ISSN 1473-9348 Volume 5 Issue 6 January/February 2006

ACNR

Advances in Clinical Neuroscience & Rehabilitation

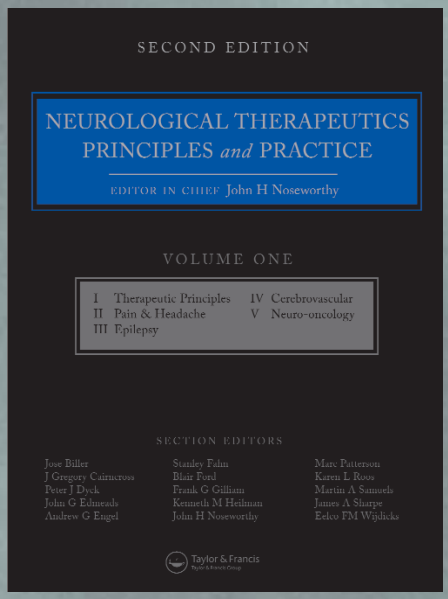
Dr Karin Stiasny-Kolster, Dr Aline Metz & Professor Wolfgang Oertel
Diagnosis and Management of Restless Legs Syndrome

Dr Sanjay Sisodiya
Genetics and Epilepsy

Professor R John Leigh & Dr Sangeeta Khanna
Neuroscience of Eye Movements

www.acnr.co.uk

Special offer available to ACNR readers: 10% discount until end of March 2006!



First Prize Winner of the Neurology Category, 2004 British Medical Association Medical Book Competition (previous edition)

'It was an undiluted pleasure to read and review this magnificent textbook ... the text is very well laid out, with clear and very helpful summary tables and algorithms ... a lot of thought has clearly gone into the arrangement of the sections and chapters ... [it] more than succeeds in its aim of covering the basics of neurotherapeutics. This is a book with a future, born to fill a hole. I have often asked the questions that this book answers. I have no hesitation in recommending it for the neurologist's bookshelf.' -

The Lancet Neurology
(of the previous edition)

Neurological Therapeutics: Principles and Practice

Second Edition

Editor-in-Chief: John H. Noseworthy, The Mayo Clinic, Rochester, USA

Neurological Therapeutics: Principles and Practice, Second Edition is a highly acclaimed, authoritative work that builds on the success of its award-winning predecessor to provide a comprehensive textbook focused primarily on therapeutics.

Key features:

- Extensive three-volume format
- Fully updated text, including new chapters addressing important issues
- Available both as a hardback and in web-formats
- Features more than 275 major topics covering the vast patient mix primarily treated by adult and pediatric neurologists
- Includes cutting-edge medical citations
- Section editors are all internationally recognized leaders in their fields
- Contains over 600 comprehensive summary tables and informative figures

A must-have resource for busy students, clinicians and clinician-scientists, this is a key reference for treatment decisions in offices of neurological practice, clinics and hospitals.

April 2006: 285x214: 3,350pp: 702 b+w and 69 colour illustrations
Hb: 1-84184-583-3: £250.00 **special offer price £225.00**

Also available from Taylor & Francis:

Restless Legs Syndrome

Edited by Ray Chaudhuri, Per Odin and C. W. Olanow

September 2004: 140pp: Hb: 1-84214-162-7: £65.00

The first professional level text dedicated solely to restless legs syndrome, this expertly written text discusses areas such as the epidemiology, pathophysiology and clinical associations of RLS, as well as the clinical features of the syndrome.

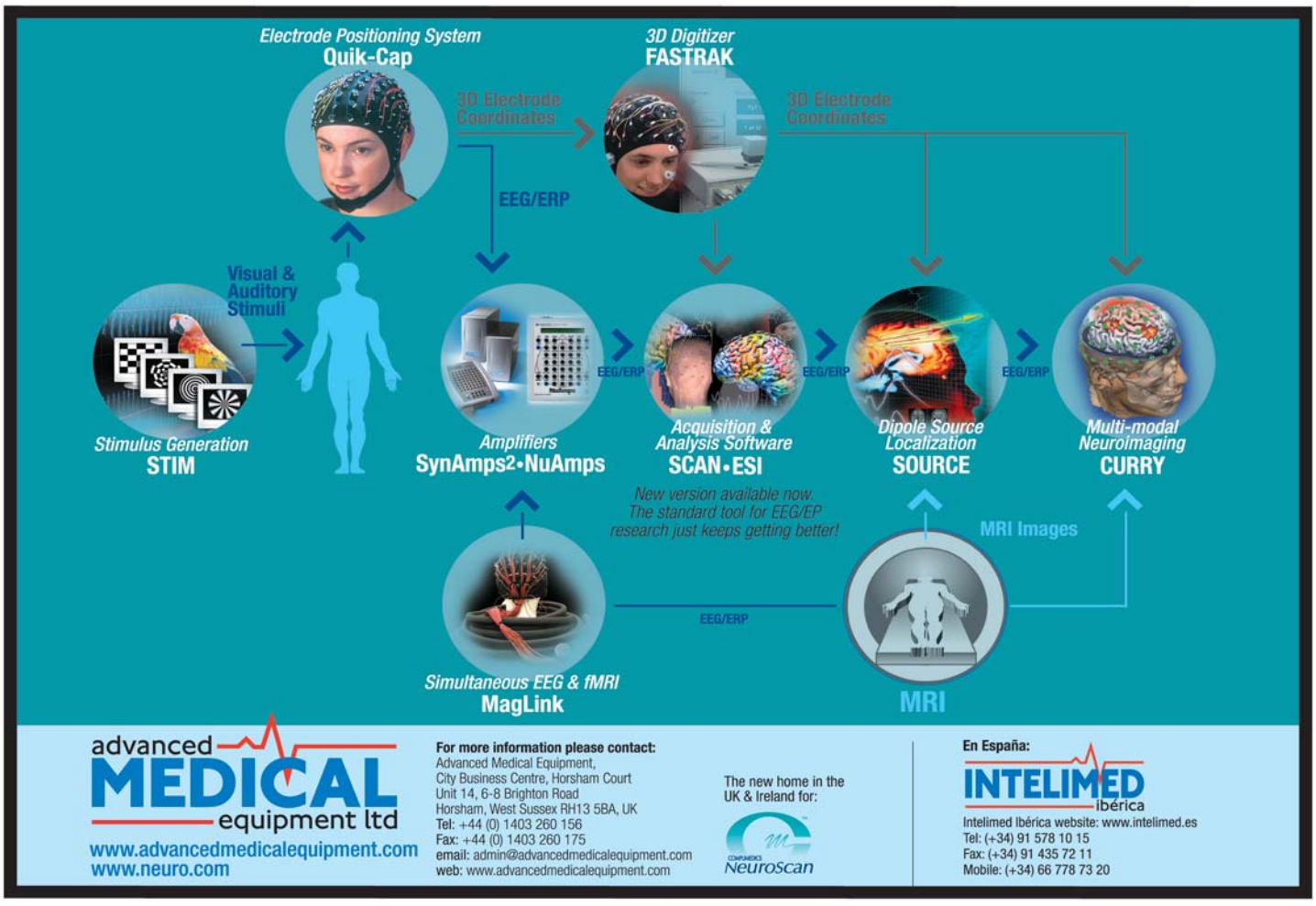
Qty	Title	ISBN	Price	Offer price	Total
	Neurological Therapeutics, 2nd Ed	1-84184-583-3	£250.00	£225.00	
	Restless Legs Syndrome	1-84214-162-7	£65.00	£65.00	

Taylor & Francis
Taylor & Francis Group
an informa business

To reserve your copy please call our credit card hotline, quoting ACNR reader offer on +44(0)1264 343071 or send this form to: Customer Services, Taylor & Francis, FREEPOST, Andover, SP10 5BR, UK (only affix stamp if posting from outside UK) Or fax: +44(0)1264 343005 Or email book.orders@tandf.co.uk
Visit our website to see our full list of Neurology titles at www.tandf.co.uk/medicine

Contents

January/February 2006



So to the final issue of our fifth year, and thank you for all your support and encouragement. The first review article takes on restless leg syndrome, which is a common neurological disorder that is often missed and for which there are effective therapies. Recently a great deal of interest has been shown towards this disorder both at an aetiological and therapeutic level. It is therefore very timely that we have this excellent short review by Wolfgang Oertel and colleagues. The article gives a brief summary on the aetiology of this condition, which leads on to an excellent description of the disorder and a comprehensive and exhaustive list of possible therapies. This latter area includes data from major trials and as one might expect from such distinguished authors allows conclusions to be drawn on drug efficacy in an evidence based fashion.

Sanjay Sisodiya discusses the area of genetics and epilepsy – a vast topic that of late has thrown up some exciting insights. This includes the channelopathies as well as the identification of susceptibility genes, although the verification of the latter and the overall clinical significance of the former are issues which are discussed in this article. However perhaps the most exciting area is in pharmacogenetics to which the author and his colleagues in London have made a major contribution. This area has major therapeutic implications in that different generic variants would modify drug strategies so allowing therapy to be more tailored to individuals.

In the second in our series on the Neuroscience of Vision we have the great honour of having Professor John Leigh and Dr Sangeeta Khanna writing about eye movements both at the level of anatomy and physiology as well as neurological practice. This is a wonderfully clear and informative account and of enormous clinical and neuroscientific interest written by great experts in this field.

Bruce Rosenthal opens our eyes to the issue of low vision in the rehabilitation article. His review begins with the sobering comment that 90% of the world's 161 million visually impaired people live in the developing world, and 75% of cases overall are due to one of four causes. This article then takes us through the panoply of assessments and devices available for such patients, which is a real education in the ingenuity of those involved in their management. Sadly though access to these services is a real issue, and remains a great challenge in the global management of this disorder.

Everyone has heard of PCR, most people can even tell you what it stands for (polymerase chain reaction) but few actually know what it means. In our Techniques in Neuroscience series Maria Ban takes us through the technique before discussing DNA sequencing, a technique for which Fred Sanger received one of his two Nobel prizes. For the non molecular among you this short review is easy to follow and even I now understand PCR and DNA sequencing.

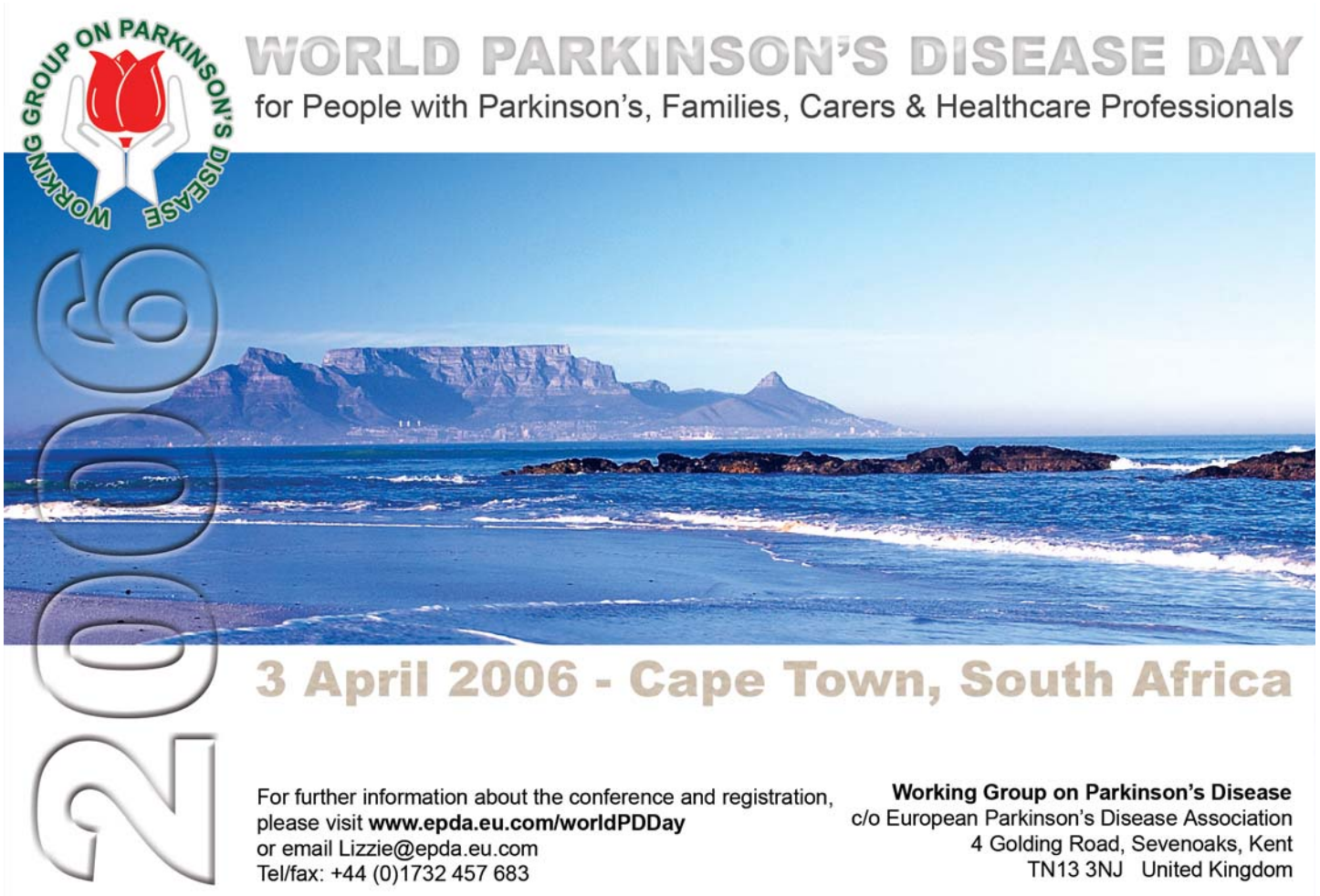
The sponsored article from Medtronic® in this issue investigates the merits of thalamic deep brain stimulation in 15 patients with post stroke pain syndromes. Of the 15 patients, 12 elected for full implantation of the deep brain stimulation apparatus with a mean improvement in symptoms of about 50% with no reported complications outside of a single lead fracture. This is an interesting article which raises many questions and possibilities not least those of health economics.

The neuropathology series moves to Edinburgh, and James Ironside with Diane Ritchie discuss CJD. This article, as one would expect from such an authoritative centre, is clear and provides much useful information including the classification of CJD using 129 PRNP genotypes. In addition it provides insights into recent developments (for example PET blotting methods) and the possibility of blood based diagnostic tests. This is a terrific account which complements our other recent articles on CJD.

In a continuation of his wonderful series of articles, Andrew Larner takes us on a tour (de force) of headache in literature. He leads us through a range of examples from well known Lewis Carroll account of migraine in *Alice's Adventures in Wonderland* to the less well known examples to be found in *the Swallows and Amazons* series by Arthur Ransome and L.Montgomery writing in *Anne of Green Gables*. As always one cannot but be impressed by Andrew's close reading of these books and his eye for descriptions of neurological disorders, although he fails to say whether the intermittent headache of Harry Potter is some form of cluster headache.

Finally we have our usual series of conference reports and journal reviews, and as always do let us know if you would like to be more involved with the journal.

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



New indication!

Now for adjunctive treatment of partial onset seizures in adults and children from 4 years of age.

Now indicated in children from 4 to 16 years

One to build with.

Strong.

- Clinically significant long-term seizure freedom[1,2]

Simple.

- No known clinically significant drug interactions[3]

Solid.

- Very well tolerated[2,4,5]

Keppra® ▼
levetiracetam

Building powerful AED therapy

KEPPRA® Prescribing Information:
Please read summary of product characteristics (SPC) before prescribing.
Presentation: Keppra 250, 500, 750 and 1,000 mg film-coated tablets containing 250, 500, 750 and 1,000 mg levetiracetam respectively. Keppra oral solution containing 100 mg levetiracetam per ml. **Uses:** Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age. **Dosage and administration:** Oral solution should be diluted prior to use. *Adults and adolescents older than 12 years of 50 kg or more*: 500 mg twice daily can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. *Elderly:* Adjustment of the dose is recommended in patients with compromised renal function. *Children aged 4 to 11 years and adolescents (12 to 17 years) of less than 50 kg*: 10 mg/kg twice daily, increased up to 30 mg/kg twice daily. Do not exceed increments or decrements of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. (For full dosage recommendations for children, adolescents and adults see SPC.) *Patients with renal impairment:* Adjust dose according to creatinine clearance as advised in SPC. *Patients with hepatic impairment:* No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended. **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Warnings and special precautions for use:** If discontinuing treatment reduce dose gradually as advised in SPC. Due to its excipients, the oral solution may cause allergic reactions (possibly delayed). **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Undesirable effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (>10%): asthenia, somnolence. *Common* (between 1%-10%): GI disturbances, anorexia, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, emotional lability, hostility, depression, insomnia, nervousness, agitation, personality disorders, thinking abnormal, vertigo, rash, diplopia, infection, cough increased. For information on post-marketing experience see SPC. **Legal category:** POM. **Marketing authorisation numbers:** 250 mg x 60 tabs: EU/1 /00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1,000 mg x 60 tabs: EU/1/00/146/024. Solution x 300ml: EU/1/146/027. **NHS price:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1,000 mg x 60 tabs: £101.10. Solution x 300ml: £71.00. **Further information is available from:** UCB Pharma Ltd., 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. medicalinformationuk@ucb-group.com **Date of preparation:** September 2005

References:
1. Krakow K, Walker M, Otoul C, *et al.* Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology.* 2001; 56: 1772-1774. **2.** Glauser TA, Gauer LJ, Lu Z, *et al.* Poster presented at IEC, Paris, 2005.**3.** Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther.* 2000; 85: 77-85. **4.** French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. *Epilepsy Res.* 2001; 47: 77-90. **5.** Glauser TA, Gauer LJ, Chen L, *et al. Epilepsia* 2004; 45: 186.

Printed in the UK

© 2005 UCB Pharma Ltd

KEP43

ucb CNS INNOVATORS™

Peaks and troughs of levodopa therapy have put limits on patient function.

When symptoms develop due to shortening of levodopa/DDCI dose effectiveness switch to Stalevo and stay in control.[1,2]

STALEVO

ORION PHARMA

Stalevo® (levodopa / carbidopa / entacapone) Brief Prescribing Information
Indication: Treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment. **Dosage and administration**: Orally with or without food. One tablet contains one treatment dose and may only be administered as whole tablets. Optimum daily dosage must be determined by careful titration of levodopa in each patient preferably using one of the three tablet strengths. Patients receiving less than 70-100mg carbidopa a day are more likely to experience nausea and vomiting. The maximum Stalevo dose is 10 tablets per day. Usually Stalevo is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone. See SPC for details of how to transfer these patients and those not currently treated with entacapone. *Children and adolescents*: Not recommended. *Elderly*: No dosage adjustment required. *Mild to moderate hepatic impairment, severe renal impairment (including dialysis)*: Caution advised. **Contraindications**: Hypersensitivity to active substances or excipients. Severe hepatic impairment. Narrow-angle glaucoma. Pheochromocytoma. Concomitant use of non-selective monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine). Concomitant use of a selective MAO-A inhibitor and a selective MAO-B inhibitor. Previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis. **Warnings and precautions**: Not recommended for treatment of drug-induced extrapyramidal reactions. Administer with caution to: patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions, or past or current psychosis; patients receiving concomitant antipsychotics with dopamine receptor-blocking properties, particularly D2 receptor antagonists; patients receiving other medicinal products which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias, monitor cardiac function carefully during initial dosage adjustments. Monitor all patients for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully. Caution when driving or operating machines. Doses of other antiparkinsonian treatments may need to be adjusted when Stalevo is substituted for a patient currently not treated with entacapone. Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dosage reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy. **Undesirable effects:** *Levodopa / carbidopa* – Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, depression, cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence. *Entacapone* – Most frequently relate to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and urine discolouration. Common: insomnia, hallucination, confusion and paroniria, Parkinsonism aggravated, dizziness, dystonia, hyperkinesias, diarrhoea, abdominal pain, dry mouth constipation, vomiting, fatigue, increased sweating and falls. See SPC for details of laboratory abnormalities, uncommon and rare events. **Legal category**: POM. **Presentations, basic NHS costs and marketing authorization numbers**: Stalevo 50mg/12.5mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40, MA numbers: EU/1/03/260/002-003; Stalevo 100mg/25mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40, MA numbers: EU/1/03/260/006-007; Stalevo 150mg/37.5mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40, MA numbers: EU/1/03/260/010-011. **Distributed in the UK by**: Orion Pharma (UK) Ltd. Leat House, Overbridge Square, Hambridge Lane, Newbury, Berkshire, RG14 5UX, England. **In Ireland information is available from**: Orion Pharma (Ireland) Ltd, c/o Allphar Services Ltd, Belgard Road, Tallaght, Dublin 24. Tel 01-4041600. Fax: 01-4041699. Full prescribing information is available on request. Stalevo is a registered trademark. Updated December 2004.

Stalevo®
levodopa, carbidopa, entacapone

Enhance the benefits of levodopa

References
1. Larsen JP *et al. Eur J Neur* 2003;**10**:137-146.
2. Rinne UK *et al. Neurology* 1998;**51**:1309-1314.

Date of preparation:
December 2004
STA1295

Diagnosis and Management of Restless Legs Syndrome

Introduction

Restless Legs Syndrome (RLS) was first described in 1672 and rediscovered by KA Ekbom in 1945[1] who extensively studied this disorder and contributed important findings which are still relevant today. The international RLS Study Group (IRLSSG) published a set of criteria to establish a diagnosis of this frequent sensorimotor disorder.[2,3]

Clinical features, definition and diagnosis of RLS

RLS is a neurological sleep disorder characterised by an almost irresistible urge to move the limbs which is most often but not necessarily accompanied by uncomfortable sensations in the legs. RLS symptoms are evoked by rest and are worse in the evening or night. The arms may also be involved. RLS occurs predominantly in the evening or during the night and has a profound impact on sleep. In addition to difficulty initiating sleep, many RLS patients have problems maintaining sleep with frequent awakenings or short arousals resulting in poor sleep efficiency.

Diagnostic criteria for RLS are characterised by four essential criteria (Table 1). To make a definite diagnosis of RLS, all four diagnostic criteria must be established.

The following supportive features have been established which are not necessary to make the diagnosis of RLS but which may, especially in doubtful cases, help to diagnose or exclude RLS.

Positive family history

A positive family history is present in more than 50% of RLS patients.

Positive response to dopaminergic treatment

Several controlled studies have shown that most patients with RLS have a positive therapeutic response to dopaminergic drugs. Based on clinical experience, more than 90% of patients report a relief of their symptoms when treated with these agents.

Periodic limb movements in sleep (PLMS)

PLMS are reported to occur in 80 to 90% of patients with RLS. However, PLMS also commonly occur in other disorders and in the elderly. A PLMS index (number of PLMS per hour of sleep) of greater than 5 is considered pathologic, although data supporting this feature is very limited. The occurrence of PLM during nocturnal periods of wakefulness (PLMW) is considered to be more specific for RLS. Thus the presence of a high number of PLM is supportive for RLS but the absence of PLM does not exclude RLS.

In addition to the essential and supportive criteria the progressive clinical course with intermittent symptoms in the beginning, the presence and character of sleep disturbances and the normal physical examination in primary cases are other features of RLS that may be helpful for diagnosis.[3]

Epidemiology

The prevalence of RLS in the general population lies between 5 and 10%, women are affected twice as often as men.[4] Most individuals suffer from primary RLS which shows a familial association in more than 50%. An autosomal-dominant mode of inheritance has been shown.[5] Genome-wide studies have been conducted to map genes that play a role in the vulnerability to RLS. So far linkage was found to a locus on chromosome 12q,[6] 14q[7,8] and 9p.[9] While most RLS cases may be idiopathic, RLS is often linked to other medical or neurological disorders. The most important associations of RLS are with end-stage renal disease or iron deficiency. RLS may also develop during pregnancy or intensify secondary to treatment with various drugs such as dopamine antagonists, typical and atypical neuroleptics, metoclopramide, or antidepressants such as tri- and tetracyclic antidepressants, serotonin reuptake inhibitors and lithium. Although supporting data are limited, peripheral neuropathies may be associated with RLS.[10]

Treatment

Pharmacological therapy should be limited to those patients who meet the specific diagnostic criteria and suffer from clinically relevant RLS symptoms. Several factors like the frequency and severity of symptoms, the temporal appearance of symptoms, the kind of sleep disturbances and the degree to which RLS interferes with the quality of life influence treatment strategies. Dopaminergic agents are considered the first-line treatment in RLS,[11] after secondary RLS associated with low iron or ferritin levels has been excluded. Even raising ferritin levels from the lower normal range frequently improves RLS symptoms.

