

# ACNR

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**ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION**

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## **WORLD EXCLUSIVE**

Further Evidence for a Recognisable Syndrome Caused by Deletion of 1p31  
– Christopher Gillberg and David FitzPatrick

Personal Perspectives: Annie's Syndrome  
– A Parental Journey to Discovery  
– Sophie Dow

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# Make a lasting impression



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So make a lasting impression – initiate Azilect monotherapy early in the course of Parkinson's disease.<sup>3</sup>

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in patients treated concomitantly with antidepressants/SNRIs and rasagiline. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. Cases of elevated blood pressure have been reported in the post-marketing period, including one report of hypertensive crisis associated with the ingestion of unknown amounts of tyramine. **Undesirable effects in clinical trials:** **Monotherapy:** >1%: headache, influenza, skin carcinoma, leucopenia, allergy, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, musculoskeletal pain, neck pain, arthritis, urinary urgency, fever, malaise. <1%: decreased appetite, cerebrovascular accident, myocardial infarction, vesiculobullous rash. **Adjunct therapy:** >1%: dyskinesia, decreased appetite, hallucinations, abnormal dreams, dystonia, carpal tunnel syndrome, balance disorder, orthostatic hypotension, abdominal pain, constipation, nausea and vomiting, dry mouth, rash, arthralgia, neck pain, decreased weight, fall. <1%: skin melanoma, confusion, cerebrovascular accident, angina pectoris. **Please refer to the SmPC for the rates of adverse events.** **Basic NHS Price:** Azilect® (tablets) 1mg x 28 £70.72 **Legal category:**

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#### References:

1. Olanow CW et al. N Engl J Med 2009;361:1268-78.
2. Parkinson Study Group. Arch Neurol 2002;59:1937-1943.
3. Horstink M et al. Eur J Neurol 2006;13:1170-1185.



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## Editorial board and contributors



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**Professor Klaus Berek**, Austria: Head of the Neurological Department of the KH Kufstein.

**Professor Hermann Stefan**, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nürnberg.

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

## Professor Ray Dolan Elected to the Fellowship of the Royal Society

The Fellowship of the Royal Society is composed of the most distinguished scientists from the United Kingdom, other Commonwealth countries and the Republic of Ireland. Professor Dolan, Wellcome Department of Imaging Neuroscience, joins eight other Fellows at Queen Square, London, UK, with a total of 26 Fellows now in UCL Neuroscience.

## Elections to the Fellowship of the Academy of Medical Sciences

Professors Nick Fox (IoN Department of Neurodegenerative Disease, London, UK), David Miller (IoN Department of Neuroinflammation, London, UK) and Geraint Rees (UCL Institute of Cognitive Neuroscience, London, UK) have joined the ranks of the UK's most distinguished medical scientists. Fellowship of the Academy is awarded to doctors and medical researchers in recognition of the excellence of their science, their contribution to medicine and society and the range of their achievements.

## Funding for Research into MS

Merck Serono and Fast Forward, LLC, a not-for-profit organisation established by the US-based National Multiple Sclerosis Society to accelerate the development of discoveries into new or improved therapies, have announced the first four recipients of funding designed to speed research advances in mutually selected high potential areas of multiple sclerosis (MS) research.

### From its Accelerating Development fund:

Innate Therapeutics Limited, Auckland, New Zealand (Project Director – Simon Wilkinson) will receive \$550,000 over 15 months to conduct a phase IIa clinical trial in patients with progressive forms of MS using MIS416, a naturally occurring agent derived from bacteria.

Cognosci Inc., Research Triangle Park, NC (Project Director – Feng Qiao Li, PhD) will receive \$330,000 over 12 months for the efficacy testing of COG112, a molecule that mimics actions of the cholesterol transporting protein Apolipoprotein E (ApoE). In the funded studies, the company will evaluate the ability of COG112 to promote myelin repair in the central nervous system (CNS) in laboratory models of MS.

### From the Accelerating Innovation Fund:

CentRion Therapeutics Limited, Greenwich, UK, (Project Director – Michael Leach, PhD) will receive \$275,000 over 12 months for studies with compounds, related to lamotrigine, an approved epilepsy therapy, which some studies suggest also can protect nerve cells from damage. CentRion will conduct research to determine the safety and efficacy of its original neuroprotective compounds in laboratory models of MS.

Oregon Health Science University, Portland, OR, (Project Director – Lawrence Sherman, PhD) will receive \$275,000 for the screening and efficacy of small molecule inhibitors of hyaluronidase, an enzyme that dissolves hyaluronic acid – a complex sugar molecule that accumulates in MS lesions. Dr. Sherman's group has found that by-products resulting from breakdown of hyaluronic acid prevent myelin repair. This project will assess whether myelin repair blockage can be overcome by inhibiting the activity of hyaluronidase.

**The RFP process for 2010 is currently underway with a goal of approving the next round of recipients expected in December. For more information see [www.nationalmssociety.org/fastforward/index.aspx](http://www.nationalmssociety.org/fastforward/index.aspx)**

## Academic Research Awards

Cambridgeshire Community Services NHS Trust's neurorehabilitation services are set to benefit from a £100,000 research grant. Andrew Bateman, Neurorehabilitation Clinical/Business Manager, The Oliver Zangwill Centre, Cambridgeshire Community Services NHS Trust, said, "We are delighted to have been awarded funds from the NHS East of England's Clinical Academic Research Awards. These awards will fund important research that will lead to real benefits for patients. Funded research activity needs to be undertaken in addition to - and under-pinning - all the wonderful clinical work our teams do. We cannot wait for others to do the research for us: it needs to be led by our own staff because this will ensure that the work is directly applicable to the needs of our own community."

Awards were presented to:

- Jackie Mercer, Occupational Therapist in the Cambridge Community Stroke Team
  - Clare Keohane, Speech and Language Therapist at the Oliver Zangwill Centre
- Jackie and Clare were awarded funds to support Masters training. Jackie is aiming to do a research project on 'vision after stroke', and Clare is interested in 'hypersensitivity to sound' after brain injury.
- Charlie Dorer, Physiotherapist in the Therapy and Rehabilitation Service based at Papworth to undertake a PhD on 'rehabilitation of upper limb paralysis after stroke'.
  - Andrew Bateman, Neurorehabilitation Clinical/Business Manager, The Oliver Zangwill Centre. Andrew received the NHS East of England Clinical Academic Post Doctoral Fellow to part fund research on 'outcome measurements in neurorehabilitation'.



Image: Peter Fraser

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**Sativex® Oromucosal Spray Prescribing Information (refer to full Summary of Product Characteristics (SmPC) before prescribing).** Presentation: 1mL contains: 38-44mg and 35-42mg of two extracts from *Cannabis sativa* L., (Cannabis leaf and flower) corresponding to 27mg delta-9-tetrahydrocannabinol (THC) and 25mg cannabidiol (CBD). Each 100 microlitre spray contains: 2.7mg THC and 2.5mg CBD. **Indication(s):** as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. **Posology and method of administration:** oromucosal use only. Treatment must be initiated and supervised by a physician with specialist expertise in MS. Direct spray at different sites on the oromucosal surface, changing site for each use of product. May take up to 2 weeks to find optimal dose, review response after 4 weeks of treatment. Re-evaluate long term treatment periodically.

**Adults:** titration period necessary; number/timing of sprays will vary between patients. Number of sprays increased daily according to SmPC table, up to maximum of 12 sprays per day with minimum 15 minutes between sprays. **Children and adolescents:** not recommended. **Elderly:** no specific studies but CNS side effects may be more likely (see Warnings and precautions) **Significant hepatic or renal impairment:** no specific studies but effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation recommended. **Contra-indications:** hypersensitivity to cannabinoids or excipients. Breast feeding. Known/suspected history or family history of schizophrenia/other psychotic illness. History of severe personality disorder/other significant psychiatric disorder other than depression due to underlying condition. **Warnings and precautions:** not recommended in patients with serious cardiovascular disease. Caution in patients with history of epilepsy/recurrent seizures. THC and CBD are metabolised in the liver. Several THC metabolites may be psychoactive. Contains approx. 50% v/v ethanol. Risk of falls if spasticity/muscle strength no longer sufficient to maintain posture/gait. CNS side effects e.g. dizziness, somnolence could impact personal safety, e.g. hot food and drink preparation. Theoretical risk of additive effect with muscle-relaxing agents, not seen in clinical trials but warn patients risk of falls may increase. No effect seen on fertility but cannabinoids shown to affect spermatogenesis in animals. Female patients of child-bearing potential/male patients with a partner of child-bearing potential should use reliable contraception. Patients with a history of substance abuse may be more prone to abuse Sativex. Withdrawal symptoms following abrupt withdrawal of long-term Sativex are likely to be limited to transient disturbances of sleep, emotion or appetite. No increase in daily dosage observed in long-term use; self-reported levels of 'intoxication' low; dependence on Sativex unlikely. **Interactions:** no clinically apparent

drug-drug interactions seen. Co-administration with food results in mean increase in  $C_{max}$ , AUC and half-life (increase less than between-subject variability in these parameters). Concomitant ketoconazole increases  $C_{max}$  and AUC of THC (and primary metabolite) and CBD. Increase less than between-subject variability. Risk of additive sedation and muscle relaxing effects with hypnotics, sedatives and drugs with sedating effects. **Pregnancy and lactation:** do not use in pregnancy unless benefit outweighs potential risks. Do not use if breast feeding. Insufficient experience of effects on reproduction - use reliable contraception during therapy and for 3 months after discontinuation. **Effects on ability to drive and use machines:** do not drive, operate machinery or engage in any hazardous activity if experiencing significant CNS side effects; warn patients may cause loss of consciousness. **Side effects:** very common - dizziness, fatigue; common - anorexia, decreased or increased appetite, depression, disorientation, dissociation, euphoria, amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment, somnolence, blurred vision, vertigo, constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort/pain, vomiting, application site pain, asthenia, feeling abnormal/ drunk, malaise, fall; uncommon - hallucination, illusion, paranoia, suicidal ideation, delusional perception, syncope, palpitations, tachycardia, hypertension, pharyngitis, throat irritation, upper abdominal pain, oral mucosal disorders e.g. discolouration, exfoliation, stomatitis, tooth discolouration, application site irritation; unknown frequency - psychiatric symptoms e.g. anxiety and mood changes, transient psychotic reactions, possible leukoplakia (unconfirmed); inspect oral mucosa regularly in long term use.

Prescribers should consult the SmPC for further information on side effects. **Overdose:** symptomatic and supportive treatment required. **Special precautions for storage:** refrigerate (2 to 8°C); once opened refrigeration is unnecessary but do not store above 25°C. **Legal Category:** POM **Package quantities and basic NHS costs:** 3 x 10mL £375.00. **MA holder:** GW Pharma Ltd, Porton Down Science Park, Salisbury, Wiltshire SP4 0JQ **MA number(s):** PL 18024/0009 **Further information available from:** Bayer Schering Pharma, Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA United Kingdom. Telephone: 01635 563000. **Date of preparation:** March 2010.

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In the first of our review articles, Alexandra Sinclair explores the greatly under-investigated, but common, condition of Idiopathic Intracranial hypertension. In this excellent short account she describes the diagnostic criteria for this condition, along with some of the new ideas on aetiology and how best to treat it – weight loss!

In our personal perspective article, Sophie Dow describes the route to finding that their daughter, Annie, had a rare chromosomal abnormality – 46,XX, arr cgh 1p31.1>1p31.3 (RP4-759M20>RP11-261J10) x 1. The discovery of this was made some 10 years after the initial diagnosis and highlights the journey that patients and their families make with scientists and clinicians as diagnostic technologies move forward – sadly much faster than treatments and cures.

A new series in this issue of ACNR, edited by Alan Carson and Jon Stone, attempts to tackle issues of neuropsychiatry through a series of clinical scenarios. This is an innovative approach suggested by Alan and Jon, and judging by the first in the series, should be hugely successful. In this article Jason Warren explores the difficult issue of dementia and MS, and what can be usefully said in a consultation about this issue. Do let us have your feedback on this new format.

Liesl Alcock discusses the features and best management of a common problem in Parkinson's disease – namely orthostatic hypotension. This succinct account reminds us of the plethora of features this condition causes and how it can best be defined and treated.

In the next of our series in paediatric neurology, edited by Anna Maw, Richard Brown takes us through the process of recognising and investigating regression in people over the age of five years old. He concludes "Patients presenting for the first time with apparent loss of skills must be carefully evaluated. The first step is defining the problem. Is this true neurodegenerative disease, with progressive loss of skills and the development of neurological signs? Or is this a pseudo-regression, where the problems derive from non-degenerative causes".

"One audit of 719 PEG procedures...demonstrated that 19% were futile and of those dying 43% did so within one week of insertion", so writes Diane Playford in her short summary of a report from a working group on PEGs. This procedure, which is often considered in neurological patients with strokes or neurodegenerative disorders is useful in the right patient at the right time. The challenge is achieving just that as this report highlights.

In a new series of articles edited by Martyn Bracewell, the historical background to the study of motor control is presented. Jonathon O'Brien and Martyn take us from the early work of Sherrington to the present day and mirror neurons!

Andrew Larner gives us another tour de force with his sixth article on headache in neurological literature, whilst also providing us with some wonderful book reviews.

We have our usual summary of conferences and journals, and we again hope you enjoy the mix of articles that is ACNR. ♦



*Roger Barker, Co-Editor.*

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

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Hypersensitivity 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. **Marketing Authorisation Number(s):** 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: £10.81; 100 mg x 14 tabs: £21.62; 100 mg x 56 tabs: £86.50; 150 mg x 14 tabs: £32.44; 150 mg x 56 tabs: £129.74; 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. **Marketing Authorisation 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:** 01/2010 (10VPE0010). Vimpat is a registered trademark. **References:** 1. Vimpat Summary of Product Characteristics, 2010. 2. Beyreuther BK et al. CNS Drug Rev 2007; 13(1): 21-42. 3. UCB Data on file. **Date of preparation:** June 2010. 10VPE0137



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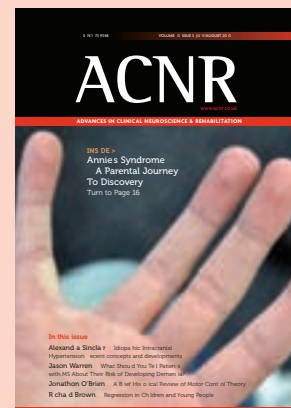
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Cover picture shows Annie Dow's hand - see our World Exclusive feature about Annie's Syndrome on page 16.



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# Idiopathic Intracranial Hypertension: recent concepts and developments



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Idiopathic intracranial hypertension (IIH) is a condition characterised by elevated intracranial pressure (ICP) and papilloedema, typically occurring in obese young women. The nomenclature of IIH has changed over the years, with previous terms including serous meningitis, pseudotumour cerebri and more recently, benign intracranial hypertension. The latter is now considered inappropriate for a condition in which affected individuals suffer with significant morbidity from chronic disabling headaches, together with progressive visual loss, which is severe and permanent in up to 25% of cases.<sup>1</sup>

### Diagnosis of IIH

The diagnostic criteria for IIH were initially suggested in 1937 by Dandy and despite recent revision,<sup>2,3</sup> further clarification is required to highlight the universal importance of excluding venous sinus thrombosis.<sup>4</sup> Additionally, a cut-off for elevated CSF opening pressure needs to be specified (Table 1).

### Pathogenesis of IIH

The pathogenesis of IIH remains unknown. Disordered cerebrospinal fluid (CSF) dynamics are fundamental although there is much inconclusive speculation in the literature as to whether this relates to enhanced CSF production at the choroid plexus or restricted CSF drainage at the arachnoid granulation tissue. The latter may, in turn, be compounded by increased venous sinus pressure. A wider review of this area is considered by Sinclair et al.<sup>5</sup>

### The role of obesity in IIH

Of particular interest in IIH, is that over 93% of patients are obese.<sup>6</sup> In the obese population the

incidence of IIH rises above 19 per 100,000, compared to 2.2 per 100,000 amongst the general population.<sup>7,8</sup> The prevalence of IIH is likely to rise in conjunction with the global epidemic of obesity (greater than 24% of adults in the United Kingdom are currently obese<sup>9</sup>) contributing to significant morbidity in young obese women over the next decade.

The association between obesity and IIH has not been satisfactorily explained and speculation regarding the role of centrally distributed adiposity and co-existing obstructive sleep apnoea remain unsubstantiated.<sup>10,11</sup> A number of case reports have linked IIH to Cushing's disease (a condition characterised by obesity and elevated circulating cortisol) as well as glucocorticoid therapy.<sup>5,12,13</sup> Although elevated serum cortisol is not observed in obesity, dysregulation of the cortisol generating enzyme, 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) is well documented.<sup>14</sup> Glucocorticoids are regulated at a systemic level through the actions of the hypothalamic pituitary adrenal axis; however, at a tissue specific level, 11 $\beta$ -HSD1 (which converts inactive cortisone to active cortisol), fine tunes local glucocorticoid availability. 11 $\beta$ -HSD1 is highly expressed in adipose tissue and has a key role in regulating adipocyte differentiation.<sup>15</sup> Additionally, and of relevance in the female dominated condition of IIH, 11 $\beta$ -HSD1 exhibits sexual dimorphism (lower levels in women than men) with activity manipulated by sex hormones.

Interestingly, 11 $\beta$ -HSD1 has also been found to have a functional role in intraocular pressure homeostasis though the secretion of aqueous humour.<sup>16</sup> Aqueous humour secretion occurs via a mechanism analogous to that occurring in the embryologically-related choroid plexus which

**TABLE: Diagnostic criteria for idiopathic intracranial hypertension**

Symptoms, if present, of raised intracranial pressure
Signs representing elevated intracranial pressure or papilloedema
Elevated CSF opening pressure in the lateral decubitus position *( $>$ 25 cmH <sub>2</sub> O, and only with great caution in those with a lower pressure)
Normal CSF composition
Imaging to exclude hydrocephalus, mass or structural lesion and *universal exclusion of venous sinus thrombosis (magnetic resonance or computed tomogram venography suggested)
No secondary cause of elevated intracranial pressure identified (anaemia, obstructive sleep apnoea, Guillain Barré syndrome, or drug effects e.g. antibiotics, non-steroidal anti-inflammatory drugs, vitamin A, lithium, cimetidine).
Adapted from the "Updated modified Dandy criteria (Friedman & Jacobson 2002) with suggested additions to the criteria marked with a star *.

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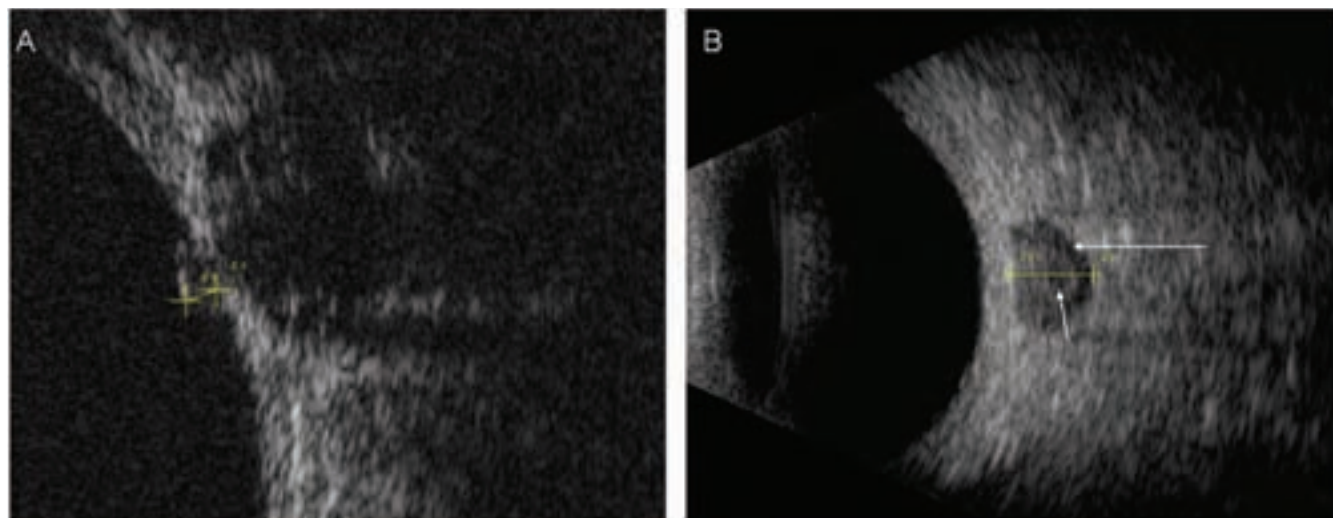
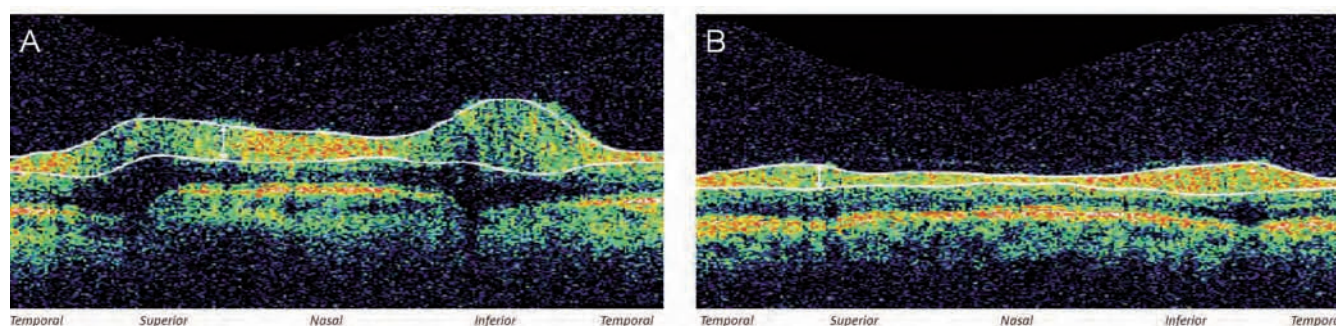


Figure 1: Ultrasonographic measurements of papilloedema. (A) Sagittal section through the orbit with the callipers measuring the maximal optic disc height (20Hz B-scan), (B) illustrates a cross section through the optic nerve sheath, the callipers mark the maximal inter-pial diameter (10Hz B-scan). The long arrow marks the hypodense signal from the cerebrospinal fluid within the distended optic nerve sheath and the short arrow marks the optic nerve.



Optical coherence tomography scan illustrating a cross sectional image acquired from scanning around the circumference of the optic disc. The arrows mark the retinal nerve fibre layer (RNFL). (A) Illustrates distension of RNFL in a patient with papilloedema, (B) illustrates the same patient following resolution of the papilloedema with a corresponding decrease in the height of the RNFL. A reduced RNFL should be interpreted in the context of the optic disc appearance and visual field assessment, as a decrease in the RNFL could also indicate progression to optic atrophy.

secretes CSF. It is possible that akin to the regulation of intraocular pressure,  $11\beta$ -HSD1 may also have a role in the regulation of CSF secretion at the choroid plexus. This is endorsed by the finding of  $11\beta$ -HSD1 activity, as well as expression of key element of the glucocorticoid signalling cascade, in the rabbit and human choroid plexus.<sup>17,18</sup> Within the eye, glucocorticoids are also known to elevate intraocular pressure through actions at the trabecular meshwork (the primary drainage tissue in the eye), as noted in topical dexamethasone induced glaucoma. Arachnoid granulation tissue has a similar structure to ocular trabecular meshwork and although little is known regarding the precise mechanisms which control drainage of CSF, glucocorticoids may also be important in manipulating CSF drainage.<sup>18</sup> Amongst individuals with IIH, global  $11\beta$ -HSD1 activity has been noted to decrease in conjunction with weight loss, improvement in symptoms and falling ICP. Furthermore, in these patients, the reduction in  $11\beta$ -HSD1 activity significantly correlated with falling ICP.<sup>24</sup> Glucocorticoids and  $11\beta$ -HSD1 may, therefore, be important in ICP dynamics and obesity in IIH and their role, along with the therapeutic potential of  $11\beta$ -HSD1 inhibitors, is currently being explored.