L-dopa

L-dopa/benserazide (Restex® and Restex® retard) was the first drug licensed for RLS in September 2000 in two European countries, Germany and Switzerland. Doses of 50/12.5 to 100/25mg standard L-dopa / DDI improve RLS symptoms about one hour after drug intake resulting in an improved quality of sleep. In correlation to the plasma half-life of L-dopa (1–2 hours) the beneficial effect decreases and RLS may persist in the second half of the night. If so, an additional application of slow release L-dopa/DDI (100/25mg given in combination with standard L-dopa/benserazide one hour prior to or at bed time) is recommended. In general, L-dopa is best used in patients with mild RLS. In patients with sporadic RLS, L-dopa can be given on demand. Tablets are generally taken at bedtime, perhaps supplemented by a dose earlier in the day to control evening or daytime symptoms.

In more severely affected patients RLS symptoms may not be adequately controlled for the whole night even with the combination of standard and sustained release preparations.

Table 1: Essential diagnostic criteria of the International RLS Study Group [76]

1. *An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs).*
2. *The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting.*
3. *The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.*
4. *The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).*

Dr Karin Stiasny-Kolster, is a Neurologist and heads the RLS outpatient clinic and neurological sleep laboratory at the Department of Neurology of Phillips University in Marburg, Germany. Her research interests include restless legs syndrome and sleep disorders associated with neurodegenerative disorders.

Dr Aline Metz is a Neurologist at the Department of Neurology of Phillips University in Marburg, Germany. Her research interests include Parkinson's disease and restless legs syndrome.

Professor Wolfgang Oertel is Director of the Department of Neurology at the University of Marburg. He has been opinion leader in the diagnosis and treatment of RLS for more than 15 years and was founder of the RLS research group in Germany. He was principal investigator in placebo-controlled national and multinational clinical trials in RLS and involved in the conception and design of studies for EMEA or FDA approval. He is speaker of the German RLS Patient Register, which was founded by the German Ministry for Education and Research (BMBF).

Correspondence to:
Dr Karin Stiasny-Kolster,
Department of Neurology,
University of Giessen and
Marburg,
Rudolf-Bultmann-Str. 8,
35037 Marburg,
Email: Stiasny@
med.uni-marburg.de

Table 2: Characteristics of dopaminergic agents in the treatment of RLS

	Half-life (hrs.)	Initial dosage	Titration	Dosage in RLS	Max. dosage
l-dopa/benserazide	*1-2*	*50/12.5 – 100/25mg*	*50-100mg / day*	*50–300mg*	*400mg*
α-dihydroergocriptine	*10-15*	*5mg*	*5mg / 3 days*	*10–40mg*	*80mg*
Bromocriptine	*3-8*	*1.25mg*	*1.25mg / week*	*2.5–5mg*	*7.5mg*
Cabergoline	*> 65*	*0.5mg*	*0.5mg / week*	*0.5–2mg*	*4mg*
Lisuride	*2–3*	*0.1mg*	*0.1mg / week*	*0.–2mg*	*4mg*
Pergolide	*7–16*	*0.05mg*	*0.05mg / 3 days*	*0.1–0.75mg*	*1.5*
Pramipexole-HCl* *(non-ergot)*	*8–12*	*0.125mg*	*0.125mg / 3 days*	*0.125–0.5mg*	*1.5mg*
Ropinirole *(non-ergot)*	*3–10*	*0.25mg*	*0.25mg / 3 days*	*0.5–4mg*	*8mg*
Rotigotine *(non-ergot)*	*(5 hrs.) constant plasma levels due to patch application*	*1.25mg (2.5cm²) or 2.5mg (5cm²)*	*1.25mg / day above 4.5mg: 2.25mg / day*	*1.25–4.5mg (2.5–10 cm²)*	*9mg*

** in some European countries declared as free base 0.088mg pramipexole = 0.125mg pramipexole-HCl*
***bold** = at least two randomised, placebo-controlled clinical trials with a sufficient number of patients*

Dopamine agonists

Due to their longer half-life dopamine agonists are preferred especially in patients with advanced daily RLS. Given once in the evening in dosages usually much lower than in Parkinson's disease dopamine agonists cover sensory and motor symptoms of RLS throughout the night and some dopamine agonists even during the day. As a consequence sleep and quality of life markedly improves in most patients. Convincing data are available for the dopamine agonists cabergoline, pergolide, ropinirole, pramipexole, and the dopamine agonist patch rotigotine. For details on the characteristics of dopaminergic agents in the treatment of RLS see Table 2.

PD ACADEMY 2005

In association with the Parkinson's Disease Section, British Geriatrics Society & Parkinson's Disease Society UK
Supported by an unrestricted educational grant from Boehringer Ingelheim Ltd

Who are these courses for? Consultants, staff grade physicians, and final year specialist registrars with an interest in Parkinson's disease wishing to advance their knowledge and skills in this area.

What will it involve? The course will advance understanding of PD and related movement disorders through taught sessions and mentorship.

What will it cost? £400 for a six month mentored course, (includes all course materials, portfolio and accommodation for the two residential modules). You are encouraged to apply to your employing Trust for Study Leave, and approval.

Dates for Parkinsnon Disease Masterclass 8
Module 1: 24th-26th May 2006,
Module 2: 29th November-1st December 2006.
Both modules need to be completed to graduate from the course.

Additional seminars and learning opportunities will be undertaken more locally with the mentor and through distance learning.

Download an application form from www.bgsnet.org.uk/Notices/meetings/April05.htm or Email redpublishing@btopenworld.com for more information.

Opioids

Opioids have shown to be effective in RLS and their analgesic or sedative effect may be of advantage in individual patients, but data from placebo-controlled trials are very limited and only available for oxycodone. Opioids may be highly effective particularly in advanced RLS and should not be withheld from appropriate patients because of fear of potential development of tolerance or dependence. If opioids are used, treatment regimens like in chronic pain syndromes should be applied. Severely affected patients may particularly profit from opioid patch applications.

Gabapentin

Gabapentin may be an alternative choice, particularly in less intense RLS, RLS in combination with a painful peripheral neuropathy or an unrelated chronic pain syndrome. Gabapentin should be used as once- or twice-daily doses in the late afternoon or evening or before sleep. A controlled trial has shown that mean doses of 1800mg/d are needed for efficacy. The anticonvulsants carbamazepin and valproic acid seem to be less effective in RLS than gabapentin.

Benzodiazepines

Benzodiazepines are sometimes employed for residual insomnia but should be used with caution in particular in older patients. Better alternatives are zaleplon, zolpidem or zopiclone.

In some patients combination therapies with dopaminergic agents, opioids, anticonvulsants or benzodiazepines may be a necessary but not formally studied option.

References

1. Ekbom, K.A., *Restless legs syndrome.* Acta Med Scand, 1945. 158: p. 4-122 (suppl).
2. Walters, A.S., *Toward a better definition of the restless legs syndrome.* The International Restless Legs Syndrome Study Group. Mov Disord 1995. 10(5):634-42.
3. Allen, R., et al., *Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institue of Health.* Sleep Medicine, 2003. 4: p. 101-119.
4. Berger, K., et al., *Sex and the risk of restless legs syndrome in the general population.* Arch Intern Med, 2004. 164(2): p. 196-202.
5. Winkelmann, J., et al., *Complex segregation analysis of restless legs syndrome provides evidence for an autosomal-dominant mode of inheritence in early age at onset families.* Ann Neurol, 2002. 52: p. 279-302.
6. Desautels, A., et al., *Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q.* Am J Hum Genet, 2001. 69(6): p. 1266-1270.
7. Bonati, M.T., et al., *Autosomal dominant restless legs syndrome maps on chromosome 14q.* Brain, 2003. 126(Pt6): p. 1485-1492.
8. Levchenko, A., et al., *The 14q restless legs syndrome locus in the french canadian population.* Ann Neurol, 2004. 55: p. 887-891.
9. Chen, S., et al., *Genomewide linkage scan identifies a novel susceptibility locus for restless legs syndrome on chromosome 9p.* Am J Hum Genet, 2004. 74(5): p. 876-885.
10. Stiasny, K., et al., *Clinical symptomatology and treatment of restless legs syndrome and periodic limb movements in sleep.* Sleep Medicine Reviews 2002. 6(4): 253-265.
11. Hening, W.A., et al., *An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine interim review.* Sleep, 2004. 27(3): p. 560-583.

Mirapexin™

pramipexole

Address the distress of Parkinson's disease

Prescribing Information UK

Mirapexin™ (pramipexole) Presentation: Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing **0.125mg**, **0.25mg** and **1.0mg** respectively of pramipexole dihydrochloride monohydrate. **Indications:** The treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa. **Dosage and Administration:** Adults and Elderly Patients: Administration: Give tablets orally with water in equally divided doses three times per day. Initial treatment: 3 x 0.125mg salt (3 x 0.088mg base) per day for first 5-7 days. Then 3 x 0.25mg salt (3 x 0.18mg base) per day for 5-7 days, and then 3 x 0.5mg salt (3 x 0.35mg base) per day for 5-7 days. Increase the daily dose by 0.75mg salt (0.54mg base) at weekly intervals to a maximum dose of 4.5mg salt (3.3mg base) per day if necessary. Incidence of somnolence is increased at doses higher than 1.5mg salt (1.05mg base) per day. Maintenance treatment should be in the range of 0.375mg salt (0.264mg base) to a maximum of 4.5mg salt (3.3mg base) per day. Adjust dose based on clinical response and tolerability; reduce doses used in titration and maintenance phases if necessary. Treatment discontinuation: Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Reduce dose by 0.75mg salt (0.54mg base) per day to 0.75mg salt (0.54mg base) per day. Thereafter reduce dose by 0.375mg salt (0.264mg base) per day. Renal impairment: See SPC for revised dosage schedules. Hepatic impairment: Dose adjustment in hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings and Precautions:** Reduce dose in renal impairment. Inform patients that hallucinations (mostly visual) can occur. Somnolence and, uncommonly, sudden sleep onset have been reported; patients who have experienced these must refrain from driving or operating machines. (A reduction of dosage or termination of therapy may be considered). If dyskinesias occur in combination with levodopa during initial titration of pramipexole in advanced Parkinson's disease, the dose of levodopa should be reduced. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. **Drug Interactions:** There is no pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules such as cimetidine and amantadine may interact with pramipexole resulting in reduced clearance of either or both drugs. Consider reducing pramipexole dose when these drugs are administered concomitantly. The dosage of levodopa should be reduced, and other Parkinsonian medication kept constant, while increasing the dosage of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. Coadministration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** Effects of pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used in pregnancy unless the benefit outweighs the potential risk to the foetus. Pramipexole should not be used during breast-feeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, confusion, dizziness and peripheral oedema (occurred more often than with placebo). More frequent adverse reactions in combination with levodopa were dyskinesias. Constipation, nausea and dyskinesia tended to disappear with continued therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin is titrated too fast. Mirapexin has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. Libido disorders (increase or decrease), pathological gambling, especially at high doses generally reversible upon treatment discontinuation. **Overdose:** There is no clinical experience with massive overdosage. Expected adverse events include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive measures may be required, along with gastric lavage, intravenous fluids and electrocardiogram monitoring. **Basic NHS Cost:** 0.125mg (0.088mg) x 30 £9.25, 0.25mg (0.18mg) x 30 £18.50, 0.25mg (0.18mg) x 100 £61.67, 1.0mg (0.7mg) x 30 £58.89, 1.0mg (0.7mg) x 100 £196.32. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. **Marketing Authorisation Number:** Mirapexin 0.088mg **(0.125mg)** x 30 tablets EU/1/97/051/001; Mirapexin 0.18mg **(0.25mg)** x 30 tablets EU/1/97/051/003; Mirapexin 0.18mg **(0.25mg)** x 100 tablets EU/1/97/051/004; Mirapexin 0.7mg **(1.0mg)** x 30 tablets EU/1/97/051/005; Mirapexin 0.7mg **(1.0mg)** x 100 tablets EU/1/97/051/006. Further information is available from Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, Berkshire RG12 8YS. **Date of preparation:** June 2005.

Code: PPX0137
Date of preparation: September 2005

Boehringer Ingelheim

Genetics and Epilepsy

The completion of the human genome project and the further availability of increasingly detailed data on human chromosomes[1] promise much for our understanding of the genetic basis of human health and disease. The entire human genome contains some 30,000 genes, more than half of which are expressed at some stage in the brain. Genetic influences on brain function and diseases are therefore pervasive. In the outbred human species, epilepsy is obviously not a constitutive phenotype: there are certain genetic variants that either directly cause or contribute to epilepsy phenotypes. Epilepsy is a heterogeneous group of conditions, and thus genetic influences on different types of epilepsy are likely to vary widely. However, whilst genes encode every protein, many proteins undergo additional modulation by factors ranging from the post-transcriptional to the macroenvironmental, so that we, and our diseases, are generally not products of a rigid genetic determinism. However, genetic factors are perhaps now more readily determined than environmental factors, so that genetic studies in epilepsy hold promise for a better understanding and more rational treatment than that which currently exists.

Genes could influence seizures, epileptogenesis and epilepsy at multiple levels. Genetic variation could affect the aetiology, susceptibility, mechanisms, syndrome, treatment response, prognosis and consequences of the epilepsies to varying degrees in different individuals. Part of the promise of genetics lies in its power to relate these facets of the overall clinical presentation to the individual patient. There has been considerable recent progress, though this has focused largely on aetiology, susceptibility and treatment response.

More and more genetic mutations are being identified that cause epilepsy. These mutations usually cause conditions that are inherited in a classical Mendelian fashion: autosomal dominant, autosomal recessive, X-linked or through mitochondrial inheritance. Mutations are rare and, even collectively, mutational causes of conditions in which epilepsy is the sole or main manifestation account for only a small proportion of cases of epilepsy. Perhaps unsurprisingly given the central position of neuronal excitability in epilepsy, most mutations so far uncovered that lead to epilepsy occur in genes encoding ion channels.[2] Sodium, potassium, calcium and chloride channelopathies have all been described, and there are likely to be others to come (Table 1). It is worth noting, in passing, that acquired epileptogenic channelopathies also exist.[3] Mutations that cause monogenic epilepsies fall into two other major categories: those that lead to structural brain malformations one clinical manifestation of which is epilepsy;[4] and those that produce the progressive myoclonic epilepsies (PMEs).[5] The latter are themselves a diverse group of conditions distinguished by particular natural histories, pathophysiologies and investigational findings, but which broadly share the common characteristics of myoclonic jerks, other seizure types and progressive cognitive decline: many PMEs can now be defined and dissected genetically (Table 2). Only a few other genetic mutations are known to lead to epilepsy as their major consequence. These include LGI1, mutations which cause a familial focal epilepsy.[6] There are of course a large number of Mendelian conditions with known underlying gene mutations that cause multisystemic conditions in which seizures are part of a broader phenotype: the number of these also continues to grow, but again account for only a small proportion of the epilepsies.

This progress in the genetic aetiology of the epilepsies is remarkable, and as yet unmatched by developments in the genetics of other aspects of disease biology, such as susceptibility or treatment response, reflecting partly the focus of researchers so far, but also the tractability of the relevant issues.

Genetic variation influencing susceptibility to non-Mendelian epilepsies has been the other major focus of research. Most epilepsies are complex traits and probably arise in individuals as a result of gene-gene and gene-environment interactions. The numbers of genes involved are unknown, and may be few or many. The resulting patterns of inheritance in the majority of cases are thus more complicated and subtle: such inheritance falls outside the Mendelian patterns to which we have become accustomed. As a corollary, large cohorts of patients are needed to extract the risks attributable to particular common genetic variants. Many positive associations between particular gene variants and defined epilepsy syndromes have been found; it is likely that many more negative results have not made it to the editor's in-tray. However, no common genetic variants are yet accepted as genuinely increasing the risk of any particular epilepsy type or syndrome.[7] Numerous problems of methodology dog this area of research. Perhaps the most important is that any one research centre is unlikely to be able to recruit sufficient numbers of patients with an appropriately homogeneous phenotype to have adequate power to detect individual gene effects which are in practice likely to be minor: a parallel with international clinical trials recruiting thousands to show minor benefits from a new treatment regime may be drawn. However, as our understanding of the genome and its vagaries improves, and with increased experience and international collaboration, it seems likely that common genetic variants driving common disease processes will emerge.

The genetics of drug response may prove to be more amenable to analysis than other aspects of genetics in epilepsy, because the proteins that are drug targets, drug transporters and drug metabolisers are to varying extents already known. Their encoding genes do not need to be picked, at random or otherwise, from 30,000 genes,[8] and many have been thoroughly characterised.[9] For example, it is well established that individuals who possess certain alleles of the CYP2C9 gene, that encodes the major metabolising enzyme of phenytoin, have significantly reduced rates of metabolism of phenytoin, necessitating lower maintenance doses,[10] although prospective genotyping is not yet undertaken in practice. Whether variants in the ABCB1 gene, that encodes the broad-spectrum multidrug transporter P-glycoprotein, influence resistance to antiepileptic drugs or not remains a hotly-debated point.[11,12] Gene variants influencing the sensitivity of targets to antiepileptic drugs are also being uncovered: for example, a splice site variation in the SCN1A gene that encodes the cerebral neuronal target of many antiepileptic drugs, has been associated with dosing of these drugs.[10] Such pharmacogenetic advances, if substantiated by further studies and proven in structured trials to be clinically significant, may permit closer modelling of treatment to the individual patient.

The genetics of most other biological facets of epilepsy have not yet even been considered in any detail, but it remains possible that genetic variation will also have an impact of clinical relevance in these other areas (eg biological consequences of epilepsy in an individual patient). Much is still expected of genetic research: careful evaluation in the clinical setting will remain critical to establishing the practical utility of such research. Close collaboration between epilepsy clinical centres, and between clinical and laboratory scientists, and accurate definition of phenotypes, will be the key to bringing epilepsy genetics to the clinic for the benefit of patients and society.

Dr Sisodiya works in the Department of Clinical and Experimental Epilepsy, Institute of Neurology, UCL, London. His clinical and research interests are in the neurogenetic, neuropathological and developmental biological aspects of epilepsy, recently focusing on genetic variation, disease susceptibility and treatment response.

Correspondence to:
SM Sisodiya MA, PhD, FRCP,
Reader in Neurology,
Department of Clinical and Experimental Epilepsy,
National Hospital for Neurology and Neurosurgery, Box 29,
Queen Square, London WC1N 3BG.
Tel: 020 7837 3611,
Fax: 020 7837 3941,
Email: sisodiya@ion.ucl.ac.uk

Table 1. Genetics of monogenic inherited epilepsies: some selected genetic data

Epileptic Disorder	Mode of Inheritance	Locus	Gene	Protein
Monogenic epileptic syndromes of early life				
Benign familial neonatal convulsions (BFNC)	*AD*	*20q (EBN1)*	*KCNQ2*	*Voltage-gated K channel*
		8q (EBN2)	*KCNQ3*	*Voltage-gated K channel*
Benign familial neonatal infantile seizures (BFNIS)	*AD*	*2q*	*SCN2A*	*α2 subunit of the voltage-gated Na channel*
Partial epilepsies				
Autosomal dominant nocturnal frontal-lobe epilepsy	*AD*	*20q13.2*	*CHRNA4*	*α4 subunit of nAChR*
		1(pericentromere)	*CHRNB2*	*β2 subunit of nAChR*
Familial lateral temporal-lobe epilepsy with auditory symptoms (ADPEAF)	*AD*	*10q*	*LGI1*	*Epitempin*
Primary generalised epilepsies				
Juvenile myoclonic epilepsy	*AD*	*6p12-11*	*EFHC1*	*EFHC1 protein*
	AD	*6p21.3*	*Unknown*	*Unknown*
		15q14	*Unknown*	*Unknown*
		5q34	*GABRA1*	*α1 subunit of the GABA(A) receptor*
Idiopathic generalised epilepsies		*3q26*	*CLCN2*	*voltage-gated chloride channel*
Generalised epilepsy with paroxysmal dystonia	*AD*	*10q22*	*KCNMA1*	*Pore-forming α subunit of BK channel*
Absence epilepsy with episodic ataxia	*AD*	*19*	*CACNA1A*	*Pore-forming α subunit of a calcium channel*
Generalised Epilepsy with Febrile Seizures +				
	AD	*19q (GEFS+1)*	*SCN1B*	*β1 subunit of the voltage-gated Na channel*
	AD	*2q31 (GEFS+2)*	*SCN1A*	*α1 subunit of the voltage-gated Na channel*
	AD	*2q31*	*SCN2A*	*α2 subunit of the voltage-gated Na channel*
	AD	*5q31 (GEFS+3)*	*GABRG2*	*γ2 subunit of the GABAA receptor*
Severe Myoclonic Epilepsy of Infancy	*De novo or transmitted*	*2q31*	*SCN1A*	*α1 subunit of the voltage-gated Na channel*
		5q31	*GABRG2*	*γ2 subunit of the GABA(A) receptor*

Note that additional loci exist for many of these disorders: the table is intended to show examples, and is not comprehensive.
AD=autosomal dominant; AR=autosomal recessive; Na=sodium; K=potassium; nAChR=nicotinic acetylcholine receptor.
Modified and updated after: Gourfinkel-An I, Baulac S, Nabbout R, et al. Monogenic idiopathic epilepsies. Lancet Neurol 2004; 3; 209-18 Table 1.

Table 2: Genetics of Progressive Myoclonic Epilepsies

Disorder	Gene	Protein
Neuronal Ceroid Lipofuscinoses		
Infantile	*CLN1*	*Palmitoyl-protein thioesterase 1 (PPT1)*
Late Infantile	*CLN2*	*Tripeptidyl peptidase 1 (TPP1)*
Finnish variant late infantile	*CLN5*	*Novel membrane protein*
Variant late infantile	*CLN6*	*Novel membrane protein*
Juvenile	*CLN3*	*Novel membrane protein*
Northern epilepsy	*CLN8*	*Novel membrane protein*
Adult (Kufs disease)	*—*	*—*
Lafora body disease	*EPM2A*	*Laforin*
	EPM2B (NHLRC1)	*Malin*
Sialidosis	*NEU1*	*Neuraminidase 1*
Unverricht-Lundborg disease	*CSTB (EPM1)*	*Cystatin B*
	EPM1B	*Not known*
MERRF	*MTTK*	*tRNALys*
Juvenile GM2, gangliosidosis type III	*HEXA*	*β N acetylhexosaminidase A deficiency*
DRPLA	*DRPLA (triplet repeat disease)*	*Atrophin 1*

Note there are other even more rare PMEs, not included in this table.

References

1. Ross MT et al. *The DNA sequence of the human X chromosome.* Nature 2005 Mar 17;434:325-37.
2. Mulley JC, Scheffer IE, Petrou S, Berkovic SF. *Channelopathies as a genetic cause of epilepsy.* Curr Opin Neurol. 2003;16:171-6.
3. Bernard C, Anderson A, Becker A, Poolos NP, Beck H, Johnston D. *Acquired dendritic channelopathy in temporal lobe epilepsy.* Science 2004;305:532-5.
4. Guerrini R. *Genetic malformations of the cerebral cortex and epilepsy.* Epilepsia 2005;46 Suppl 1:32-7.
5. Delgado-Escueta AV, Perez-Gosiengfiao KB, Bai D, et al. *Recent developments in the quest for myoclonic epilepsy genes.* Epilepsia 2003;44 Suppl 11:13-26.
6. Kalachikov S, Evgrafov O, Ross B, et al. *Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features.* Nat Genet. 2002;30:335-41.
7. Tan NC, Mulley JC, Berkovic SF. *Genetic association studies in epilepsy: "the truth is out there".* Epilepsia 2004;45:1429-42.
8. Goldstein DB, Tate SK, Sisodiya SM. *Pharmacogenetics goes genomic.* Nat Rev Genet. 2003;4:937-47.
9. Ahmadi KR, Weale ME, Xue ZY, et al. *A single-nucleotide polymorphism tagging set for human drug metabolism and transport.* Nat Genet 2005;37:84-9.
10. Tate SK, Depondt C, Sisodiya SM, et al. *Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin.* Proc Natl Acad Sci U S A. 2005;102:5507-12.
11. Siddiqui A, Kerb R, Weale ME, et al. *Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1.* N Engl J Med. 2003;348:1442-8.
12. Tan NC, Heron SE, Scheffer IE, et al. *Failure to confirm association of a polymorphism in ABCB1 with multidrug-resistant epilepsy.* Neurology 2004;63:1090-2.

Neuroscience of Eye Movements

Most diseases affecting the brain have some effect on eye movements. Indeed, identification of abnormal eye movements can often help to make a neurological diagnosis. To capitalise fully on the advantages provided by eye movements, the clinician needs to perform a systematic examination, and know how to interpret the findings. An understanding of the purpose and properties of normal eye movements guides the examination, whereas knowledge about their biological substrate aids topological diagnosis. In addition to their clinical value, eye movements are also being used as an experimental tool to probe memory and cognition.

How to approach eye movements

There are several functional classes of eye movements, each with a set of properties that suit it for a specific function (Table 1). Eye movements are of two main types: gaze holding and gaze shifting. The term gaze refers to the direction of the line of sight in an earth-fixed (not a head-fixed) frame of reference; thus gaze may remain constant if the eyes and head rotate in opposite directions by the same amount. Certain defects of eye movements, such as those made to remembered locations by patients with frontal lobe disorders, require laboratory testing. However, most disorders can be appreciated at the bedside, provided the examiner understands what properties are being tested. For a more detailed discussion of normal and abnormal eye movements, with video examples, the reader is referred to a current text.[1]

Properties of functional classes of eye movements

In general, eye movements are required for clear, stable, single vision.[2] Clear vision of an object requires that its image be held fairly steadily on the retina, especially on the central fovea (macula), which is the region with the highest photoreceptor density. Excessive motion of images on the retina degrades vision and leads to the illusion of movement of the visual environment (oscillopsia). An important limitation of eye movements mediated by visual stimuli is that they are elicited at long latency (> 100ms). Thus, during locomotion, head perturbations occurring with each footfall are too high in frequency for visually mediated movements to hold gaze steadily pointed at an object of interest. The vestibulo-ocular reflex (VOR), which depends on the motion detectors of the inner ear, generates eye movements at short latency (< 15ms) to compensate for head perturbations (rotations or displacements – translations). Individuals who have lost their VOR, due, for example, to the toxic effects of aminoglycoside antibiotics on the hair cells of the vestibular labyrinth, report that they cannot see their surroundings clearly while they are in motion.[3] Only during sustained (low-frequency) head movements can visual (optokinetic) eye movements contribute to gaze stability by supplementing the VOR. During such sustained rotations, reflexive saccades, called quick phases, reset the direction of gaze after each smooth vestibular or optokinetic movement; the overall behaviour is nystagmus. Thus, in health, vestibular and optokinetic nystagmus act to hold images steady on the retina while the subject is in motion. Pathological forms of nystagmus occur when patients are stationary and cause excessive slip of images on the retina, thereby blurring vision and leading to oscillopsia.

With the evolution of the fovea, it became necessary to be able to point this specialised region of the retina at features of interest. Thus, saccades are rapid eye movements that move the fixation point from one feature to another during visual search, including reading.[4] The speed of saccades may exceed 500 degrees/second (bigger movements are faster). Most saccades are completed in less than 100ms, and we do not appear to see during these movements. Despite their speed and briefness, most saccades are accurate, and only small corrective

There is hardly a corner of the brain that is not concerned with the control of eye movements and, for the clinician, this means that abnormal eye movements often provide useful diagnostic clues.[1]

Table 1: Functional classes of human eye movements

Class of Eye Movement	*Main Function*
GAZE HOLDING	
Vestibular	*Holds images of the seen world steady on the retina during brief head rotations or translations*
Visual Fixation	*Holds the image of a stationary object on the fovea by minimising ocular drifts*
Optokinetic	*Holds images of the seen world steady on the retina during sustained head rotation*
GAZE SHIFTING	
Smooth Pursuit	*Holds the image of a small moving target on the fovea; or holds the image of a small near target on the retina during linear self-motion; with optokinetic responses, aids gaze stabilisation during sustained head rotation*
Nystagmus quick phases	*Reset the eyes during prolonged rotation and direct gaze towards the oncoming visual scene*
Saccades	*Bring images of objects of interest onto the fovea*
Vergence	*Moves the eyes in opposite directions so that images of a single object are placed or held simultaneously on the fovea of each eye*

** Adapted from Leigh and Zee, 2006.*[1]

R John Leigh, MD, FRCP is the Blair-Daroff Professor of Neurology at Case Western Reserve University, and Staff Neurologist at Louis Stokes Veterans Affairs Medical Center, Cleveland Ohio, USA. With Dr David S Zee, he is co-author of the Neurology of Eye Movements (book/DVD), the fourth edition of which will be published in 2006.

Sangeeta Khanna, MD is a Post-Doctoral Fellow in Neuro-ophthalmology at Case Western Reserve University. She has carried out genetic and molecular studies of extraocular muscle with Dr John D Porter.

Acknowledgments:
Dr Leigh is supported by NIH grant EY06717, the Office of Research and Development, Medical Research Service, Department of Veterans Affairs, and the Evenor Armington Fund.

Correspondence to:
R John Leigh, MD,
Department of Neurology,
11100 Euclid Avenue,
Cleveland Ohio 44106-5040.
Tel: 001 216 844 3190,
Fax: 001 216 231 3461.
Email: rjl4@case.edu

Reshaping the future of Parkinson's disease.

SCHWARZ PHARMA

ROT3497

movements are usually necessary. Smooth pursuit movements make it possible to hold the image of a moving object steadily on the fovea. However, smooth pursuit may have evolved to keep the fovea pointed at a stationary feature of the visual environment during locomotion, when the optic flow of images on the remaining retina would otherwise drive an optokinetic response.[5] Finally, with the evolution of frontal vision it became necessary to place images of a single object on corresponding areas of retina (especially the fovea); this requires vergence eye movements to rotate the eyes in opposite directions. Binocular alignment is a prerequisite for stereopsis (depth vision). Misalignment of the visual axes (strabismus) may cause double vision (diplopia) or, if present in early life, lead to suppression of vision from one eye (ambylopia).

Under natural conditions, head movements accompany eye movements. Thus, the VOR generates eye movements to compensate for head movements. Voluntary gaze shifts are often achieved with a combined eye-head saccade. Similarly, we often track a moving target with smooth eye and head movements.

Neurobiological basis for eye movements

Here we use a bottom-up approach to account for how the brain controls eye movements, and briefly summarise some effects of lesions at each point.[1] Near their insertion, the extraocular muscles are surrounded by fibromuscular pulleys that guide their pulling directions and appear to dictate the geometric properties of eye rotations (Listing's law).[6] The abducens nucleus is the horizontal conjugate gaze centre; it contains motoneurons that innervate the lateral rectus muscle and internuclear neurons that project across the midline, via the medial longitudinal fasciculus (MLF), to the contralateral medial rectus motoneurons (Figure 1). Interruption of this pathway causes internuclear ophthalmoplegia (INO), with slowing of the adducting eye during horizontal saccades; this is an important sign in multiple sclerosis. The VOR for horizontal head rotations depends on vestibular afferents from the lateral semicircular canals, which relay their signal to the contralateral abducens nucleus via the medial vestibular nucleus (Figure 1). Wernicke's encephalopathy involves the vestibular nuclei and impairs the horizontal VOR. Command signals for horizontal saccades project to the abducens nucleus from the adjacent paramedian pontine reticular formation (PPRF);[7] lesions here cause slow or absent horizontal saccades. Smooth-pursuit commands reach the abducens nucleus from the vestibulocerebellum; lesions of the flocculus and paraflocculus impair pursuit. The nucleus prepositus hypoglossi (NPH), medial vestibular nucleus (MVN) and the cerebellum play an important role in holding the eyes in an eccentric position (eg., far right gaze) against the elastic pull of the orbital tissues; lesions of these structures cause the eyes to drift back to centre, leading to gaze-evoked nystagmus.

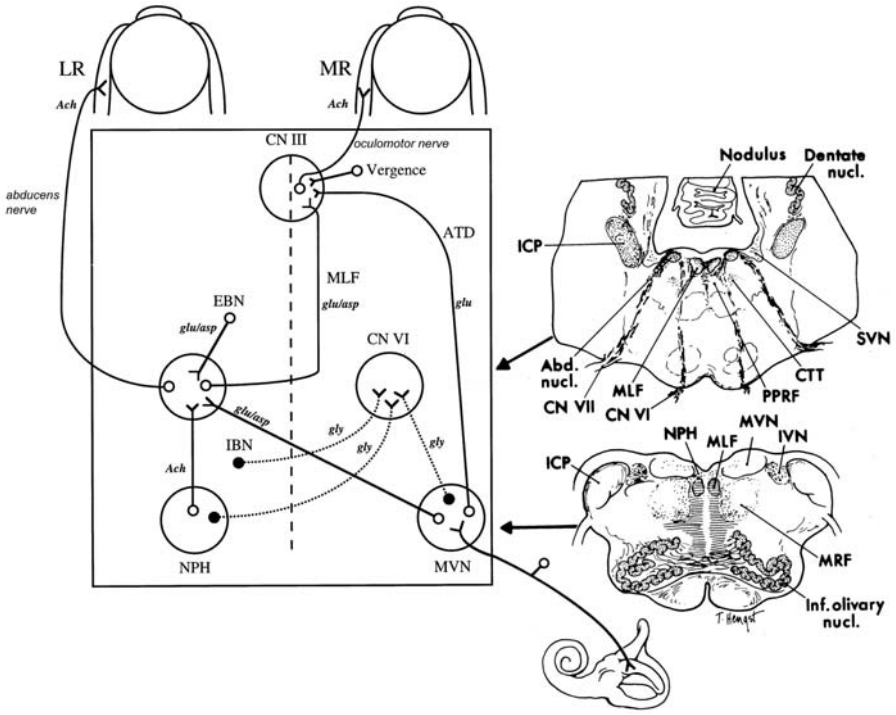


Figure 1. Anatomic scheme for the synthesis of signals for horizontal eye movements. The abducens nucleus (CN VI) contains abducens motoneurons that innervate the ipsilateral lateral rectus muscle (LR), and abducens internuclear neurons that send an ascending projection in the contralateral medial longitudinal fasciculus (MLF) to contact medial rectus (MR) motoneurons in the contralateral third nerve nucleus (CN III). From the horizontal semicircular canal, primary afferents on the vestibular nerve project mainly to the medial vestibular nucleus (MVN), where they synapse and then send an excitatory connection to the contralateral abducens nucleus and an inhibitory projection to the ipsilateral abducens nucleus. Saccadic inputs reach the abducens nucleus from ipsilateral excitatory burst neurons (EBN) and contralateral inhibitory burst neurons (IBN). Eye position information (the output of the neural integrator) reaches the abducens nucleus from neurons within the nucleus prepositus hypoglossi (NPH) and adjacent MVN. The medial rectus motoneurons in CN III also receive a command for vergence eye movements. Putative neurotransmitters for each pathway are shown: Ach: acetylcholine; asp: aspartate; glu: glutamate; gly: glycine. The anatomic sections on the right correspond to the level of the arrow heads on the schematic on the left. Abd. nucl.: abducens nucleus; CN VI: abducens nerve; CN VII: facial nerve; CTT: central tegmental tract; ICP: inferior cerebellar peduncle; IVN: inferior vestibular nucleus; Inf. olivary nucl.: inferior olivary nucleus; MVN: medial vestibular nucleus; MRF: medullary reticular formation; SVN: superior vestibular nucleus. (Reproduced, with permission from Leigh and Zee, 2006).[1]

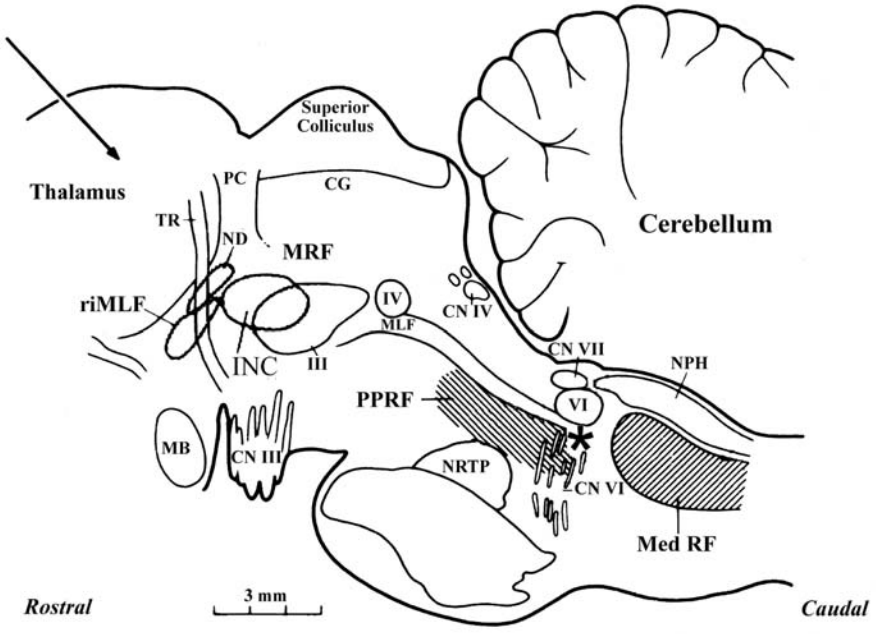


Figure 2: A sagittal section of the monkey brain stem showing the locations of premotor burst neurons: excitatory burst neurons for horizontal saccades lie in the paramedian pontine reticular formation (PPRF) and, for vertical and torsional saccades lie in the rostral interstitial nucleus of the medial longitudinal fasciculus (rostral iMLF). Burst neurons project to ocular motoneurons lying in the abducens nucleus (VI), the trochlear nucleus (IV) and the oculomotor nucleus (III). Omnipause neurons (indicated by an asterisk) lie in the midline raphe of the pons between the rootlets of the abducens nerve (CN VI) and gate the activity of burst neurons. CG: central gray; MB: mammillary body; MT: mammillothalamic tract; N III: rootlets of the oculomotor nerve; N IV: trochlear nerve; ND: nucleus of Darkschewitsch; NRTP: nucleus reticularis tegmenti pontis; PC: posterior commissure; NPH: nucleus prepositus hypoglossi; TR: tractus retroflexus; T: thalamus; Med RF: medullary reticular formation. The arrow refers to the Horsley-Clarke plane of section. (Figure adapted courtesy of Dr Jean Büttner-Ennever).

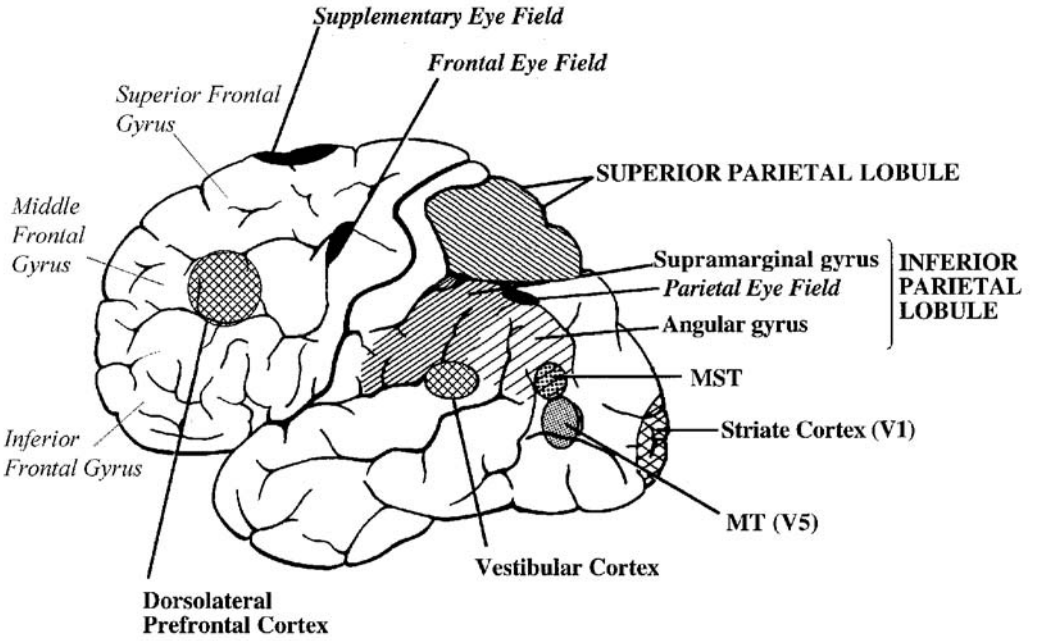


Figure 3: Probable location of cortical areas important for eye movements in human brain. MST: medial superior temporal visual area; MT: middle temporal visual area; these areas may form a contiguous cortical area. (Reproduced, with permission from Leigh and Zee, 2006).[1]

The oculomotor and trochlear nuclei (Figure 2) house the motoneurons that innervate extraocular muscles that mainly rotate the eyes vertically (superior and inferior recti) or torsionally (around the line of sight – superior and inferior oblique muscles). These motoneurons receive their saccadic input from burst neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which lies in the pre-rubral fields of the rostral midbrain.[7] Lesions involving the riMLF cause slow or absent vertical saccades (such as in progressive supranuclear palsy, PSP). The signals for vertical vestibular and pursuit eye movements ascend from the medulla and pons to the midbrain in the MLF and other pathways. The interstitial nucleus of Cajal plays an important role in holding steady vertical eccentric gaze (eg., far upward gaze). The superior colliculus is a midbrain tectal structure that is important for triggering both horizontal and vertical saccades;[8] it receives inputs from frontal and parietal cortex.

Two regions of the cerebellum contribute to the control of eye movements.[1] The vestibulocerebellum (flocculus, paraflocculus, nodulus) are important for normal smooth pursuit (eye alone or eye-head tracking), eccentric gaze holding, and adjustment of the VOR so that it is optimised to guarantee clear vision. These latter functions are all impaired in patients with vestibulocerebellar lesions such as Chiari malformation; downbeat nystagmus is also often present. Lesions of the nodulus and adjacent ventral uvula cause periodic alternating nystagmus, a form of horizontal nystagmus that reverses direction every 2 minutes; it is suppressed with baclofen. The second cerebellar region, comprising the dorsal vermis and the fastigial nucleus to which it projects, is important for saccades to be accurate. Thus, dorsal vermis lesions cause saccadic hypometria (undershoots), and fastigial nucleus lesions cause hypermetria (overshoots).

The cerebral cortex contains several areas that are important for eye movements (Figure 3).[4,9] Primary visual cortex (V1) is the "royal gateway" for vision;[10] without it, visually guided eye movements cannot be made (at least in humans). Secondary visual areas, such as the middle temporal visual area (MT, or V5), and the medial superior visual temporal area (MST) are essential for extracting information on the speed and direction of moving targets and subsequent programming of pursuit movements. The parietal eye field contributes to saccades in the context of shifts of the direction of attention. The frontal eye field is important for voluntary saccades, and suppression of saccades during steady fixation. The supplementary eye fields, and adjacent pre-supplementary motor cortex, guide saccades during complex tasks, such as sequences of movements and responses when the instructional set changes.[11] The dorsolateral prefrontal cortex is important for memory-guided saccades and programming saccades in the opposite direction (mirror image) to a visual stimulus (antisaccade).

These cortical areas project to the superior colliculus and, via pontine nuclei to the cerebellum; direct projections to the PPRF or RIMLF are sparse, and there are no projections to the ocular motoneurons. The descending pathways to the superior colliculus are both direct and also via the basal ganglia (caudate, substantia nigra pars reticulata, and subthalamic nucleus).[12] Disease affecting the basal ganglia has subtle effects on eye movements, but seems concerned with behaviours that are rewarded.[13]

Conclusions

There is hardly a corner of the brain that is not concerned with the control of eye movements and, for the clinician, this means that abnormal eye movements often provide useful diagnostic clues. This brief review deals only with abnormalities that can be appreciated at the bedside.[1] However, with laboratory measurements, eye movements have been put to use by neuroscientists to investigate topics ranging from muscle disease to memory,[9] and even free will.[11]

References

1. Leigh RJ, Zee DS. *The Neurology of Eye Movements* (Book/DVD). Fourth Edition, 4 ed. New York: Oxford University Press, 2006.
2. Walls GL. *The evolutionary history of eye movements.* Vision Res 1962;2:69-80.
3. J.C. *Living without a balancing mechanism.* N Eng J Med 1952;246:458-60.
4. Leigh RJ, Kennard C. *Using saccades as a research tool in the clinical neurosciences.* Brain 2004 Mar;127(Pt 3):460-77.
5. Miles FA. *The neural processing of 3-D visual information: evidence from eye movements.* Eur J Neuroscience 1998.
6. Demer JL. *Pivotal role of orbital connective tissues in binocular alignment and strabismus.* Invest Ophthalmol Vis Sci 2004;45:729-38.
7. Horn AK. *The reticular formation.* Prog Brain Res 2006;151:33-79.
8. Optican LM. *Sensorimotor transformation for visually guided saccades.* Ann N Y Acad Sci 2005 Apr;1039:132-48.
9. Pierrot-Deseilligny C, Milea D, Muri RM. *Eye movement control by the cerebral cortex.* Curr Opin Neurol 2004 Feb;17(1):17-25.
10. Zeki S. *The Ferrier Lecture 1995 behind the seen: The functional specialization of the brain in space and time.* Philos Trans R Soc Lond B Biol Sci 2005;360:1145-83.
11. Nachev P, Rees G, Parton A, Kennard C, Husain M. *Volition and conflict in human medial frontal cortex.* Curr Biol 2005 Jan 26;15(2):122-8.
12. Hikosaka O, Takikawa Y, Kawagoe R. *Role of the basal ganglia in the control of purposive saccadic eye movements.* Physiol Rev 2000;80(3):953-78.
13. Kobayashi S, Lauwereyns J, Koizumi M, Sakagami M, Hikosaka O. *Influence of reward expectation on visuospatial processing in macaque lateral prefrontal cortex.* J Neurophysiol 2002;87(3):1488-98.

Low Vision: Practical and Hi-Tech Solutions for Visual Impairment and Blindness

Access to care of the partially sighted and blind has been limited, for the most part, to developed nations. But that is all beginning to change in our 'flat-world' hi-tech society.[1]

On December 16, 2004, the WHO released new data on the prevalence of global blindness.[2] It was noted that, according to the figures compiled in 2002, there were 161 million people who are visually impaired.[3] Of these, 124 million are considered to have low vision[4] and 37 million are considered to be blind.[5] Of these, 90% of the world's blind live in developing countries: nine million in India, six million in China and seven million in Africa.[6]

A patient with age-related macular degeneration using a strong (microscopic) reading lens.

But only four major eye conditions result in almost 75% of the world's individuals having low vision. They include age-related macular degeneration, glaucoma, diabetic retinopathy, and cataracts.

Vision care has become very specialised in developed nations. There are anterior segment (corneal, glaucoma, contact lens, and cataract specialists) posterior segment (retinologists), paediatric, sports medicine, neuro, as well as low vision specialists. The latter are involved in the care of the partially sighted or visually impaired. The low vision clinicians include optometrists or ophthalmologists worldwide who have special training in managing individuals with reduced vision as well as irreversible vision loss in both eyes.

The specialty of low vision is considered to be a tertiary area of care in which patients are not only under the care of a low vision clinician but the care of a specialist managing the eye pathology (eg retinal or glaucoma specialist). The patient, in fact, may be managed in a multi-specialty group practice taking care of all the vision related problems. They may also be in a private practice specialising in low vision, as well as in a vision rehabilitation organisation, a university or hospital based eye clinic, as well as veterans administration blind rehabilitation centers (in the US: Chicago, Atlanta, Palo Alto, W. Haven Ct.).