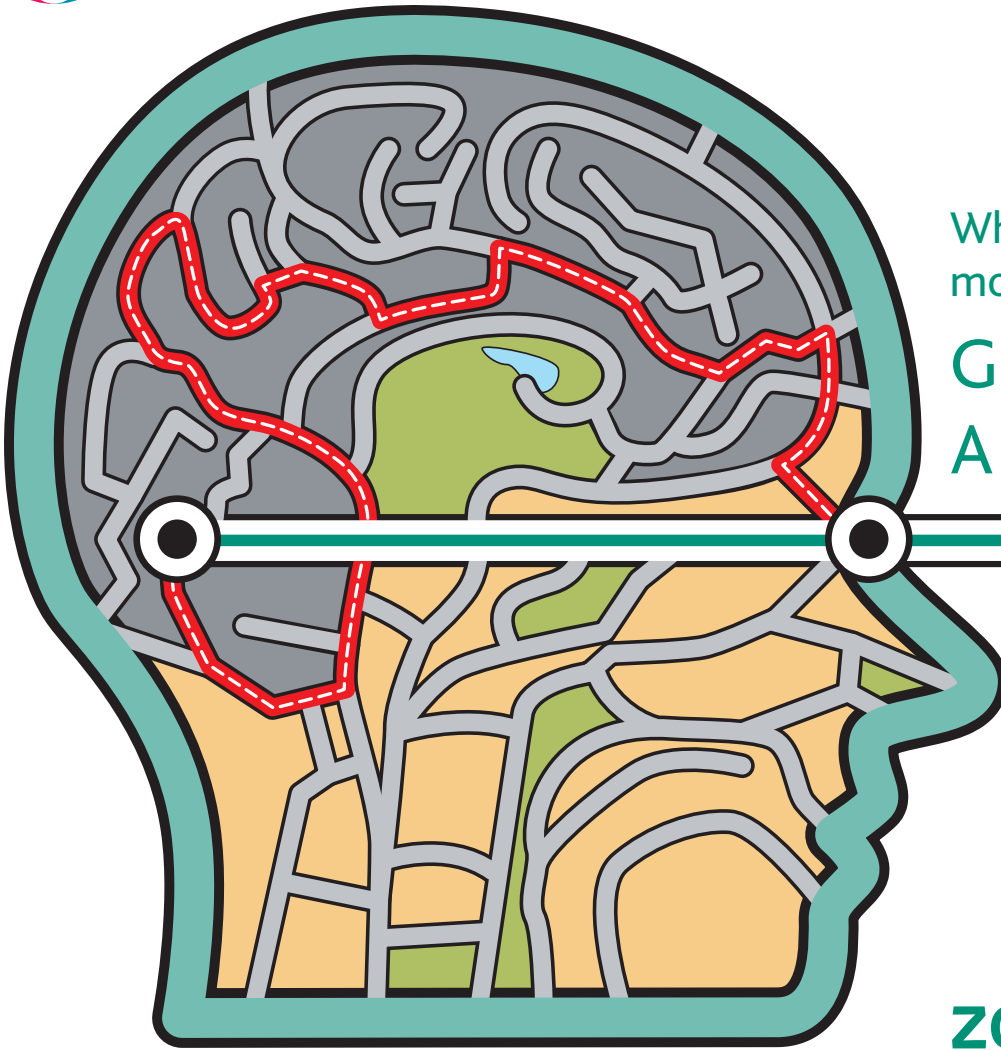
### Treatment in IIH

The 2005 Cochrane review highlighted that an evidence base for the treatment of IIH has never been established.<sup>19</sup> Medical therapies (such as acetazolamide and diuretics) are widely utilised, with surgical intervention (typically CSF shunting or optic nerve sheath fenestration) typically reserved for those with rapidly deteriorating vision.

The most recent and largest randomised controlled study to assess treatment in IIH evaluated the efficacy of acetazolamide and failed to demonstrate a beneficial effect.<sup>5</sup> Although the study was under-powered ( $n=50$ ) it highlighted that acetazolamide was extremely poorly tolerated, with 48% of subjects discontinuing acetazolamide (all at doses of less than 1500 mg per day) through choice or due to side effects, typically nausea and paraesthesia.<sup>20</sup> The current extensive use of acetazolamide in IIH needs to be questioned in light of these results and further studies are awaited to clarify the situation. The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC group) began enrolment to a multi-centre US trial in January 2010, aiming to recruit 154 patients in a randomised, placebo controlled trial of acetazolamide ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) identifier: NCT01003639); hopefully this study will shed further light on

the area. The therapeutic value of topiramate has also been considered in IIH: an open-labelled pilot study ( $n=40$ ) demonstrated a beneficial effect on the visual field grade (of a comparable magnitude to that observed in a concurrently treated cohort taking acetazolamide).<sup>21</sup> However, interpretation of this result is significantly limited as the study was not placebo controlled or masked.

One of the most frequently advocated treatments for IIH is weight loss, although until recently evidence for the efficacy of this approach has been limited to a prospective study, carried out over 35 years ago, which noted subjective improvement in the papilloedema in nine subjects with IIH on a low calorie rice diet.<sup>22</sup> This report has now been superseded by a study in which individuals with IIH ( $n=25$ ) were subjected to a three month period of observation followed by a three month intensive diet, during which subjects lost a mean of 15% of body weight (around 16kg).<sup>23</sup> The study provides the first evidence that weight loss effectively reduces ICP (measured by lumbar puncture), as well as headaches and papilloedema, in patients with IIH. These results provide important evidence for clinicians to advise and encourage patients with IIH to embark upon and maintain a weight reducing diet in order to treat



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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,

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their condition. The study was further strengthened by the use of objective outcome measures to quantify papilloedema.<sup>23</sup> Previously, evaluation of papilloedema has relied upon subjective assessment by the clinician, this study effectively utilised ultrasonography, to measure the optic disc height and optic nerve sheath diameter (Figure 1), as well as optical coherence tomography (Figure 2), to measure the peripapillary retinal nerve fibre layer (a measure of oedema and axonal detention around the optic disc).<sup>23</sup> Objective assessment of papilloedema in IIH marks a key advance likely to be widely adopted in clinical management as well as future research studies.

### Conclusions

It is now over 100 years since IIH was first described, yet progress to determine the underlying cause, and establish an evidence base for treatment, has been remarkably slow. Obesity may have an important role in the aetiology of IIH and further studies clarifying the implications of obesity, and associated metabolic changes in glucocorticoids and 11 $\beta$ -HSD1, will be of interest. The potential for weight reduction to modify obesity and treat IIH, has now been confirmed. However, the difficulties for patients to achieve and maintain weight loss are universally recognised. Practical strategies to facilitate long term weight loss, within a clinical environment, now need to be considered for patients with IIH. ♦

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### Christopher Gillberg

is a Professor of Child and Adolescent Psychiatry at the University of Gothenburg, and Chief Physician at the Child Neuropsychiatry Clinic (CNC) at Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg. He is also a Professor of Child and Adolescent Psychiatry at University College London (Institute of Child Health), University of Glasgow and at the University of Strathclyde, Glasgow. He is the founding editor of the *European Child and Adolescent Psychiatry*, the official journal of the European Society of Child and Adolescent Psychiatry since 1991. He is an elected member of The Royal Norwegian Society of Sciences and Letters since 2003.

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### David FitzPatrick,

MD, FRCP(Edin) is a consultant and professor of clinical genetics. He leads a research group in the MRC Human Genetics Unit in Edinburgh that aims to identify and understand the genetic basis of developmental disorders in humans. His particular interests are; understanding the developmental programs directing formation of the eye, face and the limbs and the use of new technologies to identify genomic causes of learning disability.

Dear Reader,

It is with great pleasure that we submit this our case report on deletion of 1p31 to this issue of ACNR.

Not only is it the first record of this specific chromosomal abnormality with a very detailed account of child development and symptoms, but it is also a first in that the scientific findings are the result of a collaboration between the family involved and us the researchers.

Sophie Dow, Annie's mother, has together with her husband, been the driving force behind our findings of this very rare chromosome deletion. The family first contacted me, Christopher Gillberg, in 2003 asking me to take a look at Annie and to try to find a more specific diagnosis than 'brain damage that occurred during pregnancy' which was, at the time, the rather unspecific conclusion of previous assessments. And the rest is history, as

you will find out when reading Dow's account of the road to discovery.

We believe that collaboration such as this between family and researchers working together in the presentation of new results to readers of a scientific journal, is a novel and helpful way of presenting a case.

We hope that it will be only the first in a new category of reports, authored not by ourselves, but by other families and other research groups.

Christopher Gillberg,  
MD, PhD, Professor of Child and Adolescent Psychiatry, University of Gothenburg, Institute of Child Health, London and University of Glasgow.

David FitzPatrick,  
MD, Honorary Consultant and Professor of Clinical Genetics,  
MRC Human Genetics Unit, Edinburgh.

## Case Report: Further Evidence for a Recognisable Syndrome Caused by Deletion of 1p31

We present our case report on an adolescent female, born to healthy and non-consanguineous parents by normal delivery at term weighing 3500g following a pregnancy complicated by pre-eclampsia. She has an older male sibling with mild dyslexia but who is otherwise well, and there is no family history of learning disability. There were no medical problems in the perinatal or neonatal periods. During the first year of life some mild global developmental delay was noted. The girl walked at 18 months of age. Significant speech and language delay was noted in the second year and later. She was seen by a number of experts over a period of several years, but no clear diagnosis was established. Assessment at the age of 12.8 years revealed mild learning disability, developmental coordination disorder (DCD), and attention-deficit/hyperactivity disorder (ADHD), mainly inattentive subtype (the combination of DCD and ADHD, with or without mild learning disability, is often referred to as "deficits in attention, motor control and perception" (DAMP) (Rasmussen and Gillberg 2000), and this was the comprehensive diagnosis assigned). The DCD was characterised by overall dyspraxia and apractic gait. A WISC-III test was performed in connection with the neuropsychiatric assessment. The cognitive profile suggested non-verbal learning disability even though the overall IQ-level was depressed. Results of the WISC-III test were as follows: Full Scale IQ 56, Verbal IQ 64, Performance IQ 45, Information (scaled score) 6, Arithmetic 2,

Comprehension 7, Vocabulary 8, Similarities 6, Block Design 4, Object Assembly 5, Coding 3, Digit Span 2, and Picture Completion 1. She had a long thin face, a broad prominent nasal bridge, and a prominent nose, hypertelorism, a large mouth, moderate pectus excavatum, thin tapering fingers (with distal broadening), and very thin feet and toes (club-shaped big toe). At the age of 17 years she developed an acute right lower lobe pneumonia requiring hospitalisation.

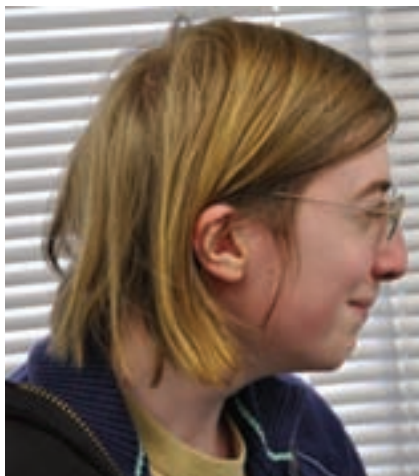
Standard karyotype and FISH 22q11.2 were normal. Array based comparative genomic hybridisation (array-CGH) analysis using the 0.5Mb 'CytoChip™' BAC microarray (BlueGnome Ltd, UK) showed del(1)(p31.1;p31.3) with the minimum and maximum sizes of the deletion being 4.86Mb (RP11-175G14> RP4-547N15 Chr1:67239552-72094826) and 6.31Mb (RP11-261J10> RP4-759M20, chr1:66677274-72983939) respectively. The DECIPHER number of this patient is 00001954.

### Discussion

Deletions of 1p31.1>1p31.3 appear to be very rare. After a review of the literature of standard cytogenetic banding reports we were able to identify only four published cases (Bene et al., 1979; Lai et al., 1991; Mircher et al., 2003; Petersen and Warburg, 1987), plus one further case with a significantly larger, but overlapping, deletion identified by array CGH analysis (Shaw-Smith et al., 2004). Clinically and cytogenetically the case presented here most



photos David FitzPatrick 2009



resembles the two cases reported by Lai et al. In particular the prominent nose, long face, arachnodactyly and motor developmental problems (DCD) are common to all three cases.

There are at least 21 different genes in the deleted region. Only three of these have been linked to human disease; IL23R as a protective factor in inflammatory bowel disease, and biallelic mutations in RPE65 and CTH as causes of Leber congenital amaurosis and cystathionuria, respectively. It has not been possible to attribute obvious genotype-phenotype correlations to the other genes in the region.

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# Annie's Syndrome – A Parental Journey To Discovery



## Sophie Dow

Sophie Dow is a journalist and founder of Mindroom ([www.mindroom.org](http://www.mindroom.org)) an organisation that works to create awareness about all kinds of learning difficulties. She has a daughter, Annie aged 19 who is the inspiration behind Mindroom. Sophie was born and raised in Sweden, lived 12 years in London, where she worked as correspondent for Swedish press, radio and TV (arts and culture). Moved to Edinburgh 1994 where she still lives.

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"Well, Mrs Dow," said the extremely curly-haired, highly recommended child psychologist from Harley Street as he sat in my kitchen, "you've got a problem. According to my tests, your daughter is mentally handicapped."

I smiled politely and complimented him on his briefcase – beautifully worn leather in just the right colour. Exactly what I'd been looking for. Plenty of room, with lots of useful pockets, a zipped pocket for your wallet, a small one for your keys and big enough for newspapers.

"But," Mr Flowers MA (Hons), Dip Teach, Ed. Psych, MNZ, PSSC Psychology, continued mercilessly, "having seen how sociable and communicative she is, I'm not sure that I agree entirely with the tests."

He had tested Annie according to the book for more than three hours, using two different tests: one to test the child's practical abilities and the other the child's social skills. Apparently the two combined provide a reasonably accurate picture of what the future holds.

Mr Flowers proved to be impeccably professional and immune to my desperate attempts to play down the results of the tests. With an aching heart, I withdrew into a corner of our spacious kitchen. Deep down I knew that something wasn't right but I was desperate to reassure myself, to seduce myself, into

believing that it was only a matter of a couple of courses of penicillin, or at worst, that we'd have to go to an OT for a term or two.

Mentally exhausted, we said goodbye to Mr Flowers on the front step. "Thank you for coming. Have a good day. Lovely weather, isn't it? Oh, and where did you buy that briefcase?" In a kind voice he explains that he bought it before he moved to the UK. A proper New Zealand school bag, and yes, thank you, he would have a good day.

Self-preservation had already kicked in, bubble-wrapping the shocking news and numbing it with comforting politeness and small talk.

That day of reckoning was the 20th May, 1994 and Annie was three years and four months old. Today, 16 years later, we know that Annie has a unique chromosome deletion of 1p31, chromosome 1.

But first things first, and just like the DNA chain of logical events, the parental adjustment to such an unexpected, life changing scenario needs to proceed at its own pace.

The impossible and rhetorical questions that came tumbling into our unsuspecting parental world that very day all those years ago, do unfortunately to some extent still apply.

- What does mentally handicapped actually mean?

- Will Annie be able to lead an independent life?
- What about school?
- Can she train herself to overcome her difficulties?
- Surely to God, there must be an oracle somewhere that can help her?
- Perhaps somewhere farflung like China?
- Can we protect her and help her?
- What will happen to her when we die?

Falling outside the norm, as Annie and so many others do, places you in a multi-faceted and complex world. The facets involved include the mind, the soul, the environment, the ongoing medical research, the educational system, social services and your own inner feelings, self esteem – and of course, your fears. The complexities are the interplay between them all.

In some ways the term 'learning difficulties' applies just as much to society as to the children and adults involved. Our society seems to have a blind spot – its own form of learning difficulty – towards people with different needs, and its inability to meet their needs is both part of, and adds, to the problem.

A few years later I set up Mindroom, a charity dedicated to creating awareness of learning difficulties. We now collaborate across the field with leading experts within the field of neurodevelopmental disorders, with politicians, health and education professionals as well as provide direct help and support to families who are living with learning difficulties.

The second day of reckoning for us, was the 18th July 2007, when we received the news about the chromosome deletion, from Dr David FitzPatrick, Professor of Clinical Genetics at MRC Genetics Unit in Edinburgh.

After a third assessment in 2003, which failed to pinpoint the cause of Annie's disabilities, and at the suggestion of Christopher Gillberg, Professor of Child and Adolescent Psychiatry, University of Gothenburg, Institute of Child Health, London and University of Glasgow, Annie was tested for FISH 22q11.2.

Annie has amongst other features; a high/prominent nasal bridge, thin/long face, arachnodactyly, dyspraxia/apraxia including gait apraxia, short attention span, extraordinarily big club shaped big toes and mental retardation/developmental delay.

Although results came back as normal, we felt we were now on the right track.

The answer would most probably be found within the rapid unraveling of the human genome. However, our team; Gillberg, FitzPatrick, Sharkey, myself and my husband Robin, were ahead of the technology needed to solve the genetic mystery. It was agreed that Professor FitzPatrick would keep Annie's blood sample until such technological break through would present itself.

Four years later, the brown window envelope arrived, by 2nd class post, carrying the fundamental information of 'a small but significant missing fragment on the short arm of chromosome 1'. The technique used was new, called array CGH, and no other case with a deletion of this precise region of chromosome 1 had been detected worldwide to date.

The code for Annie's array CGH analysis is: 46,XX,arr cgh 1p31.1>1p31.3 (RP4-759M20->RP11-261J10) x 1

As a journalist and as the founder of Mindroom, I was very excited by the news. I felt we were right at the heart of a genetic detective novel. But as a mother, I and our family will always be up against a void in Annie's genome of about 6 million base pairs of DNA, which is less than 3% of the total length of chromosome 1.

That particular void is irreparable, and perhaps the upside of such an absolute is a blessing, as we are spared the hunt for a cure. But it is the other void, the further scientific understanding of what role those missing 21 genes would have played, had Annie arrived in tact, with a complete count of genes, that needs to be filled. Professor FitzPatrick and his colleagues, are at present unable to answer those questions, which to a layperson seems almost incredible when we have such sophisticated answers to so much in today's world.

Here we are once again, waiting for technology to catch up with our hypothesising – is there a connection between Annie's aunts ulcerative colitis and the fact that three of the missing genes are linked to human disease; IL23R as a protective factor in inflammatory bowel disease?

Or could one of the missing genes have been a contributing factor to Annie's two episodes of acute lobar pneumonia which required hospitalisation at the ages 12 and 17 years, with the latter episode associated with a severe unclassified mucocutaneous disorder?

What we do know though, is that deletions of 1p31.1-1p31.3 are very rare. A review of standard genetic banding by Professor FitzPatrick and his team, revealed only five cases with a further case identified with a significantly larger, but overlapping deletion.

Having done our own genetic detective work, we have checked with the excellent UNIQUE, the rare chromosome disorder support group based in Surrey, who have as complete a database on all known chromosome differences as is possible, and so far Annie is the first person to be identified with this particular chromosome profile. Her specifics are now registered with UNIQUE and available to the world. [www.rarechromo.org](http://www.rarechromo.org)

It is in the hope that by writing up Annie's case so far, we will be able to identify other Annie's out there, thus creating a syndrome from which affected families can draw information and create a frame of reference.

On the wall in my study, within my line of vision and as a thought provoking reminder of who I am, sits a badge from a Parliamentary Reception at the Scottish Parliament that simply says 'Sophie Dow – Rare chromosome disorders and Mindroom'.

Who could have predicted such a deviation in life?

*Sophie Dow, June 2010*

For more information on Mindroom, please visit [www.mindroom.org](http://www.mindroom.org)

Mindroom's fifth international conference No Mind Left Behind, 29-30 March 2011 at Glasgow Royal Concert Hall, features over 50 of the worlds leading experts within the field of social communication and learning difficulties.

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

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

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Series Editor

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Series Editor

### Jon Stone

Series editor Jon Stone is a Consultant Neurologist and Honorary Senior Lecturer in the Department of Clinical Neurosciences in Edinburgh. Since 1999 he has developed a research and clinical interest in functional symptoms within neurology, especially the symptom of weakness. He writes regularly on this topic in scientific papers and for textbooks of neurology and psychiatry.

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Welcome to a new series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to write short pieces

in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.

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# What Should You Tell Patients with MS About Their Risk of Developing Dementia?

## Case

A 35-year-old man with a new diagnosis of relapsing remitting multiple sclerosis comes for clinic review. His only residual symptom is a bit of tingling in his left leg. His lawyer wife has written a letter to you before the clinic to say that she has read conflicting information on the internet about the effects of MS on cognition and is now very concerned about the risks of dementia. She has not discussed this with him but wanted to find out what the risks were and to have a discussion of this at his next clinic appointment. What should you tell them? There are at least four questions implicit in this scenario. What is meant by 'dementia' (in the context of MS)? How frequently does it occur? What are the implications for this patient? And finally, what should I tell them?

### What is 'MS dementia'?

Cognitive dysfunction in MS has a spectrum of severity ranging from mild task-specific deficits to severe global cognitive decline, with most cases falling toward the milder end of that spectrum.<sup>1</sup> As predicted from the distribution of brain damage, in most cases the profile of cognitive impairment predominantly reflects involvement of subcortical pathways, impacting particularly on attention and concentration, processing speed, encoding of new information, working memory, executive functions and affect. This profile is non-specific and (in itself) of limited diagnostic usefulness: similar deficits occur in most 'subcortical dementias'. Moreover, the spectrum of cognitive dysfunction in MS is likely to be broader than can generally be captured by conventional screening instruments, extending to affect complex behaviours and aspects of social cognition.<sup>2</sup> Certain deficits (such as aphasia and apraxia) occur seldom; however involvement of most cognitive domains has been described, and the specific cognitive presentation shows wide individual variation and correlates only loosely with physical disability. In addition, cognitive dysfunction is frequently associated with fatigue, itself a functionally important symptom in MS. Though classical disconnection syndromes are rare, the cognitive effects of MS may reflect at least in part disruption of cortico-subcortical networks, including ascending cholinergic and

other neurotransmitter pathways.<sup>3,4</sup> In general the severity of cognitive impairment in MS correlates broadly with disease burden, duration and overall severity,<sup>1,5</sup> though there is no simple relation to longer term functional outcome. The effect of age is more difficult to assess.<sup>6</sup> Neither brain atrophy measures nor total lesion load entirely account for the extent of cognitive dysfunction in MS.<sup>7</sup> White matter lesion volume has been shown to be the best MRI predictor of overall cognitive function after five years in primary progressive MS,<sup>3</sup> however the role of cortical damage is increasingly recognised.<sup>3,7</sup> As with any cognitive syndrome, neuropsychometry (if available) is valuable for delineating deficits more fully and for assessing change. Since cognitive deterioration can signal progressive disease in the absence of increasing physical disability, there is a need for simple and reliable cognitive metrics that can be incorporated into the routine assessment of patients.

### How frequently does it occur?

Estimates of the frequency of cognitive decline in MS vary depending in part on how it is defined and measured, but it is common – somewhere in the order of 40-70% of patients will exhibit cognitive deficits at some stage during the course. Although the overall prevalence of cognitive deficits increases with disease duration,<sup>5</sup> significant dementia eventually develops only in a variable minority<sup>1</sup> and even

**Table 1: Cognitive dysfunction in MS: at a glance****How commonly does it occur?**

Cognitive dysfunction is common (over half of patients over the course of the disease) but frank dementia is unusual.

**How does it manifest?**

Typically, memory, attention and executive functions are predominantly affected.

**What is the cognitive outlook?**

Cognitive impairment tends to correlate broadly with disease stage and overall severity, and with progressive disease, however prognosis in the individual patient is difficult. Heavy white matter burden on initial MRI is a predictor of cognitive decline in the intermediate to longer term. Cognition is not usually the major determinant of overall functional status.

**Is it all just MS?**

The possibility of a second disease process should be kept in mind, and pursued particularly if cognitive dysfunction is dominant or rapidly evolving in relation to other disease indices, where atypical brain imaging findings (e.g. focal atrophy) are present or if there is a strong family history of dementia

**Can it be treated?**

Management focuses mainly on mood, fatigue, iatrogenic and other factors that can contribute to cognitive dysfunction. The role of cholinesterase inhibitors and other symptomatic therapies and the impact of disease-modification on cognitive function remain under evaluation.

after follow-up intervals of 10 to 30 years a substantial proportion of all patients (as many as a half in some series) do not exhibit cognitive decline<sup>5,6</sup> Apparent discrepancies between studies are likely to reflect not simply the duration of the follow-up interval but the particular neuropsychological indices chosen. Although cognitive symptoms are observed across disease subtypes, cognitive decline tends to be more significant in primary and secondary progressive MS, probably reflecting the relative extent of white matter damage. A meta-analysis in relapsing-remitting MS indicates that cognitive decline is moderate in this group and tends to be more severe in older patients and in females.<sup>8</sup> Dementia as a presentation of MS is unusual enough (<5% of cases in a recent large series from the Mayo Clinic<sup>9</sup>) to call the diagnosis into question. Unfortunately, MS itself is sufficiently common that second pathologies causing cognitive decline do need to be considered: clues to this situation include dementia as an early or prominent feature, a 'biphasic' course where significant cognitive decline supervenes on longstanding MS that is apparently otherwise stable, a strong family history of dementia, or the presence of focal brain atrophy on MRI.

**What are the implications for my patient?**

For individual patients with MS and their families, cognitive decline understandably bulks large among the most feared accompaniments of the disease and indeed, it contributes importantly to social handicap over and above the degree of physical impairment as well as potentially limiting the scope of physical rehabilitation.<sup>5</sup> The risk of developing significant cognitive decline in the individual case is difficult to estimate with any precision, at least until the passage of time has revealed the overall course of the disease more clearly. The question of treatment inevitably arises. In principle, cognition should benefit from restriction of accumulated disease lesion load in relapsing remitting MS; however, there is relatively little evidence concerning the cognitive impact of disease modification, perhaps because trials have tended to include cognition as a secondary outcome measure. This means that cognitive considerations alone do not, in general, presently drive therapeutic decision making, though there are indications this may change.<sup>10</sup> Various symptom-modifying agents have been tried in small numbers of patients, including several of the same drugs used for fatigue, however results to date have been largely inconclusive.<sup>14</sup> There is modest evidence for a useful benefit from acetylcholinesterase inhibition (Donepezil) on learning and memory and everyday functioning,<sup>14</sup> though side effects may be relatively more frequent in patients with MS than with Alzheimer's. For the present, the use of cholinesterase inhibitors for MS is not covered by NICE guidelines in the UK, and this seems unlikely to change in the foreseeable future. The evidence base for nonpharmacological cognitive rehabilitation programmes in MS is similarly limited. One important practical issue is to address treatable factors that may contribute to cognitive dysfunction where these arise. One such factor is the drugs used to treat other symptoms in MS: examples include centrally acting spasmolytic agents such as baclofen or tizanidine (which often produce sedation), and anticholinergic agents to treat urinary urgency (agents with relatively lower CNS activity are preferable to oxybutynin). Other key factors are fatigue and depression: both are common in MS, and treatment may substantially improve overall quality of life. The relationship between depression and cognitive decline is not straightforward, since mood alterations may be less severe in patients who lack insight due to cognitive deterioration, while conversely, depressed patients are more likely to report subjective cognitive complaints.

**What should I tell them?**

In the light of the available information, what should I tell this patient (and his wife)? Unsurprisingly, there is no simple answer to the question of 'dementia risk' (see Table 1): this must take into account the specific characteristics of the individual patient's MS and its evolution. The first step is to try to uncover what is behind the question, and the concerns of the

patient (besides those of his wife); what do they each understand by 'dementia'? Patients in this age group are typically embroiled in a difficult matrix of social, occupational and not least family planning issues. All this needs to be probed gently at the consultation. If indeed the patient wants more information, my policy is to be honest while (ideally) attempting to tread a path between insouciance and despondency. I would tell them that cognitive symptoms are common in MS, but generalised intellectual decline ('dementia' in the traditional and popular sense) is uncommon. Typically everyday memory, concentration and aspects of organisational and planning ability (i.e., executive functions) are most vulnerable, whereas a number of specific cognitive capacities are spared. More precise cognitive prognosis in the individual case is difficult; however, this patient appears to have relapsing-remitting disease which, on current evidence, would place him in a relatively favourable prognostic group. While there is no very effective treatment for cognitive symptoms per se, there is a need for vigilance to ensure that potentially treatable factors that may affect cognitive function in MS are detected and treated wherever possible – and amongst these, one of the most important is mood. Given the current level of clinical and research interest, it also seems fair to suggest that new information relevant to the question will soon be forthcoming. ♦

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# A Brief Historical Review of Motor Control Theory



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In this edition, we begin a series of primers on motor control. Topics to be covered include the motor cortices, basal ganglia and cerebellum. Naturally such a series cannot be comprehensive, but we hope our contributors, drawn from the UK and farther afield, will convey both some of the fundamentals and some of the exciting new developments in motor neuroscience. We start with an historical overview. Rather than take the traditional perspectives of neurophysiology and neuroanatomy, we have chosen to review what seem to us some of the key conceptual advances in thinking about motor control since the late nineteenth century. Although Charles Sherrington will (we hope!) be a familiar name, some of the other authors discussed may not be to those of you who benefitted from a traditional medical school curriculum.

*Martyn Bracewell, Series editor*

### Introduction

The field of motor control explores the ways in which the nervous system co-ordinates the musculoskeletal system to produce movement. This review describes some key theoretical contributions to the field from the nineteenth century through to the present day.

### From Sherrington to Bernstein

For Sherrington<sup>1</sup> the reflex arc, consisting of a receptor, a conductor and an effector motor neuron, was the basic unit of analysis. The motor neuron acted as the final common path for stimuli from other reflex arcs throughout the organism. Reflexes might be combined simultaneously, with one dominant and multiple subordinate arcs converging on the common path. They could also form a consecutive chain, with one reflex initiating the next, as in the process of swallowing. Sherrington also demonstrated that the simultaneous excitation and inhibition of synergistic muscles acting at a joint was a product of the same reflex, a phenomenon labelled reciprocal innervation. Overall, voluntary and automatic movements were seen as resulting from such co-ordinated reflex responses.

Other researchers questioned this emphasis on movement as a reaction to external stimuli. Woodworth,<sup>2</sup> for example, investigated human hand movements and noted that the accuracy of very rapid movements seemed unaffected by visual or muscular feedback. Woodworth concluded that these movements were guided by impulse control, independent of sensory feedback. This initial impulse, he argued, comprised the action goal and the concomitant muscular activations, and therefore encompassed the whole movement. Lashley<sup>3</sup> explored this idea in a case study of a man with complete anaesthesia in the left lower limb. When deprived of visual feedback the patient could nonetheless place his leg following instruction, demonstrating accuracy comparable with a

healthy control. Lashley maintained that these movements were controlled centrally, with the impulse spreading from its origin to downstream motor centres.

Bernstein<sup>4</sup> made a number of contributions that built on earlier ideas and pointed in new directions. He shared the view that movements are directed towards a pre-specified goal and therefore the central nervous system (CNS) must contain a guiding engram or advance program for the entire movement. While this implied a hierarchical organisation for the nervous system, Bernstein stressed that movement resulted from the interaction of the CNS, the musculoskeletal apparatus and environmental forces. A further development was a closed circle model of motor control including, among other components, a central command, sensory receptors and a comparator which assessed the discrepancy between the motor program and the unfolding action. Movement could be initiated from any point in this circle and Bernstein suggested this overcame the opposition of centrally directed and reactive movements which had marked earlier debates. Finally, he noted that the abundance of available articular configurations, muscle elasticity and the unpredictability of external influences meant that any motor problem was solvable in a potentially vast number of ways. He contended that an overarching goal for research was to specify how the motor system co-ordinated these factors. Generally known as the degrees of freedom problem, it has remained a key challenge in the field.

### From World War Two to the 1970s

Experience of war led to interest in human-machine interaction and the development of cybernetics, the study of control and communication systems.<sup>5</sup> With this came a tendency to see human motor and machine engineering problems as analogous. Craik,<sup>6</sup> for example, portrayed the motor system as an intermittent correction servo,

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meaning that trajectory corrections in human movements were predictive and based on extrapolation from earlier feedback rather than current conditions. Fitts,<sup>7</sup> also working in this tradition, was concerned to understand the information capacity of the human motor system. He defined this as the ability to generate a uniform movement response when faced with a range of alternatives; the greater the number of available alternatives, the higher the information capacity of the response. The minimum information needed for a specific movement was labelled its index of difficulty (Id). In his studies of movement amplitude and duration, Fitts noted that Id was a function of the width of the target and the distance to be moved. Thus speed, distance and accuracy requirements were interlinked. These interrelationships were given a mathematical formulation, now known as Fitts' Law, which is still widely applied in motor research.

Von Holst,<sup>8</sup> also influenced by cybernetics, was concerned to identify mechanisms by which a visual signal produced by moving the eyeball with an external force could be distinguished from a visual signal produced by an active eye movement. The problem was to explain why, in the first case, the visual world appears to move, whereas in the second it remains still. He proposed that when the CNS issues a command to move, or an efference, then a replica of that command, the efference copy, is stored in a lower CNS mechanism. Reafference from an active movement cancels out the efference copy and the visual world remains static. Ex-afference from an externally produced movement, however, does not have this effect and the visual world appears to move. This concept of efference copy has continued to be crucial in movement theory.

An influential paper by Keele<sup>9</sup> reviewed many earlier studies and helped spark renewed academic interest in the field. This paper also outlined a modified version of Fitts' Law suggesting that, as very rapid movements are not reliant on visual feedback, so movement time would not depend on accuracy requirements. This modification was widely referenced in subsequent discussion. Ultimately, however, the chief legacy of this paper was a broader awareness of the concept of the motor program. Keele defined the program in terms reminiscent of Bernstein and Woodworth, although only the latter author was referenced in the paper.

In 1975 Schmidt<sup>10</sup> criticised earlier models, arguing that cerebral storage capacity did not allow for every individual movement to have its own motor program, as previously suggested. Rather there were generalised motor programs for categories of movement, with adjustable parameters, for example for force or speed. During repeated movements the interrelationships of certain components, such as sensory feedback and accuracy, were abstracted from to form a motor schema for the movement. The schema would then allow the selection of an appropriate response to

## While the field progresses, investigators will still be compelled to draw on past achievements...

achieve a desired result. This selection involved the specification of the parameters to be modified and the triggering of the appropriate motor program. Schmidt's multifaceted model addressed problems with existing approaches and has continued to provoke debate.

### Motor theory today

The dominant concept in contemporary theory is that of the internal model which simulates movement. This has two constituents. First, a forward model predicts the future state of the system by combining knowledge of its present condition with an efference copy of the motor command. Second, an inverse model calculates the motor command needed to cause a desired sensory state, allowing feedforward control of action in advance of feedback.<sup>11</sup> The internal model thus facilitates a two-way transfer of motor and sensory information, allowing the acquisition of motor skill.

Jeannerod<sup>12</sup> has argued that motor simulation is based on the activation of hard-wired motor rules, and is central in predicting the outcome of action and in understanding the actions of others. His model relies heavily on evidence regarding mirror neurons. These were an accidental discovery by Rizzolatti and colleagues,<sup>13</sup> who identified neurons in monkey pre-motor cortex which are active during the execution and observation of goal-directed hand movements. They are now thought to occur in primate (including human) inferior parietal, ventral pre-motor and caudal inferior frontal cortices<sup>14</sup> and, in Jeannerod's view, underpin the formation of the internal model.

One dissenting position in contemporary discussion is that of the equilibrium point hypothesis (EPH). Feldman and Latash, advocates of EPH, suggest internal models are unable to explain a mundane problem in movement control identified by Sherrington.<sup>15</sup> That is, how can movement take place against a background of postural stability without the stabilising mechanisms dragging the limb back to its initial posture? EPH posits that this can be achieved by one centrally controlled

variable, the point  $\lambda$  at which the tonic stretch reflex activates the muscle as it is stretched. The ratio of muscle force and length, when muscle force is balanced by an opposing force and posture is stabilised, is labelled the equilibrium point (EP). EP and its attendant torques and joint angles are considered emergent properties which cannot be pre-programmed as the internal model approach suggests. The ratio can be changed by a voluntary adjustment of  $\lambda$ , leading to a shift to a new EP, overcoming postural inertia and allowing movement.

### Conclusion

This has been a necessarily selective review of an extensive literature. We hope to have highlighted some of the key contributions over the last 115 years and shown how similar concerns have occupied researchers in that time. Both motor program and internal model concepts, for example, sought to answer how rapid movements are controlled without sensory feedback. EPH, on the other hand, has placed renewed emphasis on reflex control in movement. This suggests that, while the field progresses, investigators will still be compelled to draw on the past achievements we have outlined. ♦

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

affected by a fixed contracture. **Undesirable effects:** The following adverse reactions were reported with Xeomin®: Frequency by indication defined as: Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100). **Blepharospasm:** Common: ptosis, dry eyes. Uncommon: paraesthesia, headache, conjunctivitis, dry mouth, skin rash, muscle weakness inflicted injury. **Spasmodic torticollis:** Common: dysphagia, muscle weakness, back pain. Uncommon: headache, tremor, eye pain, dysphonia, diarrhoea, dry mouth, vomiting, colitis, skin rash, erythema, pruritus, increased sweating, skeletal pain, myalgia, asthenia, injection site inflammation, injection site tenderness. **Post-stroke spasticity:** Common: injection site pain, injection site haematoma, muscular weakness. Uncommon: feeling hot, asthenia, oedema peripheral, pain in extremity, joint swelling, myalgia, dysphagia, nausea, dry mouth, dysaesthesia, headache, hypoaesthesia, haematoma, cough, erythema. **Xeomin® may only be used by physicians with suitable qualifications and proven experience in the application of Botulinum toxin. Prescriber should consult the SmPC for full information regarding side effects. Legal Category:** POM. **Basic NHS Price:** 100 U/vial £129.90. **Product Licence Number:** PL29978/0001. **Marketing Authorisation Holder:** Merz Pharmaceuticals GmbH, 60048 Frankfurt Main, Germany. **Further information available from:** Merz Pharma UK Ltd., 260 Centennial Park, Elstree Hill South, Elstree, Hertfordshire WD6 3SR. **Date of revision of text:** December 2009. Xeomin® is a registered trademark of Merz GmbH. Botox® is a registered trademark of Allergan Inc.

# Focus on the EFNS

25-28 September, 2010, Geneva, Switzerland



Gian Luigi Lenzi

## Dear Colleagues,

The 14th Congress of the EFNS will be hosted in Geneva in September 2010. I estimate that more than four thousand neurologists, the majority of them younger than 40, coming from all over Europe – and from outside Europe as well – will gather to attend lectures, workshops, teaching courses and presentations. In after-congress hours they will stroll along the shores of Lake Lemman (Lake Geneva), will climb the streets of the old town, will indulge in inexpensive window-shopping, will admire beautiful ladies zooming from one fashionable boutique to the next and all will taste Swiss cuisine without any prejudice.

They will probably all become permeated smoothly by the slow efficacy of daily life in Switzerland, by the activity and low-level bustle of busy schedules, interrupted occasionally, for a few minutes, by noisy foreign students going out to ersatz Irish pubs or bistros.

What will remain in these four thousand neurologists' neurons once back home from Geneva? Will they have understood why Geneva was chosen as the site for the League of Nations, created to avoid a new genocide after the 1st World War, though regrettably missing its target? Will they understand why Calvin chose Geneva as the stronghold where he built his Academy, to forge new missionaries against the corruption of the Roman Popes, calling for overdue reform?

Will the "normal" neurologist have understood the reasons why J.J. Rousseau illuminated European thought here in Geneva; what was the cultural background that brought him to value individuals' intrinsic qualities of more than family status or blood lineage?

Why did Voltaire choose to have his second house here in Geneva?

Why is the World Health Organisation based in Geneva?

To attempt an answer to all these "whys", we need to grasp the cultural and political significance of this very special corner of Europe. We have to return to that historical time when to be a BOURGEOIS, the inhabitant of a bourg or small town, and FREE from the rule of "established powers", be those the Church with its taxes and future hell, or feudal landlords with similar taxes and actual dungeons, was radical and activist. The bourgeoisie waged war against the establishment, history and the customs of tradition. To be a bourgeois meant to fight against professional soldiers. It meant one risked being killed, imprisoned, tortured or burned, because of the affirmation of a

remarkable new idea; that it is man's right to be his own master.

This is the contribution of Geneva and its citizens to our civilisation, from the first uprising against Amadeus VIII, Duke of Savoy, in 1530, to the final constitution voted in 1847, through the struggles of Europe out from the Feudal Order to the changes due to the French Revolution and Napoleon's years. The bourgeoisie of Geneva succeeded in this remarkable enterprise.

So, if today we are all free neurologists in training or established neurological practitioners, to come to Geneva from the more remote borders of Europe, the East or Far East, from Australia or Canada (often taking this extraordinary freedom for granted!) this is because of the not inconsiderable amounts of blood offered and spilt as sacrifice for freedom in the world on the walls of Geneva. If we are free to discuss different ideas and proposals rather than to receive wisdom, and are free to agree or disagree, this is also in no minor part due to bourgeois blood spilt in Geneva.

Let me finish on a less dramatic and slightly romantic note. Let me presume that this same freedom was what Empress Sisi was seeking for on the shores of Lake Lemman where unfortunately she found only the blade of her murderer.

This then is the message and invitation to Geneva I make on behalf of my colleagues of the Congress Programme Committee: come and attend our Congress in Geneva. Come to Geneva not only to attend a sequence of scientific gatherings, but also the complete merging of the neurological community in a town that has FREEDOM as its crest. We will all be members of a community of free people, of people who care for freedom in the world, freedom for neurons and for the unfettered products of neural work - human feelings, ideas and actions.

And, please, let us feel the beauty and the importance of this aspect.

In this respect, we, the neurologists, are privileged.

Because who better than we neurologists and students of the neurosciences can know that freedom without peace, welfare, education and science, is not the freedom that Geneva gave us, is not the freedom that was created, defended and originally affirmed, here in Geneva.

*Gian Luigi Lenzi,  
Chairperson,  
Congress Programme Committee.*



# TAKE CONTROL IN ALZHEIMER'S DISEASE

Proven efficacy across key AD symptom domains – cognition, function and behaviour<sup>1-7</sup>

No titration required – the only AD treatment with a therapeutic dose from the start<sup>8-15</sup>

The only AD treatment to offer carers and patients the convenience of an orodispersible formulation<sup>9,16</sup>

**Aricept**<sup>®</sup> donepezil hydrochloride    **Aricept Evess**<sup>®</sup> donepezil hydrochloride

**RIGHT FROM THE START**

#### ABBREVIATED PRESCRIBING INFORMATION

**ARICEPT<sup>®</sup> (donepezil hydrochloride film-coated tablet)**

**ARICEPT EVESS<sup>®</sup> (donepezil hydrochloride orodispersible tablet)**

Please refer to the SmPC before prescribing ARICEPT 5 mg, ARICEPT 10 mg, ARICEPT EVESS 5 mg or ARICEPT EVESS 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration: Adults/elderly;** 5 mg daily which may be increased to 10 mg once daily after at least one month. Aricept Evess orodispersible tablets should be placed on the tongue and allowed to disintegrate before swallowing with or without water. Aricept film-coated tablets are taken orally. Treatment with Aricept or Aricept Evess should be initiated and supervised by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Monitor regularly to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. **Children;** Not recommended. **Contra-Indications:** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in Aricept or Aricept Evess. **Pregnancy:** Donepezil should not be used unless clearly necessary. **Lactation:** Excretion into human breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinus pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. No data available for patients with severe hepatic impairment. In three 6-month clinical trials in individuals with vascular dementia (VaD), the combined mortality rate was numerically higher, in the donepezil group (1.7%) than in the placebo group (1.1%), but this difference was not statistically significant. In pooled Alzheimer's disease studies (n=4146), and in Alzheimer's disease studies pooled with other dementia studies including vascular dementia studies (total n=6888), the mortality rate was numerically higher in the placebo group than in the donepezil group.

Aricept film-coated tablets contain lactose and should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Donepezil has minor or moderate influence on ability to drive/use machines so this should be routinely evaluated. **Drug Interactions:** Interaction possible with inhibitors or inducers of cytochrome P450; use such combinations with care. May interfere with anticholinergic agents. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Very common effects ( $\geq 1/10$ ): diarrhoea, nausea, headache. Common effects ( $\geq 1/100$ ,  $< 1/10$ ): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, vomiting, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, fatigue, pain, accident. Uncommon effects ( $\geq 1/1,000$ ,  $< 1/100$ ): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film-coated tablets marked 5 and Aricept, packs of 28 £59.85 ARICEPT 10 mg; yellow, film-coated tablets marked 10 and Aricept, packs of 28 £83.89 ARICEPT EVESS 5 mg; white, embossed, orodispersible tablets marked 5 and Aricept, packs of 28 £59.85. ARICEPT EVESS 10 mg; yellow, embossed, orodispersible tablets marked 10 and Aricept, packs of 28 £83.89. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. ARICEPT EVESS 5 mg; PL 10555/0019 ARICEPT EVESS 10 mg; PL 10555/0020. **Marketing authorisation holder:** Eisai Ltd. **Further Information from:** Eisai Ltd, EKC, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM. **Date of preparation:** December 2009.

Adverse events should be reported. Reporting forms and Information can be found at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk). Adverse events should also be reported to Eisai Ltd on 0208 600 1400 or [Lmedinfo@eisai.net](mailto:Lmedinfo@eisai.net)

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ART-EU2181



EBTARP-10-193

Preparation date: May 2010



#### PRESCRIBING INFORMATION – UK AND ROI

**REBIF® 8.8 MICROGRAMS AND 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE**

**REBIF® 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE**

**REBIF® 44 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE**

**REBIF® 8.8 MICROGRAMS/0.1ML AND REBIF® 22 MICROGRAMS/0.25ML SOLUTION FOR INJECTION IN CARTRIDGE**

**REBIF® 22 MICROGRAMS/0.5ML SOLUTION FOR INJECTION IN CARTRIDGE**

**REBIF® 44 MICROGRAMS/0.5ML SOLUTION FOR INJECTION IN CARTRIDGE**

#### Interferon beta-1a

**Presentation** Rebif 8.8µg and 22µg: Pre-filled glass syringe containing 8.8µg or 22µg of Interferon beta-1a in respectively 0.2 or 0.5ml. Rebif 22µg or 44µg: Pre-filled glass syringe containing 22µg or 44µg Interferon beta-1a in 0.5ml. Rebif 8.8µg/0.1ml and Rebif 22µg/0.25ml: Pre-filled glass cartridge containing 132µg of Interferon beta-1a in 1.5ml. Rebif 22µg/0.5ml or Rebif 44µg/0.5ml: Pre-filled glass cartridge containing 66µg or 132µg of Interferon beta-1a in 1.5ml. **Indication** Treatment of relapsing multiple sclerosis. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Initiate under supervision

of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection. Recommended dose: Weeks 1 and 2: 8.8µg three times per week (TIW); weeks 3 and 4: 22µg TIW; week 5 onwards: 44µg TIW (22µg TIW if patients cannot tolerate higher dose). Rebif solution for injection in cartridge is for multidose use and should only be used with the RebiSmart autoinjector device following adequate training of the patient and/or carer. Follow the instructions provided with the RebiSmart device. Limited published data suggest that the safety profile in adolescents aged 12–16 years receiving Rebif 22 TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24h afterwards, an antipyretic analgesic is advised to decrease flu-like symptoms. Evaluate patients at least every second year of the treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, or to any of the excipients; treatment initiation in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver

disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44µg. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6–12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. If overdose occurs, hospitalise patient and give supportive treatment. **Side effects** In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. **Very common:** flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. **Common:** injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia, severe elevations of transaminase. **Serious side effects include:** injection site necrosis, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures,

# Rebif®: established, effective treatment for people with relapsing–remitting multiple sclerosis (RRMS)<sup>1,2</sup>

Delivered through innovation to help address adherence

- Rebif® is available in multidose cartridges for use with the RebiSmart™ electronic autoinjector device
- Up to 70% of RRMS patients treated with DMDs are non-adherent with therapy\*<sup>3</sup>
- RebiSmart™ is the only device in MS which allows adherence to be reviewed

thromboembolic events, thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, suicide attempt, Stevens-Johnson syndrome, dyspnoea, retinal vascular disorders. Consult the Summary of Product Characteristics for more information relating to side effects. **Legal category** POM. **Price** Rebif 8.8µg and 22µg: 6 (0.2ml) + 6 (0.5ml) syringes – £552.19; Rebif 22µg: 12 syringes (0.5ml) – £624.77; Rebif 44µg: 12 syringes (0.5ml) – £813.21; Rebif 8.8µg/0.1ml and 22µg/0.25ml: 2 cartridges – £406.61; Rebif 22µg/0.5ml: 4 cartridges – £624.77; Rebif 44µg/0.5ml: 4 cartridges – £813.21; For prices in Ireland, consult distributors Allphar Services Ltd. **Marketing Authorisation Holder and Numbers** Merck Serono Europe Ltd, 56 Marsh Wall, London, E14 9TP; EU/1/98/063/007; 003; 006; 010; 008; 009. **For further information contact:** **UK:** Merck Serono Ltd, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono, 3013 Lake Drive, Citywest Business Campus, Dublin 24. Tel: 01 4661910. **Date of Preparation** January 2010.

Adverse events should be reported. Reporting forms and information can be found at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk). In the Republic of Ireland information can be found at [www.imb.ie](http://www.imb.ie). Adverse events should also be reported to Merck Serono Limited - Tel: +44(0)20 8818 7373 or email: [medinfo.uk@merckserono.net](mailto:medinfo.uk@merckserono.net).

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\*Retrospective analysis of 1606 RRMS patients treated with interferon-β-1a (44µg sc tiw or 30µg im qw) or interferon-β-1b; adherence was defined as a medication possession ratio of ≥85% over a period of 360 days.

DMD: disease-modifying drug. sc: subcutaneous. tiw: three times weekly. im: intramuscular. qw: once weekly.

# European Federation of Neurological Societies (EFNS)

The EFNS was founded in 1991 in Vienna, Austria.

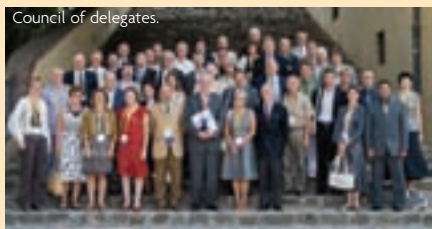
The role of the EFNS is

- To advance the development of neurology as an independent specialty caring for all patients with a disease of the nervous system
- To support that these services being made available to all Europeans
- To support research and dissemination of research results throughout Europe
- To organise and support neurological teaching at the pregraduate as well as the post-graduate level throughout Europe
- To handle the current political issues in European neurology on behalf of its members

The EFNS is a federation of 44 European national neurological societies, 8 associate member societies and welcomes individual members from all over the world.

The federation is governed by a Council constituted of one representative elected by each affiliated national neurological society in Europe. The Council delegates the day-to-day management of the EFNS to the Management Committee, empowered to decide on all matters of the Federation when such decisions cannot be delayed until the next Council meeting. Important decisions made by the Management Committee must subsequently be ratified by the Council.

Council of delegates.



The European Federation of Neurological Societies is based in Vienna, Austria. We also have Branch Offices in Florence, Italy, and Prague, Czech Republic.

## Committees and Scientist Panels:

The EFNS has 8 standing committees and 25 Scientist Panels. The standing committees perform the ongoing functions vital to the EFNS on a long-term basis.

- Congress Programme Committee
- Education Committee including the CME, E-learning, European Co-operation and Teaching Course Sub-committees
- Liaison Committee
- Scientific Committee

The aims of the scientist panels are:

- to co-ordinate clinical research at a European level
- to disseminate good neurological practice throughout European countries
- to assist the Congress Programme Committee in organising congresses
- to assist the EFNS in training neurologists

and in supporting continuing medical education.