Vision rehabilitation services and teamwork are generally required and provided, regardless of whether it is a congenital, early onset, or adventitious aetiology. The vision rehabilitation team includes the optometrist or ophthalmologist specialising in low vision and care of the partially sighted. It is their primary responsibility to perform the low vision evaluation as well as prescribe and design low vision devices. The other members of the vision rehabilitation team include the social worker to deal with issues such as: vision loss, depression, family dynamics, and loss of independence. The team also includes a vision rehabilitation specialist or occupational therapist (OT) to instruct patients in the use of the low vision devices as well as to teach them independent living skills. Mobility specialists may be called upon, as well, for the teaching of independent travel, along with educators of the visually impaired and job placement specialists.

The Clinical Low Vision Examination

The specialised low vision evaluation is a functionally oriented examination to determine patient specific objectives and needs, to maximise the residual vision with prescriptive lenses, low vision devices, and hi-tech solutions. These objectives may include such diverse demands as, reading the label on a prescription medication bottle, reading the daily newspaper, being able to access the computer screen, travelling independently and safely in an unfamiliar area, being able to see the Professor's PowerPoint presentation in college, being able to see the markings on the insulin gauge, reducing glare in the environment, accessing your PIN code, seeing the menu at a fast food restaurant, or using the ATM in the Bank. The history will also investigate comorbidities, such as diabetes or stroke and how they may affect the patient's goals and objectives as well.

The low vision examination also consists of a specialised battery of tests designed to evaluate the patient's visual function. It includes specially designed vision charts that measure even the lowest levels of vision. The preferred visual acuity chart for testing is the ETDRS (Early Treatment of Diabetic Retinopathy) chart which is also used for all clinical trials in the United States.[7] These logarithmic charts have been statistically validated to record changes in vision over time as well as to record vision as low as 1/40 (20/800). Patients with vision of less than 2/40 (20/400) may have need of other vision rehabilitation services such as mobility in order to learn how to travel safely and independently in their environment. Individuals possessing only light perception or no vision al all (functionally blind) will also be referred for mobility training in the use of a cane.

Contrast sensitivity functional (CSF) testing was added to the low vision battery of tests by the author and Eleanor Faye, MD in 1981. CSF measures the ability to see objects (eg print, road signs), as the contrast decreases. That is, how black does an object have to be, before it can be seen. Contrast sensitivity is becoming an important outcome measure in patient management as it relates to quality of life issues. It is affected by the major pathologies such as macular degeneration, cataracts, and diabetic retinopathy. Magnification, the usual method of improving performance, may not be as effective as much as enhancing the contrast by strategies such as increasing the illumination in all environments.

It is important to map out the visual field using automated perimetry, as well, in eye diseases such as glaucoma, optic nerve disease and systemic conditions such as stroke. Trauma may also lead to significant loss of the visual field as does retinitis pigmentosa. The latter is a progressive disease that generally results, not only in a loss of the peripheral vision but night blindness, and significant mobility problems. There is no treatment at this time to slow the degeneration of the peripheral retina but exciting genetic research (eg ABCR gene)[8] may lead to a cessation of progression. Again mobility, or newer hi-tech methods such as use of the GPS, especially when the visual field is severely compromised, will be essential for independent travel.

The other examination components include a specialised low vision refraction test to determine whether a spectacle correction will be beneficial for distance, intermediate, and near tasks, an Amsler grid to evaluate the central 20 degrees of the visual field, as well as an ocular health analysis.

The ability to enhance visual function is one of the objectives of the evaluation and magnification and

Dr Bruce P Rosenthal is the Chief of the Low Vision Clinical Practice at Lighthouse International in New York City, Adjunct Professor at Mt Sinai Hospital, Distinguished Professor at State University of New York, and Chair of the Scientific Advisory Board of the AMD Alliance International. He lectures throughout the world, has authored of eights books on visual impairment and macular degeneration as well as over 100 scientific articles.

Correspondence to:
Email: BROSENTHAL@lighthouse.org

enhancing the CSF are ways of achieving this objective. Increasing the magnification can be done in three ways: relative size, relative distance, and angular magnification. In relative size magnfication, the object of regard can be physically enlarged such as the print in a large print book. The object of regard can be brought closer to the eye, in relative distance magnification, so that the object subtends a larger retinal image and appears much larger. In angular magnification the object can be made to appear to be closer to the eye and thus appear larger (eg seeing the train or airport departure board).

Low vision devices will generally allow the user to bring an object closer to the eye and thus magnify the retinal image size. Enhancing the contrast is a different story and may require a hi-tech device, a filter, as well as techniques such as using a bold line pen when writing.

In addition to prescriptive lenses for distance (televison, theatre), intermediate (reading music, the computer screen), and near tasks (reading) are specialised low vision devices. The low vision devices includes strong reading lenses (microscopic lenses), magnifying systems (hand and stand magnifiers), telescopic systems (for use in museums, independent travel or, classroom work), absorptive lenses and filters (for reducing glare as well as increasing the contrast), and hi-tech devices that are known as closed-circuit televisions.

High plus microscopic lenses are readily available up to 12x (48 diopters – focal distance of less than 2.03cm) magnification. Optical magnification, for all practical purposes is good up to 6x (24 diopters; focal distance 4.1cm). Most individuals cannot manage the close working distance or the restricted depth of field in high magnification systems. Illuminated magnifiers, especially illuminated stand magnifiers that sit on the page are available up to 15x (60 diopters). The image stays in focus since the magnifier sits on the page but the field of view as well as ease in reading significantly decreases as the magnification increases.

That is where the closed circuit television comes into play. As the world moves ahead to a hi-tech age, so will the field of low vision, enabling individuals with the most profound vision loss access to information on the web. The closed-circuit television, which is a dedicated system that can enlarge print up to over 40 times the size of the original print as well as enhance contrast, has been around for 35 years. The ability to reverse polarity, that is changing the black letters on a white background to white on black is perhaps the major feature of the closed-circuit television. There are brightness and contrast controls as well as systems that allow a user to isolate a line. This feature is extremely beneficial when it is difficult to locate or isolate a line of print. It is also helpful in the loss of the visual field from a stoke or tumour.

Assistive technology has become much more common in the workplace in the United States. Microsoft found that 27% of computer users have a vision difficulty and have added much greater accessibility in their programme updates. These include screen enlargers that move around the screen like a magnifier, screen readers that present graphics and text as speech, speech recognition systems that allow for voice input commands, screen synthesisers also known as text to speech systems that allow blind users to play back their Word document including the words, numbers, and punctuation. Other programmes for the blind include refreshable Braille in which a line of print is displayed and then will refresh to play another line, a Braille embosser that has the capability of transferring computer generated images into embossed Braille, talking word processors, as well as large print processors.[9] In addition Microsoft has included tutorials for the blind and visually impaired for programmes ranging from Windows XP to accessing the internet.

Accessing the ATM has been difficult if not impossible for the blind and partially sighted. This has begun to change with the Northern Bank and Clydesdale Banks in Belfast and Glasgow as well as Bank of America in San Francisco launching systems that are truly accessible. The Northern Bank's 'cashpoint' is used by plugging a set of headphones into a jack, which is fitted to the front of the ATM. The machine uses an automated voice to give instructions about the exact location of items such as the numbers on the keypad, the cash dispenser and all other devices on the machine. It also talks through each stage of the process, whether a user wants to check a balance or withdraw cash. Sighted users can also use the machine by following instructions displayed on screen.[10,11]

Even shopping in mega stores such as WalMart in the United States is becoming more accessible. WalMart has begun to install state-of-the art point of sale devices in their stores to protect the privacy and security of shoppers with visual impairments. They explain that the[12] new devices have tactile keys arranged like a standard telephone keypad and will allow shoppers who have difficulty reading information on a touchscreen to privately and independently enter their PIN and other confidential information.

But the holiday season will also be accessible throughout the world with talking catalogues, accessible accounting and cheque writing programmes for the blind and visually impaired, talking barcode readers, as well as talking mobile phones and PDAs.[13]

One of the ways to keep up with innovations for the blind and visually impaired is through the use of websites such as VisionConnection from Lighthouse International in the United States. VisionConnection allows for customisation of the screen with the ability to change the font size as well as enhance the contrast.

Additional vision rehabilitation services may be indicated when the vision is severely compromised. As mentioned mobility may be indicated when the visual field is reduced, especially when it is less that 6 to 8 degrees in diameter. Cane travel is generally taught by individuals who have lost their vision later in life from conditions such as macular degeneration. It is generally the most frequent recommendation by vision rehabilitation organisations in the United States. Individuals with congenital and early childhood loss however, may be taught the use of guidedogs as well. There is a significant dichotomy in the preferred method of travel among the different vision rehabilitation organisations in the US.

One of the newer methods of travel is by use of the GPS systems such as Trekker. They have adapted the system for people who are blind or visually impaired and allow them access to talking menus, talking maps and GPS information. There are other features enabling the user to determine his or her position, including the street address and the surrounding intersections.

There are traditional as well as hi-tech strategies that will significantly improve the quality of life, regardless of the extent of vision loss. And accessing those strategies is easy for everyone through websites such as http://www.VisionConnection.org/[14]

Access to low vision care, as well as access to reimbursement for low vision devices varies tremendously around the world. The Medicare programme in the United States, for example, does not cover the cost of a low vision evaluation or low vision devices. Governments as well as non-governmental organisations have to begin recognising the low vision health crisis throughout the world as well as include the visually impaired in health care programmes. We have the solutions for improving the quality of life in visually impaired people of all ages. We must now look for the collective strategy as well as funding to increasing access and availability, regardless of level of vision impairment, as well as socio-economic status.

References

1. Friedman TL. *The World is Flat.* A Brief History of the Twenty-first Century Farrar, Straus, and Giroux, NY, 2005.
2. http://www.worldsightday.ca/facts.htm
3. Visual impairment is vision loss involving the loss of an area of visual function (e.g. Visual acuity, visual field, contrast sensitivity, color vision)
4. The definition of low vision used by the WHO: Low vision is visual acuity less than 6/18 (20/60) and equal to or better than 3/60 (in the better eye with best correction).
5. Blindness refers to a total loss or no usable vision.
6. http://www.worldsightday.ca/facts.htm
7. Ferris Fl3rd, Kassoff A, Bresnick GH, Bailey I. *New visual acuity charts for clinical research.* Am J Ophthalmol 1982;94:91-96.
8. Foundation Fighting Blindness; http://www.blindness.org/
9. Resource Guide for Individuals with Visual Difficulties and Impairments;http: //www.microsoft.com/enable/guides/vision.aspx
10. VisionConnection http://www.visionconnection.org/Content/Technology/News/AnotherBankIntegratesTalkingATMsIntoIts Services.htm
11. VisionConnection; http://www.visionconnection.org/Content/Technology/News/EuropesFirstTalkingCashpoint.htm
12. VisionConnection; http://www.visionconnection.org/Content/Technology/News/WalMartMakesShoppingMoreAccessible.htm
13. VisionConnection; http://www.visionconnection.org/Content/Technology/News/WebSymposiumtoFocusonAccessibleGiftsfortheHolidays.htm
14. http://www.visionconnection.org/VisionConnection/default.htm

DNA Sequencing and PCR Methods

In the past three decades there have been several key innovations, namely the development of novel techniques for DNA sequencing in the 1970s and the development of the polymerase chain reaction (PCR) in the 1980s that have made a significant difference in the field of molecular genetics. The principles and methods of these two techniques are briefly described below.

PCR Principles and Method

A major breakthrough in molecular biology was the invention of the polymerase chain reaction (PCR) in 1985 by Kary Mullis[1] who received a Nobel Prize for his discovery. This technique involves the rapid amplification of a specific fragment of DNA so that numerous copies can be made. This is essential in order to have enough starting DNA template to complete further experiments such as sequencing.

The process is completed in three main steps which are shown in Figure 1. The first is denaturation, where the reaction is heated to 95°C so that the double-stranded DNA molecules separate into single-strands and all enzymatic reactions are stopped. The second stage is annealing, where the temperature is lowered to allow the primers to bind to the complementary sequence on the DNA template. Primers are a short strand of DNA, generally between 15-20 nucleotides in length, that are synthesised based on the sequence flanking the genomic region of interest. Within the reaction there are primers constantly attaching and breaking away from the template DNA. When the primers bind to the exact complementary piece of sequence, these bonds are more stable allowing the DNA polymerase to attach and begin extension of the PCR product which is the third and final stage. In the extension stage, the temperature is increased to 72°C as this is the ideal working temperature for the DNA polymerase to synthesise the new strand by incorporating deoxynucleotide triphosphates (dNTPs) to the 3′ end of the primer. The addition of the dNTPs is based on the sequence of the template DNA to which the primer is bound. Once the DNA polymerase begins to extend the copied DNA strand, the ionic bonds become stronger than those which pull them apart, therefore allowing the template DNA to be copied as the primer does not break away. Those primers that do not have a perfect match to the template DNA become free again due to the higher extension temperature. Extension of these products therefore does not occur, limiting the amplification of non-specific products. The PCR cycle of denaturation/annealing/extension is repeated 30-40 times in order to increase the amount of DNA copies. As both strands of the DNA are copied, the DNA copy number increases exponentially.

Sequencing Principles and Method

The aim of DNA sequencing is to determine the order of the four nucleotides (adenine, guanine, cytosine and thymine – A, G, C and T) that make up the genetic code in a DNA sample. While there are several methods for sequencing DNA, the most popular and commonly used DNA sequencing method today is based on the method developed by Frederick Sanger in 1977,[2] who was also awarded a Nobel Prize for his discovery. This method involves direct sequencing of the DNA which replaced the laborious task of having to determine the DNA sequence from the protein sequence.

The dideoxy sequencing method is accomplished by utilising fluorescently labelled dideoxynucleotides (ddNTP - ddATP, ddCTP, ddGTP and ddTTP) which are added to the reaction in addition to the dNTPs. The dideoxynucleotide differs from a deoxynucleotide in that it has a hydrogen atom attached to the 3' carbon atom rather than an – OH group as shown in Figure 2. Therefore once a ddNTP is incorporated into the newly synthesised DNA strand, the strand can no longer be elongated due to the absence of the 3'–OH group. This leads to termination of the reaction, thus this technique is also known as the chain termination method.

The initial stage of sequencing (like that of PCR) is denaturation to produce single-stranded DNA. The reaction is then cooled to allow the sequencing primer to anneal to the template and then extension of the product by the DNA polymerase. In dideoxy sequencing, DNA extension will occur as normal until the DNA polymerase randomly incorporates a fluorescently labelled ddNTP. For this reason, an excess amount of the four dNTPs and limiting amounts of the four ddNTPs are added to the sequencing reaction. This allows a whole succession of strands to be created prior to the chain being terminated by the ddNTP. As millions of copies of DNA are being generated and the incorporation of the ddNTP is random, at the completion of the reaction there will be millions of different sized strands.

The sequence of the samples can then be ascertained by

Dr Maria Ban is a Post-Doctoral Research Associate in the Department of Clinical Neurosciences, Cambridge University. Her research interest is in identifying the genetic factors involved in susceptibility to multiple sclerosis.

Correspondence to:
Dr Maria Ban,
Neurology unit - Department of Clinical Neurosciences,
Cambridge University,
Box 165,
Addenbrooke's Hospital,
Hills Road,
Cambridge, UK, CB2 2QQ.
Email: mb531@medschl.cam.ac.uk

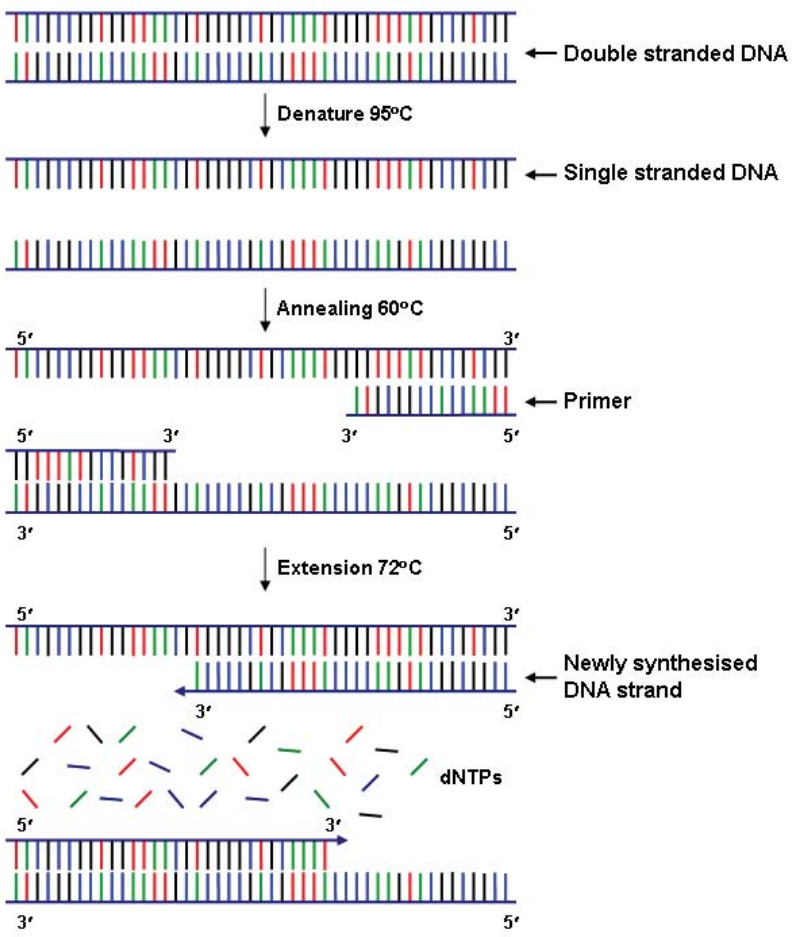


Figure 1: The diagram shows the three stages involved in PCR. Each blue line represents a strand of DNA with the four nucleotides indicated by different colours (T-red, A-green, C-blue, G-black). The first stage in PCR is denaturation where the high temperature leads to single stranded DNA. This leaves the strands exposed so that the primer can bind to the complementary region of the template DNA strand. The temperature is lowered in the annealing stage to allow the primers to bind to the template DNA. The primer is then extended in the third and final stage through the addition of dNTPs to the 3' end of the primer by a DNA polymerase, leading to a new copy of the DNA strand.

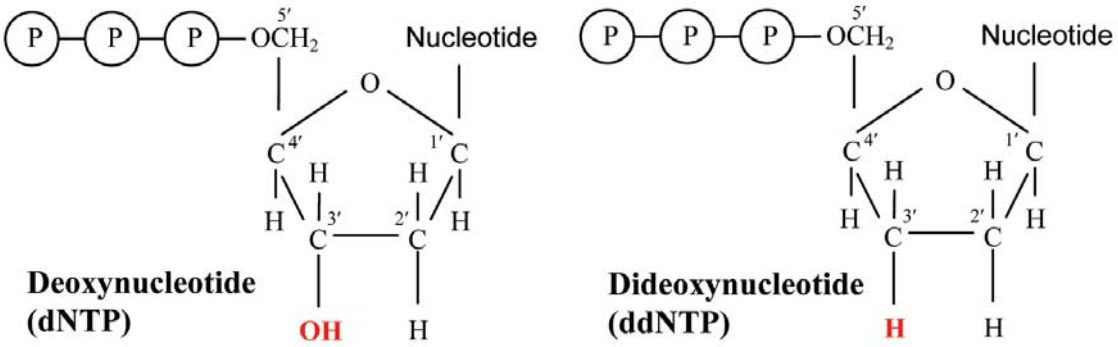


Figure 2: The formula for a deoxynucleotide triphosphate (dNTP) is shown on the left. On the right is the formula for a dideoxynucleotide (ddNTP), which unlike the dNTP has a hydrogen atom at the 3′ carbon. Consequently once a ddNTP is added to the DNA strand, the extension of the strand is terminated as another nucleotide cannot be added due to the absence of the –OH group at the 3' carbon.

separating out the DNA fragments by size (with each fragment being one base pair longer than the previous) and establishing the last ddNTP that was incorporated into the strand. The original method used by Sanger involved the use of radioactively labelled DNA primers and a separate sequencing reaction was performed for each of the four nucleotides. Once completed, the reactions were run in four separate lanes (one for each nucleotide reaction) on a polyacrylamide gel to determine the sequence. With technological improvements and the ability to multiplex four nucleotides into the one reaction (as each nucleotide has a different fluorescent label), the detection and reading of a sequence is now completed by an automatic capillary array DNA sequencer. Each sample is loaded into a capillary through which the fragments are separated out according to their size. A laser is used to detect the fluorescence specific for each nucleotide as the DNA migrates to the bottom of the capillary. Sequencing software is then applied to analyse the output from the DNA sequencer and provide a chromatogram of the DNA sequence, the end product (Figure 3).

Conclusion

While the discovery of novel DNA sequencing methods has been invaluable, the invention of PCR has facilitated its use by enabling the rapid amplification of DNA which has had a far reaching impact across many fields. The many uses of PCR range from the increased sensitivity and specificity it provides in diagnostic testing in the medical field to amplifying DNA found in fossils for evolutionary biology studies. Finally, the development of these sequencing techniques has led to the complete sequencing of the entire human genome, with the first draft version published in 2001.[3,4] The substantial knowledge gained and the rapid advancement in our understanding of the nature and complexity of the human genome and its application to human health would have been inconceivable at present without the development of these sequencing and PCR methods.

References

1 Mullis K, Faloona F, Scharf S, Saiki R, Horn G, Erlich H. *Specific enzymatic amplification of DNA in vitro: the polymerase chain reaction.* Cold Spring Harb Symp Quant Biol 1986;51Pt1:263-73.

2 Sanger F, Nicklen S, Coulson AR. *DNA sequencing with chain-terminating inhibitors.* Proc Natl Acad Sci USA 1977;74:5463-7.

3 Lander ES, Linton LM, Birren B et al. *Initial sequencing and analysis of the human genome.* Nature 2001;409:860-921.

4 Venter JC, Adams MD, Myers EW et al. *The sequence of the human genome.* Science 2001;291:1304-51.

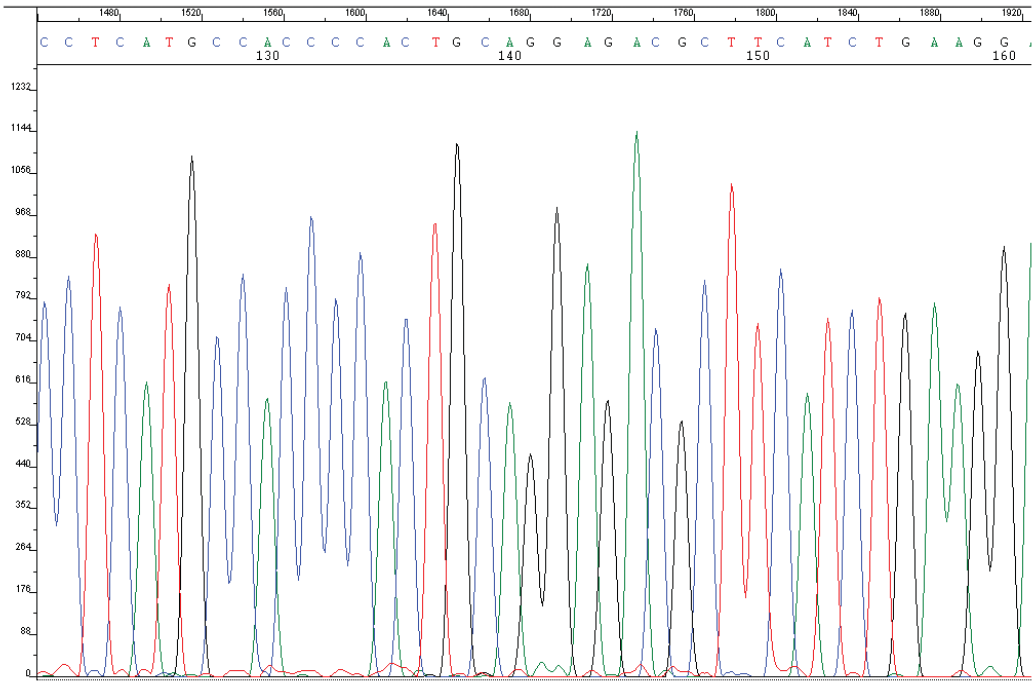


Figure 3: The chromatogram shows an example of a DNA sequence obtained from an automatic DNA sequencer. Each nucleotide is represented by a different colour (T-red, A-green, C-blue and G-black) and is shown in the order in which they were detected, from the smallest to the largest fragment along the x-axis. The y-axis indicates the fluorescence intensity.