- to develop European Neurological Guidelines

## Topics:

Amyotrophic Lateral Sclerosis, Autonomic Nervous System disorders, Critical Care, Dementia, Demyelinating Diseases, Epilepsy, Genetics, Headache, History, Infectious Diseases, EFNS/MDS-ES, Muscle Disorders, Neuroimaging, Neuro-immunology, Neuro-oncology, Neuro-ophthalmology, Neuropathic Pain, Neuropathies, Neurorehabilitation, Neurotraumatology, Palliative Care, Public Health, Sleep Disorders, Stroke, Substance Abuse.

## Congresses and meetings:

At its annual congresses, usually taking place in September, the EFNS provides an unmatched opportunity for neurologists to join over 5,000 colleagues to study and disseminate the latest research, clinical practices and treatments.

- 14th EFNS Congress, Geneva, Switzerland – 25-28 September 2010
- 15th EFNS Congress, Budapest, Hungary – 10-12 September 2011
- 16th EFNS Congress, Stockholm, Sweden – 8-11 September 2012
- 17th EFNS Congress, Istanbul, Turkey – Autumn 2014

Furthermore, the EFNS organises Regional Teaching Courses in Eastern Europe as well as in Africa. At these courses participants only pay for travel and accommodation. EFNS-RTCs are specially designed to disseminate best neurological practice directly to the countries in the East so that younger neurologists do not have to travel long distances to congresses which may not be affordable for them. RTCs provide basic teaching in neurology and contribute to the development of collaboration and friendship between neurologists in different European countries.

EFNS Academy 2010.



At the annual EFNS Academy in the Czech Republic, 120 young neurologists from all over Europe meet and listen to contributions by European experts. Participants only pay for their travel.

## Grants and Awards

### Bursaries to EFNS Congresses:

The EFNS offers up to 200 bursaries consisting of free registration to the congress and hotel

accommodation for four nights to European neurologists up to the age of 35 who are not yet in permanent positions and whose abstracts have been accepted for presentation at the congress.

### Department-department co-operation programme

Up to 80 young neurologists per year, each receive a grant of €500 plus travel expenses up to €300. The purpose of this award is to support their board and accommodation expenses in the host city. The grant is designed to allow for a visit of up to six weeks. If a participant is able to accept a low budget board, it may be possible to stay longer than six weeks in the hosting department. Candidates from all European countries are eligible. Applicants must be under the age of 40, and must be fluent in English or in the local language.

### Fellowship programme

The EFNS offers up to eight scientific and four educational fellowships per year to support young European neurologists to carry out research projects in clinical and basic neurology. The objective is to support young and active neurologists wishing to expand their knowledge in neurology by working on scientific projects, and most of all, to study the practice of neurology in different countries, and thereby also create new international connections. Accordingly, the research work must be carried out at a European academic neurological department outside the country of residence.

Amount: Net salary in accordance with the salary scale of the host institution up to a maximum of €2,000 per month plus travel expenses.

### Investigator award:

All free presentations (short communications, posters), selected for presentation at the annual EFNS Congress automatically compete for an Investigator Award. The EFNS Scientist Panels are responsible for the evaluation process (independent from other awards and the programme organisation). The award for each selected presentation will be €500, a diploma, and the winners will be announced in the *European Journal of Neurology* and the *EFNS Newsletter*. The award will be given to the first author, who is also required to present the work at the congress.

### Tournament for young neurologists

A tournament for young neurologists takes place at each EFNS Congress. It will be carried out in two groups, one on clinical related research, and one on basic neurological science. Neurologists in training not older than 35 years are entitled to participate. The Congress Programme Committee will select six candidates for each tournament on the basis of the contents of the abstracts submitted. The clinical subjects should be received from authors who work and carry out their projects in Europe.

Candidates selected for the tournament receive a bursary consisting of free registration to the Congress, up to four nights hotel accommodation, and a travel grant.

Prize: The winner of each group will receive the Uschi Tschabitscher Prize for Young Neurologists consisting of: Free registration at the upcoming EFNS Congress, up to four nights hotel accommodation, a travel grant, as well as €1,000.

#### **CME articles online**

All registered users of the EFNS website do have the possibility of answering questions related to articles selected from the *European Journal of Neurology* and receiving a CME certificate.

#### **Partners and collaborators**

Our Partners and Collaborating Societies consist of:

- European organisations dedicated to any associated speciality related to clinical neurology
- European subgroups of clinical neurology
- European patient organisations and
- Neurological organisations outside of Europe.

Collaboration with the EFNS promotes co-operation and co-ordination in mutual areas of interest and creates more representative (and therefore more powerful) influence on national health authorities and the European Union.

#### **Our partners are:**

European Association of Young Neurologists and Trainees, European Brain Council, European Board of Neurology, European Federation of Neurological Associations,

European Federation of Autonomic Societies, European Headache Federation, European Epilepsy Academy, European Neurological Society, Movement Disorders Society-European Section, World Federation of Neurology

#### **Publications**

*European Journal of Neurology* (EJoN): 12 issues per year – FREE OF CHARGE online access for members of the EFNS.

*The European Journal of Neurology* covers all areas of clinical and basic research in neurology, including pre-clinical research of immediate translational value for new potential treatments. Emphasis is placed on major diseases or disorders with a large clinical and socio-economic importance (dementia, stroke, epilepsy, headache, multiple sclerosis, movement disorders, and infectious diseases).

The journal provides a forum for European activity in clinical neuroscience and medical practice and helps strengthen the links between research workers and clinicians in Europe and other parts of the world. The journal also publishes the official EFNS taskforce papers and CME Articles which can be read to gain CME credits. ISI Journal Citation Reports® Ranking: 2008: 52/156 Clinical Neurology; 104/219 Neurosciences New 2008 Impact Factor: 2.732

<http://www.europeanjournalofneurology.com>

#### **EFNS Newsletter**

Four issues per year; free of charge for members and non-members alike.

#### **European Handbook of Neurological Management**

*The European Handbook of Neurological Management*, is a unique book that brings together peer-reviewed guidelines for the treatment and management of neurological disease. For the first time, neurologists can find advice on management aspects of most neurological disorders that is either evidence-based or, where the evidence is inadequate, the consensus guidance of an international European panel of experts. Each chapter of the handbook is written by task forces with a multinational European authorship in accordance with prespecified guidance for collecting evidence and reaching consensus. Whenever possible, these task forces have collaborated with the corresponding disease-specific European society. In some cases societies and authors from outside Europe have contributed.

EFNS Guideline papers are included in the *European Journal of Neurology, Handbook* and are also available to all FREE OF CHARGE on the EFNS website. An important aim of the EFNS is to establish European standards of diagnosis, treatment and care within the various subfields of neurology. Teaching course syllabi are available in the e-education area of the EFNS website as well as on CD-Rom.

**For further details and information on the EFNS, please visit the EFNS Website [www.efns.org](http://www.efns.org) or contact**



## The Vision and Missions of the European Federation of Neurological Societies

### **Vision: excellence in European Neurology**

The European Federation of Neurological Societies, better known by its abbreviation EFNS, aims to make European neurology the equal of the best in the world. It provides a common home for European neurological patient care, research, education and partnership. Our annual congress is an important, and the most visible, manifestation of our vision but not the only one. The EFNS Council has affirmed ten missions.

### **Mission 1. A strong organisation of European Neurology**

There are national neurological societies in every European country and 44 have elected delegates to represent their country on the

Council of the EFNS. The Council meets annually at our Congress. It elects the officers who form its Management Committee and conduct the day to day business of the Federation. The EFNS has its Head Office in Vienna which is managed by our Executive Director, Lisa Müller, and branch offices in Florence and Prague. This managerial and administrative structure underpins the nine other missions of the EFNS.

### **Mission 2. Taking care of neurological patients in Europe**

The EFNS aims to advance the development of neurology as the major medical specialty caring for patients with neurological disorders. As medicine becomes more and more specialised we have seen some groups of diseases fall

increasingly into the hands of other specialties, pain under the care of anaesthetists, sleep disorders under respiratory physicians, stroke under elderly care physicians and chronic disorders under rehabilitation specialists. Communication and collaboration with these related specialties is helpful and should be encouraged but we should not abandon the care of these primarily neurological disorders to other specialties. Their pathology is the pathology of the nervous system and advances in care are most likely to come from neuroscience of which we should be the masters. We have a scientific committee chaired by Professor Michael Brainin (pictured overleaf), Austria, which oversees 24 scientist panels covering all the major sub- (or super-) specialties



**RICHARD HUGHES**  
PRESIDENT OF THE EFNS

within neurology. The panels are well placed to encourage and supervise the development of their fields.

### Mission 3. High quality of neurological health care

We aim to strengthen the standard, availability, and uniformity of neurological services in Europe. The Scientist Panels have set up task forces which have written guidelines on the management of important neurological diseases which are freely available on line on the EFNS website. The first 41 guidelines were published in the first edition of the *European Handbook of Neurological Management* edited by myself with Professor Michael Brainin and Professor Nils Erik Gilhus, Norway, in 2006. The second edition edited by Professors Nils Erik Gilhus, Michael Brainin and Michael Barnes with 40 updated guidelines will be published at this Congress. The guidelines are evidence based where possible but where not are based on the consensus of experts from different European countries and are in any case peer reviewed by the Scientific Committee. The guidelines form a benchmark to which all European neurologists can aspire and against which individuals and individual countries can audit their practice.

### Mission 4. Multidisciplinary collaboration and partnership

We aim to strengthen collaboration between ourselves and related professional and lay organisations. We particularly appreciate a close liaison to the point of merging with the management committees of European sub-specialty organisations and have negotiated close working arrangements with the Movement Disorders Society – European Section, European Headache Federation and European Federation of Autonomic Societies. We would welcome others. Just as, or even more important, is our close alliance with our sister patient organisation the European Federation of Neurological Associations (see [www.efna.net](http://www.efna.net)) which helpfully brings together all the European organisations of people with different neurological diseases. Their enthusiastic support and contribution under the indefatigable presidency of Mary Baker MBE are particularly welcome. The Good Life sessions which they organise at each EFNS congress should not be missed for being thought provoking and enjoyable at the same time. The backing of EFNA was key to the formation of the European Brain Council with the EFNS. The EBC (see [www.europeanbraincouncil.org](http://www.europeanbraincouncil.org)) was founded in 2002 and is formed by ourselves, EFNA, the European organisations responsible for neurosurgery, psychiatry, basic neuroscience and industry. The EBC aims to increase the European resources devoted to research, teaching and care of brain diseases. It has been successful in increasing the neurological share of the European Union research budget from 260 million € in 2000 to 381 million € in 2007.

### Mission 5. Excellence in clinical neurological research - the cornerstone of progression

We aim to improve the quality of European neurological research through supporting research activities, encouraging collaboration, and promoting dissemination of research results. The annual congress, organised by the Congress Programme Committee and chaired by Professor Gian Luigi Lenzi, Italy and from now by Professor Nils Erik Gilhus, Norway, attracts about 5000 delegates from about 106 countries within and outside Europe. Twelve main topics, 15 focused workshops, about 1500 posters and special sessions are presented during the congress. To further support and encourage training in research the EFNS awards 8 scientific research fellowships each year to enable neurologists in training to spend up to 12 months in another European scientific department undertaking a research project. The scientist panels undertake research projects at a European level and use the Congress as an opportunity to hold collaborative meetings. If you have research interests that would benefit from a European dimension you are encouraged to contact the relevant panel chair who can be identified through the



Professor Michael Brainin



Professor Nils Erik Gilhus

EFNS website. The EFNS owns the *European Journal of Neurology* which has a high and rising profile in the international clinical neurology publishing scene. For those interested in such statistics, the impact factor has increased to 2.7 and the journal has risen into the top third of clinical neurology journals.

### Mission 6. Clinical and basic neuroscience – two interacting themes

We aim to strengthen the integration between basic neuroscience and clinical neurology by promoting bidirectional translational research. The EFNS congresses include basic science lectures in the main themes and workshops and many basic science abstracts are accepted for oral and poster presentations. Each scientist panel awards prize certificates for the best presentation in their specialty. Two Uschi Tschabitscher prizes for neurologists in training are awarded at each Congress, one for a basic science presentation. Basic science underpins much of the work of the scientific committee and scientist panels.



Award Winners 2009.

### Mission 7. High standards in neurological education throughout Europe

We aim to strengthen the standard, availability and equality of pre-graduate and post-graduate neurological education for neurologists and related professionals throughout Europe. The newly formed Training and Education committee, chaired by Professor Jean-Marc Léger, France, oversees several sub-committees disseminating postgraduate neurological training. The Teaching Course sub-committee has, as usual, organised 26 teaching courses which will provide Continuing Medical Education to attendees at this Congress. Professor László Csiba, Hungary, and Professor Detlef Kömpf, Germany, have the responsibility for organising popular regional teaching courses in Eastern European countries. Courses will be held in Odessa, Ukraine, Ufa, Russia and Chisinau, Moldova in 2010. Professor Pavel Kalvach organises an annual academy for 120 neurologists in training in Staré Splavy, Czech Republic. An e-learning sub-committee chaired by Professor Thomas Berger is charged to set up an e-learning programme which will bring the EFNS neurological training programmes to an even wider constituency.



Professor Jean-Marc Léger



Professor Detlef Kömpf



Professor Thomas Berger

### Mission 8. A platform for teaching activities at European level

We aim to provide a common platform for the integration of high quality, standardised neurological teaching activities at the European level. We collaborate with the European Neurological Society and Union of European Medical Specialists to form the European Board of Neurology (UEMS-EBN) which sets annual examinations to test proficiency in neurology. The second examination will take place at this Congress. The examination builds on the work of the Education Committee to provide neurologists in training the opportunity of testing themselves against pan-European standards.

### Mission 9. Raising public awareness about neurological disorders in Europe

We aim to raise awareness in the European lay public and among health care providers and politicians about the importance and implications of neurological disorders.



Journalists are welcomed at our annual Congress where there is a press office and the Congress is regularly reported in the medical and lay press. At a political level, our major lobbying is done by the European Brain Council which is co-chaired by a Member of the European Parliament and has the ear of Brussels. Five years ago, we sponsored an important initiative to measure the cost of neurological disorders in Europe (*European Journal of Neurology* 2005 volume 12 supplement 1). We are now sponsoring an update led by Professor Jes Olesen, former President of the EFNS.

### Mission 10. Contributing to neurological health care worldwide

We aim to strengthen the collaboration between European neurology and related international health organisations. We are holding talks about increasing co-operation with the European Neurological Society so that we can work together to make European neurology the finest in the world. We have from our foundation in 1991 been a constituent part

of the World Federation of Neurology (WFN) and form its European section. We have an agreement with the WFN that we will not hold an EFNS congress in a year when there is a World Congress of Neurology in Europe. This last happened in 2001 when I chaired the Congress Programme Committee in London and will next happen in 2013 when the World Congress will be in Vienna. We have close relationships with the neurological societies in neighbouring regions, including the Mediterranean societies of Algeria, Egypt, Jordan, Lebanon, Libya, Morocco, Syria and Tunisia, and the Pan-Arabic Union of Neurological Societies with whom we exchange representatives at our Congresses. Looking slightly further afield, we have been delighted to join leading African neurologists in organising teaching courses for the growing number of neurologists in Africa. These courses are also sponsored by the WFN and the International Brain Research Organisation. So far courses have been held in Senegal and Ethiopia and at the time of writing one is planned for the Ivory Coast.

## TEACHING COURSES

### SATURDAY, SEPTEMBER 25, 2010

#### 09.30 – 11.00

Free Teaching Course: How do I examine...

#### 11.30 – 13.30

Teaching Course 1: Movement disorders

– basic clinical knowledge

Teaching Course 3: Acute stroke management

– update on practical issues – basic clinical knowledge

Teaching Course 5: An update on MS diagnosis

– basic clinical knowledge

Teaching Course 7: Luigi Amaducci teaching course on dementia

– basic clinical knowledge

Teaching Course 9: Treatment of epilepsy, what every clinician should know – basic clinical knowledge

Teaching Course 11: Pain therapy in neurology

– Differential diagnosis and management of craniofacial pains

Teaching Course 13: Emergencies in neurology

Teaching Course 15: Neuro-ophthalmology

Teaching Course 17: Therapy in neurology I

Teaching Course 19: Controversies in neurology

#### 14.30 – 16.30

Teaching Course 2: Movement disorders – advanced

Teaching Course 4: Challenging stroke syndromes – advanced

Teaching Course 6: Update on the immunological attack in MS

– advanced

Teaching Course 8: Luigi Amaducci teaching course on dementia

– advanced

Teaching Course 10: Diagnostic advances in epilepsy for the clinician – advanced

Teaching Course 12: Neuromuscular diseases

Teaching Course 14: Autonomic disturbances

Teaching Course 16: Palliative care in neurology

Teaching Course 18: Therapy in neurology II

### SUNDAY, SEPTEMBER 26, 2010

#### 07.30 – 09.00

Teaching Course 22: Therapy in BPPV: all kinds of manoeuvres

Teaching Course 23: EMG – practical demonstration

#### 15.30 – 17.00

Teaching Course 20: FREE Teaching Course: How do I write a scientific paper?

#### 20.30

Scientific Raclette Dinner: The changing world of stroke

Chairperson and speaker: Vladimir Hachinski, London, ON, Canada

### MONDAY, SEPTEMBER 27, 2010

#### 07.30 – 9.00

Teaching Course 24: Doppler sonography

– practical demonstration

#### 15.30 – 17.00

Teaching Course 21: Free Teaching Course: Methods and their pitfalls in clinical science

### TUESDAY, 28 SEPTEMBER 2010

#### 07.30 – 09.00

Teaching Course 25: Nerve conduction

– practical demonstration

## MAIN TOPICS

### SUNDAY, SEPTEMBER 26, 2010

#### 08.30 – 10.30

Main topic 1: Parkinson's disease and movement disorders:

expanding the boundaries of current practice

Main Topic 2: Biological markers of disease activity

Main Topic 3: Infections of the peripheral nervous system

Main Topic 4: New developments in pain

### MONDAY, SEPTEMBER 27, 2010

#### 08.30 – 10.30

Main Topic 5: New aspects in stroke

Main Topic 6: A pragmatic approach to the management of three common neuromuscular disorders

Main Topic 7: New frontiers in behavioural neurology

Main Topic 8: Huntington's disease: new venues

### TUESDAY, SEPTEMBER 28, 2010

#### 08.30 – 10.30

Main Topic 9: New oral treatment of multiple sclerosis

Main Topic 10: The vegetative state

Main Topic 11: Molecular concepts in degenerative dementias

Main Topic 12: Emerging concepts in non-convulsive status epilepticus

### TUESDAY, SEPTEMBER 28, 2010

#### 12.00 – 13.00

EFNS Lecture on Clinical Neurology: Out of Balance

Thomas Brandt, Munich, Germany

## FOCUSED WORKSHOPS

### SUNDAY, SEPTEMBER 26, 2010

#### 15.30 – 17.00

Focused Workshop 1: Assessment of neuropathic pain:

how useful are new neurophysiological methods?

Focused Workshop 2: Clinical phenotypes of myasthenic syndromes

Focused Workshop 3: Nutrition and stroke

Focused Workshop 4: Gender issues in epilepsy

Focused Workshop 5: Vestibular-evoked potentials and reflexes

### MONDAY, SEPTEMBER 27, 2010

#### 15.30 – 17.00

Focused Workshop 6: Manganese and neurological disease

Focused Workshop 7: Advances in the management of gliomas

Focused Workshop 8: Aphasia as a part of different neurological disorders

Focused Workshop 9: New clinical indications of botulinum toxin therapy

Focused Workshop 10: Fitness to drive in neurological disorders

### TUESDAY, SEPTEMBER 28, 2010

#### 15.00 – 16.30

Focused Workshop 11: Atypical parkinsonian disorders: from bench to bedside

Focused Workshop 12: State of the art in clinical and molecular diagnosis of hereditary spastic paraplegia

Focused Workshop 13: Sleep and neurology

Focused Workshop 14: Transient loss of conscience and orthostatic intolerance; definitions and descriptions of key autonomic syndromes

Focused Workshop 15: Evidence-based guidelines for the management of transient ischemic attack (TIA) and stroke in clinical practice

## SPECIAL SESSIONS

### SUNDAY, SEPTEMBER 26, 2010

#### 14.30 – 17.00

European Basal Ganglia Club (EBGC)

#### 15.00 – 17.00

EFNS-EFNA Special Session: "The Good Life" – Practical rehabilitation in regaining quality of life: the ethical perspective

17.30 – 18.40

European Association of Young Neurologists and Trainees Session

### MONDAY, SEPTEMBER 27, 2010

#### 15.00 – 17.00

EFNS-EUREPA-Epilepsy Symposium: Treatment of Epilepsies

#### 15.00 – 17.00

EFNS – EFNA Awareness Session: Extremes of Prevalence in Neurology – the contrast in the management of dementia and rare illnesses

### TUESDAY, SEPTEMBER 28, 2010

#### 10.30 – 12.00

History and art: Neurological disorders of famous composers

#### 14.30 – 16.30

Joint Session EFNS – Mediterranean Neurological Societies: STROKE & COGNITIVE COMPLICATIONS AFTER CARDIAC SURGERY

# Regression in Children and Young People



**Dr Richard Brown**

is a Consultant Paediatrician in Peterborough. Following undergraduate studies at Oxford and St. Mary's, he trained in paediatrics at Guy's and St. Thomas', before moving to East Anglia. His special interests of neurology, neurometabolic disease, and medical education were fostered in Cambridge and at Sydney Children's Hospital.

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**Acknowledgement:**

Thanks to Dr Anna Maw for her editorial comments.

Adult neurologists practising outside tertiary units can expect to see young people presenting with concerns about regression. Furthermore, they often care for young adults who may be living with a disease of childhood onset, causing progressive intellectual and neurological deterioration. It is of great importance that these young people are assessed in an appropriate way, and that their condition is placed within the context of their overall developmental level. This series of articles has covered some of these issues already, and this article will focus on elements of the diagnostic process in regression. The focus will be on those disorders likely to present in children and young people over the age of five; younger than this, and diagnosis is very likely to be the domain of paediatric neurologists.

Regression is classically associated with neurodegeneration. These illnesses are progressive, so the clinician will expect to uncover a loss of previously acquired skills. Underpinning such diseases are abnormalities of structural or enzyme proteins – but the exact metabolic error or genetic defect may not yet have been isolated. This can make it tricky to prove the diagnosis with a single test, so there is ongoing emphasis on careful history taking, family investigation and neurological examination, followed by special tests. The tests most often needed are biochemical, neuroimag-

ing, neurophysiology, and expert review by ophthalmology.

The take home message of this article is, however, that most referrals about regression are evaluated to be due to non-neurodegenerative disease.

**“Seeming to regress” – non-neurological causes**

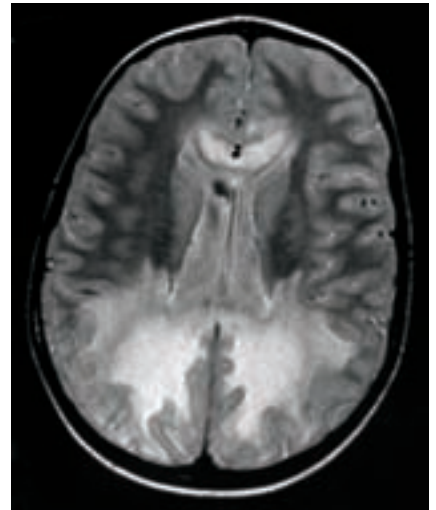
Most children and young people who present to paediatric or adult neurologists with concerns about school performance do not have a neurodegenerative disease. Worsening grades may derive from bullying or stress, from school absence (which may itself derive from a medical cause), or from previously unidentified developmental disorders such as dyslexia or autism. As children go through school, what we expect of them in academic and social terms increases and this may uncover a long standing problem that had previously gone unrecognised – thus an apparent regression or loss of skills is actually a static problem revealed by a change in environment. Sadly, adolescents are the archetype for factitious illness; for this reason, an in-depth social history should be taken, including any recent bereavement, moving house, parental separation and so on. This is an opportunity to be justifiably nosy. More rarely, autoimmune disease, vasculitis and endocrine disorders may present with failure in school.

**TABLE: Disorders producing changes in density or signal on MRI brain imaging**

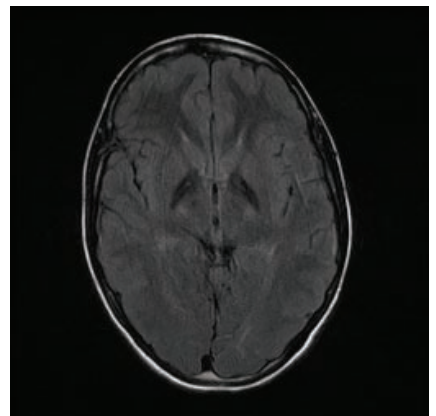
White Matter	Grey Matter
Genetic	
Leukodystrophies	Alpers
Mitochondrial Encephalopathies	Gangliosidosis GM1, GM2
Refsum	Mucopolysaccharidoses
L-hydroxyglutaric aciduria	Fucosidosis
Phenylketonuria	Wilson
Maple Syrup Urine Disease	Lafora Body Disease
Mucopolysaccharidoses	Niemann-Pick A,C
Giant Axonal Neuropathy	Mucopolysaccharidoses
Congenital Muscular dystrophies	Gaucher
Farber	Mitochondrial
Trichothiodystrophies	Menkes
Acquired	Huntington
Diffuse post-anoxic encephalopathy	
Periventricular leukomalacia	
Toxic leukoencephalopathy (methotrexate, radiotherapy, immunosuppression)	
Viral infections eg HSV encephalitis, SSPE	

**TABLE – Possible tests in neurodegeneration**

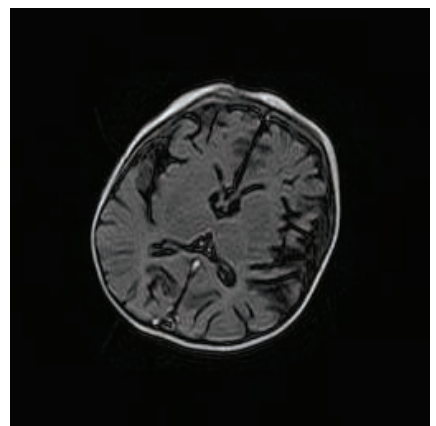
Condition	Test
Mitochondrial	Muscle biopsy. Respiratory chain enzymes
NCL – juvenile	White cell enzymes. Electron microscopy of skin: 'fingerprint' inclusions in neurones
NBIA/PKAN	MRI – iron deposition in the basal ganglia followed by the 'tiger eyes' sign as necrosis develops. Genetics
Refsum	Phytanic acid
HIV dementia	Viral load, CD4 estimation
Niemann-Pick C	Cholesterol transport/storage in cultured fibroblasts
Unverricht-Lundborg	EPMI mutation
Friedreich ataxia	Frataxin mutation
vCJD	MRI – bilateral pulvinar high signal
Wilson	Caeruloplasmin, Urine copper excretion, penicillamine challenge
SSPE	CSF measles PCR
Lafora Body disease	Biopsy axilla – Lafora bodies in sweat glands
Huntington	Genetics
Cerebrotendinous Xanthomatosis	Cholesterol levels



Adrenoleucodystrophy age two.



Tiger-eye sign in PANK (Hallervorden Spatz) age four.



Menkes atrophy age one.

### Seeming to regress – non-degenerative neurological conditions

Not all neurological causes of apparent regression are neurodegenerative.

Other causes to consider include:

- **Drugs** – Centrally acting drugs, such as anti-epileptic medications or recreational drugs (including alcohol), may be implicated.
- **Sensory impairment** – The young person may be losing visual acuity or becoming deaf.
- **Raised intracranial pressure** – this is classically associated with change in behaviour and deterioration at school.
- **Psychiatric disorder** – Psychosis and depression may cause difficulty accessing the educational curriculum.
- **Epilepsy** – disorders such as Landau-Kleffner can cause apparent regression. Landau-Kleffner may have an insidious (or rarely abrupt) onset, and is characterised by language deficit – loss of verbal comprehension, followed by loss of oral expression. There may be auditory agnosia, but crucially there may be few (or no) classical seizures.
- **Autism** – Regression is common in autism, occurring in 30% of cases but usually under the age of three. Incidental EEG abnormalities are common (21-68% have an 'epileptiform sleep EEG'), but they are independent of regression, suggesting no evidence of causality. There is no evidence that treatment with anti-epileptic medication improves core deficits in autism. The National Autism Plan for Children 2003 (UK) proposed that an EEG should only be considered in autistic children where there were clinical epileptic features, or where there is
  - A fluctuating clinical course
  - Coming and going of Skills
  - A fluctuating movement disorder or unusual behaviour

- Possible regression in the second year. If features of non-neurodegenerative disorders predominate and there are no neurological signs, then the focus should be on addressing the root cause. Thereafter, the role of the health professional lies in communicating with education regarding appropriate assessment in school – which would usually involve an educational psychologist.

### Neurodegenerative disease

Psychomotor regression may be difficult to objectively demonstrate in clinic in the early stages. Tests of parietal, temporal and frontal lobe function will be familiar to adult neurologists, and adolescents will be able to participate in tests for astereognosis, sensory inattention and so on.

It must be emphasised that investigation in suspected neurodegenerative disease should be targeted. This is guided by information from the history, examination and investigations. Perhaps one exception to this rule of targeting is the near-ubiquitous use of MRI brain scanning in these patients. This is largely because this investigation has the single greatest diagnostic yield, and provides useful hints as to the 'next step'.

The British Paediatric Surveillance Unit has been collecting data on the clinical presentation of progressive intellectual and neurological deterioration for eleven years. All individual causes of neurodegeneration are rare, but for adolescents presenting with true regression, the most common cause has been variant Creutzfeldt-Jakob disease.

In all things – first comes the history.

- Is there myoclonus? Subacute sclerosing panencephalitis, Lafora-body disease, Unverricht-Lundborg and variant Creutzfeldt-Jakob disease (vCJD) may all present with this.
- If the predominant school complaint is deterioration in behaviour, then juvenile neuronal ceroid lipofuscinosis (NCL),

Wilson disease and juvenile Huntington should be considered.

- A vary rapid rate of regression may suggest neurodegeneration with brain iron accumulation (NBIA, formerly known as Hallervorden-Spatz).
- Examination may be fruitful, particularly in terms of looking at the co-ordination of movement.
- Extra-pyramidal signs may suggest juvenile Huntington, NBIA, Wilson and vCJD.
  - Ataxia may point to Niemann-Pick Type C, vCJD, Refsum, cerebrotendinous xanthomatosis (CTX), or Friedreich ataxia (FA).

- The loss of deep tendon reflexes promotes Refsum or FA. A large liver suggests Wilson or Refsum.

Clues from the MRI brain scan are invaluable in the evaluation of infants and younger patients with regression, but are still of considerable value in older children.

- NBIA may demonstrate the tiger eye sign – a symmetrical bilateral hypointense signal on T2 in the globus pallidus, surrounding a hyperintense signal anteriorly.
- A hint to vCJD may be found in bilateral intensities in the posterior thalamus.

It is hard to overstate the importance of an experienced neuroradiologist in the interpretation of these images. If you don't have local access to such an opinion, it is often well worth going the extra mile to get the scans reported at another institution.

Ophthalmological assessment may be a valuable screening tool.

- Early optic atrophy points towards juvenile NCL, and this may be supported by attenuation of the ERG. Optic atrophy may also be found in SSPE.
- Retinitis pigmentosa may be found in NBIA or Refsum.
- A cherry red spot is found in many childhood causes of regression, but in this age group Niemann Pick type C is promoted (a vertical gaze palsy is nearly always present).
- Cataracts may be found in CTX.
- Progressive central visual loss has been associated with SCA 7 mutation.

- Kayser-Fleischer rings are as important in paediatric practice as they are for 'grown-up' neurologists!

**Summary**

Patients presenting for the first time with apparent loss of skills must be carefully evaluated. The first step is defining the problem. Is this true neurodegenerative disease, with progressive loss of skills and the development of neurological signs? Or is this a pseudo-regression, where the problems derive from non-degenerative causes (including neurological, social, psychiatric and 'other')?

Where neurodegenerative disease is suspected – focus investigation on those conditions suggested by your initial assessment, the MRI findings, and the ophthalmology review. ♦

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*Most children and young people who present to paediatric or adult neurologists with concerns about school performance do not have a neurodegenerative disease*

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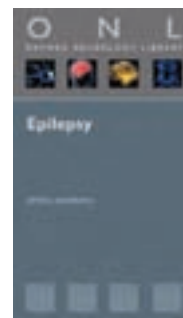
**Epilepsy**

There are many books which deal with subspecialties in neurology. Epilepsy has been a favourite subject for authors, and there have been many books dealing with all aspects of care of this complex but common condition. Professor Shorvon has contributed to or edited the seminal UK textbooks on this topic, which made the idea of reviewing this latest offering such a pleasure.

On receiving the book, I did notice that it is, to put it kindly, rather small. I suppose in this environmentally aware, post-credit crunch time, the notion of a small book should tick many of the important boxes. This pocket size would allow the book to be carried around while working (if anyone was allowed to wear the bacterial Death Star that is the white coat – but I digress). Accommodating this diminutive stature, however, the font size has had to be reduced to a level small enough to be a recurrent reminder of my imminent old age.

But enough of this griping about form. The content is the important thing, and it is clear that the information contained in is as relevant, clearly written, and pithy as the author's pedigree would promise. There is no wasted space, and the chapter headings are well chosen. Despite its size, the book delivers a breadth of information that is easy on the brain if not easy on the eye. Each aspect of epilepsy care is dealt with and includes sections on patient subsets that leave no group neglected.

I would thoroughly recommend this book to trainees or consultants in general medicine, or to SpRs needing a primer on the basics of epilepsy care. And since time spent on education is never a waste, I would add that consultants - even those with a special interest in epilepsy - will find much to enjoy and commend in this easily digestible book, even if the finishing is accompanied by an acute desire for a pair of half-moon gravitas-adding glasses. Now, where's my cardigan ....?



**Author:** S Shorvon  
**Published by:** Oxford University Press (2009)  
**Price:** £5.99  
**ISBN:** 9780199560042

**Reviewed by:**  
 John Paul Leach,  
 Southern General  
 Hospital, Glasgow.

# Head Injury: A Multidisciplinary Approach 1st Edition

This is another valuable guide to the care of patients who have suffered head injuries. One may ask whether there is a need for a book which, after a first glance at the contents page, appears to be a series of topic review chapters. In this era of rapid online publication such a volume might be expected to have a short shelf life as more recent reviews become available. However, this volume provides a comprehensive overview of all aspects of head injury management which will appeal to a wide audience of neuroscience specialists and is likely to stand the test of time.

The management of the head injured patient requires input from many different disciplines and the editors of this book aim to provide a concise overview of each of those disciplines. The target audience is, therefore, members of each of those disciplines and the editors have undoubtedly achieved their aim in the 27 chapters which systematically deal with each.

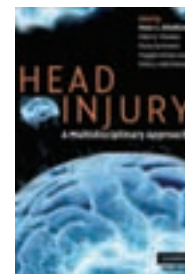
The volume opens with a discussion of the epidemiology of head injury by Giles Critchley and Anjum Memon. This chapter sets the tone for the book. In just ten pages Critchley and Memon define why head injury is such an important problem, describe the basic principles of epidemiology and how this applies to head injury. Their discussion is packed full of the most essential information drawn from a massive body of literature and manages to include a discussion on sporting head injuries in addition to those injuries which more commonly come to the attention of neurosurgeons and neuro-intensivists. The reader is left at the end of their chapter with a summary of take home facts which serves to highlight how important this clinical and public health problem is and serves as a commanding lead-in to the rest of the book.

The subsequent chapters keep to this pattern of dealing with each topic succinctly and this defines the style of the

book which remains compact at 309 pages. The chapters are to-the-point, punchy and in many ways down-to-earth in the way they deal with the subject matter. Furthermore, figures are used sensibly to illustrate key points and concepts judiciously. The reader is taken through the key aspects of the neuropathology, clinical assessment, and neuroimaging of head injury, and key aspects of essential neurophysiology and monitoring of the head injured patient. Perhaps what is most noteworthy about this volume, however, is the inclusion of chapters which cover areas which many neuroscience practitioners would not necessarily have had time to read about very extensively. For example, chapter 3 discusses experimental models of head injury which highlights just how heterogeneous this condition is and how important the use of a wide range of outcome measures is in order to achieve the translation from preclinical research observations to clinical benefits for patients.

The latter chapters describe the issues surrounding the surgical management of head injury thoroughly, including excellent chapters on craniofacial trauma and cranioplasty. The final six chapters of this book cover different aspects of rehabilitation, neuropsychology, outcome and prognosis, and medico-legal aspects of head injury and maintain the momentum of the opening chapters.

There is no comparable volume available on the market which takes this multi-disciplinary approach and this makes this volume unique. It should be available to all those involved in the care of the head injured patient or involved in head injury research. In addition to being a must have for every clinical neurosciences department this will also be a valuable guide for individual clinicians and researchers, especially those who are new to the field.



**Editors:** Peter Whitfield, Eflyn Thomas, Fiona Summers, Maggie Whyte, and Peter Hutchinson  
**Published by:** Cambridge University Press (2008)  
**ISBN:** 13:9780521697620

**Reviewed by:** Reuben Johnson  
 Lecturer in Neuroanatomy, Exeter College, Oxford; Specialist Registrar in Neurosurgery, John Radcliffe, Oxford.

# Neurological Disorders in Famous Artists. Part 3.

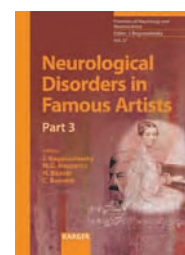
The two previous volumes in this series have received the reviewer's "thumbs-up" (see ACNR 2005;5(5):37 and 2008;8(1):52) and the latest offering achieves the same rating. It taps into a possibly infinite seam of mixed fact and speculation, which probes the possible interactions between neurological disease and creativity, a subject likely to be of interest not only to many neurologists but also to a lay audience. Here are to be found visual artists (da Vinci, Klee, de Chirico, Schiele, Warhol), composers (Schubert, Robert and Clara Schumann, Wolf, Berlioz, Shostakovich, Bartok), and writers (Stendhal, Cendrars, Pascal, Hemingway, Ramuz, Shakespeare). Diagnostic possibilities investigated include cerebrovascular disease, systemic sclerosis, dystonia, neurosyphilis, opiate misuse, motor neurone disease, chronic pain syndromes, amputation, migraine, autism (from Ioan James, reprising material previously reviewed in these pages: ACNR 2006;6(5):36), and out-of-body experience. Verily, then, a textbook of neurology.

To select one or two morceaux: Brandy Matthews contributes two chapters, one on "Neurology at the opera" which contains the (dismaying?) information that an opera has been written based on Sacks' "The man who mistook his wife for a hat", and one on Shakespeare's portrayal of neurological illness and physicians. The latter seems to perpetuate the face-value acceptance of Iago's assertion of Othello's "epilepsy" (cf.

<http://bmj.com/cgi/eletters/333/7582/1335>, 2 January 2007), and a diagnosis of dementia with Lewy bodies is suggested for King Lear. Would you believe it, but a diagnosis of prion disease has even been advanced for Macbeth (notably not in a neurological journal: Clin Infect Dis 2006;42:299-302)? A section on Shakespeare as therapy concludes with the refrain All's well that ends well, surely a misreading of a "problem play" wherein the King's last couplet (V;iii:327) begins "All yet seems well" (the slogan for any autocracy?).

The most scholarly piece, to my mind, is that of Sebastian Dieguez on Ernest Hemingway. Clearly Dieguez is conversant not only with the oeuvre but also the criticism engendered by it, in framing the multiple diagnostic possibilities (personality disorder, bipolar disorder, head trauma, alcoholism). However, I was surprised to see haemochromatosis in the mix (p. 184,188) since even if, as seems likely, Hemingway had this condition, I thought doubts remained about whether this causes neurological problems (iron does not normally cross blood-brain barrier?). The discussion of "repetition compulsion" in Hemingway's work (p. 196) might also help to explain some of the output of de Chirico ("replay syndrome", p. 44) and Warhol (p. 171), and presumably explains the allure of the Teletubbies.

So, much to enjoy in a generously illustrated volume. Part 4 is keenly awaited!



**Editors:** Bogousslavsky J, Hennerici MG, Bázner H, Bassetti C  
**Published by:** Karger, (2010)  
**Price:** €88  
**ISBN:** 978-3-8055-93304

**Reviewed by:** AJ Lerner, WCNN, Liverpool.



### Dr Andrew J Larner

is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

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# Neurological literature: Headache (Part 6)

"...all went to Pitcombe Church this Afternoon. I stayed at home having a little Head-Ache and thinking also that they would be crowded at Church."<sup>1</sup>

Thus the Reverend James Woodforde's diary for 30 July 1786, indicating that the impact of headache on day-to-day occupation is nothing new, although increasingly recognised in recent times.

Further literary historical accounts of the occupational impact of headache may also be given, for example from Dr Oliver Wendell Holmes (1809-1894), speaking of a school mistress, Helen Darley, aged "22 or 23 years old" in 1861:

"She was consequently ... overworked, and an overworked woman is always a sad sight ... because she is so much more fertile in capacities of suffering than a man. She has so many varieties of headache, – sometimes as if Jael were driving the nail that killed Sisera into her temples, – sometimes letting her work with half her brain while the other half throbs as if it would go to pieces, – sometimes tightening round the brows as if her cap-band were a ring of iron."<sup>2</sup>

This account is quoted, in part, by two books devoted to the history of anaesthesia<sup>3,4</sup> as illustrations of the 19th century willingness to treat pain by means of anaesthetic agents. In this context, it is of interest that both chloroform and ether were at times used to treat headache.<sup>5</sup> For example, in the story *Sur l'eau* (*Alloat*, 1888) by Guy de Maupassant (1850-1893), the narrator breathes ether to relieve migraine. However, anaesthetic agents had adverse effects as well, and sometimes had fatal consequences, for example the case of Miss Mary Duff "Found dead in a bathhouse":

"The charitable construction put upon the terrible tragedy is that young Titus administered to his sweetheart [Miss Mary Duff] a dose of chloroform to dispel a headache, and that she took an overdose that caused her death. In the despair following her death, it is believed that he killed himself."<sup>6</sup>

Christopher Isherwood (1904-1986), enjoying a brief renaissance with the recent popularity of the film *A Single Man*, diverging though it does from his novella, is perhaps best remembered for *Goodbye to Berlin*, hailed as one of the most popular novels of the 20th century. Besides obliquely chronicling the rise of the Nazis, it also contains some casual examples of headache: Otto Nowak, a working class boy from Berlin, aged 16 or 17, "had a touch of sunstroke, and went to bed early, with a headache" whilst holi-

daying on Reugen Island in summer 1931. Frau Landauer is reported to have "tairrible headaches" by her daughter Natalia, such that she cannot be left, but she never has a headache when the narrator proposes going out with Natalia. Interestingly, when he does take Natalia out, to hear Mozart concertos, he finds that "The audience plainly regarded the concert as a religious ceremony. Their taut, devotional enthusiasm oppressed me like a headache".<sup>7</sup> Isherwood was briefly a medical student, as may perhaps be evidenced by the clinical detail in the final pages of *A Single Man*.

The author JD Salinger (1919-2010) is remembered chiefly for his novel *The catcher in the rye*, a paperback copy of which was held, infamously, by Mark Chapman on the night he shot John Lennon. The novel's anti-hero protagonist, Holden Caulfield, at one stage "had a helluva headache all of a sudden", "felt lousy" and "even had a sort of stomach-ache" which felt a little better after coffee but later felt worse. Prior to this, in his peregrinations about New York, Caulfield had evidently missed sleep and meals, and consumed alcohol. Interestingly Holden's mother also complains of a splitting headache, and is said to get headaches quite frequently. "Take a few aspirins" suggests her 10-year-old daughter Phoebe.<sup>8</sup> Diagnosis: migraine?

Phoebe Caulfield's suggestion of aspirin is perhaps not an unreasonable one, particularly from a 10-year-old, but it is now recognised that this is not so straightforward a therapeutic avenue as was once thought:

"Years ago ... if you had a headache you would have thought aspirin the best you could hope for, wouldn't you? Now, you would be wrong. Endless shelves of medicine are now common, specific medicines for specific headaches. Is it a sinus headache or a migraine headache? Now, it makes a difference."<sup>9</sup>

Will improved recognition, identification and treatment spell the end of headache as a major neurological problem? A tantalising glimpse into the future, specifically the 26th century, as provided by Yevgeny Zamyatin (1884-1937) does not seem to augur well:

After what happened yesterday, my head's been in tight bandages. Or rather, no – it isn't a bandage, but more like a hoop, a merciless hoop made of glass steel and riveted to my head.

Compressed inside the tight hoop, my temples were pounding,

My head was on fire and pounding. I sat up the whole night like this and fell asleep only around seven in the morning

... my head killing me.<sup>10</sup> ♦

# Oral Feeding Difficulties and Dilemmas

A guide to practical care, particularly towards the end of life. Report of a working party 2010. Royal College of Physicians and British Society of Gastroenterology.



## Dr Diane Playford

is Clinical Lead of the Rehabilitation Services at the NHNN, where she is responsible for two rehabilitation wards: an 18-bedded supra regional service looking after young adults with stroke, spinal cord injury and MS; and a 10-bedded district based service with predominantly stroke patients.

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The take home message of this report is simple. Insertion of a PEG is not something to be undertaken lightly, and should only be taken after consultation with a full multidisciplinary team consisting of physician, dietitian, speech and language therapist and nurse, having provided the patient and family with appropriate information about the risks and benefits of PEG feeding and its alternatives.<sup>1</sup> Why is a report needed to state this simple fact? The answer lies in some shocking figures. The authors of the report quote one audit of 719 PEG procedures which demonstrated that 19% were futile and of those dying 43% did so within one week of insertion.<sup>2</sup> Even in the best units 30 day mortality is 6% with 10% morbidity.<sup>3</sup>

The underlying causes of this mortality and morbidity are simple to diagnose but may be complex to treat. In the 1970s large bore tubes were used for nasogastric feeding, which were poorly tolerated and rarely used for more than a few days. Gastrostomies were rarely performed and had significant morbidity rates. In the early 1980s fine bore nasogastric tubes and endoscopic placement of PEG tubes were introduced. Since then the number of PEGs inserted has increased enormously and it is clear that many are now inserted unnecessarily. Prevalence figures for enteral feeding in the community suggest that nearly 22,000 people are enterally fed at any one time. While the proportion with cancer continues to rise, 58% of these will have neurological diagnoses, with stroke being the most common cause, these patients will often have associated cognitive and communication deficits.<sup>1</sup>

So why have numbers risen so high? A number of themes emerge from this document. Poor communication with families, failure to consider alternatives, and lack of relevant skills all appear to contribute. In the acute setting, a relatively common scenario seems to be family distress at a sick relative's being 'starved', when PEG is seen as a solu-

tion. Careful explanation of the alternatives is essential here. In many cases, if the patient is not hungry then nothing further needs to be done. If swallowing is impaired, then careful definition of the risks, altered consistencies, safe swallowing techniques and hand feeding, taking enough time to do this properly, may be appropriate. If feeding support cannot be offered this way, or if it is needed for less than six weeks, then an NG tube may be the appropriate choice. Taking the time to make a careful multidisciplinary decision with family and patient involvement is critical.

The report recommends that a multidisciplinary nutrition support team of healthcare professionals, ideally but not inevitably led by a doctor with special expertise in nutrition, also consisting of a nutrition nurse specialist, dietitian and speech and language therapist, and involving the GP and any community team, that is in a place to obtain the best results. Although this is feasible in hospitals, it is clearly more difficult to implement within the community. Dietitians and nutrition nurse specialists are not readily available in all community teams. Management structures do not always facilitate timely discussion of the issues. Although in principle NG tubes may be more appropriate for patients needing them for less than six weeks, ensuring they are correctly positioned before each feed is difficult, and replacing a dislodged tube may involve distressing visits to A&E for replacements if community staff feel they haven't the skills. This is of particular relevance to the nearly 7,000 people with PEGs in nursing and residential homes.

Despite these issues the report can at times appear unduly negative about PEG feeding. A section addressing the negative aspects of PEG feeding highlights not only the 30 day mortality, but also social consequences for the patients including the fact that patients can be deprived of the pleasure of eating. This seems to be based on an

*Too many PEGs are inserted resulting in unnecessary morbidity and mortality. Careful oral feeding may result in better quality of life for patients and carers*

assumption that insertion of PEG equates to 'nil by mouth'. This is clearly untrue. PEGs may be a source of augmentative feeding when eating is tiring or takes a long time; eating small amounts can then be used as a source of pleasure. Although it is true that a PEG can remove meal times as a source of structure for the day and social interaction, from a carer's perspective hand feeding, which takes a long time and is associated with a risk of coughing, can be extremely stressful. In addition rehabilitation interventions now focus on repetitive practice, this applies to swallowing as much as to walking or dressing.<sup>5</sup> Patients with PEGs (or NGs) inserted who might expect a slow recovery need to continue practice swallowing, at first with a skilled speech and language therapist paying attention to safe swallow techniques and then by a trained carer.

Even when these issues are addressed, the placing of PEG tubes can involve complex ethical decisions. The third chapter of this document is an excellent summary of the complex ethical issues. The arguments advanced consider many basic principles and are applicable in situations beyond the dilemmas posed by oral feeding. Issues such as sanctity of life, the intrinsic and instrumental value of life, the principle of ordinary and extraordinary means intended and foreseeable consequences are

discussed. The very topical issues surrounding withholding and withdrawing life prolonging treatment, and best interests decision making, euthanasia, killing and letting die are also considered. The role of the mental capacity, best interest decision making and surrogate decision making are also considered. The distinction between medical treatment and basic care is considered with the report acknowledging the consensus view of the courts, professional bodies and the overwhelming majority of ethical and medical opinion is that nasogastric or gastrostomy feeding is medical care. The detail in this chapter highlights the complex issues that may need to be considered when making decisions in difficult and challenging clinical situations. This chapter is followed by a comprehensive review of the legal considerations, reviewing issues now familiar to many clinicians such as capacity, and competence, and how best interests are determined.

In conclusion, this report is a timely reminder that PEG insertion should only occur after careful consideration of the risks and benefits with careful explanation of these and alternatives to the family. The benefits of PEGs, in carefully selected patients, to maintain body weight, as a form of augmentative feeding combined with judicious eating should also not be underestimated. ♦

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The Encephalitis Society  
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## ENCEPHALITIS PROFESSIONAL SEMINAR

# Some Solutions and Emerging Challenges



Monday 29th November 2010, 13.30 – 18.30 – Wellcome Centre, Euston, London

The Seminar presents current studies that contribute to a fuller understanding of the pathogenesis, epidemiology and outcomes of the encephalitis

### Keynote Speakers:

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Dr Sarosh R Irani, John Radcliffe Hospital Oxford  
Julia Granerod, HPA Centre for Infections, London

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# American Academy of Neurology Annual Meeting

Conference details: April 10-17, Toronto, Canada. Reviewed by: Alasdair Coles, University Lecturer in Neuroimmunology at Cambridge University.