Clinical and Neuropathological Investigations in Creutzfeldt-Jakob Disease

Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, are a group of rare and invariably fatal degenerative diseases of the central nervous system affecting humans as well as a number of animal species.[1] Enormous public and scientific attention has focused on prion diseases, not only because of their unique biological properties, but also because of their impact on animal and public health, particularly with the emergence of bovine spongiform encephalopathy (BSE)[2] and variant Creutzfeldt-Jakob disease (variant CJD) in the United Kingdom.[3] Unlike other forms of CJD, infectivity is readily detectable within lymphoid tissues in variant CJD,[4] raising concerns over the potential spread of variant CJD by iatrogenic means, particularly through surgical procedures and surgical instruments, as the infectious agent shows an alarming resistance to conventional decontamination methods. More recently it has been shown that variant CJD also appears to be transmissible by blood transfusion, heightening concerns over secondary human-to-human spread of the disease via contaminated blood products.[5,6]

In humans, prion diseases occur in three main groups; they may occur sporadically, by autosomal dominant inheritance through mutations or insertions in the prion protein gene (PRNP), or by secondary transmission through either dietary or medical exposure to the infectious agent.[7] Traditionally, human prion diseases are classified according to their major clinical features into Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), fatal familial insomnia (FFI) and kuru (Table 1). All forms of prion disease share four neuropathological features (spongiform vacuolation, neuronal loss, astrocytic and microglial proliferation and in certain cases the presence of amyloid plaques), which although characteristic of these disorders are not entirely specific.[8]

All prion diseases are associated with the conversion of the normal cellular host encoded prion protein, PrP^{C}, to an abnormal disease-associated isoform, PrP^{SC}. PrP^{SC} is not only a diagnostic marker of disease, but has been proposed as the sole or principal component of the transmissible agent in prion disease. According to the 'prion hypothesis', PrP^{SC} is derived from the normal cellular protein (PrP^{C}) by a post-translational mechanism, which appears to involve a conformational change.[9] This involves refolding of the protein to a structure containing a high beta sheet content, which readily forms aggregates and is more resistant to denaturation by proteases than PrP^{C}.

Genetic and molecular aspects of sporadic CJD

The most common form of human prion disease is sporadic CJD, which accounts for around 85% of all human prion diseases, with a world wide incidence of around 1-1.5 cases per million of the population per annum. Like all human prion diseases, much phenotypic heterogeneity exists within sporadic CJD in terms of clinical and pathological features.[10] This heterogeneity has been linked with the polymorphism found at codon 129 on PRNP which encodes either methionine (M) or valine (V).[11] This polymorphism has also been identified as an important risk factor in sporadic CJD; most cases occur in individuals who are homozygous for methionine at codon 129, who present with the most 'typical' clinical and pathological features. Cases of sporadic CJD in heterozygotes and valine homozygotes are rarer and display more 'atypical' phenotypes (Table 2).[12]

The physicochemical properties of PrP^{SC} also play an important role in influencing the disease phenotype in sporadic CJD. Western blot analysis of the protease resistant core of PrP^{SC}, referred to as PrPres, has identified two kinds of heterogeneity within the brains of patients with CJD. Firstly, differences occur in the mobility of the protease resistant core, presumably relating to different PrPres fragment sizes after proteinase K-mediated N-terminal truncation, and secondly, variation occurs in the relative abundance of the three PrP glycoforms (diglycosylated, monoglycosylated and nonglycosylated). Following the classification of Parchi et al.[13] two distinct PrP^{SC} types or PrPres isotypes, have been identified after proteinase K digestion: one with a mobility on western blot of around 21kDa named PrPres type 1, and the second, which is slightly smaller with a molecular weight of around 19kDa named PrPres type 2 (Figure 1).[13] This classification system has been further subdivided to incorporate PrPres isotype combined with codon 129 PRNP genotype (MM, MV, VV) resulting in six different sporadic CJD subtypes.[14] Examination of the clinical and pathological data from each of these subtypes shows that although not all have a distinct phenotype, there does appear to be a good correlation between clinical and neuropathological features and disease subtype (Table 2). More recently, the observation of CJD patients with more than one PrPres isotype within the brain has combined to increase the heterogeneity and complexity observed in sporadic CJD.

The presence of distinct strains of the infectious agent in prion diseases has been established for some time, particularly in relation to scrapie in sheep. However, the presence of individual strains remains difficult to explain within the bounds of the prion hypothesis, which proposes that all the information required for individual strain phenotypes is contained within the prion protein itself.[9] In sporadic CJD, the different conformations of PrPres as determined by western blot analysis have been proposed to represent different biological profiles of the transmissible agent, which may in turn relate to different biological strains. Confirmation that these different molecular conformations or isoforms of the prion protein do indeed correspond to distinct strains will require analysis of the biological properties (such as incubation period and pat-

Table 1: Classification of human prion diseases

Aetiology	*Disease*
Sporadic	*Sporadic Creutzfeldt-Jakob Disease* *Sporadic Fatal Insomnia*
Familial	*Familial CJD* *Gerstmann-Sträussler-Scheinker* *Fatal Familial Insomnia*
Acquired	*Kuru (human source)* *Iatrogenic CJD (human source)* *Variant CJD (bovine source)*

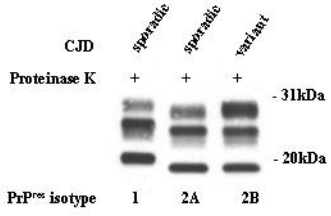


Figure 1: Western blot analysis of PrPres from the frontal cortex of two different sporadic CJD (s) patients, showing the type 1 and type 2 mobility variants. The distinctive type 2B pattern found in variant CJD (v) patients, with a predominance in the diglycosylated PrPres is also shown.

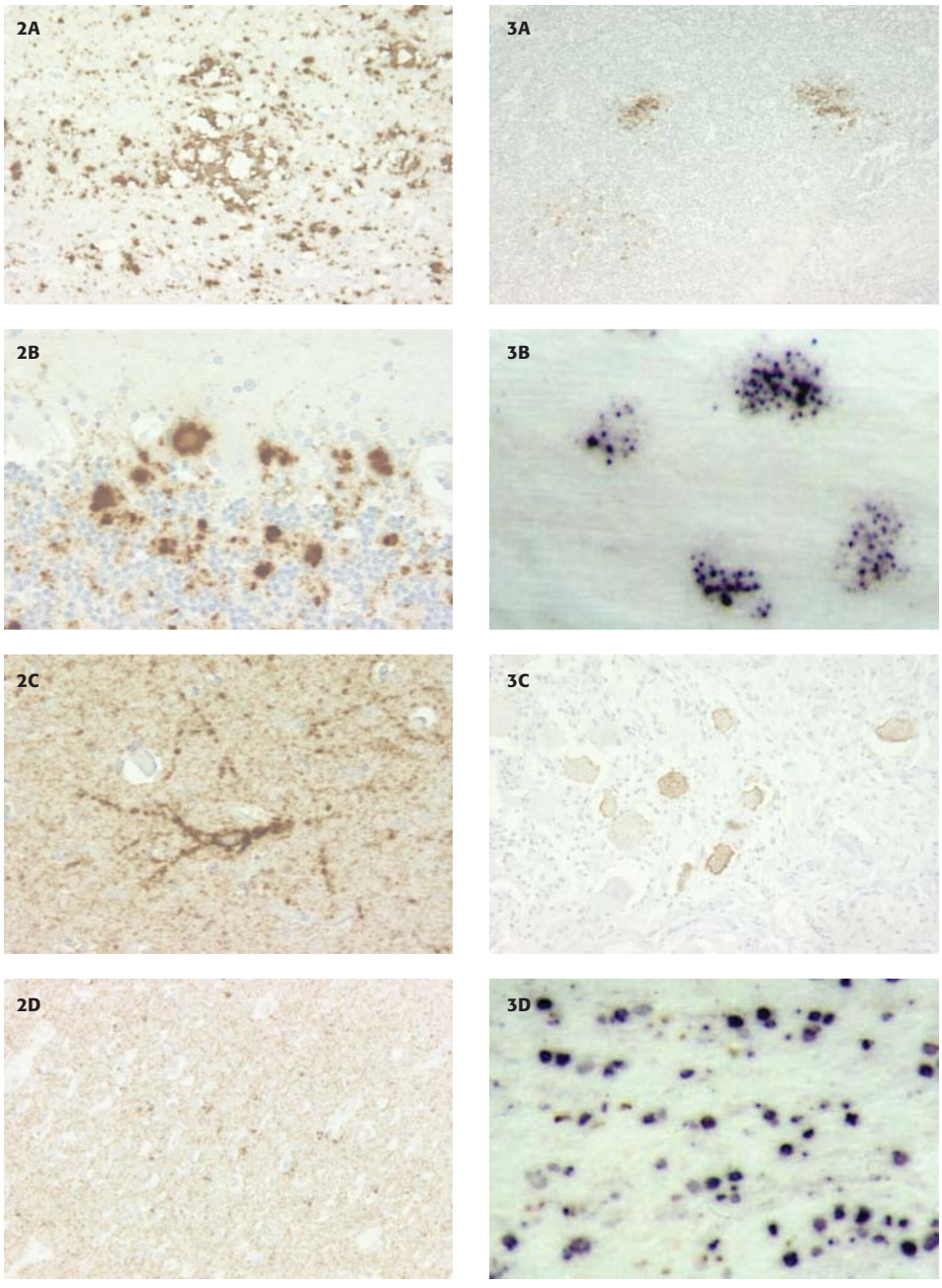
Professor James Ironside is a Neuropathologist in Edinburgh who has been involved in the National CJD Surveillance Unit since 1990. In 1996, he and his colleagues identified variant CJD, the new human prion disease which is linked to BSE. His current research interests include the tissue distribution of infectivity in all forms of CJD, and the neuropathology of paediatric gliomas.

Diane Ritchie started her career in prion diseases at the Institute for Animal Health, Neuropathogenesis Unit, under the guidance of Professor Moira Bruce looking at experimental models of scrapie. Currently she is studying at the National CJD Surveillance Unit looking at human prion diseases with Professor James Ironside, where she has refined the PET blot technique for use on human tissue.

Correspondence to:
Ms Diane L Ritchie,
National CJD Surveillance Unit,
Western General Hospital,
Edinburgh EH4 2XU, UK.
Tel: 0131 537 1980
Fax: 0131 537 3056
Email: diane.ritchie@ed.ac.uk

Table 2: Clinical and pathological features of sporadic CJD subtypes (adapted from Parchi et al, Ann Neurol 1999)[14]

Sporadic CJD Subtype	Mean disease duration (months)	Clinical symptoms	Patterns of PrP deposition
MM1/MV1	*3.9*	*Cortical visual impairment (41% of cases), rapidly progressive dementia, involvement of the pyramidal and extrapyramidal systems, Myoclonus.*	*Widespread and intense perivacuolar deposits around areas of confluent spongiform change with synaptic labelling throughout the cerebral cortical layers.*
MM2 (cortical variant)	*15.7*	*Progressive dementia.*	*Intense perivacuolar labelling around areas of confluent spongiform change.*
MM2 (thalamic variant)	*15.6*	*Ataxia and cognitive impairment with the addition of insomnia.*	*PrP depositions less intense in this subtype; widespread synaptic positivity particularly targeting the occipital cortex; cerebellum relatively spared.*
MV2	*17.1*	*Dementia at clinical onset (50% of cases) often with ataxia or extrapyramidal signs.*	*Intense labelling of kuru plaques, most obvious in the cerebellum. Synaptic positivity present in the granular layer of the cerebellum.*
VV1	*15.3*	*Progressive dementia.*	*Weak and widespread synaptic labelling; cerebellum is relatively spared.*
VV2	*6.5*	*Progressive ataxia with dementia developing during later stages.*	*Perineuronal positivity within the cerebral cortex and intense plaque like deposits in the basal ganglia.*



terns of neuropathology) after transmission to laboratory mice. In variant CJD, which is recognised as a distinct human prion strain closely related to the BSE strain in cattle,[15] the biological profile on western blot analysis is also distinct from other human prion diseases, with a mobility much like that found in type 2 sporadic CJD cases, but with a unique glycoform ratio in which there is a predominance of the di-glycosylated band.[16] The PrPres isotype of variant CJD patients is referred to as type 2B to distinguish it from the type 2 found in sporadic CJD (Figure 1). The PrPres isotype of variant CJD cases resembles that of BSE in cattle and in a range of other species, which has helped confirm that BSE was undoubtedly the source of variant CJD.[16]

Diagnosing human prion disease

Although clinical criteria for the diagnosis of human prion disease with a high degree of certainty have been agreed,[17] a definitive diagnosis requires the examination of biopsy or post-mortem brain material for the presence of PrP^{SC}. Immunohistochemical detection using antibodies raised against the prion protein is invaluable in the pathological diagnosis of

Figure 2: Immunohistochemistry for the prion protein (PrP) in sporadic CJD subtypes. All sections are immunolabelled with the KG9 anti-PrP antibody and counterstained with Haematoxylin. (A) Frontal cortex in the sporadic CJD MM1 subtype showing intense perivacuolar positivity around areas of confluent spongiform change. Original magnification x200. (B) Cerebellum in the sporadic CJD MV2 subtype showing intense positivity of kuru plaques in the granular layer. Original magnification x400. (C) Perineuronal labelling in the occipital cortex in the sporadic CJD VV2 subtype. Also shown is the widespread deposition of synaptic positivity. Original magnification x400. (D) Faint synaptic labelling within the cerebral cortex in the sporadic CJD VV1. Original magnification x200.

Figure 3: Detection of the prion protein (PrP) in peripheral organs in variant CJD comparing the PET blot analysis (3F4 anti-PrP antibody) and immunohistochemistry (KG9 anti-PrP antibody). (A) Immunohistochemistry and (B) PET blot analysis in the tonsil in variant CJD. (C) Immunohistochemistry and (D) PET blot analysis in a dorsal root ganglion in variant CJD.

prion diseases, but since all readily available anti-PrP antibodies recognise both PrP^{C} and PrP^{SC}, a number of pre-treatments (autoclaving, formic acid treatment, and partial digestion with proteinase K) are required to denature any PrP^{C}, leaving PrP^{SC} for diagnosis. Immunohistochemistry has demonstrated the numerous patterns of PrP^{SC} accumulation within sporadic CJD ranging from the light synaptic depositions to the more intense and distinctive kuru plaques (Figure 2). These different patterns of PrP deposition have been studied extensively and attempts have been made to correlate these with the individual disease subtypes (Table 2).[14] The advent of immunohistochemistry has witnessed an ever-increasing number of anti-PrP antibodies targeting different epitopes on the prion protein; these combined with the increasing number of improved immunodetection kits available has improved the sensitivity of immunohistochemistry. In certain cases, the detection of PrP^{C} in immunohistochemistry can prove problematic in the interpretation of staining results. Since only limited proteinase K digestion can be performed on tissue sections for histology, PrP^{C} is not always completely degraded, particularly in brain biopsy material. This problem is not encountered with western blot analysis of frozen tissue, where a more rigorous digestion with proteinase K results in the complete digestion of PrP^{C} leaving only the protease resistant core of PrP^{SC}. A combination of technical aspects from immunohistochemistry and western blot techniques has lead to the development of the paraffin embedded tissue blot technique (PET blot).[18,19] This method uses fixed paraffin tissue sections blotted on to nitrocellulose membrane to investigate the presence of PrP^{SC}. As in western blot methods for PrP^{SC}, the PET blot has an extensive pre-treatment step with proteinase K ensuring the complete digestion of PrP^{C}, but has the advantage of retaining some of the tissue architecture and some of the cellular detail of immunohistochemistry. The PET blot method has been utilised in a number of studies and has demonstrated increased sensitivity and specificity in the detection of PrP^{SC}, for example in peripheral organs in variant CJD (Figure 3).[19-21]

Future developments

The recent detection of PrP^{SC} in tissues such as muscle in sporadic CJD[22] has reinforced the need for more sensitive and specific detection techniques for PrP^{SC}. Many exciting developments have been made using experimental models of prion disease in the development of diagnostic screening tests and screening assays for PrP^{SC}, which may also prove applicable in human prion diseases. The recent detection of low levels of PrP^{SC} within blood samples of scrapie-infected hamsters has been described using protein misfolding cyclic amplification (PMCA) technology.[23,24] This in vitro method has the ability of converting undetectable levels of PrP^{SC} into larger PrP^{SC} aggregates, by incubating with an excess of PrP^{C}. Repeated stepwise sonication of the newly formed PrP^{SC} aggregates allows the conversion of further PrP^{C} molecules, resulting in larger PrP^{SC} aggregates at levels which are easily detected by western blotting. This work is continuing by looking at the detection of PrP^{SC} in blood from infected animals during the presymptomatic incubation period as well as investigating the detection of PrP^{SC} in plasma and blood products. Whilst a diagnostic blood test for CJD may not be imminent, the potential for a blood-detection method is of prime concern in prion research and could potentially offer a valuable minimally invasive pre-clinical test for variant CJD, which may also have important implications in verifying the safety of donated blood and blood products, and in estimating the number of individuals in the UK who are infected with BSE.

Enormous public and scientific attention has focused on prion diseases, not only because of their unique biological properties, but also because of their impact on animal and public health

References

1. Prusiner SB. *The prion diseases.* Brain Pathol 1998;8:499-513.
2. Wells GA, Scott AC, Johnson CT, Gunning RF, Hancock RD, Jeffrey M, Dawson M, Bradley R. *A novel progressive spongiform encephalopathy in cattle.* Vet Rec 1987;121:419-20.
3. Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG. *A new variant of Creutzfeldt-Jakob disease in the UK.* Lancet 1996;347:921-5.
4. Bruce ME, McConnell I, Will RG, Ironside JW. *Detection of variant Creutzfeldt-Jakob disease infectivity in extraneural tissues.* Lancet 2001;358:208-9.
5. Llewelyn CA, Hewitt PE, Knight RS, Amar K, Cousens S, Mackenzie J, Will RG. *Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion.* Lancet 2004;363:417-21.
6. Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. *Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient.* Lancet 2004;364:527-9.
7. Ironside JW. *Prion disease in man.* Pathol 1998;186:227-34.
8. Budka H. *Histopathology and immunohistochemistry of human transmissible spongiform encephalopathies (TSEs).* Arch Virol Suppl 2000;16:135-42.
9. Prusiner SB. *Novel proteinaceous infectious particles cause scrapie.* Science 1982;216:136-44.
10. Gambetti P, Kong Q, Zou W, Parchi P, Chen SG. *Sporadic and familial CJD: classification and characterisation.* Br Med Bull 2003;66:213-39.
11. Alperovitch A, Zerr I, Pocchiari M, Mitrova E, de Pedro CJ, Hegyi I, Collins S, Kretzschmar H, van Duijn C, Will RG. *Codon 129 prion protein genotype and sporadic Creutzfeldt-Jakob disease.* Lancet 1999;353:1673-4.
12. Ironside JW, Ritchie DL, Head MW. *Phenotypic variability in human prion diseases.* Neuropathol Appl Neurobiol 2005;31:565-79.
13. Parchi P, Castellani R, Capellari S, Ghetti B, Young K, Chen SG, Farlow M, Dickson DW, Sima AA, Trojanowski JQ, Petersen RB, Gambetti P. *Molecular basis of phenotypic variability in sporadic Creutzfeldt-Jakob disease.* Ann Neurol 1996;39:767-78.
14. Parchi P, Giese A, Capellari S, Brown P, Schulz-Schaeffer W, Windl O, Zerr I, Budka H, Kopp N, Piccardo P, Poser S, Rojiani A, Streichemberger N, Julien J, Vital C, Ghetti B, Gambetti P, Kretzschmar H. *Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects.* Ann Neurol 1999;46:224-33.
15. Bruce ME, Will RG, Ironside JW, McConnell I, Drummond D, Suttie A, McCardle L, Chree A, Hope J, Birkett C, Cousens S, Fraser H, Bostock CJ. *Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent.* Nature 1997;389:498-501.
16. Collinge J, Sidle KC, Meads J, Ironside J, Hill AF. *Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD.* Nature 1996;383:685-90.
17. UK National Creutzfeldt-Jakob Disease Surveillance Unit. http://www.cjd.ac.uk 2005.
18. Schulz-Schaeffer WJ, Tschoke S, Kranefuss N, Drose W, Hause-Reitner D, Giese A, Groschup MH, Kretzschmar HA. *The paraffin-embedded tissue blot detects PrP(Sc) early in the incubation time in prion diseases.* Am J Pathol 2000;156:51-6.
19. Ritchie DL, Head MW, Ironside JW. *Advances in the detection of prion protein in peripheral tissues of variant Creutzfeldt-Jakob disease patients using paraffin-embedded tissue blotting.* Neuropathol Appl Neurobiol 2004;30:360-8.
20. Koperek O, Kovacs GG, Ritchie D, Ironside JW, Budka H, Wick G. *Disease-associated prion protein in vessel walls.* Am J Pathol 2002;161:1979-84.
21. Head MW, Peden AH, Yull HM, Ritchie DL, Bonshek RE, Tullo AB, Ironside JW. *Abnormal prion protein in the retina of the most commonly occurring subtype of sporadic Creutzfeldt-Jakob disease.* Br J Ophthalmol 2005;89:1131-3.
22. Glatzel M, Abela E, Maissen M, Aguzzi A. *Extraneural pathologic prion protein in sporadic Creutzfeldt-Jakob disease.* N Engl J Med 2003;349:1812-20.
23. Castilla J, Saa P, Soto C. *Detection of prions in blood.* Nat.Med 2005;11:982-5.
24. Saborio GP, Permanne B, Soto C. *Sensitive detection of pathological prion protein by cyclic amplification of protein misfolding.* Nature 2001;411:810-3.

Headache

A number of physicians and physiologists have given accounts of their migraine over the past 200 years, most particularly the aura, with or without headache: examples include Caleb Hillier Parry,[1] Emil Du Bois-Reymond,[2] Sigmund Freud,[3] Karl Lashley,[4] and, in our own time, Miller Fisher[5] and Graeme Hankey.[6] Another notable migraineur was the philosopher Immanuel Kant.[7]

Such is the prevalence of headache in general and migraine in particular that it might be anticipated that such phenomena might also stimulate accounts from non-medical authors, possibly influencing or occurring in their imaginative works, whether or not they themselves were sufferers. For example, it has been suggested that Charles Lutwidge Dodgson's experience of migraine may (or may not) have contributed to Lewis Carroll's depiction of Alice's strange experiences of expanding and contracting in size (macro- and microsomatognosia) in *Alice's Adventures in Wonderland* (1865), hence the 'Alice in Wonderland syndrome'.[8] The only direct reference to headache in Carroll's Alice books of which I am aware is in chapter 4 of *Through the looking-glass and what Alice found there* (1872), wherein Tweedledum excuses his lack of bravery, and hence unwillingness to fight Tweedledee, by saying that he has a headache, and Alice agrees that he may look a little pale.

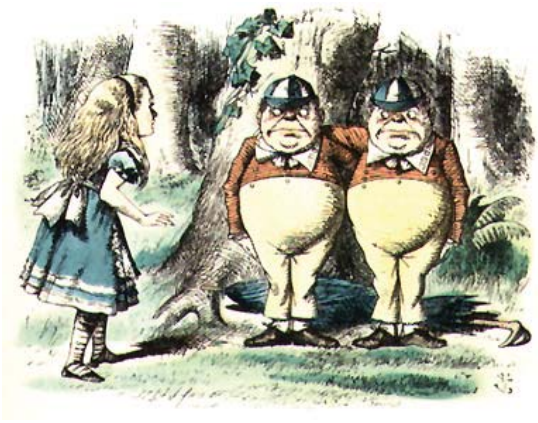
However, just as there is a paucity of neurologists willing to declare a special interest in headache, despite it being the most prevalent of 'neurological" conditions, so literary accounts of headache seem to me to be few compared, say, to illnesses with more dramatic potential, such as the inability to walk (paraplegia?) which miraculously improves: think of Mrs Clennam in Charles Dickens's *Little Dorrit* (1857); Clara Sessman in Johanna Spyri's *Heidi* (1880); Colin in *The Secret Garden* by Frances Hodgson Burnett (1911); and *Pollyanna* (1913) by Eleanor H Porter. Nonetheless, some literary accounts of headache have come to my attention, and readers may be aware of others.