## A 92-year-old rescues a miserable meeting

Even before the volcanic ash cloud trapped European neurologists in Toronto for days, the meeting was not going well. At least in multiple sclerosis research, there was nothing new to learn. The educational sessions were off-puttingly expensive and the plenary sessions failed to thrill. Perhaps the lowest moment was the Presidential address. At this keynote moment of the whole conference, with literally thousands of neurologists in attendance, the President declared emotionally that the principal purpose of the American Academy of Neurology was to protect the remuneration scales of American neurologists. Goodness knows what delegates from developing countries made of that.

It took a 92-year-old English psychologist to save the day. Brenda Milner, who gave her first presentation to the AAN in 1953, was back! Tiny and frail, she spoke fluently, enthusiastically and charmingly about her famous patient 'HM'. When she finished, she got a standing ovation, the crowd delighted to have something unequivocally good to celebrate.

Brenda Milner had studied psychology in Cambridge and then went to do a PhD in Montreal in 1950, with the task of understanding the function of the temporal lobes, working on the epilepsy surgery patients of Wilder Penfield. She explained that Penfield always prohibited bilateral temporal lobe surgery, out of an instinctive concern that this would be harmful. On the other hand, he and his assistant, Dr Rasmussen, regarded unilateral surgery of the anterior temporal lobe as fairly harmless. However, the team had a shock when a 47-year-old engineer suffered devastating working memory loss after a routine unilateral operation. Penfield speculated that he must have had undetected hippocampal damage on the non-operated side. Eight years later, when the patient came to post-mortem, this proved to be true. In the intervening years, though, Brenda Milner publicised the hypothesis that bilateral temporal lobe damage would lead to a devastating amnesic syndrome. This attracted the attention of a neurosurgeon in Hartford, US. Dr Scoville had been performing bilateral hippocampectomies in people with intractable epilepsy. One of these, 'Henry M', had developed a syndrome similar to that reported by Penfield & Milner. So Milner took the night train down to Hartford, "an obscure young psychologist from Montreal" to meet the patient who would make her world-famous. He was 27 at the time and in December 2008 he died at the age of 82. During all that time, he never recognised Milner.



CN Tower, Canada.

Milner's 'breakthrough' came when she found that some aspects of HM's memory were intact. She took down to Hartford the 'mirror drawing task' in which patients (or monkeys!) have to draw around a star, visualising the task in a mirror. HM learnt this task as quickly as any normal person. At the end of the experiment, after performing the task for the 30th time, HM had no memory of previous attempts and said "I thought that was going to be difficult, but I did it rather well".

It is hard for us to understand now the importance of HM. At the time, memory was considered a unitary function and dependent on the mass of the cortex. But his case showed that memory was fractionated (his 'motor memory' was intact) and that working memory was specifically localised to both hippocampi.

## Supermice and the humble astrocyte

A goal of transplantation into the brain has always been restoration of components that are lost or never made. The potential – and the limitations – of this aim were beautifully illustrated by Steve Goldman's work on the shiverer mouse. This animal fails to myelinate its neurons and develops ataxia and dies

young. Goldman's group have worked out a way of generating A2B5 positive human oligodendrocyte precursors from middle trimester spontaneously aborted foetuses (usually due to placental problems). When injected into the shiverer mice, these oligo precursors myelinate neurons nicely, restore normal electrophysiology and even induce the formation of new nodes of Ranvier. So far, so good. Unfortunately, when the embryonic oligo precursors migrate in the brain, they lose their capacity to remyelinate and become astrocytes. So, to achieve a useful therapeutic result, the embryonic cells need to be injected into multiple white matter sites. This really does not sound like a terribly viable option for adults with multiple sclerosis.

On the other hand, this treatment might be helpful for the inherited leukodystrophies. Transplantation of human embryonic oligo precursors into the developing shiverer had fascinating effects. There was a slow remyelination of the entire neuraxis over weeks, much as in the normal mouse. The human cells also generated astrocytes, pushing the residual mouse astrocytes out of the way towards the cortex. One unexpected effect of this was the generation of 'supermice'. The mice made up of mouse neurons and human oligos and astrocytes actually performed better on memory tasks than normal mice. The explanation for this offered by Goldman is that the human astrocytes have many more processes, and are much more effective at promoting synaptic transmission, than ordinary mouse astrocytes. I have never had much time for astrocytes, but it seems I may have underestimated them!

## The best of the rest

- Mostly children get anti-NMDAR encephalitis. Since Dalmau's description of the first 100 cases in *Lancet Neurology*, his group has collected 240 more patients. The big news is that many of the new cases are children. In total, 40% of all cases are now under age 18. In this younger age group, 25% will have a tumour, whereas the rate is 50% for those aged over 18.
- Tysabri and pregnancy. Of the 125 on the Tysabri Pregnancy Exposure Registry, there have been 20 miscarriages and some terminations, of the 99 live births, eight malformations were reported in six pregnancies – two which involved twin births. The average maternal age in these cases was 29 years. 64,600 patients have been put on Tysabri up to December 2009.
- H1N1 Infection can cause acute cerebellitis.

That is it! I was underwhelmed. ♦

# Association of British Neurologists Conference 2010

**Conference details:** 11-14 May 2010, Bournemouth, UK. **Reviewed by:** Biba Stanton, Chair ABN Trainees Committee (ABNT) and Beth Mallam, ABNT Research Representative.

This year's ABN conference was the largest ever, with over 600 delegates attending. Held at the Bournemouth International Centre, overlooking Bournemouth's miles of sandy beaches, the programme was as impressive as the location.

As at last year's meeting, the format included parallel sessions providing a clinical and scientific teaching programme alongside presentations of high quality original research. Teaching included subjects that have sometimes been under-represented at neurology conferences, such as neuro-oncology, pain and neuro-otology. This provided an excellent opportunity for both trainees and consultants to update their knowledge and hear from national experts in their respective fields. The members' papers were well attended and led to stimulating discussions. Highlights included Dr N Paul presenting data from Oxford on the high early risk of stroke following recurrent 'capsular warning syndrome' TIAs, Dr Simon Mead extending the phenotypic spectrum of familial prion disease to include chronic diarrhoea, and Dr W Brown presenting an impressive array of data suggesting that the recent relaxation of DVLA post-seizure driving rules may be too lenient.

Plenary lectures from invited international speakers included Josep Dalmau on autoimmune encephalitis, Stephen Hauser on multiple sclerosis and Johan Aarli on historical perspectives on hysteria. Yves Agid presented his view of the role of the basal ganglia in sub-conscious motor and emotional processing



Beach huts on Boscombe Beach, Bournemouth.

with great erudition and panache. The ABN medal was presented to Michael Swash, in recognition of his major contribution to science and clinical practice in motor neurone disease over a long and distinguished career.

For the first time, the conference hosted a half-day 'road-show' for medical students and foundation doctors interested in neurology. By providing practical information and also some inspiration, the ABN hopes that the road-show will help our efforts to continue attracting the very best medical graduates into our specialty. An extremely entertaining CPC discussion by Martin Turner, and a challenging quiz from the President Elect were highlights of this well-attended session. The ABN Research Forum took place later that day, with 20 posters showcasing neurological research from across the country and time for networking by those interested in setting up research projects. This

unique event looks set to become an annual feature, with plans to expand next year to include an overview presentation.

As always, the meeting's social programme provided a valuable opportunity for colleagues from around the country to meet. The gala dinner was made particularly memorable by musical performances from talented members of the association, not least the mellifluous Queen Square Mellow-tonins. The trainees' dinner, held for only the second time, was also a success and will hopefully become a tradition.

As Heather Angus-Leppan ends her term as chair of the ABN's meetings committee, her successor has a lot to live up to. The 2011 meeting is to be held in October, in another stunning waterside location in Newcastle-Gateshead. But if you can't wait that long, look out for details of an international meeting to be held in Cuba in April. ♦

## The ABN Second Annual Research Forum: May 2010, Bournemouth

The 2nd Annual Research Forum was held at the May ABN Meeting in Bournemouth. The format this year was a poster fair, displaying the research interests and opportunities of all the major neurology centres in the UK. We were delighted with the response to the invitation to present at the forum: 17 academic centres were represented, in addition to presentations by the Academy of Medical Sciences, the Wellcome Trust and the National Institute of Health Research (NIHR).

The event was advertised via email through the ABN to all neurology trainees, posters put up by the ABNT Regional Representatives in neurology departments and junior doctors' messes, and on the Doctors.net neurology forum. Attendance for the event was difficult to assess as people were free to come and go due to the open setting of the poster session. Having the Research Forum on the same day

as the medical students/FY doctors neurology road show was a definite plus: a number stayed on to find out more about research opportunities as well. Some centres have reported that they have since received interest from trainees wishing to set up research projects. We will be contacting all the presenters for feedback on this event in due course.

The opportunity and potential of this event cannot be underestimated: a showcase of UK neurology research bringing together those in research and those who would like to be. Looking to the future, it is felt that an overview presentation might bring attention and focus to the event and help improve the number of people attending. Other useful talks could be commissioned, for example the Wellcome Trust has offered to give an insider's guide to grant applications and fellowship interviews. A brief introduction of those presenting the posters has also been suggested as some atten-

dees commented that they weren't sure who to speak to. The highlight of the event will remain the unique opportunity for informal networking and information gathering from representatives of the various societies promoting research in the UK.

The ABNT is contributing to the ongoing revamp of the ABN website, in particular we are working on establishing the Research Network. The Research Network is hoped to be a permanent resource containing much of the information that was available at the Research Forum. Please look for the Research Network on the ABN website over the coming months.

We would like to hear any comments that people have – whether they were presenters, attendees, or are future participants – regarding the Annual Research Forum: please email us at [josieshew@theabn.org](mailto:josieshew@theabn.org)

## ABN continued: List of Poster Presentations and Contact Details:

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### The Academy of Medical Sciences

Contact: <http://www.acmedsci.ac.uk/>

### Neurology/Neuroscience Research at University of Birmingham,

Contact: Prof Karen E. Morrison, [k.morrison@bham.ac.uk](mailto:k.morrison@bham.ac.uk)

### Institute of Clinical Neurology at Bristol

Contact: Professor Neil Scolding, [n.j.scolding@bristol.ac.uk](mailto:n.j.scolding@bristol.ac.uk)

### Research Opportunities in the Department of Clinical Neurosciences, University of Cambridge

Contact: Professor Alastair Compston, [kd203@medschl.cam.ac.uk](mailto:kd203@medschl.cam.ac.uk)

### Research in the academic department of Neurology, Cardiff University and the University Hospital of Wales

Contact: AE Rosser, [CaffynMR1@cf.ac.uk](mailto:CaffynMR1@cf.ac.uk)

### Neurology research training opportunities in Edinburgh

Contact: Siddharthan Chandran, [siddharthan.chandran@ed.ac.uk](mailto:siddharthan.chandran@ed.ac.uk)

### Glasgow Neurosciences

Contact: Professor Hugh J Willison, [h.j.willison@clinmed.gla.ac.uk](mailto:h.j.willison@clinmed.gla.ac.uk)

### Liverpool Brain Infection Group

Contact: Professor Tom Solomon, [tsolomon@liv.ac.uk](mailto:tsolomon@liv.ac.uk)

### Neuroscience at King's College London

Contact: Ms Sophie Morris, [sophie.morris@kcl.ac.uk](mailto:sophie.morris@kcl.ac.uk)

### UCL Institute of Neurology

Contact: Professor Alan Thompson, [a.thompson@ion.ucl.ac.uk](mailto:a.thompson@ion.ucl.ac.uk)

### Clinical Neurodegeneration Research in Manchester: Linking Genotypes and Cognitive Phenotypes

Contact: Professor Karl Herholz, [Karl.Herholz@manchester.ac.uk](mailto:Karl.Herholz@manchester.ac.uk)

### Poster presentation by the National Institute for Health Research Trainees Coordinating Centre (NIHR TCC)

Contact: <http://www.nihr.ac.uk/Pages/default.aspx>

### Research training opportunities in Newcastle and the North East of England

Contact: Professor Patrick Chinnery, [p.f.chinnery@ncl.ac.uk](mailto:p.f.chinnery@ncl.ac.uk)

### Research in Nottingham

Contact: Dr Cris Constantinescu, [Cris.Constantinescu@nottingham.ac.uk](mailto:Cris.Constantinescu@nottingham.ac.uk)

### Opportunities For Neuroscience Research In Oxford, Department Of Clinical Neurology, University Of Oxford

Contact: Professor Christopher Kennard, [chris.kennard@cneuro.ox.ac.uk](mailto:chris.kennard@cneuro.ox.ac.uk)

### Research Opportunities in Plymouth

Contact: Professor C Oliver Hanemann, [Oliver.Hanemann@pms.ac.uk](mailto:Oliver.Hanemann@pms.ac.uk)

### Academic Neurology Unit, University of Sheffield: Current research activities and opportunities.

Contact: Professor Pamela Shaw, [pamela.shaw@sheffield.ac.uk](mailto:pamela.shaw@sheffield.ac.uk)

### Poster presentation by the Wellcome Trust

Contact: <http://www.wellcome.ac.uk/>

## Headache Disorders in Focus – The Migraine Trust and the 2nd EHMTIC

**Conference details:** October 29-31, Nice, France. **Reviewed by:** Peter J Goadsby, Medical Trustee, The Migraine Trust, Russell Square London, UK.

PREVIEW

Since the inception of *ACNR* the editors have recognised headache as an important topic in clinical neuroscience, addressing the problem of migraine management in the very first issue.<sup>1</sup> From October 29th until 31st this year the 2nd European Headache and Migraine Trust International Conference will be held in Nice, France. The programme will cover the latest advances in the understanding and management of headache disorders. It will feature invited lectures and teaching courses ranging from primary care and allied health professionals to scientific methods. There will be discussion and debate, and I expect, indeed hope, disagreements, for it is robust interaction that is the stuff of good science. The marriage of the two meetings has been a happy one for the couple and we hope for our constituency.

This is the 18th International Congress that has borne the name of the Migraine Trust and a very special one it is, since it is the first time the Symposium has been held off-shore in its now 34 year uninterrupted history. The trust meetings were first held at Queen Square under the leadership of MacDonald Critchley who once told me as I prepared for a lecture

bearing his name that what was known about migraine in his time could be written on the back of a postage stamp...with space left over. Much has changed, perhaps most importantly the increasing recognition of the very significant disability that attends migraine, and thus the crucial acknowledgement through the meeting of the need for research. By combining the meeting of the European Headache Federation and the Migraine Trust concentrate and focus the presentation of headache research every two years in what is always a meeting, where advances are presented and issues vigorously discussed.

Despite the multi-billion euro cost of migraine in Europe,<sup>2</sup> and the very clear realisation of that cost by a recent All-Party Parliamentary Group in the UK,<sup>3</sup> research spending on headache remains at an all-time low. The latest estimates from the National Institutes of Health are now below \$8m dollar per annum in the US for all headache disorders, the successful European Union funding program that spawned EuroHead, and drove the first migraine aura mouse model,<sup>4</sup> lapsed for want of political will to continue its funding, and in the UK the funding situation was

reflected accurately when the All-Party Parliamentary Group held a meeting on research at the House of Commons and neither the Medical Research Council, nor the National Institute for Health Research bothered to attend. Only a concerted effort between patients, doctors and researchers interested in headache will break the funding drought and give the EHMTIC its next 34 years in which to redouble our efforts to refine the understanding and treatment of headache disorders. ♦

#### References

1. Boes CJ, Matharu MS, Goadsby PJ. *Management of difficult migraine*. *Advances in Clinical Neuroscience and Rehabilitation* 2001;1:5-8.
2. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J. *Cost of disorders of the brain in Europe*. *Eur J Neurol* 2005;12(Suppl 1):1-27.
3. A Report of the All-Party Parliamentary Group on Primary Headache Disorders (APPGPHD). *Headache Disorders- not respected, not resourced*. House of Commons, London UK, 2010.
4. van den Maagdenberg AMJM, Pietrobon D, Pizzorusso T, Kaja S, Broos LAM, Cesetti T, et al. *A *Ca<sub>v</sub>1* knock-in migraine mouse model with increased susceptibility to cortical spreading depression*. *Neuron* 2004;41:701-10.

## The Birmingham Neurosurgery Clinical Meeting

**Date:** Tuesday 30th November and  
Wednesday 1st December 2010

**Venue:** Post Graduate Medical Centre, Queen Elizabeth Hospital  
Metchley Park Road, Edgbaston, Birmingham, B15 2TH

*This is the second such event to be organised by Aesculap Academia. The choice of Birmingham reflects the growing reputation that we have as a unit which offers its staff and trainees a wide range of experience, covering both general neurosurgery and a variety of specialist subjects.*

### Topics to include:

- Battlefield injuries - Brain implants - Cerebral gliomas -
- Craniofacial reconstruction - Interventional radiology -
- Modern management of stroke - Neurological rehabilitation -
- Neurosurgical sepsis - Protecting the damaged brain -
- Spinal cord injuries - Spinal fixation - Syringomyelia -
- Veterinary neurology - Regeneration in the central nervous system -

### Invited Faculty:

Professor Garth Cruickshank, Professor Keith Porter,  
Professor Ann Logan, Mrs Rosalind Mitchell, Mr Graham Flint,  
Dr Richard West, Mr Spencer Harland, Dr Nandan Gautam,  
Dr Don Sims, Mr Steve Dover, Dr Imad Soryal,  
Professor James van Dellen, Mr Ameen Ameen,  
Dr Clare Rusbridge, Mr Wagih El Masri

### Registration Details:

The course fee is £75.00 (Including VAT at 17.5%).

For further information or to register please contact the events team:

Tel: 0114 225 9057

academia.bbmuk@bbraun.com

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Taking place over three days, the symposium features a scientific meeting and a clinical meeting.

### Scientific meeting

Proposed platform session themes

- RNA biology in ALS
- Lessons from other diseases
- Emerging disease models
- Translational strategies
- Genetics and genomics
- Axonal function and pathology
- Glial cell biology
- Cell biology and pathology

### Clinical meeting

Proposed platform session themes

- Autonomy and quality of life
- Care education and practice
- Surrogate markers
- Epidemiology
- Cognitive and psychological assessment and support
- Clinical trials
- International perspectives on care practice
- Holistic care
- Respiratory and nutritional management

For more information and to register, contact the conference team by email [symposium@mndassociation.org](mailto:symposium@mndassociation.org) or register online at [www.mndassociation.org/symposium](http://www.mndassociation.org/symposium).



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

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***Do FES and robotics improve recovery of the upper limb?***

Marie-Helene Boudrias, Institute of Neurosciences, London  
***What human neuroimaging can teach us about motor control.***

Dr Martin Monti, Postdoctoral Researcher, University of Cambridge  
***The aware mind in the still body: fMRI of the vegetative state***

Dr Stephanie E. Baldeweg, Consultant Physician in Diabetes & Endocrinology, University College London Hospital  
***Hormones after head injury or what really happened to Tintin?***

Another four speakers to be confirmed

For further details and application enquiries please contact:

**Nick Hall, Conference Organiser • Email: [nicholas.hall@homerton.nhs.uk](mailto:nicholas.hall@homerton.nhs.uk) • Tel: 020 8510 7970**

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 The Centre Administrator, Tel: 0113 812 5918, Fax: 0113 812 3416  
 Email: [cnsenquiries@leedsmet.ac.uk](mailto:cnsenquiries@leedsmet.ac.uk)

Courses developed in association with: NeuroEducation, Epilepsy Action, Multiple Sclerosis Society, Multiple Sclerosis Trust, Parkinson's UK

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**RAaTE 2010** is delighted to announce this year's keynote speaker as Dr. Martin Ferguson-Pell, the Dean of the Faculty of Rehabilitation Medicine at the University of Alberta, Canada. Dr. Ferguson-Pell's background is in Biomedical Engineering and he is a registered Clinical Scientist. He has extensive experience working in clinical-academic settings developing engineering solutions to overcome barriers experienced by people with physical disabilities.

**RAaTE 2010** is now accepting papers for this year's Conference under the following categories:

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- AT for Older People/ Telecare & Telehealth
- Innovative Access & Innovative Wheelchair Control - AT in Education

To book your place at **RAaTE 2010** register online at [www.raate.org.uk](http://www.raate.org.uk) Cost is £125 inclusive of VAT.

For more information on sponsorship opportunities or to book an exhibition stand please contact [hdti.info@coventry.ac.uk](mailto:hdti.info@coventry.ac.uk)





**2nd European Headache and Migraine Trust  
INTERNATIONAL CONGRESS – EHMTIC  
NICE, FRANCE | OCTOBER 28-31, 2010**

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**2nd Global Symposium  
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To list your event in this diary, email brief details to John Gustar at [editorial@acnr.co.uk](mailto:editorial@acnr.co.uk) by 6th August, 2010

# 2010

## JULY

**European Life Science meeting: Human autoimmune disease: learning from models**

2 July, 2010; Hertfordshire, UK  
E. [enquiries@euroscicon.com](mailto:enquiries@euroscicon.com)  
[www.regonline.co.uk/autoimmunemodels09](http://www.regonline.co.uk/autoimmunemodels09)

**Clinical Reasoning in Soft Tissue Repair: Using the evidence to maximise recovery using manual therapy, exercise and electrotherapy**

3 July, 2010; Essex, UK  
[www.physiok.co.uk](http://www.physiok.co.uk)

**FENS Forum 2010: The latest developments in Brain Research**

3-7 July 2010; Amsterdam, The Netherlands  
T. 020 7738 0424

E. [elaine@snell-communications.net](mailto:elaine@snell-communications.net)  
[www.snell-communications.net](http://www.snell-communications.net)

**European Life Science meeting: Cytokines in translational research: bench to bedside**

8 July 2010; Hertfordshire, UK  
E. [enquiries@euroscicon.com](mailto:enquiries@euroscicon.com)  
[www.regonline.co.uk/cytokines10](http://www.regonline.co.uk/cytokines10)

**The Society for Research in Rehabilitation Summer Meeting**

7-8 July, 2010; Sheffield, UK  
T. 01142255336

E. [conference21@shu.ac.uk](mailto:conference21@shu.ac.uk) or  
[srr\\_secretary@srr.org.uk](mailto:srr_secretary@srr.org.uk)

**7th International Congress on Neuroendocrinology**

10-15 July, 2010; Rouen, France  
T. +33 149 284 676

E. [william.rostene@st-antoine.inserm.fr](mailto:william.rostene@st-antoine.inserm.fr)

**6th National Autism Today Conference**

12-13 July, 2010; London, UK  
E. [anne.haylock@markallengroup.com](mailto:anne.haylock@markallengroup.com)

**Warwick University Short Course: Techniques and Applications of Molecular Biology: A Course for Medical Practitioners**

12-15 July, 2010; Warwick, UK  
T. 024 7652 3540

E. [charlotte.moonan@warwick.ac.uk](mailto:charlotte.moonan@warwick.ac.uk)  
[www.warwick.ac.uk/go/bioscienceshortcourses](http://www.warwick.ac.uk/go/bioscienceshortcourses)

**XII International Congress on Neuromuscular Diseases**

17-22 July, 2010; Naples, Italy  
[www.icnmd2010.naples.org](http://www.icnmd2010.naples.org)

**3rd INBR Congress**

24-30 July, 2010; Abuja, Nigeria  
E. [polycarpnwoha@yahoo.com](mailto:polycarpnwoha@yahoo.com)

## AUGUST

**4th Migrating Course on Epilepsy**

15-22 August, 2010; Sercock, Poland  
E. [petra@epilepsy-academy.org](mailto:petra@epilepsy-academy.org)  
[www.epilepsy-academy.org](http://www.epilepsy-academy.org)

**15th World Congress of Psychophysiology - the Olympics of the Brain - IOP2010**

30 August - 4 October, 2010; Budapest, Hungary  
Mark Molnar,

T. 61 350 1854

E. [worldcongress2010@world-psychophysiology.org](mailto:worldcongress2010@world-psychophysiology.org)

## SEPTEMBER

**3rd International Congress Biotechnologies for Spinal surgery**

1-4 September, 2010; Amsterdam, Netherlands  
E. [meisel@bergmannstrost.com](mailto:meisel@bergmannstrost.com)  
[www.biospine.org](http://www.biospine.org)

**Cambridge Memory Disorders Workshop**

2-3 September, 2010; Cambridge, UK  
T. 01223 217557

E. [fiona.aschmann@addenbrookes.nhs.uk](mailto:fiona.aschmann@addenbrookes.nhs.uk)  
[www.ozc.nhs.uk](http://www.ozc.nhs.uk)

**Computers for Therapy, one day course**

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T: 0208 780 4500 x5140

E. [pdenning@rhn.org.uk](mailto:pdenning@rhn.org.uk)

[www.rhn.org.uk/nec\\_001.asp](http://www.rhn.org.uk/nec_001.asp)

**XVIIIth International Congress of Neuropathology**

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Brigitte Millán-Ruiz, T. 43 1 404 005 573

E. [brigitte.millan-ruiz@meduniwien.ac.at](mailto:brigitte.millan-ruiz@meduniwien.ac.at)

**Parkinson's Disease SpR Masterclasses**

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[www.neurosurgeon.org](http://www.neurosurgeon.org)

**OZC – Understanding Brain Injury**

17 September, 2010; Ely, UK

T. 01353 652173

E. [Rachel.everett@ozc.nhs.uk](mailto:Rachel.everett@ozc.nhs.uk)

**Evolving MS Services**

17 September, 2010; Maidstone, UK

T. 0208 438 0809

E. [pcrossman@mssociety.org.uk](mailto:pcrossman@mssociety.org.uk)

**Understanding and Dealing with Behaviour Problems following ABI**

17-18 September, 2010; Gatwick Airport, London, UK

E. [enquiries@braintretraining.co.uk](mailto:enquiries@braintretraining.co.uk)

[www.braintretraining.co.uk](http://www.braintretraining.co.uk)

**Clinical Reasoning in Soft Tissue Repair: Using the evidence to maximise recovery using manual therapy, exercise and electrotherapy**

18 September, 2010; Bath, UK

[www.physiok.co.uk](http://www.physiok.co.uk)

**Second Meeting of the European Societies of Neuropsychology**

22-24 September, 2010; London, UK

E. [dana.samson@nottingham.ac.uk](mailto:dana.samson@nottingham.ac.uk)

**14th Congress of the European Federation of Neurological Societies (EFNS 2010)**

25-28 September, 2010; Geneva, Switzerland

T. 41 229 080 488

E. [efns2010@kenes.com](mailto:efns2010@kenes.com)

**2nd World Parkinson Congress**

28 September-1 October, 2010; Glasgow, UK

T. Elizabeth Pollard, (001) 212.923.4700

E. [info@worldpdcongress.org](mailto:info@worldpdcongress.org)

**10th Annual Brain Injury Legal Seminar**

30 September, 2010; London, UK

T. 07501483989

E. [chloe\\_hayward@hotmail.com](mailto:chloe_hayward@hotmail.com)

**3rd National Autism and Depression Conference**

30 September-1 October, 2010; London, UK

E. [anne.haylock@markallengroup.com](mailto:anne.haylock@markallengroup.com)

**OCTOBER**

**6th International Symposium on Neuroprotection and Neurorepair**

1-4 October, 2010; Rostock Germany

T. +49 (0)341240596-50

F. +49 (0)341240596-51

E. [johannes.boltze@izi.fraunhofer.de](mailto:johannes.boltze@izi.fraunhofer.de)

**XIX Symposium Neuroradiologicum**

4-9 October, 2010; Bologna, Italy

E. [marco.leonardi@symposiumneuroradiologicum.org](mailto:marco.leonardi@symposiumneuroradiologicum.org)

[www.symposiumneuroradiologicum.org](http://www.symposiumneuroradiologicum.org)

**Global Symposium on Dietary Treatments for Epilepsy and other Neurological Disorders**

5-8 October, 2010; Edinburgh, UK

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**AANEM Annual Scientific Meetings**

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**European Life Science meeting: Induced pluripotent stem cells: production and utility in regenerative medicine**

7 October 2010; Hertfordshire, UK

E. [enquiries@euroscicon.com](mailto:enquiries@euroscicon.com)

[www.regonline.co.uk/IPS09](http://www.regonline.co.uk/IPS09)

**ABN Annual General Meeting**

11-14 October, 2010; Bournemouth, UK

E. [enquiries@euroscicon.com](mailto:enquiries@euroscicon.com)

[www.regonline.co.uk/IPS09](http://www.regonline.co.uk/IPS09)

**7th World Stroke Congress**

13-16 October, 2010; Seoul, Korea

T. +41 22 908 0488 x966

E. [dhuriel@kenes.com](mailto:dhuriel@kenes.com)

[www.kenes.com](http://www.kenes.com)

**2010 Congress of the European Committee for Treatment and Research in Multiple Sclerosis**

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E. [pdenning@rhn.org.uk](mailto:pdenning@rhn.org.uk)

[www.rhn.org.uk/nec\\_001.asp](http://www.rhn.org.uk/nec_001.asp)

**Discover the Thorax with LJ Lee**

15-17 October, 2010; Sutton, UK

[www.physiok.co.uk](http://www.physiok.co.uk)

**Thoracic Outlet Syndrome: Assessment, Differential Diagnosis and Hands on Treatment**

16 October, 2010; Bristol, UK

[www.physiok.co.uk](http://www.physiok.co.uk)

**British Neuropsychological Society Autumn Meeting**

20 October, 2010; London, UK

E. [dana.samson@nottingham.ac.uk](mailto:dana.samson@nottingham.ac.uk)

**UKNG Education/Update: Ischaemic Stroke**

22 October, 2010; London, UK

E. [Annie.Sellar@sellarannie@hotmail.com](mailto:Annie.Sellar@sellarannie@hotmail.com)

**10th International Congress of Neuroimmunology**

26-30 October, 2010; Barcelona, Spain

Francesca Mariani,

T. 39 0 65 193 499,

F. 39 0 65 194 009

E. [mariani@eemservices.com](mailto:mariani@eemservices.com)

**Neurology Symposium**

27 October, 2010; Edinburgh, Scotland

E. [patricia@oncologynews.biz](mailto:patricia@oncologynews.biz)

**EHMTIC 2010 – Migraine**

October 28-31, 2010; Nice, France

T. +41 22 908 0488

E. [ehmtic@kenes.com](mailto:ehmtic@kenes.com)

[www.ehmticcongress2010.com](http://www.ehmticcongress2010.com)

**The 4th World Congress on Controversies in Neurology (CONY)**

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E. [info@comtecmed.com](mailto:info@comtecmed.com)

[www.comtecmed.com/cony](http://www.comtecmed.com/cony)

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## EDITOR'S CHOICE

## EPILEPSY: Golden Oldies

There are few double-blind randomised clinical trials worthy of the name in epilepsy and those that do exist are fraught with difficulties including diagnostic heterogeneity. Childhood absence epilepsy is common and is easier to define than most types of epilepsy, although even this condition may be mistaken for other idiopathic epilepsies or occasionally for focal epilepsies. So it is a good condition to study and these authors have looked at very respectable numbers of patients (453 in total) and randomised them to receive ethosuximide, valproate or lamotrigine. They increased the dose incrementally until they achieved seizure-freedom. Bedside hyperventilation and one hour of video EEG were used to monitor whether seizure-freedom had been achieved at 16 weeks. This is an important measure as patients are not always aware of their own absences. Patients "failed" if they had ongoing absences, a single tonic clonic seizure, adverse effects or predefined changes in serum markers. 209 children had not failed treatment at 16 weeks (ethosuximide 53%, valproate 58% and lamotrigine 29%). Failures were due to lack of seizure control in 24% and adverse effects in 22% (valproate 12%, ethosuximide 14% and lamotrigine 47%). Adverse effects occurred in 24% of patients taking valproate and ethosuximide

and in 17% of patients taking lamotrigine. They also used something called the Connors' continuous performance test to assess cognitive function and quality of life in these children, whose activity had previously been interrupted by very regular absences. Valproate patients did significantly worse than the other two groups. So in conclusion, lamotrigine did not work well at controlling seizures whereas valproate and ethosuximide both worked well but ethosuximide had less neurocognitive adverse effects. Insofar as we understand the basis of absence epilepsy, there is an abnormality of thalamocortical function in which T-type calcium channels play a key part. Ethosuximide acts on T-type calcium channels so is the closest we have to a magic bullet in epilepsy. It is an endorsement of research into the understanding of basic biological mechanisms that this relatively purely targeted drug is more successful in this study than the other agents tested. Don't forget this drug in IGE, even in older patients. Moreover, it confirms that newer is not always better, but those of us who are longer in the tooth already know that.

– **Mark Manfred**

**Glauser T, Cnaan A, Shinnar S et al.**

**Ethosuximide, valproic acid and lamotrigine in childhood absence epilepsy. NEJM 2010;362:790-9.**

## 'And the deep lane insists on the direction'

That micro-electrodes can be inserted into distinct relevant parts of the brain of rat pups before their eyes have unsealed (~postnatal day 15, P15), and by recording, while they navigate for the very first time, reveal that representations of direction, and to a lesser degree spatial location, are relatively hard-wired, is staggering. These are two back-to-back papers from the teams of John O'Keefe at University College London ('Team Place') and Edvard and May-Britt Moser at the Kavli Institute, Trondheim, Norway ('Team Grid'). O'Keefe and colleagues are known for their identification in 1971 of cells in cornu ammonis 1 (CA1) of hippocampus that fire maximally if a rat is in a particular position in space: place cells. Taube identified head-direction responsive cells in 1990. The Mosers identified in 2005 cells in medial entorhinal cortex (MEC) that fire maximally when a rat passes a virtual point in space matching a vertex of a regular grid of equilateral triangles: grid cells. But how much of this tripartite hardware is generated from experience and learning, and how much is a pre-determined not-so-blank slate? Team Place recorded from P14 to P30 from rats foraging for food. Directional cells were present at P14, mostly in para-subiculum, place cells developing over P16 to P17, and grid cells at P20, rapidly developing to P22. Team Grid measured from P13, and also found directional cells first, P15, at the level found in adult rats. Place cells were seen at P16, with only a subsequent modest rise, and rudimentary grid cells were seen at P16 but only attained strict periodicity by P28. The groups disagree on the timing and development of nascent grid cells, and issues of cross-communication between cells are unresolved in these studies, but both groups show that experience (trial number) had a far weaker effect on cell number than age. Bartsch et al provide a nice human study, in the same issue of Science, of 14 patients with acute transient global amnesia, CA1 lesions and impaired place memory in a virtual Morris water maze.

– **Mike Zandi**

**Wills et al. (O'Keefe) Development of the Hippocampal Cognitive Map in Prewanling Rats. SCIENCE 2010;328:1573-6. Langston et al. (Moser) Development of the Spatial Representation System in the Rat. SCIENCE 2010;328:1576-80.**

**Palmer and Lynch. A Kantian View of Space. SCIENCE 2010;328:1487-8.**

**Bartsch T. et al. Focal Lesions of Human Hippocampal CA1 Neurons in Transient Global Amnesia Impair Place Memory. SCIENCE 2010;328:1412-15.**

**Eliot T.S. East Coker. London : Faber, 1940**

Immune cells and the brain  
new functions and interactions

There has always been a great deal of interest in the dialogue between the immune system and the brain, and we have regularly reviewed this area in the context of disease states such as MS and paraneoplastic or autoimmune conditions targeting receptors or ion channels. Of late though there have been a number of papers linking inflammation to neurodegenerative disorders and more recently epilepsy.

In this latter area, Maroso et al have shown in experimental work and human post mortem data that inflammation may be important in epilepsy and not just an incidental consequence of the pathological insult and/or ongoing ictal activity. These authors show that a variety of cells in the brain, such as microglia and possibly even astrocytes and neurons, secrete the well known intracellular chromatin associated protein; high-mobility group box 1 (HMGB 1)!! This protein seems to be released in some situations by these cells in epileptic tissue, and it then binds to the Toll-like receptor 4 (TLR4). This receptor is normally involved in the immune response of the organism to bacterial infections, and works through the release of inflammatory mediators such as interleukin 1 beta. Maroso et al have now shown that this receptor binds HMGB1 in animal models of epilepsy, which in turn causes a number of downstream effects in the different cell compartments, and that this may underlie the propagation of further ictal events such that blocking this system at an early stage may have significant anti-epileptic properties in terms of the severity and chronicity of epilepsy, a possibility reinforced in this paper by human post-mortem data on resected hippocampal tissue from patients with chronic temporal lobe epilepsy.

Another new area where the immune system may be having a role in CNS function is in the area of adult neurogenesis; a process by which new, mature, adult neurons are added to the hippocampus and olfactory bulb in the fully developed mammalian brain. In two recent papers, Hunt et al have shown that cyclosporin is good for this process, and Wang et al show that activated T-cells are bad for it!!

In the study of Wang et al, they show that activated T-cells can release granzyme B (GrB) and that this then binds to a G-protein associated receptor in the human neural precursor cells (NPCs) with a reduction in intracellular cAMP level. This process in turn causes an increase in the expression of the voltage dependent potassium channel, Kv1.3, in



these NPCs, which leads to an inhibition of NPC neurogenesis. The authors also show that these processes have some *in vivo* relevance and then try to link it to MS, by reporting that patients with MS have elevated levels of CSF GrB compared to controls. They do not, however, show that in MS, this process of altered neurogenesis is present nor relevant to disease course.

In the second study Hunt et al have shown that cyclosporin A (CyA) has a direct proliferative effect on NPCs *in vitro* and *in vivo*, and that this effect was not associated with any alteration in the differentiation profile of the cells derived from those NPCs. The exact mechanism by which CyA achieves this effect is not clear, but may relate to actions on cell adhesion within the NPC clones. Furthermore it is not clear exactly what this means *in vivo* given this study only looked at NPC turnover rather than differentiation, integration and function. Nevertheless this study adds further weight to the evidence that CyA has direct neurorestorative properties, independent of any effects it has on the T-cells, and that this may be of increased significance as we move towards the first clinical trials of allografted stem cells for patients with neurological disease.

– Roger Barker

Maroso M et al.

**Toll-like receptor 4 and high-mobility group box-1 are involved in iktogenesis and can be targeted to reduce seizures.**

NATURE MED 2010;16:413-19.

**Hunt Jet al. Cyclosporin A has direct effects on adult neural precursor cells.** J NEUROSCI 2010;30:2888-96.

**Wang T, et al. Activated T-cells inhibit neurogenesis by releasing Granzyme B: Rescue by Kv1.3 blockers.** J NEUROSCI 2010;30:5020-7.

## NMDA receptor-antibody mediated encephalitis?

The question of autoantibody pathogenicity in neurology has been investigated since the discovery of AChR antibodies in myasthenia gravis. In this disease, and subsequently in the peripheral nervous system diseases of Lambert-Eaton myasthenic syndrome and neuromyotonia, passive transfer of patient IgG to experimental animals mimicked some of the physiological and behavioural effects seen in the clinic (reviewed by Vincent 2006). Hughes et al examined the *in vitro* pathogenicity of N-methyl-D-aspartate receptor antibodies (NMDAR-Abs) in central nervous system neurons. NMDAR-Abs have recently been described in patients with an encephalitis characterised by psychosis, seizures, a characteristic movement disorder, dysautonomia and a reduction in consciousness (Dalmau et al 2007, 2008). Although initial reports suggested a very strong female predominance (around 8.5 females to 1.5 males) with the majority of patients having ovarian tumours, more recent studies have shown a predominance of non-paraneoplastic cases and upto 30% of cases being male (Irani et al 2010). Most patients respond to immunotherapies and/or oophorectomy and many regain independent function. Although NMDAR-Abs target the extracellular domain of the NR1 subunit of the excitatory NMDAR and NMDAR-Ab titres correlate well with outcomes in individual cases, the pathogenicity of these antibodies is yet to be formally, experimentally confirmed.

Hughes et al used various electrophysiological and immunofluorescent techniques to show that NMDAR-Abs were able to internalise NMDARs on the surface of hippocampal cultures and reduce surface NR1 subunit levels. In addition, and possibly more surprisingly, total cellular NR1 content was also reduced. Moreover, this downregulation did not affect the expression/localisation of the other receptors or postsynaptic proteins examined and did not alter the morphology or viability of the neurons. The reduction in NMDAR-density was also seen in hippocampi of mice infused with NMDAR-IgG for two weeks and humans who died of the condition. The magnitude of the effect was proportional to the concentration of the NMDAR-Abs. While this study strengthened the previous *in vitro* observations of Dalmau et al (2008), some important questions remain unanswered:

1. NMDAR-Abs are known to be predominantly of the complement fixing subtypes (IgG1-IgG3). No study has yet been presented to specifically examine the role of this potential cytotoxic or chemotactic mechanism.
2. If it is shown that NMDAR-Abs, when injected into experimental animals, can reproduce some of the clinical correlates of the human dis-

ease, this will have important therapeutic implications for patients, particularly those with emerging variants of the typical NMDAR-antibody encephalitis.

– Sarosh R Irani, Department of Clinical Neurology, Oxford.  
Hughes EG, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J NEUROSCI. 2010;30:5866-75.  
and Vincent A. ACTA NEUROL SCAND 2006;Suppl;183:1-7.  
Dalmau et al. ANN NEUROL 2007;61:25-36.  
Dalmau et al. LANCET NEUROLOGY 2008;7:1091-8.  
Irani et al. BRAIN 2010;133(Pt 6):1655-67.

## On the bus-like arrival of ALS genes: eyeing up a new protein

For some 15 years there had been essentially only one model of ALS: mutant SOD1. Things changed in 2006 with the realization that ALS (except SOD1 ALS) is characterised by TDP-43 pathology, and with the subsequent discovery of ALS-linked mutations of *TDP-43* and *FUS*. This has led to intense investigation of the role of RNA-processing in neurodegeneration. Somewhat like the buses, in the past 12 months, four more genes have been linked with ALS. Homozygous *spatacsin* mutations cause a very slowly progressive autosomal recessive juvenile ALS (Orlacchio et al 2009). Heterozygous mutations in *FIG4* cause ALS, which in some cases has an upper motor neuron phenotype (Chow et al., 2009). A single family with typical ALS was recently linked to a dominant mutation in *D-amino acid oxidase (DAO)* (Mitchell et al 2010). A fourth gene, *OPTN* encoding optineurin, is perhaps the most intriguing.

*OPTN* mutations were found in a handful of Japanese ALS cases (Maruyama et al 2010). Two different homozygous mutations, both predicted to cause premature termination, were found in consanguineous families. A further missense mutation was found in autosomal dominant kindreds. The pathogenicity of the homozygous mutations is likely to be due to a loss of function as a result of nonsense-mediated decay of mRNA transcripts. The dominant missense mutation may act through an as yet unknown toxic gain of function. Interestingly, *OPTN* mutations are a cause of primary open angle glaucoma (Rezaie et al 2002).

Maruyama et al went on to conduct pathological studies demonstrating that a case with the missense *OPTN* mutation had typical TDP-43 inclusions as seen in ALS. Interestingly, these inclusions were also positive for optineurin. Furthermore, they also found optineurin to be a component of inclusions in sporadic ALS, suggesting that optineurin may have a broader role in ALS pathogenesis. Even more surprisingly it appeared that optineurin was also a component of inclusions in SOD1 linked ALS. Their pathological studies were conducted in a somewhat unorthodox manner as they retained pathological specimens rather than taking consecutive sections and staining separately for ubiquitin, TDP-43 and optineurin. Nevertheless, it is intriguing that while TDP-43 seemed to separate SOD1 ALS from sporadic ALS, optineurin appears to be a common denominator.

Although its functions remain unclear, optineurin is an ubiquitously expressed, cytoplasmic and perinuclear protein. It associates with the golgi apparatus and is implicated in vesicle transport, apoptosis and transcription, mechanisms that have previously been implicated by other ALS genes. ALS-linked optineurin mutants were found by Maruyama et al to lack the ability to inhibit activation of the transcription factor NF- $\kappa$ B, while the mutation commonly associated with glaucoma retained this property. Further genetic and pathological studies are needed to determine the wider role of optineurin in ALS pathogenesis. It will also be interesting to elucidate how *OPTN* mutations can cause neurodegeneration in such seemingly disparate locations as the retina and the motor pathways.

– Jemeen Sreedharan, Guy's and St Thomas' NHS Trust, London.

Maruyama H et al. Mutations of optineurin in amyotrophic lateral sclerosis. NATURE 2010;465:223-6.

and Orlacchio A, et al. SPATACSIN mutations cause autosomal recessive juvenile amyotrophic lateral sclerosis. BRAIN 2010;133:591-8.

Chow CY, et al. Deleterious variants of FIG4, a phosphoinositide phosphatase, in patients with ALS. AM J HUM GENET 2009;84:85-8.

Mitchell J et al. Familial amyotrophic lateral sclerosis is associated with a mutation in D-amino acid oxidase. PROC NATL ACAD SCI USA 2010;107:7556-61.

Rezaie T, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. SCIENCE 2002;295:1077-9.

## Torsins and LAP-1: explaining neuronal vulnerability in DYT1 dystonia

A curious feature of many genetic conditions is that mutations in widely expressed genes cause tissue-specific illness. One example is DYT1 dystonia, a dominantly inherited form of primary dystonia which causes patients to suffer involuntary movements or postures due to co-contraction of antagonistic muscles. DYT1 dystonia is caused by a 3 base-pair deletion in the *TOR1A* gene which results in removal of a glutamic acid from the protein torsinA. This protein normally resides in the endoplasmic reticulum/nuclear envelope endomembrane system, but nobody really knows what it does. In animal models of DYT1 dystonia, neuronal nuclear membranes in all brain regions show characteristic abnormalities on electron microscopy (outpouchings originating from the inner nuclear membrane or blebs), whereas non-neuronal cells look normal. Is torsin A doing something different in neurones, or are neurones more vulnerable to this condition (and if so, why)?

Kim and colleagues began by focussing on one protein known to interact with torsinA – lamina-associated polypeptide 1 (LAP1). They disrupted the gene which encodes LAP1 and showed that the neurones of homozygous mutant mice exhibited the same nuclear membrane abnormalities as *TOR1A* mutant mice. They also showed that eliminating torsinA function in LAP1 heterozygotes caused the same blebs in neural and non-neural cells, supporting the functional relationship between torsinA and LAP1 and indicating that they are operating together in all tissues.

TorsinA is a member of a family of proteins which includes torsinB, torsin2 and torsin3. The authors postulated that these torsins may share redundant cellular functions and that differing expression patterns of family members may account for the neuronal vulnerability seen in DYT1 dystonia. They began by showing that torsinB protein levels were significantly higher in non-neural tissues than in neural tissue. They then showed that by selectively reducing torsinB levels (using lentivirus-mediated RNA interference), there was a dramatic increase in the frequency of nuclear membrane blebs in mutant torsinA cortical neurones and non-neuronal cells (fibroblasts in this case).

The paper argues that expression of torsinB in non-neuronal cells is largely responsible for protecting them from the disease mutation underlying human DYT1 dystonia. Other proteins also interact with torsinA (such as 'pritor' and 'nesprin-3 $\alpha$ ') and they too might contribute to the cell-specific phenotype caused by torsinA dysfunction. The authors make the interesting point that polymorphisms in LAP1 and torsinB may affect penetrance of the *DYT1* mutation (which is incomplete) or alter the severity of symptoms in patients with DYT1 dystonia.

– **David P Breen, Cambridge Centre for Brain Repair, University of Cambridge.**

**Kim CE, et al. A molecular mechanism underlying the neural-specific defect in torsinA mutant mice. PNAS 2010;107:9861-66.**

## Occult PML

When faced with a patient with sub-acute cognitive decline and characteristic white matter changes on MRI, progressive multifocal leukoencephalopathy (PML) tends only to come into the differential diagnosis if the patient is immunosuppressed, whether from HIV, haematological malignancy or drugs. Ghuens et al describe five cases of CSF PCR+ or histologically-confirmed PML with minimal/occult immunosuppression and a literature review of similar cases. They found an additional 33 cases and of the total, 7 had hepatic cirrhosis, 5 renal failure, 2 were pregnant, 2 had dementia, 1 dermatomyositis, and 22 no diagnosis (of these, 5 had low CD4 counts). 71% of all cases were fatal within 120 months (median 8 months) and interestingly some patients stabilised or improved (after treatment with mirtazepine or interferon alpha, follow up only to 6-9 months).

There are problems with this study, acknowledged by the authors; a relatively large group of 19 patients had not been tested for HIV. The authors (although I'm not sure I agree!) felt the patients were very unlikely to have had HIV because 12 cases were before the AIDS epidemic, 16 had no histological features of HIV at autopsy and 14 had no haematological features of HIV. Furthermore, not all had had a thorough work up for immunosuppression since PML was unsuspected in life and

found only at autopsy (19 cases from table 1 had PML diagnosed on autopsy with no CSF PCR data so it could be assumed the cases without 'thorough work up' are these, although this is not elaborated upon in the paper).

It is clear those patients with, for example hepatic and renal failure have changes to their cellular immune system, and one could speculate that these changes were enough to predispose to PML. The 22 cases with no identified disease (assuming nothing was missed on pre-mortem testing) are also very interesting - the authors mention 5 cases with idiopathic low CD4 counts and mention that CD4 counts can fluctuate, thus speculating that the other cases may also have had changes in T cells normalised by the time their blood was tested. Speculatively, these cases may have had signalling defects downstream of lymphocyte numbers.

That 3 cases stabilised or improved (albeit with a short follow up time) is interesting and raises the possibility that cases with occult/ minimal immunosuppression do better and respond to treatment. It highlights also the importance of making an early diagnosis: although PML is untreatable, some agents hold promise (mirtazepine, mefloquine, IL2) and reversal of immunosuppression may improve outcome (as we have seen from the HAART era). If there is clinical suspicion for PML even in apparently immunocompetent patients, the CSF should be tested for JCV. And, as in many cases of rapidly progressive dementia with no clear cause and MRI changes, a brain biopsy should be considered and may test positive even if CSF JCV is negative (particularly given that post HAART, the sensitivity of PCR in the CSF decreases, and it could be speculated that the sensitivity of CSF PCR may be lower in patients with minimal immunosuppression).