Arthur Ransome, famed for the *Swallows and Amazons* series of books, gives an account in *We didn't mean to go to sea* (1937) of what sounds (to this neurologist) like childhood migraine, apparently induced by seasickness or at least by the motion of the sea:

> …Titty suddenly clutched the coaming of the cockpit and leant over it.
>
> "She's being sick," said Roger …
>
> "Leave me alone," said Titty, "… It's only one of my heads. I'll be all right if I lie down for a bit."
>
> … Down in the fore-cabin Titty scrambled into her bunk. Something was hammering in her head as if to burst it.[9]

In *Northern Lights* (1995), the first book in Philip Pullman's trilogy *His Dark Materials*, the young heroine, Lyra Belacqua, wakes with a "sick headache", ascribed to her proximity to the gas fumes of a boat engine near which she is in hiding.[10]

In L.M. Montgomery's *Anne of Green Gables* (1908), "warnings of a sick headache", presumably migraine, prevent Marilla Cuthbert from escorting Anne Shirley to church shortly after the latter first arrives at Green Gables, with the result that the young orphan indulges her wish to adorn her hat with wayside flowers, much to the astonishment of the other parishioners. The episodic nature of Marilla's headaches later becomes evident, necessitating Anne to attend to the housework whilst Marilla rests. She



has to lie down, and their effect is to leave her weak, "tuckered out", and "somewhat sarcastic". She feels they are becoming worse and worse and that she must see a doctor about them. Her local attendant, Dr Spencer, insists she see a specialist, who turns out to be an oculist, whose recommendation is that Marilla should give up reading, sewing, and any kind of work that strains the eyes. If she is careful not to cry, and wears the glasses he gives her, he thinks her eyes may not get any worse and the headaches will be cured; if not, she will be stone blind in six months.[11] Even today, consulting an optician about headaches in the belief they originate from 'eye strain' is common, and sometimes even suggested by general practitioners,[12] even though refractive errors rarely a cause of headache.

The social consequences of headache are also noted by the creator of *Just William*, and arch social critic, Richmal Crompton:

> …Mrs Jones had a lively sense of her own importance… there was no doubt at all that people weren't making enough fuss of her, so she rose and said with an air of great dignity:
>
> "Mrs Hawkins, I am suffering from a headache. May I go into your drawing room and lie down?"
>
> She had often found that that focused the attention of everyone upon her. It did in this instance. They all leapt to their feet solicitously, fussed about her, escorted her to the drawing room, drew down the blinds and left her well pleased with the stir she had made.[13]

Another archetypal boy hero, Harry Potter, uses the pretext of headache to escape from Professor Trelawney's divination class at Hogwarts after seeing an apparition of his arch-enemy Voldemort.[14]

Social realism is also to be expected from Anton Chekhov (1860-1904). As a doctor, he was certainly familiar with headache in his clinical practice,[15] and a number of his characters profess, or are reported to be suffering from, headaches: Ivanov (in the play of the same name, 1887), Olga (in *Three Sisters*, 1901), and Shipoochin (specifically "a migraine"; *The Jubilee*). The character Lyebedev suggests that Ivanov's headache is because he thinks too much; Olga supposes that she gets a continual headache (tension-type?) "because I have to go to school every day and go on teaching right into the evening".[16]

Jane Austen, another keen social observer, reports in *Sense and Sensibility* (1811, chapter 16) that Marianne

Andrew 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.

Correspondence to:
AJ Larner,
Walton Centre for Neurology and Neurosurgery,
Lower Lane,
Fazakerley,
Liverpool,
L9 7LJ, UK.
Email: a.larner@thewaltoncentre.nhs.uk

Dashwood, following the departure of her beau, Mr Willoughby, is;

> … awake the whole night … She got up with an head-ache, was unable to talk, and unwilling to take any nourishment.

Are these simply the consequences of young and unrequited love, or does she have a migraine (perhaps triggered by young and unrequited love)? In *Pride and Prejudice* (1813, chapter 7), Jane Bennet develops "sore throat and head-ache" which worsens as her feverish symptoms increase, having ridden (at her mother's suggestion) to Netherfield in the rain to see Mr Bingley; her illness requires the attendance of her sister, Elizabeth Bennet, which brings her into the social orbit of Mr Darcy. Later (chapter 33), Elizabeth has a headache, and hence is unable to go to tea at Rosings, at which time Mr Darcy calls unexpectedly to make his first (unsuccessful) proposal of marriage: obviously Elizabeth's indisposition will not help his case. Jane Austen is also alert to the potential dangers of new (fashionable?) headache treatments, as evinced in her novel *Sanditon*, left unfinished at her death in 1817:

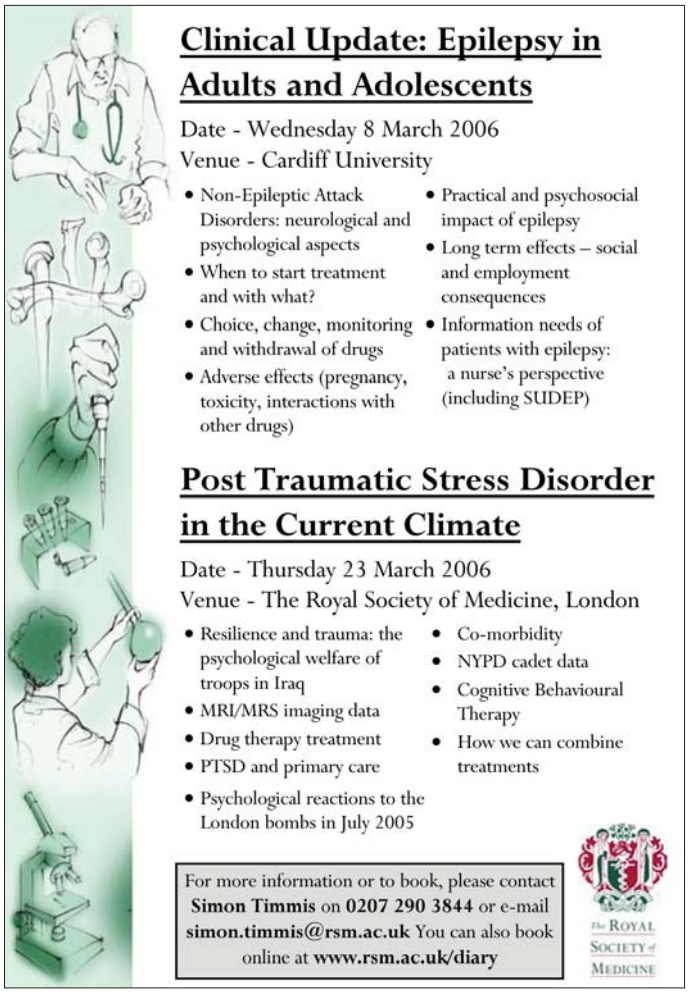
> "[Susan] has been suffering much from the headache and six leeches a day for ten days together relieved her so little that we thought it right to change our measures – and being convinced on examination that much of the evil lay in her gum, I persuaded her to attack the disorder there. She has accordingly had three teeth drawn, and is decidedly better, but her nerves are a good deal deranged. She can only speak in a whisper – and fainted away twice this morning …"[cited in 17]

Before we indulge in the condescension of posterity after reading this passage, it may be worth considering which current headache treatments might be held up to ridicule in a century or two (acupuncture? botulinum toxin injections?).

Perhaps it is purely a chance observation or selection bias, but readers may note that all the physicians and physiologists who wrote about their migraine and are referred to in this article were men,[1-6] which might be considered unusual since migraine is more prevalent in women, whereas all the literary accounts of migraine or presumed migraine, with the exception of Chekhov's Shipoochin,[16] relate to women.[9-11,13,17] Could it be that literary discourses may sometimes reflect the human condition more accurately than professional medical discourses?

References

1. Larner AJ. *Neurological contributions of Caleb Hillier Parry.* Advances in Clinical Neuroscience & Rehabilitation 2004;4(3):38-9.
2. Pearce JMS. *Historical aspects of migraine.* J Neurol Neurosurg Psychiatry 1986;49:1097-103.
3. Pearce JMS. *Freud's migraine, and contributions to neurology.* In: Fragments of neurological history. London: Imperial College Press, 2003:615-21.
4. Lashley KS. *Patterns of cerebral integration indicated by the scotomas of migraine.* Arch Neurol Psychiatry 1941;46:331-9.
5. Fisher CM. *Late-life (migrainous) scintillating zigzags without headache: one person's 27-year experience.* Headache 1999;39:391-7.
6. Hankey GJ. *Recurrent migraine aura triggered by coronary angiography.* Practical Neurology 2004;4:308-9.
7. Podoll K, Hoff P, Sass H. *The migraine of Immanuel Kant.* Fortschr Neurol Psychiatr 2000;68:332-7.
8. Larner AJ. *The neurology of "Alice".* Advances in Clinical Neuroscience & Rehabilitation 2005;4(6):35-6.
9. Ransome A. *We didn't mean to go to sea.* Harmondsworth: Puffin 1969 [1937], p 135.
10. Pullman P. *Northern lights.* London: Scholastic, 1995, p 150.
11. Montgomery LM. *Anne of Green Gables.* Godalming: Colour Library, 1994 [1908], p 125,256-7,345-6,469,473-4.
12. Larner AJ. *What role do optometrists currently play in the management of headache? A hospital-based perspective.* Optometry in Practice 2005;6:173-4.
13. Crompton R. *William – the good.* In: *The Just William Collection.* London: WH Smith, 1991, p 193-4.
14. Rowling JK. *Harry Potter and the goblet of fire.* London: Bloomsbury, 2000, p 501.
15. Coope J. *Doctor Chekhov: a study in literature and medicine.* Chale: Cross Publishing, 1997, p 109.
16. Fen E (transl). *Chekhov: Plays.* Harmondsworth: Penguin, 1959, p 86,250,449.
17. Larner AJ. *Acupuncture use for the treatment of headache prior to neurological referral.* J Headache Pain 2005;6:97-9.



Clinical Update: Epilepsy in Adults and Adolescents

Date - Wednesday 8 March 2006
Venue - Cardiff University

- Non-Epileptic Attack Disorders: neurological and psychological aspects
- When to start treatment and with what?
- Choice, change, monitoring and withdrawal of drugs
- Adverse effects (pregnancy, toxicity, interactions with other drugs)
- Practical and psychosocial impact of epilepsy
- Long term effects – social and employment consequences
- Information needs of patients with epilepsy: a nurse's perspective (including SUDEP)

Post Traumatic Stress Disorder in the Current Climate

Date - Thursday 23 March 2006
Venue - The Royal Society of Medicine, London

- Resilience and trauma: the psychological welfare of troops in Iraq
- MRI/MRS imaging data
- Drug therapy treatment
- PTSD and primary care
- Psychological reactions to the London bombs in July 2005
- Co-morbidity
- NYPD cadet data
- Cognitive Behavioural Therapy
- How we can combine treatments

For more information or to book, please contact **Simon Timmis** on **0207 290 3844** or e-mail **simon.timmis@rsm.ac.uk** You can also book online at **www.rsm.ac.uk/diary**

The Royal Society of Medicine

Neuro-ophthalmology clinical course

At the Institute of Neurosciences
Beaumont Hospital, Beaumont, Dublin 9

Monday 24th April - Friday 28th April 2006

This course covers clinical neuro-ophthalmology with emphasis on clinical demonstrations and teaching sessions. Relevant basic sciences will also be covered during the course

Course organiser:
Ms P Logan
Faculty:
Professor L Cassidy
Mr T Buchanan
Dr F Hamroush

Course Fee: €800 (euros)

Applications to:
Emma Flynn
The Eye Department
Beaumont Hospital, Beaumont
Dublin 9
Eire
Tel: +353 1 809 2609

To list your event in this diary, email brief details to Patricia McDonnell at events@acnr.co.uk by January 27th, 2006

2006

January

Regional Asian Stroke Conference
5-8 January, 2006; Chennai, India
W. www.stroke-india.org/main.asp

Attention and Executive Skills
12-13 January, 2006; Ely, UK
Alison Gamble
T. 01353 652165
E. alison.gamble@ozc.nhs.uk
W. www.ozc.nhs.uk

The Society for Research in Rehabilitation Winter Conference
17 January, 2006; Manchester, UK
T. 0161 295 7014
E. j.fletcher@salford.ac.uk
W. www.srr.org.uk

NEW
BISWG National Study Day – Brain Injury and the Family
20 January, 2006; Edinburgh, UK
Fen Parry – T. 0131 537 6853
E. fen.parry@edinburgh.gov.uk

NEW
Cognitive Rehabilitation Workshop following brain injury
20-21 January, 2006; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

NEW
BISWG South Wales and West Regional Meeting
25 January, 2006; Cardiff, UK
Kate Coles
T. 02920 224871
E. kate.coles@hughjames.com

Latsis Colloquium: Early Language Development and Disorders
26-28 January, 2006; Geneva, Switzerland
W. www.unige.ch/fapse/PSY/LATSIS/

February

International Neuropsychological Society (INS) 34th Annual Meeting
1-4 February, 2006; Boston, USA.
Info. International Neuropsychological Society T. + (614) 263-4200
F. + (614) 263-4366,
E. ins@osu.edu
W: www.the-ins.org/meetings

3rd International Meeting on Neuromuscular and Visual Disorders
1-5 February, 2006; Havana, Cuba
E. jgut@infomed.sld.cu or milalatin@aol.com

International Congress on Gait & Mental Function
3-5 February, 2006; Madrid, Spain
T. +972 3 9727555
E.gait@kenes.com

International Comprehensive Update on Diagnostics and Therapeutics in Epilepsy (CUTE)
4-5 February, 2006; New Delhi, India
W. www.iamst.com

3rd Mediterranean Congress of Neurology in conjuction with 7th Cairo International Neurology Conference
8-11 February, 2006; Sharm el Sheikh, Egypt
T. +357 25 720554,
E. congress@congresswise.com

British Neuropsychiatry Association Annual Meeting
9-10 February, 2006; London, UK
Info. Jackie Ashmenall
T/F. 020 8840 9266 E. admin@bnpa.org.uk or jashmenall@yahoo.com

4th World Congress of Neurorehabilitation
12-16 February, 2005; Hong Kong
F. +852 2547 9528, E. info@wcnr2006.com

International Stroke Conference 2006
16-18 February, 2006; Kissimmee, FL, USA
W. http://strokeconference.americanheart.org/portal/strokeconf

NEW
American Skull Base Society – 17th Annual Meeting
16-19 February, 2006; Phoenix, Arizona, USA
W. www.nasbs.org

7th International Conference on New Trends in Immunosupression and Immunotherapy
16-19 February, 2006; Berlin, Germany
W. www.kenes.com/immuno/prog.asp

NEW
AANS / CNS Cerebrovascular Section and American Society of Interventional & Therapeutic Neuroradiology 20th Annual Meeting
17-20 February, 2006; Orlando, Florida, USA
W. www.aans.org

Short Courses: Neurological Anatomy
20-22 February, 2006; London, UK
E. neurosurgery@rcseng.ac.uk
T. 020 7405 3474

World Parkinson Congress
22-26 February, 2006; Washington, USA
E. info@worldPDcongress.org
W. www.worldpdcongress.org

NANOS 2006 Meeting
25 February - 2 March, 2006; Tucson, AZ, USA
W. www.nanosweb.org/meetings/nanos2006/

March

The Social Brain II - See The Bigger Picture
March 2006; Glasgow, UK
T. +44 (0)141 331 0123
E. registration@mindroom.org

The Annual Global Conference on Neuroprotection and Neuroregeneration
1-3 March, 2006; Uppsala, Sweden
W. www.gcnpnr.org/2006/gcnn2006.html

NEW
The National Centre for Young People with Epilepsy (NCYPE) Open Day
2 March, 2006; Lingfield, Surrey, UK
Karen Styles
T. 01342 832 243
W. www.ncype.org.uk

Annual Meeting of the American Society of Neuroimaging
2-5 March, 2006; San Diego, CA, USA
W. www.asnweb.org/

International Symposium on Clinical Neurology and Neurophysiology
6-8 March, 2006; Tel Aviv, Israel
W. www.neurophysiology-symposium.com

RSM Clinical Update: Epilepsy in Adults and Adolescents
8 March, 2006; Cardiff, UK
Info. Simon Timmis
T. 0207 290 3844
E. simon.timmis@rsm.ac.uk

NEW
RCN 11th European Mental Health Nursing annual conference and exhibition The future of mental health is… working together
10–11 March, 2006; Belfast, UK
E. mentalhealth@rcn.org.uk

NEW
Commonwealth Nurses' Federation, 6th European Regional Conference Commonwealth nurses' advancing nursing care: collaboration in Europe
10–11 March, 2006; Warwickshire, UK
E. jane.edey@rcn.org.uk

NEW
BISWG West Midlands Regional Meeting
13 March, 2006; Stourbridge, UK
Lucy Devlin
T. 01384 244654
E. lucy.devlin@dgoh.nhs.uk

Birmingham Movement Disorders Course 2006
15-17 March, 2006; Birmingham, UK
E. c.e.clarke@bham.ac.uk
T. 0121 507 4073

NEW
Simposio Internacional de Dolencias Cerebro – Vasculares Sociedad de Neurocirurgia del Cono Sud
17-18 March, 2006; Porto Alegre, RS
E. marketing@maededeus.com.br

NEW
XVIII Symposium Neuroradiologicum
19-24 March, 2006; Adelaide, Australia
W. www.snr2006.sa.gov.au/

NEW
RCN International Nursing Research Conference
21–24 March 2006; York, UK
E. research@rcn.org.uk

NEW
British Neuropsychological Society Spring Meeting
22-23 March, 2006; Cambridge, UK
E. georgina.jackson@nottingham.ac.uk
W. www.icgp.org

50. Jahrestagung der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung
22-26 March, 2006; Gießen, Germany
E. Manfred.Kaps@neuro.med.uni-giessen.de

RSM Post Traumatic Stress Disorders in the Current Climate
23 March, 2006; London, UK
Info. Simon Timmis
T. 0207 290 3844
E. simon.timmis@rsm.ac.uk

Neural Networks ICNN 2006
24-26 March, 2006; Wien, Austria
W. www.ijci.org/icnn2006/

NEW
Sleep Medicine Course
27 March - 1 April, 2006; Edinburgh
E. enquiries@sleeping.org.uk

NEW
BISWG and Child Brain Injury Trust (CBIT) South Yorkshire – Understanding Acquired Brain Injury and Adolescence
30 March, 2006; Sheffield, UK
Linda Eldred
T. 0870 1500 100
E. linda.eldred@irwinmitchell.com

1st International Conference on Hypertension, Lipids, Diabetes and Stroke Prevention
30 March - 1 April, 2006; Paris, France
E. strokeprevention@kenes.com

April

European Congress of Endocrinology 2006
1-6 April, 2006; Glasgow, UK
Info. Liz Brookes,
E. conferences@endocrinology.org,
T. 01454 642210.

American Academy of Neurology 58th Annual Meeting
1-8 April, 2006; San Diego, USA
T. 001 651 695 1940
E. web@aan.com

NEW
BSS Spring Meeting
2-4 April, 2006; Cirencester, UK
E. enquiries@sleeping.org.uk

NEW
Neurology for Neuroscientists (XI)
6-7 April, 2006; Oxford, UK
W. www.ion.ucl.ac.uk/neurochemistry/N4N
E. n.neuroscientists@ion.ucl.ac.uk

38th International Danube Symposium for Neurological Science and Continuing Education
6-8 April, 2006; Brno, Czech Republic
E. tarabova@traveller.cz,
T/F. +420 543 211134

NEW
Insight Workshop - understanding awareness problems
7-8 April, 2006; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

Cognitive Neuroscience Society Annual Meeting
8-11 April, 2006; San Francisco, USA
W. www.cogneurosociety.org/content/meeting

ABN Spring Scientific Meeting
19-21 April, 2006; Brighton, UK
E. info@theabn.org

NEW
American Academy of Neuroscience Nursing (AANN) Annual Meeting
22-25 April, 2006; San Diego, USA
E. info@aann.org

NEW
AANS 74th Annual Meeting
22-27 April, 2006; San Francisco, California, USA
W. www.aans.org

MS Convention
23 April, 2005; Manchester, UK
E. CBray@mssociety.org.uk

NEW
Oxford Sleep Seminar in Dental Sleep Medicine
24 April, 2006; Oxford, UK
E. enquiries@sleeping.org.uk

NEW
Parkinson's Awareness Week
24 April, 2006.
T. 020 7931 8080 F.020 7233 9908
W. www.parkinsons.org.uk

Annual Scientific Meeting of The British Pain Society (IASP Chapter)
24-27 April, 2006; Harrogate, UK
T. 020 7631 8870,
E. meetings@britishpainsociety.org,
W. www.britishpainsociety.org

8th Congress of the European Headache Federation
26-29 April, 2006; Valencia, Spain
T. +41 22 9080488,
E. kenesinternational@kenes.com
W. www.ehf-org.org/8ehf

International Symposium: Evidence for Stroke Rehabilitation - Bridging into the Future
26-28 April, 2006; Goteborg, Sweden
E. stroke2006@gbg.congrex.se
W. www.congrex.se/stroke2006

BRAIN AWARENESS WEEK: 13-19 MARCH 2006
A global celebration of the latest brain science
To organise an event or get involved:
Contact Jennifer Gilmartin on tel: 020 7019 4914
Email: enquiries@edab.net or see **www.edab.net**

4th World Congress for NeuroRehabilitation

WCNR 2006, Hong Kong

12-16 February 2006

Hong Kong Convention and Exhibition Centre

www.wcnr2006.com

MAIN SYMPOSIA

Neuroplasticity and Recovery of Brain Function
Motor Control in Neurorehabilitation
Rehabilitation: Human / Machine Interface
Genes, Plasticity and Recovery

PARALLEL SESSIONS

Disease-specific Rehabilitation
Rehabilitation of Neurological Complications
Cognitive Rehabilitation
Cross Cultural Issues and Traditional Chinese/Alternative Rehabilitation
Neuroscience, Technology & Outcome Measurement

CALL FOR ABSTRACTS

Deadline for Submission: 30 September 2005

DEADLINE FOR EARLY BIRD REGISTRATION

31 October 2005

Patron

The Hon. Mr. Donald Tsang
Chief Executive, Hong Kong SAR

Organizer

WFNR
World Federation for Neurorehabilitation

Host Organizers

Hong Kong Association of Rehabilitation Medicine

Hong Kong Neurological Society

Diamond Sponsor

Pfizer

Gold Sponsors

IPSEN

Satellite Symposium Sponsors

ALLERGAN

Bristol-Myers Squibb Company

sanofi aventis

Lunch Symposium Sponsors

NOVARTIS

Pfizer

For more information, please visit our website at www.wcnr2006.com
For enquiry, please contact WCNR 2006 Congress Secretariat at Tel : (852) 2559 9973 Fax : (852) 2547 9528 Email : info@wcnr2006.com

UCL

INSTITUTE OF NEUROLOGY
in association with the
National Hospital for Neurology and Neurosurgery,
Queen Square, London WC1

'Neuropsychiatry'

given on Wednesday evenings

- First lecture starts at 5.15pm
- break for coffee at 5.50pm
- Second lecture starts at 6.05pm
- Venue: Wolfson Lecture Theatre, National Hospital

Please note that these lectures are open only to those practicing and researching in the relevant specialism or associated disciplines. Those interested are invited to attend, free of charge, on production of a staff/student identity card.