– **Wendy Phillips, Neurology Unit, Addenbrooke's Hospital, Cambridge, UK. Ghuens S, et al. Progressive multifocal leukoencephalopathy in individuals with minimal or occult immunosuppression. J NEUROL NEUROSURG PSYCHIATRY 2010;81(3):247-54.**

## Rehabilitation: are variations in pulse after brain injury due to deconditioning or uncoupling?

Autonomic instability is a well-documented feature of the early stages of recovery following a severe brain injury. This may manifest with any of the signs or symptoms of sympathetic over-activity and has a putative neuroanatomical basis in lesions of the frontal lobe. Over time, unexpected variations in heart rate and blood pressure gradually resolve, and cardiovascular instability is not usually considered in the longer term amongst the survivors of acquired brain injury. This study looks at heart rate at rest and under conditions of submaximal exercise in a group of young males (age 7 – 13) surviving a severe brain injury. Given that ambulation was an inclusion factor, the group had all made a reasonable physical recovery. The control group was made up of age and BMI-matched subjects without health problems. Both groups had their heart rates measured at rest and on mobilisation at their "comfortable walking velocity". The brain-injured group had significantly higher resting and walking heart rates. Given that exercise should, at least in theory, form part of the longer term rehabilitation strategy for survivors of acquired brain injury, the potential for autonomic dysfunction perhaps needs to be considered. It would be enlightening to have a sense of the longer term cardiac morbidity and mortality in this patient group. While this is an important issue, given the increasing long-term survival rates following severe brain injury, there are a number of important questions that this study fails to address. What is the contribution of deconditioning? The study group had all sustained their brain injuries at different (undefined) points in the past and presumably were in hospital for different lengths of time. Adequate analysis of these variables or a more appropriate control group may have gone some way to addressing this fundamental issue.

– **Lloyd Bradley, Western Sussex Hospitals Trust Katz-Leurer M et al. Heart rate and heart rate variability at rest and during exercise in boys who suffered a severe traumatic brain injury and typically-developed controls. BRAIN INJURY 2010;24(2):110-14.**

# Orthostatic Hypotension in Parkinson's Disease



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Orthostatic hypotension (OH) has been recognised as a feature of Parkinson's disease (PD) for many years, but has, until recently, been largely attributed to a side effect of dopaminergic medication. Recent interest in the 'multisystem' nature of PD has led to wider recognition of the 'non motor' features of PD, including renewed focus on the dysautonomia associated with the disease.

Using the standard definition of OH (20mmHg fall in systolic or 10mmHg fall in diastolic blood pressure within three minutes of standing or head up tilt to at least 60°) between 20-58% of patients with PD have a 'pathological' orthostatic blood pressure drop.<sup>2</sup> Extending tilting beyond the three-minute guidance will identify an additional 'late OH' group. Correlation of orthostatic symptoms (dizziness, drowsiness and characteristic 'coat-hanger' ache across the shoulders) with objectively measured OH is poor however, regardless of the length of tilt employed.<sup>3,4</sup> Why symptoms are so poorly correlated with objective signs is unclear: OH is associated with cognitive decline, particularly with impairment in attentional reserve,<sup>5</sup> and this may in part explain why some patients with objective OH fail to volunteer expected symptoms. Conversely, poor reproducibility of OH may result in a high 'false negative' diagnostic pool, thereby negatively impacting on correlation of blood pressure changes with symptoms.

Fatigue is the most common non motor symptom in PD, affecting nearly 60% of patients.<sup>6</sup> Studies in non parkinsonian patients have shown an association between autonomic dysfunction and fatigue severity.<sup>7</sup> Little is known about the potential relationship between OH and fatigue in PD, and given the significant negative impact of fatigue on quality of life in PD this is a high priority area for future research.

Perhaps because of the methodological difficulties in clearly 'capturing' OH in PD, correlation with falls is surprisingly poor. Disease duration, disease severity and history of previous falls remain the strongest individual predictors of future falls. Any association with OH is weaker, some studies supporting an association, others with conflicting results.<sup>8,9</sup>

Dysautonomia in PD is related to both peripheral and central autonomic pathology. Studies using metaiodobenzylguanidine (MIBG) as a marker of sympathetic nerve activity show reduced uptake in even the earliest stages of clinical PD.<sup>10</sup> Subjects with PD and OH show reduced resting noradrenaline levels,

supersensitivity to exogenous noradrenaline and upregulation of peripheral  $\alpha 2$  adrenoceptors, findings consistent with peripheral sympathetic dysfunction.<sup>11</sup> Neuropathological studies confirm the presence of Lewy body pathology in peripheral autonomic ganglia and lower brainstem autonomic nuclei in the presymptomatic phase of the disease. As pathological changes 'ascend' through the brainstem and into the cerebral cortex disease severity increases and, alongside the development of neuropsychiatric features of the disease, other 'higher level autonomic centres' become involved.<sup>12</sup> Both the insular cortex and anterior cingulate area are sites of predilection for Lewy body pathology in PD: As sites of integration of autonomic with limbic and motor function respectively, it is likely that involvement of these higher cortical centres will contribute to the severity of OH in PD. Initial studies are supportive of this hypothesis, demonstrating higher cortical Lewy Body counts in patients with PD and OH compared to subjects with PD alone.<sup>13</sup>

Treatments for OH in PD are largely based on strategies to compensate for poor peripheral autonomic function. Non pharmacological therapies such as compression stockings, caffeine, exercise and avoidance of warm weather and hot baths reduce vascular capacitance, whilst reduction of nocturia through elevation of the bed head alongside increasing salt and fluid intake increase plasma volume. A number of different medications are used in the treatment of symptomatic OH in PD, but the evidence to support efficacy in this condition per se is weak, relying primarily on extrapolation of outcomes from studies on patients with other hypotensive conditions: Medications acting on blood volume (erythropoietin), blood vessel tone (etilefrine, midodrine), sympathetic pathways (pyridostigmine) and for the prevention of postprandial hypotension (octreotide) are used within this context.

A double blind cross over trial of the mineralocorticoid fludrocortisone (0.1mg daily), perhaps the most widely used antihypotensive agent, and the D2 antagonist domperidone (10mg three times daily) in subjects with PD and OH has shown some interesting and disease specific results. Both treatments improved symptoms of orthostatic dizziness and although the measured reduction in postural drop did not reach statistical significance, there was a trend towards improved haemodynamic response which was greatest in the domperidone treatment phase.<sup>14</sup>

A recent study of the sympathomimetic drug droxidopa has shown encouraging preliminary results. The synthetic catecholamine, which is metabolised to norepinephrine in vivo, appears to be well tolerated by patients with PD and OH and effective in reducing symptoms of orthostatic dizziness.<sup>15</sup>

Non motor features, including dizziness and fatigue, have significant impact on the quality of life of patients with PD. With increasing understanding of the interplay between peripheral and central autonomic pathology in PD, it should be possible to target treatment of the autonomic symptoms, including OH, more effectively. There are very few studies of treatments for OH specifically in PD, and larger clinical trials would be welcome. ♦

*Recent interest in the 'multisystem' nature of PD has led to wider recognition of the 'non motor' features of PD, including renewed focus on the dysautonomia associated with the disease.*

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## 2nd Parkinson's UK Research Conference

*Conference details:* 1-2 November, 2010; Royal York Hotel, York.

PREVIEW

**PARKINSON'S<sup>UK</sup>**  
CHANGE ATTITUDES.  
FIND A CURE.  
JOIN US.

Following the great success of the first Parkinson's UK research conference 'Progress: Advancing Parkinson's Research' in 2008, and we're delighted to be hosting this event again in 2010.

### Conference aims

"We aim to bring researchers working in fields from molecular biology to physiotherapy and everything in between together to share ideas, discuss challenges and develop new collaborative projects. Through international keynote speakers, poster sessions, short oral presentations and plenary lectures we can work together to advance Parkinson's research in the UK."

*Dr Kieran Breen,*

*Director of Research and Development.*

### Keynote speakers

Our line up of international keynote speakers reflects the diversity and breadth of Parkinson's research that is happening in the UK.

#### **Dr Mark Cookson**

Dr Cookson is an investigator in the Laboratory of Neurogenetics at the National Institute of Ageing in Washington. His group uses cellular and molecular biology tools to

study inherited neurodegenerative disorders such as Parkinson's, attempting to understand the mechanisms leading to nerve cell damage.

#### **Dr Deniz Kirik**

Dr Kirik is the Head of the Brain Repair and Imaging in Neural Systems (BRAINS) Unit, and co-director of the Bioimaging Center at Lund University in Sweden. Dr Kirik has over 15 years' experience in the field of cell and gene therapy. His more recent work in this field focuses on using PET and MR imaging techniques to track disease progression and treatment related changes in the brain.

#### **Dr Valerie Voon**

Dr Voon has been based at the National Institutes of Health in the US until she recently made the move to join Cambridge University. Her research focuses on the neuropsychiatric symptoms that can affect many people with Parkinson's, such as impulse control disorders and depression, what causes them and how they can be treated.

#### **Success of our 2008 Conference**

Two years ago 172 delegates from around the UK gathered in York for the first Parkinson's UK

research conference. Keynote speeches on the advances in gene therapy, clinical studies and physiotherapy set the tone for 27 stimulating presentations and 82 scientific posters.

"The best thing the charity has done for years! It was an excellent meeting which was truly representative of the Parkinson's research community in the UK. A great opportunity for networking and should be essential for any PhD student in the UK working on Parkinson's." ♦

#### **Find out more about the 2010 Conference**

For further details please visit our website: [www.parkinsons.org.uk/researchconference](http://www.parkinsons.org.uk/researchconference)

During the conference you'll be able to:

- follow us on twitter: [www.twitter.com/parkinsonsuk](http://www.twitter.com/parkinsonsuk)
- or read our conference blog at <http://talkparkinsons.blogspot.com/>

And after the conference you'll be able to download the full abstract booklet, see keynote presentations online and listen to our conference podcast.

**Hope to see you all in York!**

## Karolinska University Hospital acquires Leksell Gamma Knife Perfexion

Karolinska University Hospital recently acquired Elekta's fifth generation radiosurgery system, Leksell Gamma Knife® Perfexion™. Since January, Karolinska clinicians have been using the system to treat more patients per day and tumours that used to be hard to reach. Physicians also are much more easily treating multiple metastases in a single session.

While Karolinska clinicians are currently treating traditional Gamma Knife indications (metastases, meningiomas, arteriovenous malformations, dural fistulas, acoustic neuromas), the immediate impact Perfexion has made is the ease with which physicians can treat two or more metastases in one session.

"We treat five to ten metastases on a regular basis, because the automated collimator makes it possible to rapidly plan and treat multiple tumour isocenters," Karolinska neurosurgeon Dr Ernest



Dodoo explains. "Suddenly, it is feasible to treat everything we see. Now, the question is not 'Is it technically possible?' but rather 'Does it make sense clinically from a therapy standpoint?'"

For more information see [www.Elekta.com](http://www.Elekta.com) or [E.michelle.lee@elekta.com](mailto:E.michelle.lee@elekta.com)

## Warfarin Comparison Study to enrol 90% of atrial fibrillation patients with high risk of stroke

New data from a warfarin comparison study shows that the health characteristics of the patients enrolled on the ROCKET AF trial (Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) more closely reflect the typical AF patient population than four other recent major trials.

The baseline demographic data, from Bayer Schering Pharma's study, were presented at the 19th European Stroke Conference, Barcelona; the study is designed to assess the safety and efficacy of once-daily oral rivaroxaban (Xarelto®) against warfarin in 14,269 AF patients.

Healthcare professionals widely use the CHADS tool to assess stroke-risk and subsequent need for anticoagulation therapy in patients with AF. A high CHADS score (three and above) corresponds to a greater risk of stroke. The ROCKET AF study specifically targeted AF patients with the greatest need for a stroke-preventing anticoagulant. Of those enrolled, 90% have a CHADS score of three or higher.

"ROCKET AF is a study with a patient population that reflects clinical practice advocated in current guidelines," said Dr Luis Felipe Graterol, Medical Director, Bayer Schering Pharma. "We are looking forward to the results of the study and hope that this trial provides us with much needed information on how to effectively reduce the risk of stroke for patients with atrial fibrillation."

The abstract is available online at [www.eurostroke.eu/pub\\_ongoings.asp](http://www.eurostroke.eu/pub_ongoings.asp)

## Oxford Biosystems half price evaluation kit

Oxford Biosystems supplies a range of Neurological Biomarkers, including: Annexin V, Glial fibrillary acidic protein (GFAP), Neuron Specific Enolase (NSE), S100bb, C-reactive protein (CRP), sRAGE, Heart type fatty acid binding protein (h-FABP), High-Mobility Group Box 1, sTNFR-1, Phosphorylated Neurofilament H (pNF-H), Gold Dot NR2 Antibody, Amyloids, Catecholamines/Neurotransmitters, CVDefine<sub>α</sub> (anti-PC IgM), Glutamate, Glutamine, Tryptophane, Kryptopyrrole, Glycin, γ Aminobutyric Acid (GABA), Phenylalanin/Tryptophan ratio.

These markers are provided as Enzyme Linked Absorbant Assays (ELISA) for laboratory use only. A half price kit is supplied for the initial evaluations with discounts available for future volume purchases.



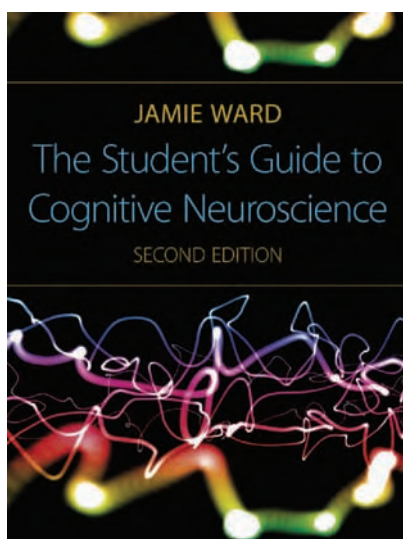
Please contact **John Coombes** on [jcoombes@oxfordbiosystems.com](mailto:jcoombes@oxfordbiosystems.com) for price and availability.

## The Student's Guide to Cognitive Neuroscience, 2nd Edition

This title, by Jamie Ward, was published by Psychology Press in January 2010. Reflecting recent changes in the way cognition and the brain are studied, this thoroughly updated edition of the best-selling textbook provides a comprehensive and student-friendly guide to cognitive neuroscience. Jamie Ward provides an easy-to-follow introduction to neural structure and function, as well as all the key methods and procedures of cognitive neuroscience, with a view to helping students understand how they can be used to shed light on the neural basis of cognition.

Robert H Logie, Professor of Human Cognitive Neuroscience, University of Edinburgh, UK, says "I thought the first edition was the best textbook I have come across on cognitive neuroscience. This second edition is even better."

A complimentary examination copy is available. For more information see [www.psypress.com/ward](http://www.psypress.com/ward)



## New data supporting Cladribine Tablets

New data providing further understanding on Cladribine Tablets as a potential new therapeutic option for relapsing forms of multiple sclerosis (MS) were presented at the 62nd Annual Meeting of the American Academy of Neurology (AAN).

Cladribine Tablets, Merck Serono's proprietary investigational oral formulation of cladribine, is currently under regulatory review in a number of countries.

"The relevance of the CLARITY study is further substantiated by the series of additional analyses presented at the AAN," said Bernhard Kirschbaum, Merck Serono's Head of Global Research and Development. "We are committed to continuing to work with regulatory authorities to bring Cladribine Tablets to patients at the earliest point in time." The data presented at the AAN are from pre-specified and post-hoc analyses of the Phase III CLARITY clinical trial.

For more information see [www.merckserono.com](http://www.merckserono.com)

## SonoSite point-of-care ultrasound systems hit the spot

SonoSite point-of-care ultrasound systems, including an M-Turbo® and three S-Nerve® instruments, are changing the approach of anaesthetists in regional anaesthesia at the Nottingham University Hospitals NHS Trust. Dr Nigel Bedforth, Consultant Anaesthetist at the QMC campus of the hospital, explained, "Both the M-Turbo and S-Nerve systems have great image resolution, offering excellent visibility of nerve structures. As a result, anaesthetists who are using point-of-care ultrasound are developing better awareness of internal anatomy; we're realising that a more thorough understanding of muscles, tendons, vessels, bones and other structures is really important for being skilful at finding nerves, rather than relying solely on landmarks. Our SonoSite systems allow us to

place nerve blocks more safely and accurately, even, for example, for the more difficult blocks like supraclavicular, which were often previously avoided due to the risk of pneumothorax."

Dr Bedforth added, "I use the M-Turbo for virtually everything I do, while the S-Nerve systems suit less frequent users because they are even easier to use, with a minimum of buttons and controls. We are keen to pass on our techniques to other anaesthetists and, as part of our relationship with SonoSite, we have jointly run ultrasound-guided anaesthesia courses for a number of years."

**For more information T. +44 (0)1462 444 800,  
E. [ukresponse@sonosite.com](mailto:ukresponse@sonosite.com), [www.sonosite.com](http://www.sonosite.com)**



## Implanted neural prosthesis signals liberation for stroke sufferers

An implantable drop foot stimulator that compensates for the lack of control of the ankle joint and aids stroke patients suffering from drop foot has been launched in the UK by Otto Bock Healthcare. The 'ActiGait®' system restores a steadier and more natural walking pattern to the wearer, meaning users can focus on their outer environment and return to more normal daily activities.

Drop foot is the inability to raise the foot due to a weakness in or paralysis of the dorsiflexor muscles. This condition is a frequent result of damage to the central nervous system following a stroke. ActiGait® is implanted beneath the skin of the thigh with the control unit worn comfortably on a belt and is easy to

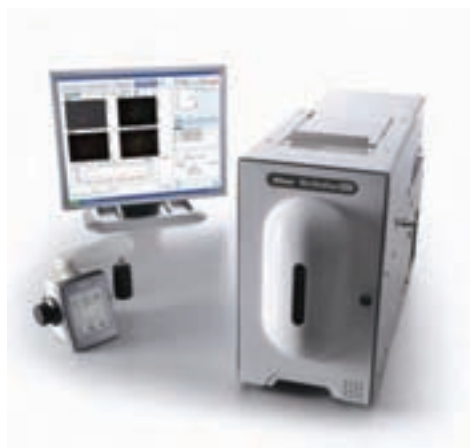
use, even for patients with impaired arm functionality. The system is wireless with implanted electrodes.

Patient studies in Denmark illustrated an increase in distance patients could walk in a four minute period and in walking speed over 20 metres, without the help of another person. Furthermore, qualitative responses highlighted improvement in confidence with less fear of falling, promoting the long-term potential to provide a positive effect on personal well-being, safety and performance.

**For more information contact Gaynor Norris,  
E. [gaynor.norris@ottobock.com](mailto:gaynor.norris@ottobock.com)**



## Simple solution for long term live cell imaging



Adding to Nikon's series of BioStation incubator imaging systems, which offer excellent cell care throughout imaging, the new BioStation IM-Q allows users with minimal microscopy experience to conduct live cell imaging without a steep learning curve. This compact system incorporates a microscope, an incubator and a high sensitivity, cooled quantitative CCD camera integrated into a single package. Providing a stable environment for live cells and advanced phase and fluorescence imaging solutions for simple, long term, cell friendly timelapse data acquisition, the BioStation IM-Q eliminates the need for a darkroom, meaning it can be installed anywhere.

The BioStation IM-Q provides fully motorised control from a PC, allowing users who are not accustomed to operating a microscope or

camera to easily conduct timelapse imaging.

Integrating cell culture and image capture functions, no complex setup or alignment procedures, that conventional timelapse observation systems require, are necessary. Providing thermal and mechanical stability, BioStation IM-Q greatly reduces focus drift, enabling reliable imaging even over long periods.

Two high performance monochrome Nikon Digital Sight camera options are available, and two kinds of analysis software.

**For further information  
E. [info@nikoninstruments.eu](mailto:info@nikoninstruments.eu), or see  
[www.nikoninstruments.eu/Products/  
Cell-Incubator-Observation/BioStation-IM-Q](http://www.nikoninstruments.eu/Products/Cell-Incubator-Observation/BioStation-IM-Q)**

**To feature your news in ACNR, please contact Rachael Hansford,  
T. 01747 860168, E. [rachael@acnr.co.uk](mailto:rachael@acnr.co.uk)**

## S-Nerve offers greater insight for Paediatrics

With intuitive controls and a wide range of transducers, SonoSite's S-Nerve™ point-of-care system offers anaesthetists easy access to ultrasound guidance for line placement and regional nerve blocks. The paediatric anaesthetics department at Leeds General Infirmary has taken advantage of this user-friendly instrument to ensure accurate and safe regional anaesthesia, as well as post-surgery multimodal analgesia. Consultant Paediatric Anaesthetist Dr Duncan Johnson explained, "Ultrasound guidance is of particular benefit to paediatric specialities, as the anatomy of a premature infant has little in common with that of a 17 year old. Use of ultrasound to guide nerve blocks offers an easy route to safer, more reliable blocks, enabling the anaesthetist to visualise the needle adjacent to the



nerve, while avoiding other important structures."  
"Leeds is a national referral centre for hand surgery, specialising in transplants and improving

motor function for children with congenital abnormalities. These procedures are generally performed in very young children, and effective nerve blocks can be difficult to achieve. Ultrasound guidance is very helpful, and the small footprint of the S-Nerve's hockey stick probe is very well suited to this application. The anaesthesia-focused controls of the instrument make it very quick and easy to operate during procedures, obtaining good quality images with a minimum of adjustments."

For more information T. +44 (0)1462 444 800,  
E. [ukresponse@sonosite.com](mailto:ukresponse@sonosite.com) or see  
[www.sonosite.com](http://www.sonosite.com)

## Elekta acquires Resonant Medical Inc.

Elekta recently announced the acquisition of Resonant Medical Inc., Montreal Canada. Through this acquisition, Elekta adds exciting new solutions for image guidance as well as highly skilled R&D resources in the field of oncology imaging and motion management.



Resonant Medical Inc. ("RMI") develops systems for image guided radiation therapy of soft tissues using latest generation, 3-D ultrasound technology. RMI's integrated software solutions have been developed in cooperation with leading academic institutions to improve treatment accuracy for cancer in the prostate, breast, liver, cervix, uterus, bladder as well as head and neck. RMI's equipment is in daily clinical use in the US, Canada, Italy, The Netherlands and Ireland and its research collaborators are considered among the world leaders in their field.

Elekta's President and CEO Tomas Puusepp said, "This further enhances Elekta's state-of-the-art solutions in IGRT, by adding RMI's leadership in soft tissue visualisation and tracking. In addition, given Elekta's dedication to open architecture, the technology will be made available to customers with other vendors' equipment, making it possible to improve IGRT processes everywhere."

RMI will provide useful additions to Elekta's MOSAIQ® treatment planning solutions by displaying soft tissue structures, not easily seen on X-ray computed tomography but in exact spatial correlation with these CT images, and offering a suite of automatic segmentation and contouring tools.

For further information, E. [todd.powell@elekta.com](mailto:todd.powell@elekta.com)

## MEG System for monitoring the brain in action

Elekta has unveiled its next generation magnetoencephalography (MEG) system, Elekta Neuromag® TRIUX\*.

A platform that addresses key requirements critical for monitoring normal and abnormal brain activity, Elekta Neuromag TRIUX was designed to operate in virtually any clinical environment.

Implementing a MEG program will be more practical for most clinical environments with the Elekta Neuromag TRIUX system's dynamic range, which has been increased three-fold, in addition to built-in active shielding, which protects its ultrasensitive sensor array from magnetic interference. These improvements make Elekta Neuromag TRIUX suitable for siting in even the busiest hospitals and research centres.

Elekta Neuromag TRIUX also provides several features designed to simplify day-to-day use of the system and enhance patient experience. These include a new connector panel—with easy to access connectors—and an all-new gantry that allows clinicians and researchers to conduct MEG measurements with the patient in a more comfortable upright position.



Elekta Neuromag TRIUX will be available as a turn-key system or as a hardware / software upgrade for certain Elekta Neuromag models. To learn more, visit [www.elekta.com/MEG](http://www.elekta.com/MEG).

## Nikon Instruments opens Microscopy Centre in Budapest

Nikon Instruments has partnered with the Institute of Experimental Medicine of the Hungarian Academy of Science KOKI in Budapest, Hungary to open the first Nikon Microscopy Centre (NMC) in Central Europe. The centre will allow neuroscience researchers access to state-of-the-art microscopy and imaging systems provided by Nikon. Systems include the Eclipse Ti-E with TIRF and the new super-resolution N-STORM and the Eclipse FN1 with C1plus, ideal for live cell and deep tissue imaging.

"The centre will make an important contribution to the development of neuroscience imaging techniques and further our research immensely, enabling us to maintain our position in the international mainstream of neuroscience research. We were pleased to partner with Nikon, who have collaborated with other leading

organisations to launch several similar centres in the past," commented Professor Tamas Freund, Director of the Institute.

The Institute of Experimental Medicine is the only research institute in Hungary dedicated exclusively to medical research. Its activity focuses on basic biomedical research, primarily in the field of neuroscience, including studies on neurotransmission, learning and memory, behaviour, ischaemic and epileptic brain damage, as well as the central and peripheral control of hormone secretion.

For further information contact Nikon Instruments Europe, T. +44 (0)208 247 1718,  
E. [info@nikoninstruments.eu](mailto:info@nikoninstruments.eu)



L-R: Marjan Vasic, Nikon GmbH Austria, Harald Bayer, Nikon GmbH Austria, Peter Drent, Nikon Instruments Europe, Mr Eimori, President, Nikon Instruments Europe at the opening of the NMC at IEM, Budapest.



## 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. Limited published data suggest the safety profile of 20mg administered sub-cutaneously once daily is 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 vasodilation, 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. Other undesirable effects more than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group: 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: £513.95. **Product Licence Number** – 10921/0023

**Further Information** – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. **Date of Preparation** – December 2009.

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

Date of Preparation: May 2010

C0210/610a



**COPAXONE®**  
(glatiramer acetate)

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