Wednesdays:
25th January - 15th March 2006

The lecture programme is available on our website at www.ion.ac.uk or from the Students Office, Institute of Neurology, 23 Queens Square, London WC1N 3BG
Tel: 020 7829 8740 · Fax: 020 7278 5069
Email: J.Reynolds@ion.ucl.ac.uk · www.ion.ucl.ac.uk
The Institute of Neurology promotes teaching and research of the highest quality in neurology and the neurosciences

The International League Against Epilepsy
(UK Chapter)
Annual Scientific Meeting

20th-22nd September 2006

The Hilton Hotel, Bottle Bank, Gateshead, Newcastle

Sessions include:

- Basic Science Session and Novel Research
- Sleep and Epilepsy
- Channels and Epilepsy
- Paediatric Interactive Session on Diagnosis
- Depression and Epilepsy
- SANAD Study
- New Ways of Working

Download forms from www.ilae-uk.org.uk

For details of the Annual Scientific Meeting contact:
Conference 2k, *Capstan House, Western Road, Pevensey Bay, East Sussex, BN24 6HG. Office Tel: 01691 650290, Fax: 01691 670302, Direct Tel: 01323 740612, Mobile: 07802 376938*
Email: denise@conference2k.com/Website: www.conference2k.com

UCL

INSTITUTE OF NEUROLOGY
in association with the
National Hospital for Neurology and Neurosurgery,
Queen Square, London WC1

Short Courses

8-19 May 2006

Neuroimaging	(8 May)
Stroke	(9 May)
Dementia	(10 May)
Statistical Parametric Mapping	(11, 12 and 13 May)
Epilepsy	(15 May)
Neuro-ophthalmology	(16 May)
Movement Disorders	(17 May)
Multiple Sclerosis	(18 May)
Neuromuscular Disease	(19 May)

Course fee £175 per day
(£125 for 5 or more days;
£150 per day for clinical trainees;
£125 per day student rate) to include refreshments.
£600 for the three-day SPM course.

For further details please contact:
The Assistant Secretary for Students
Institute of Neurology,
National Hospital for Neurology and Neurosurgery
Queen Square, London WC1N 3BG
Tel: 020 7829 8740
Fax: 020 7278 5069
Email: J.Reynolds@ion.ucl.ac.uk
www.ion.ucl.ac.uk

The Institute of Neurology promotes teaching and research of the highest quality in neurology and the neurosciences

XVIIIth World Congress of Neurology

Sydney, Australia, 6-11 December, 2005.

Sydney is deservedly developing a reputation for managing large scale events of global significance - first the Olympics and now the XVIIIth World Congress of Neurology. Both attending and reporting on the congress demand a highly selective approach: two days of teaching courses, five days of the conference proper (running 0700 to 1930 with up to eight parallel sessions) and almost 1700 posters. One of the concerns of attending a conference of this scale is that, having come to terms with the fact that at any one time you're missing at least five-sixths of what's going on, the additional leap into truancy to miss the sixth isn't so hard. As the conference was competing for attention with one of the world's most beautiful cities set in a cluster of near perfect beaches, it is a tribute to the organisers that the standard of the programme in a flawless conference centre seemed to pull the crowds in off the harbour bay.

Over the course of one week the entire canon of neurology was reviewed. Having, by necessity, missed huge chunks of the meeting (due to the parallel programme design rather than the call of extracurricular pursuits) I can only give a very personal account of the meeting highlights.

The core programme of the WCN is a series of invited reviews rather than presentations of original work. Coming at the end of the specialist conference season, this provides encouragement to go to all the sessions one would normally avoid, allowing oneself to be brought up to date in the obscure backwaters of neurology, like Parkinson's disease and stroke. Those who made the mistake of going to their 'home' sessions (especially during the teaching programme) seemed invariably to compensate for the fact they were not the invited lecturer by providing a running commentary in their less-informed neighbour's ear. This latter unfortunate frequently seemed to be me, allowing me to perfect my trick of functional unilateral auditory neglect.

From the main programme, the 'Frontiers of Neuroscience' lectures boasted two Nobel laureates among the five speakers. Whilst any of the speakers could have filled the time recapping their CVs, all appeared to consciously avoid this, providing the peaks of the conference with a series of excellent overviews. Peter Doherty in particular exemplified the nature of these sessions in his address comparing the CNS and the immune system, exploring concepts of self and memory, drawing from a wide range of work from several disciplines.

Revealing too much of what was new to me in the teaching courses and review lectures would unfortunately betray the pre-existing gaps in my knowledge. I shall thus give only the main points gleaned per subject area:

Parkinson's disease: The North Americans have unbounded enthusiasm for Neuroprotection – it would seem the main national debate is whether to put fluoride or selegeline in the water. Rasagiline is creating interest and seems to be finding a place in very early treatment, combining symptomatic relief with a hint of the holy grail of neuroprotection. L-dopa seems very good or very bad depending on your choice of study.

Headache: The tip of asking whether photophobia was bilateral (96% of migraine) or unilateral (>90% cluster headache) – a discriminator I have been using to great effect since. Aura does not exclude a diagnosis of cluster headache.

Idiopathic intracranial hypertension remains an evidence free zone, open to all opinions and therapeutic options.

Menstrual migraine may be due to too much or too little of one or several sex hormones and may or may not respond to hormonal alteration (this talk was a little short on specifics).

New persistent daily headache are four words which, when put together, seem to form an allowable diagnosis – albeit one without a specific prognosis, aetiology or treatment.

Epilepsy: The MESS trial results show no benefit in the long term from immediate rather than delayed treatment of first seizures, which is a reassuring validation of conventional practice. A simple model of risk for further seizures can be generated from the data which is dependent on number of seizures, EEG abnormalities and pre-existing brain pathology.

Genetics: there was an excellent session on genetics for amateurs which, for me, captured the purpose of the congress – perfectly pitched for people who knew a bit about the subject but don't do it everyday and don't get to keep up with the literature. I am not revealing anything from this session - I have laminated my notes on the genetics of peripheral neuropathy and the SCAs for cheating at clinical meetings.

Sleep: There is a complex interaction between the sleep disorders and the neurodegenerative disorders, which should raise their profile in clinical practice.

Some neurologists take an interest in obstructive sleep apnoea (a revelation in itself).

Hypocretin deficiency in narcolepsy is mostly restricted to forms associated with cataplexy and there is emerging evidence that the aetiology of this combination might be a destructive monophasic autoimmune disease – an interesting prospect for future therapies.

Multiple sclerosis: the pathologists continue to disagree on the fundamental point of whether there is more than one subtype of disease, but continue to be nice to one another in public. The clinicians also have disagreements, but are much less coy about expressing themselves.

Stroke: Palm Beach is where they film Home and Away and is exceptionally beautiful.

Mitochondrial disease: is commoner than previously thought (UK estimate 6.6/100 000). The genotype/phenotype correlations appear increasingly blurred, but the mechanisms whereby specific mutations lead to differing phenotypes is being clarified.

Outside the mainstream programme were a series of special feature meetings. Each day started with a 'Meet the Professor' session. Many of these were familiar names from the UK, so most delegates seemed to settle for the 'Meet the Consultant' breakfast session which, if you weren't too fussy about which consultant you wanted, could be done in any of the city centre hotels up to about 11 am, thus saving an early morning trip to the conference centre.

Poster 416 was on 'Marathon Related Death'. I fear this is the outcome for anyone who braved the completely overwhelming poster hall. In the absence of any discernable reviewing policy (I'd be fascinated to see what actually did get rejected), I took the free CD home to review at leisure. Haven't quite got round to it yet.

From the sponsored symposia, I attended the world première of 'Brainstorm', a specially commissioned play by Polly Toynbee. The appearance of five actors in matching white pyjamas (the doctor given away by a white coat – a subtle touch), accompanied by suitably dramatic electronica should have set the alarm bells ringing, evoking suppressed memories of well meaning sixth form drama groups. 'Distilled essence of horror' and 'watch in silent mortification' are quotes from the play which conveniently double as reviews. The saintly good doctor of the piece at one point cries in desperation that the saintly patient 'needs to join a support group'. After 45 minutes of it all, she wasn't the only one. Apparently it is going to be made available on DVD, but unfortunately not in time for this Christmas, for those who were stuck for an idea for their Clinical Director.

In a year when England reclaimed the Ashes, national expectations were high for the international 'Tournament of the Minds'. The heats saw the UK through to the final four. There appeared to be certain injustices in the scoring system which resulted in the final four becoming six on appeal and the elimination of the Irish team, who, despite having eligibility criteria laxer than those for their international football team, mistakenly went for looks, charm and integrity – none of which appeared to count (this last line may reflect the only moment of personal bias in this article). The UK went on to take the final on a narrow finish. Somehow the event missed the national tabloid press, but I suspect will be picked up next year as consolation for defeat in the World Cup.

While the host city easily leads to a rose-tinted view of the week, this really was an excellent conference. When so many meetings get bogged down in overly edited presentations of complex original work, or invited reviews where the speaker rarely strays beyond their own two most recent papers, this was a genuinely comprehensive refresher course in clinical neurology leaving me a lot more educated and enthused than when I arrived. The next congress is set for Bangkok in 2009. I advise planning to go, but don't bring a poster.

Martin Duddy, Consultant Neurologist, Newcastle-Upon-Tyne, UK.

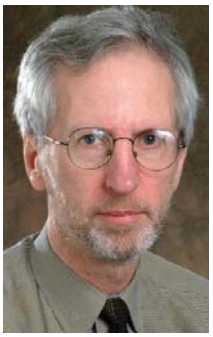
Joint meeting of the Association of British Neurologists and Society of British Neurological Surgeons, with the Netherlands Society of Neurology and Netherlands Society of Neurosurgeons

Torquay, UK, 7-9 September, 2005.

The usual suspects of ABN members gathered once again, this time in faded Torquay, to fraternise and debate research. Clinical Neurosciences 2005 was much enlivened by the presence of good friends from Dutch neurology and – dare I say - even more so by UK and Dutch neurosurgeons. I am afraid that, more than once, the parallel neurosurgery sessions were more interesting and lively than the neurology programme. There was a particular emphasis in the neurological platform sessions on neurological workforce issues which contained either little or no research, to the exclusion of vastly better work confined to poster presentation.

The main messages of the meeting for this reviewer were:

Stick at it! Charles Warlow, on accepting the ABN Gold Medal, resisted the temptation to maudlin reminiscence. Instead he assembled a powerful argument for prolonged and repeated observation of disease, based on the accomplishments of former teachers and colleagues. At the heart of his case, in more than one way, was the example of John Fry, his former family GP, who made a systematic epidemiology of his practice.



Professor Charles Warlow was awarded the ABN Gold Medal.

The management of low grade glioma is confused. In a combined neurology-neurosurgery session, five distinguished doctors discussed their approach to a case and four management plans were offered, ranging from doing nothing to giving chemotherapy. Reassuring, rather than enlightening.

Neurologist-assisted suicide is imminent. The final session of the meeting was devoted to a lively discussion of the prospective Assisted Dying Bill in the UK. Those neurologists who contributed were against the bill. However, the message sent to Lord Joffy by the ABN on our behalf was rather neutral.

Cerebral AVMs presenting as haemorrhage are more likely to bleed in the future than AVMs presenting in other ways. This paper, from Edinburgh, following the fate of 229 people with untreated AVMs since 1999, rightly won Al-Shahi the ABN platform prize.

Many spastin mutations can cause HSP. McDermott, from Sheffield, gave a lovely account of the clinical and genetic features of 61 patients with 47 different mutations in the spastin gene. On the whole, they had a 'pure HSP' phenotype and the mutations seem to converge on a hot spot in exon 1.

Atrophy in multiple sclerosis MRI scans is due to axonal loss. Proving this axiom of multiple sclerosis research has been difficult. But Trip and colleagues, from Queen Square, nicely show that atrophy of the optic nerve correlates with loss of thickness of the retinal nerve fibre layer measured by optical coherence tomography, a technique with a bright future.

GPs refer patients with headache for social reasons. An analysis of 489 people presenting to their GP with headache, by Ridsdale at King's, suggested the following: an average GP will see one patient with headache a week and refer one per year to a neurologist. Those referred were more likely to be men, to believe there was a physical explanation for their symptoms and to consult more frequently.

Microvascular decompression works for hemifacial spasm. Coakham, from Frenchay, reported the long-term (6 months to 22 years) follow-up of 126 patients with hemifacial spasm treated with microvascular decompression. In all cases, a compressive vessel was seen at surgery (PICA in 59%). 8 patients required a second operation, CSF leak was caused in 3% and deafness in 9%. At follow-up 80% were classified as cured.

Nogo is found in the spinal cord of ALS and MS patients. Nogo inhibits axonal regeneration and trials into neutralising its effect in spinal injury are already taking place. The implication of this study, from Durrenberger at Imperial, is that similar manoeuvres might help in degenerative diseases.

The immune response in head injury might be beneficial. Cox, from Cambridge, won the ABN poster prize with her study comparing clinical outcomes, radiology and immune responses in acute head injury.

Alasdair Coles, University of Cambridge, UK.

Torquay Harbour.

The Neurosurgical Perspective

Clinical Neurosciences 2005 was hosted by the Department of Clinical Neurosciences, Peninsula Medical School. The meeting opened with a Trainees teaching session, entitled 'Getting out of trouble'. This was a great success – firstly, because it was free, and secondly, because the trainees had not previously known that their consultants had ever been in trouble. However, the topics remained professional, and some useful insights and experiences were eloquently passed on to the next generation. This session occurred in parallel with a Neurosciences Nurses Session, a first and long overdue addition to the SBNS meetings. With the increasing role that nurses are playing in the clinical and academic neurosciences, we anticipate that this successful session will set a precedent for future meetings.

Delegates then were welcomed to the meeting proper by Mr James Palmer and Professor John Zajicek, with a historical perspective covering the naval connections and development of Neurosurgery in the region. The move from lectures towards debate has become a trend in recent meetings that continued here with a lively session on 'Neurologists should look after patients with subarachnoid haemorrhage'. Voting involved each member of the audience pointing to a yes or no section of the stage with a laser pointer. Some interesting points were energetically made, but the only clear conclusion was that neurosurgeons had steadier hands with laser pointers.

The second plenary session was a high quality combination of four talks representing Neurosurgery and Neurology from the UK and Holland. Mr Richard Kerr, Oxford, presented the latest data from the International Subarachnoid Aneurysm Trial (including 7 year mortality data) and Dr Martin van den Bent, Rotterdam, presented the results of a phase III study of combination chemotherapy for anaplastic oligodendroglioma.

The sponsored satellite symposia were a great success, with Professor David Miller chairing developments in the treatment of MS, and Professor John Pickard presiding over current opinions on normal pressure hydrocephalus and its management. The delegates were then witness to the delights of Torquay by night, and the sponsors' contributions were both enjoyed and appreciated.

The third plenary session provided an excellent synopsis of the current management of low-grade glioma with contributions from both sides of the Atlantic. Professor Peter Black, Boston, USA, provided a contemporary view on the surgical management of low-grade gliomas, where important advances in technology, notably intra-operative MRI scanning, were demonstrated. Clearly this intervention will have a significant impact on whether and how patients are treated early with radical resection over watchful waiting.

The breakout SBNS sessions comprised neurovascular, neuro-oncology, spine/trauma, movement disorder and audit. There was a lively session chaired by Mr Richard Nelson (Bristol) and Mr Peter Whitfield (Plymouth) on neurovascular developments in the management of subarachnoid haemorrhage, while Mr James Palmer (Plymouth) and Mr Michael Powell (London) looked over advances in tumour management with a particular focus on adjuvant therapies. Mr Robin Johnston (Glasgow) and Mr Lou Pobereskin (Plymouth) chaired an eclectic session that could have been titled 'pain in the neck', covering topics such as the role of neuronavigation in cervical surgery to the problems we face in getting neurotrauma patients to appropriate centres quickly. Finally, Mr Ken Lindsay (Glasgow) and Miss Anne Moore (Plymouth) chaired an interesting session on the surgical management of movement disorder.

The meeting concluded with a debate on physician assisted dying with arguments presented by Deborah Annetts from the Voluntary Euthanasia Society, Dr Bert Keizer discussing physician assisted dying in Holland, and Dr Helen Watt, ethicist. As anticipated, strong views were expressed by both speakers and audience. The pros and cons of the Joffe Bill, due to go before the House of Lords, in November were discussed at length.

Overall, Clinical Neurosciences 2005 was a hugely successful meeting with healthy interaction between surgeons / physicians and Dutch / British alike. An enjoyable social programme, the pinnacle of which was a Gala Banquet at the Britannia Naval College, Dartmouth, supported its strong scientific content.

PJ Hutchinson and RJ Mannion,
Derriford Hospital, Plymouth, UK.

Acknowledgements

Many thanks to the local organising committee comprising James Palmer, Peter Whitfield, Anne Moore, John Zajicek, Martin Sadler, Simon Edwards, Louise Davies, Jo Henley and Tracey Holman.

The 17th Annual Scientific Meeting of the British Sleep Society

Cambridge, UK, 25-27 September, 2005.

Having previously been a peripatetic symposium, the 2005 BSS scientific meeting was held for a fifth consecutive year at Robinson. A negative view might suggest this implies (small 'c') conservatism and a fear of change. However, the positive alternative is true. There exists a growing and compelling seasonal urge that keeps the eclectic British sleep community returning to this corner of Cambridge. Some propose this has a basis in melatonin secretion and breeding habits, others are probably attracted by the superb Robinson cuisine. One not altogether fanciful reason for return is that the BSS meeting invariably coincides with a visit from a fun-loving group of Portuguese proctologists famed for their disinhibited dancing techniques. Rather more soberly, however, the excellent nearby parking probably provides the main rationale. Whatever the reasons for coming, the meeting invariably provides the delegate with a veritable pot pourri of reviews and new data, relating to every conceivable aspect of sleep medicine. This year was certainly no exception with a stated theme of 'From Genotype to Phenotype: what's sleep got to do with it?'

The programme kicked off with an evening symposium chaired by Jonathan Bird that addressed sleep from a psychiatric perspective, stretching from cradle to grave. It is a sobering thought that psychiatrists receive even less training than neurologists in sleep medicine, yet probably see a greater proportion of patients with significantly disordered sleep. Distinguishing between the deleterious effects of mood disorder on sleep and the consequences of a defined sleep disorder on mood is a minefield within which even those experienced in sleep medicine tread carefully. This is particularly true at the extremes of age. Professor Gregory Stores, an acknowledged expert in adolescent sleep problems, addressed the area with an overview of those sleep disorders frequently mistaken for psychiatric or psychological distress. Dr Chris Hawley then addressed the issue of excessive daytime sleepiness, as opposed to fatigue, in a general psychiatric population, emphasising a much needed systematic approach to assessment and treatment. This meat of the symposium was enclosed by two entertaining and enlightening personal reviews by Dr Paul Gringras and Dr Avi Dhariwal. The former discussed how herbs, hormones and hypnotics are used (and abused) in children, the latter how sleep problems may severely affect the elderly, yet remain completely off the radar of the physicians in charge.

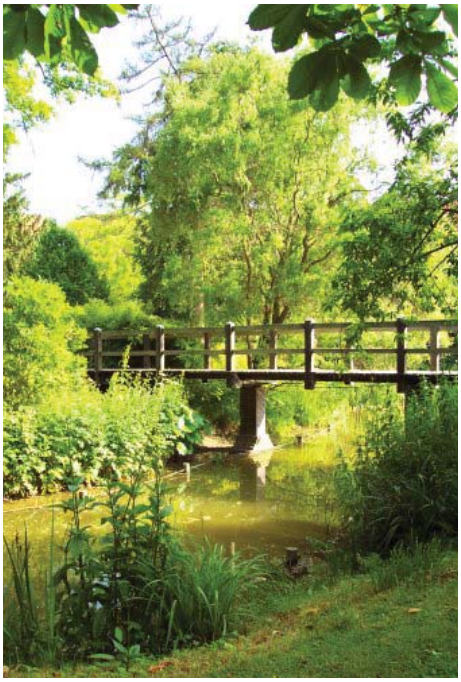
The first day of the meeting proper started with a superb overview of gene research in the field of intracellular clock mechanisms by Simon Archer from Surrey University. Having leapt to popular fame on a recent Robert Winston sleep documentary, Simon gave an authoritative and particularly comprehensive account of 'clock' genes, highlighting the surprising extent to which humans remain hostage to our internal clocks. He focused particularly on how polymorphisms in certain key clock genes may determine whether we are 'night owls' or ''morning larks' and therefore better suited to careers as croupiers or milkmen. Cyclical production and degradation of a small number of proteins as they pass between

the nucleus and cytoplasm provides the basis of circadian timing. The tightly orchestrated mechanism is essentially the same in fruit flies as it is in humans and represents a truly fascinating area of biology. We are only just beginning to comprehend the effects these primitive processes have on functions such as repair, metabolism and the immune system. The potential application of such knowledge is colossal.

The second keynote speaker was Patrick Levy from Grenoble whose pivotal work in unravelling the unholy trinity of (visceral) obesity, the metabolic syndrome and obstructive sleep apnoea is widely acknowledged. The talk focused on how intermittent hypoxia due to OSA may independently lead to impaired glucose tolerance and leptin (the 'satiety' peptide) gene dysregulation. One current theme of such research is that OSA sufferers will gain visceral fat independently and directly because of their fragmented sleep, thereby worsening their OSA. Whether appropriate treatment of OSA can offset this proposed vicious cycle remains an area of debate. Subsequent talks through the morning addressed these issues further, broadening the topical discussion to include the potential damaging effects of increased cytokines and oxidative stress secondary to severe OSA.

The first afternoon was dominated by further insights into the metabolic consequences of OSA, followed by the 'free communications' session. The latter included talks on topics as diverse as CRP levels in sleep-disordered breathing and the effects of behavioural intervention for sleeplessness in autistic children. There then followed a relatively painless AGM before the feverishly anticipated gala dinner. With so much education in the previous 10 hours on matters germane to sleep hygiene and the metabolic syndrome, one might have expected a sober and reflective evening. Of course, the adage 'do what I say, not what I do' applied with the inevitable consequences of overindulgence and sleep deprivation the following morning for the majority.

The second day of the meeting was dominated by matters paediatric, from womb to adolescence, a much neglected area of sleep medicine particularly in the UK. Fascinating material was presented concerning the activity-rest cycles of the foetus and their relations to autonomic function and dysfunction. It is extremely interesting to reflect that the foetus in its latter stages of development spends well over 50% of its existence in a state akin to REM sleep, a fact rarely incorporated into theories of REM (dream) sleep. Moving into the first year of life, a lecture by Dr Helen Ball, an anthropologist from Durham University, was equally enlightening and somewhat leftfield to those of us working in more conventional areas of medicine. It mostly dealt with how we sleep, or, rather, don't sleep, with our infant offspring. Since Victorian times or a little before, it can be argued that humans in Westernised societies have fought an evolutionary and natural instinct to sleep along side our infants. Certainly in 'underdeveloped' cultures, it is the norm to sleep with the very young and breast feed through the night. Interesting video data were shown, outlining how the maternal position is generally stereotyped in the shared bed. When deviations from this pattern were observed, accompanying problems with sleep for the mother and infant became evident. A cogent argument was made that having infants sleeping in distant beds or rooms to the parent was often the primary cause of psychosocial problems and disrupted sleep. The final talk of the paediatric session was an inspirational and wide-ranging discourse from Ron Dahl, a professor from Pittsburgh, on 'Sleep and Emotion Regulation in Children and Adolescents'. Combining 'hard' data with psychological theory, he addressed the myriad of potential sleep problems and associated behavioural difficulties that can affect teenagers.



The final session of the meeting was devoted to 3 case studies from different areas of sleep medicine, each of which had a 'message'. We heard from Sophie West about a patient with dreadful OSA, diabetes and extreme obesity (BMI > 50) whose long term management was helped immensely by gastric (bariatric) surgery. Renata Riha presented an interesting parasomnia case with videos showing a young man exhibiting a so-called 'rhythmic movement disorder' of sleep. This is thought to represent the persistence into adulthood of a disorder akin to 'head banging', a common childhood sleep phenomenon, usually at sleep-wake transition. The rhythmical movements can involve various body parts and affect the patient in any sleep stage, including REM. Invariably it is the bed partner who suffers in this situation. Indeed, one commonly held theory is that the movements are, in a sense, gratifying to the subject and best viewed as a form of sleep-related tic. The third case from Ron Dahl was a teenager with delayed sleep phase syndrome, a not uncommon circadian rhythm disorder, usually misdiagnosed as 'lazyitis'. Good evidence suggest that sufferers have an inherent phase delay in their circadian timing such they are compelled to sleep a few hours later than average, the resulting lay-in often causing major upset with parents and educators alike. Cultural and sociological factors are also clearly important in fuelling the abnormal sleep-wake pattern. The case study described one behavioural way of treating this problem which, paradoxically, involved sequentially delaying sleep further by 3 hours each night over 6 days until a conventional sleep onset time was achieved. This tight schedule appeared successful in the patient discussed and the need for medication obviated.

In conclusion, speaking as a veteran of the last 6 annual BSS meetings, I think this was probably the most rewarding to date, despite concentrating on areas largely foreign to my clinical practice. Particular credit must go to Dr Mary Morrell from the National Heart and Lung Institute who was the main driving force on the scientific committee that organised the meeting. It never ceases to amaze me how broad are the horizons for sleep medicine. Although it is still very much a 'Cinderalla' discipline in the UK, even compared to continental Europe, the enthusiasm generated by mutli-disciplinary meetings such as those organised by the BSS bodes well for the future. A working knowledge of sleep biology and the wide-ranging consequences of when it goes wrong should surely be essential to all health practitioners dealing with the brain and mind.

Paul Reading,
James Cook University Hospital,
Middlesbrough, UK.

Additional web content www.acnr.co.uk

EuroYapMeet - European Conference for Younger People with Parkinson's disease, was held in Dublin, 7-9 October 2005.
For a report on this event see www.epda.eu.com/

For a report on 'Innovations in Brain Injury Rehabilitation' (Manchester, September 28-30 2005),
see www.acnr.co.uk/events.htm

Deep brain stimulation for the alleviation of post stroke neuropathic pain

Introduction

Intractable neuropathic pain affects 2-8% of patients after a stroke.[1] Typically, a burning hyperaesthesia and aching affect areas that are rendered numb after a stroke. Such pain usually resists medical therapy leaving these patients with no symptom alleviation. In the UK, an estimated 28,000 people will suffer from this predicament.

Although motor cortex stimulation has been reported as a mode of therapy for this condition the published literature quotes extremely variable results.[2,3] Therefore, deep brain stimulation has been the preferred mode of therapy for neuropathic pain at Oxford since 1999. During this period, 15 post stroke patients with neuropathic pain were treated with deep brain stimulation. Here we present the clinical results.

Tipu Aziz

Professor Tipu Z Aziz is a Consultant Neurosurgeon at the Radcliffe Infirmary, Oxford and Charing Cross Hospital London. He is an expert in functional neurosurgery and has a special interest in the surgical treatment of movement disorders.

Sarah LF Owen

Miss Sarah Owen qualified as an Operating Department Practitioner from Selly Oak, Birmingham in 1988, and later gained her first neurosurgical position at the Radcliffe Infirmary in 1989. She subsequently read for a BA (hons) in Anthropology with a special interest in the evolution of the primate brain at Oxford Brookes University, where she qualified in 2004. She is currently reading for a DPhil at Brasenose College, University of Oxford. Her research involves investigating the sensory pathways involved in pain.

Correspondence to:
Professor TZ Aziz
Department of Neurosurgery,
Radcliffe Infirmary,
Woodstock Road,
Oxford, OX2 6HE.
Tel: 01865 228425,
Email: tipu.aziz@
physiol.ox.ac.uk

Patient population and surgery

Of the 15 patients in the study the average age was 58.6 years, there were 3 female and 12 male patients, 5 had cortical and 10 subcortical strokes of which 8 were thalamic, 1 pontine, and 1 in the internal capsule. Average duration of pain prior to surgery was 5.2 years. The most disabling aspect of the pain syndrome was a burning hyperaesthesia in the area of numbness that affected 7 of the 15 patients. Also described was a severe cramping or crushing sensation.

Provided there were no over riding medical or psychological contraindications, deep brain stimulation of the periventricular area and sensory thalamus were offered to these patients. Both targets were chosen after existing literature by different authors quoted both as being effective.[4] Also there was no indication of any superiority of one target over another. Preoperatively they filled in pain charts using a visual analogue scale and the McGill questionnaire. They also underwent a comprehensive neuropsychological assessment. Deep brain stimulation for neuropathic pain has approval of the local ethics committee.

All patients had a T-1 weighted axial MRI scan prior to surgery, and a CRW base ring was applied to the patients' head under local anaesthesia. A stereotactic CT scan was then performed and using the Radionics Image Fusion, and Stereoplan, programme the MRI scan is volumetrically fused to the sterotactic CT scan. This is a technique that has been adopted since 1995 to eliminate the errors of using MRI sterotaxy alone that arise from the spatial distortions intrinsic to magnetic fields. The co-ordinates for the PVG and VPL were then calculated. Patients with strokes in the sensory thalamus were only implanted in the PVG/PAG with a Medtronic 3387. The VPL was implanted with a Medtronic 3387 electrode where stimulation induced parasthesia in the area of pain and the PVG/PAG with a Medtronic 3387 electrode where stimulation induced relief of pain or a sensation of warmth in the area of pain. The deepest electrode was noted to be in a satisfactory position if eye bobbing was induced at an intensity of stimulation at least twice that required for sensory effects. The electrodes were fixed to the skull with a miniplate prior to externalisation.

In all patients the electrodes were externalised for a week of trial stimulation. Pain was assessed before surgery and during stimulation by a self-rated visual analogue scale. Post stroke pain during the trial period responded better to stimulation of the PVG compared to the VPL. If the patients were satisfied with the degree of pain relief, full implantation of a Medtronic pulse generator was performed in the following week under general anaesthesia.

Results

During a trial period of one week following surgery, 3 patients did not feel there was significant pain relief to proceed to full implantation of the pacemaker and the electrodes were removed under local anaesthesia. The 12 remaining underwent full implantation of the extension cables and the pacemaker (SYNERGY, Medtronic Inc). Although dual channel, all patients were implanted with a SYNERGY because of the longer battery life, if one channel is used a plug is used to close off the inactive channel. The patients were then reviewed a month later to optimise the settings for maximum pain relief and were reviewed 6 monthly thereafter.

Follow up

Average follow up was 15 months. Nine patients preferred chronic stimulation of the PVG, one in the VPL and three preferred both electrodes to be activated. The results are summarised in Table 1. Overall the reduction in pain scores was 48.8% (SD 2.2, $p<0.001$). The average reduction in the cortical strokes subgroup was 42% (SD 2.7, $p=0.023$) and in the sub cortical stroke group was 54% (SD 1.9, $p<0.001$). If burning hyperaesthesia was present this was markedly reduced. An analysis of the McGill questionnaire was also performed, by looking at pain scores in the four word groups sensory, affective, evaluative and miscellaneous. In each group the average pain score was reduced postoperatively as follows: sensory from 8.5 to 8.0, affective from 9.1 to 7.3, evaluative from 4.6 to 4.3 and miscellaneous from 11.2 to 6.5. Of the 12 patients, 7 stopped all analgesics (of these 4 were on opiates, 3 on Gabapentin) and 5 changed from regular opiate analgesia to as

Table 1: Changes in VAS scores

	Pre-op VAS	Post-op VAS	% reduction	SD	P value
Cortical	9.7	6.7	31		
	7.3	7.3	0		
	8.2	1.9	77		
	6.7	4.8	28		
	10	4	60		
Mean	**8.4**	**4.9**	**42**	**2.7**	**0.023**
Subcortical	8.5	6.8	20		
	7.2	3.7	49		
	9.2	5.3	42		
	9.1	2	73		
	8.1	2	75		
	6.6	4	39		
	6	1.2	73		
Mean	**7.8**	**3.6**	**54**	**1.9**	**<0.001**
Total Mean	**8.1**	**4.1**	**49**	**2.2**	**<0.001**

We would like to thank Medtronic for sponsoring this article. For more information email Clive Woodward clive.woodward@medtronic.com or telephone Medtronic on 01923 212213.

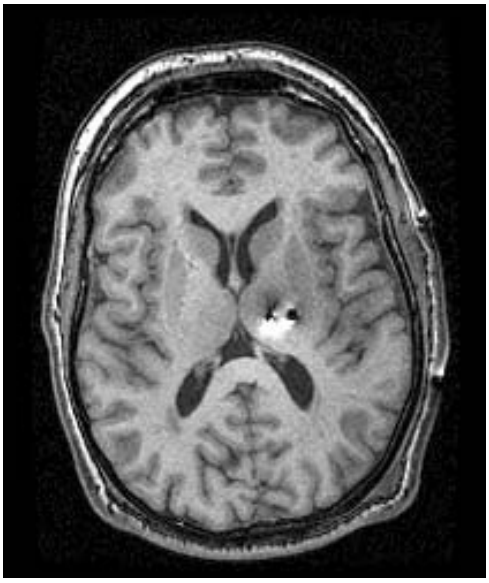


Figure 1: An axial MRI scan showing electrodes in the VPL (lateral) and PVG (medial) nuclei.

required non-opiates. There was one complication in this series. One patient struck the top of his head against a lintel and a few hours later the neuropathic pain returned, as the lead had fractured which required surgical revision with return of pain relief.

Discussion

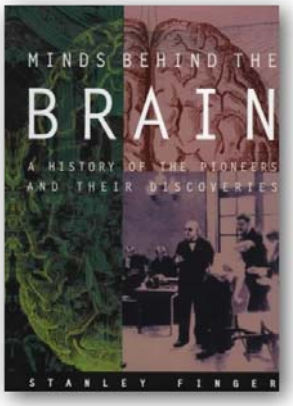
This prospective study demonstrates that deep brain stimulation of the PVG/PAG and sensory thalamus may have a useful role in the management of post-stroke central pain. In our experience, those patients who symptomatically suffer from severe burning hyperaesthesia appear to respond best. In this series the average pain relief is of the order of 48.8% which is of the region of 50% relief often quoted as the bench mark for useful pain relief. The site of the stroke may be of relevance as we have observed that cortical stroke patients had less relief than sub-cortical strokes but given the small numbers there was no statistical difference. One disadvantage put forward against deep brain stimulation is the onset of tolerance. In our experience the effect is not that of tolerance but that once patients lose the intolerable burning hyperaesthesia, the background crushing aching sensation becomes more noticeable. Nevertheless, the effectiveness of the procedure can be confirmed in an N of 1 study[5] in which the patient records pain scores and the stimulator is randomly turned on or off. The mechanism of the effects are still unclear. There is some evidence to suggest that PVG/PAG stimulation has an inhibitory effect on the sensory thalamus.[5] However, the analgesic effects of deep brain stimulation can last for over 24 hours after a period of stimulation. This confounds on/off studies[3] but does support studies that indicate that that PVG/PAG stimulation results in the release of endogenous opiates.[6] Deep brain stimulation has been tried with success in the past but due to overall poor results and poor patient recruitment into two trials in the 1980s this technique was largely abandoned. However, with the resurgence of functional surgery for movement disorders the use of MRI scans for sterotactic target localisation, safer electrodes than those used in the early days (internalised stylet), more reliable pacemakers, the knowledge gained from some early studies does mean that this important indication should be revisited.

References

1. Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ. *Motor Cortex Stimulation For Chronic Neuropathic Pain: A Preliminary Study Of 10 Cases.* Pain 2000;84:431-7.
2. Coffey RJ. *Deep Brain Stimulation For Chronic Pain: Results Of Two Multicentre Trials and a Structured Review.* Pain Med 2001;2(3):183-92.
3. Green AL, Shad A, Watson R, Nandi D, Yianni J, Aziz T. *N-of-1 Trials for Assessing the Efficacy of Deep Brain Stimulation in Neuropathic Pain.* Neuromodulation 2004;7(2):76-81.
4. Katayama Y, Tsubokawa T, Yamamoto T. *Chronic Motor Cortex Stimulation For Central Deafferentation Pain: Experience With Bulbar Pain Secondary To Wallenberg Syndrome.* Stereotactic Functional Neurosurgery 1994;62: 295-9.
5. Nandi D, Smith H, Owen SLF, Joint C, Stein J, Aziz T. *Periventricular Grey Verses Motor Cortex Stimulation For Post Stroke Neuropathic Pain.* Journal of Clinical Neuroscience 2002;9(5):557-61.
6. Young RF, Bach FW, Van Norman AS, Yakash TL. *Release Of Beta-Endorphin and Methionine-Enkephalin Inro Cerebrospinal Fluid During Deep Brain Stimulation For Chronic Pain. Effects Of Stimulation Locus and Site Of Sampling.* Journal of Neurosurgery 1993;79(6):816-25.

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o rachael@acnr.co.uk

Minds Behind the Brain: A History of the Pioneers and their Discoveries

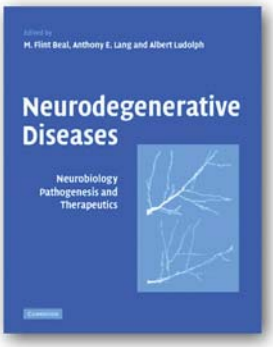


Stanley Finger
Published by: Oxford University Press
Price: £18.99
ISBN: 0195181824

This book is entertaining and informative with plenty of personal detail and insights into the working practices and conditions of some of the major contributors to what we now call neuroscience. Prof. Finger states that the purpose of the book 'is to look at the lives and discoveries of some of the major Western thinkers who contemplated how the brain may work'. He wants to cover a great period of time, not pick anyone too contemporary, and not discount anyone because their ideas would be deemed 'wrong' by our current understanding of brain function. He comes up with 19 principal characters (each with their own supporting cast) and covers them in 16 chapters ordered by time. As is inevitable with any Hornby-esque list one is struck by omissions as much as by inclusions so Broca gets in but there is no place for Wernicke or Dejerine (who doesn't even make the bench). The project really only fails in its attempt to justify itself as a coherent book, which will only bother those who were expecting a common thread or overview to emerge from this voyage that cannot stop at every port of call. The structure of the book demands that the ideas presented must be pinned to 'giants' of the past even when this is, by the author's own admission, impossible. Thus, most of the (very interesting) material in the first two chapters has to be attributed to two physicians, Egypt's Imhotep and Greece's Hippocrates. The writings attributed to the former (whose period of existence can only be roughly estimated as 3000BC) are a series of 48 fascinating military cases, but the papyrus dates to 1650BC, suggesting that the ancients suffered from an even more frustrating peer-review delay than we do even now. Similarly the Corpus Hippocratum, compiled at least 50 years after the presumed date of Hippocrates's death, is acknowledged to be an accumulation of works from multiple authors. Again, the sections on Luigi Galvani, Otto Loewi and Henry Dale, good as they are, have nothing to say about the brain (although a lot good to say about nervous transmission and the conflict been those who thought that electrical currents directly animated muscles and glands, and those who interposed the 'soup' of neurotransmitters). The author himself seems to be aware of these problems and in the short summary chapter (best avoided) he is reduced to speculating on common factors that may link his disparate heroes, such as personality and upbringing. But these are minor carps about an otherwise interesting collection of 'nutshell' profiles of some of the more influential workers in the field of nervous system research; the work is well referenced and will readily point readers towards more detailed accounts of the subject matter, should they require it.

Alex Leff, FIL, Queen Square, London, UK.

Neurodegernative Diseases: Neurobiology, Pathogenesis and Therapeutics



Edited by: MF Beal, AE Lang, A Ludolph
Published by: Cambridge University Press
Price: £220.00
ISBN: 0-521-81166-X

The objective of the distinguished editors of this massive tome from CUP is 'to present the latest research into the genetics, pathogenesis, biochemistry, animal models, clinical features, and treatment of neurodegenerative diseases.' There are 62 chapters, divided into 10 parts, the largest devoted to 'basic aspects of neurodegeneration' such as free radicals, oxidative stress, excitotoxicity, calcium, apoptosis, and protein misfolding. Sections on neuroimaging (structural/functional) and therapeutic approaches (gene therapy, stem cells) are followed by more clinical sections covering normal ageing, Alzheimer's disease, other dementias, parkinsonian syndromes, cerebellar degenerations, motor neurone diseases, and other neurodegenerative diseases. It might be argued that multiple sclerosis is, at least in part, a neurodegenerative disorder and hence merits a chapter.

Hence, there is a large amount of information, which will repay careful reading, perhaps especially for those new to the field. The book has high production values and a thorough (though not perfect) index. Presumably the hope is to attract both scientists and clinicians as potential purchasers, although the science may in parts be challenging for the clinician, and there may be too much clinical material for the laboratory-based neuroscientist. Moreover, those wanting the 'latest research' may be disappointed: the editors admit that the 'rapid pace of research … challenges the ability of any textbook to maintain its currency', but in fact the challenge is due more to the slow pace of textbook production. Published June 2005, only 20/62 chapters have references dating to 2004 (one chapter clearly postdates the Alzheimer's Disease Conference in Philadelphia in July 2004), and 'The neuropathology of Alzheimer's disease in the year 2005' bears a striking resemblance to how I recall it being in 2004, a conclusion supported by the absence of any reference later than 2003 in this chapter. The variable rate at which authors produce chapters may also lead to disconcerting effects: the gene defect in AOA2 is reported to be unidentified (731) but is discussed (senataxin) elsewhere (742,762). Creatine is stated not to have been used in the treatment of MND (918) but such a trial, reported in 2003, is discussed elsewhere (779). Variable authorial effort is also evident: some chapters are comprehensive accounts (eg MSA, SBMA), some have the feel of being produced in a hurry. There are plenty of typos, my favourite was Leigh syndrome described as 'subacute narcotizing encephalopathy' (915). Those who think this is mere pedantry may be interested, as I was, to learn that the original mapping of PARK4 to the short, rather than long, arm of chromosome 4 was due to a typing error (589). The same chapter subsequently states PARK6 to be autosomal dominant (591), rather than recessive. At £220, one expects better proofreading and/or editorial input. Nonetheless, a highly desirable addition for the departmental library.

AJ Larner,
Cognitive Function Clinic,
WCNN, Liverpool, UK.

Save £20 on
The Neurology of Eye Movements

The Neurology of Eye Movements, Fourth Edition, by John Leigh and David Zee is the only book to combine basic and clinical syntheses about eye movements. It is comprehensively rewritten with updated references, with boxes to summarise anatomy and features of clinical disorders.

The book provides clinicians with a synthesis of current scientific information that can be applied to the diagnosis and treatment of disorders of ocular motility. Basic scientists will benefit from descriptions of how data from anatomical, electrophysiological, pharmacological, and imaging studies can be directly applied to the study of disease.

New for this edition: A free CD-ROM with every book, including the entire text, hypertext links, and 60 video clips demonstrating the major disorders of eye movements.

Readers of ACNR are entitled to order the new edition for £100 (normal price £120). Please call +44 (0) 1536 741727 quoting the code ABNEM06. ISBN 0-19-530090-4.

EDITOR'S CHOICE

Anti-epileptic drugs and pregnancy – the best data to date

Pick a common disease area with heavy pharmaceutical interest, something to do with children and long term outcomes for the emotional interest and something to do with sexuality to add a little zest and you have research money for life. The Belfast group need to be congratulated for their pre-science. More importantly they have produced data which those of us at the coal face use every day to try and help our patients with tough decisions about their treatment. For nearly a decade this register has been collecting pregnancy outcomes of patients with epilepsy. The patients have to be reported to the study before any outcome is known, including before any antenatal scans and so is truly prospective and avoids selection bias towards abnormal outcomes that affects retrospective ascertainment. From the prevalence of epilepsy in the UK, the authors estimate that about half of all pregnancies in women with epilepsy are reported into the study. They measured major congenital malformations (MCM), requiring medical intervention, minor malformations and pregnancy loss. By March 2005, 4414 pregnancies were reported into the study and 2598 (72%) were on monotherapy, 21.3% on polytherapy and 6.7% on no treatment throughout pregnancy. 207 (5.7%) pregnancies were lost, 21 with a birth defect, 13 MCM. The rate of MCM was 3.5% for no AED, 3.7% for all monotherapy outcomes and 6.0% for polytherapy outcomes, which was significantly worse. Only 3 drugs had large enough numbers to compare monotherapy outcomes; carbamazepine 900, valproate 715 and lamotrigine 647. The next largest was phenytoin with 82 and the others were very much "also ran". MCM rate was 2.2% for carbamazepine, 6.2% for valproate (P<.001), 3.2% for lamotrigine and 3.7% for phenytoin. It is perhaps worth mentioning that 2 of 28 pregnancies on topiramate resulted in MCM. The spectrum of disorders was similar with the three main drugs. Valproate caused neural tube defects in 1% and facial clefts in 1.5%. Carbamazepine was associated more with cardiac abnormalities (0.7%) than NTD (0.2%) and the commonest abnormality seen with lamotrigine was hypospadias (0.9%). There was no significant difference in the dose of valproate or carbamazepine between those patients who had MCM and those who did not but there was a significant difference between those on lamotrigine with and without MCM. For all the drugs there was a fairly clear trend of a dose-response curve. Carbamazepine <400mg, 1.7% MCM and >1g, 3.3% MCM. Valproate <600mg, 4.1% and >1000mg, 9.1% MCM. For lamotrigine the dose effect was most marked (<100mg, 1.3%; 100-200mg, 1.9% and >200mg 5.4%). Polytherapy combinations containing valproate (9%) were significantly worse than those not containing valproate with an odds ratio 1.31-4.70. 141 pregnancies exposed to valproate and lamotrigine – a good combination for some IGE patients had a 9.6% risk of MCM. So what are the take home messages. Avoid polytherapy – nothing new there. As far as we know, carbamazepine is as good as it gets and especially with newer contraceptive methods there is no reason to change on account of 'women's issues'. Valproate is a real problem even without the recent considerations of possible mild cognitive problems in children without MCM. But it is not as simple as valproate bad, lamotrigine good. In doses over 200mg daily the risk from lamotrigine was comparable to valproate <1000mg daily. This is without taking into consideration the efficacy of the drug for the mother's epilepsy, which is the reason for stepping into this vipers' pit in the first place and that should never be forgotten. As for the new drugs, we await the next 10 years with interest. - ***MRAM***

Morrow JI, Russell A, Gutherie E, Parsons L, Robertson I, Waddell R, Irwin B, Morrison P, McGivern C, Craig J.
Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK epilepsy and Pregnancy register.
BMJ
http://jnnp.bmjjournals.com/cgi/rapidpdf/jnnp.2005.074203v1.pdf

SPINAL CORD TRAUMA: New anti-Nogos get the nod

★★★ RECOMMENDED

Martin Schwab, in Zurich, has published on the molecular biology of neuronal growth since the mid 1970s. Perhaps his most important contribution has been the identification of Nogo-A, a membrane protein found especially in CNS myelin that inhibits neurite outgrowth. Key experiments from 1990 onwards showed that inhibition of Nogo-A with an antibody called IN-1 resulted in long-distance regeneration of lesioned fibres in the spinal cord of adult rats and improved functional recovery from animal models of stroke and traumatic spinal cord and brainstem lesions. The trouble with the antibody, IN-1, is that it is an IgM and is administered by the cumbersome technique of actually grafting the hybridoma cells onto the animals. Cesar Milstein would have despaired! So their study in October's Annals examined the utility of two IgG anti-Nogo-A monoclonals (7B12 and 11C7) that could be administered by infusion through catheters placed in the subdural space over the spinal cord. The spinal cord was cut and antibody was dripped over the lesion for two weeks……and the outcome tested. When the Schwab machine moves into action, it is impressive. Histology of the cord demonstrated that there was long-distance tract regeneration and sprouting in the corticospinal tract with the anti-Nogo-A monoclonals. Fibres actually formed bridges over the lesioned areas, unlike in the control antibody animals. And there were functional improvements in the ability of the antibody animals to run, swim, walk along narrow beams and ladders. Their footprints were better! And then the poor things were put through a fMRI protocol, which showed increased cortical activation following forepaw activation in the antibody animals. All in all, very impressive. But it is ever so slightly unrealistic that we will be able to get epidural catheters into people immediately after their spinal cord trauma! Much more pragmatic was their study in December's Annals, which showed the effect of intra-ventricular infusion of the 7B12 anti-Nogo-A monoclonal in aged adult rats one week after a MCA occlusion stroke. The 7B12 animals were no better off to begin with. But, by 8 weeks after the stroke, their performance on behavioural tasks exceeded controls and continued to improve faster than controls until the end of the study at 14 weeks post-stroke. Rather unexpectedly this improvement seemed to arise, using fMRI pictures, from plasticity within the thalamus - an area not involved in the original stroke. Intriguing… So, perhaps the future management of stroke will be thrombolysis in the community, followed by admission to the neurosurgical theatre for intraventricular catheter placement for infusion of anti-Nogo-A antibody, CNTF, BDNF and whatever else is good for neuronal regeneration… - ***AJC***

Markus TM, Tsai SY, Bollnow MR, Farrer RG, O'brien TE, Kindler-Baumann DR, Rausch M, Rudin M, Wiessner C, Mir AK, Schwab ME, Kartje GL.
Recovery and brain reorganization after stroke in adult and aged rats.
ANNALS OF NEUROLOGY
2005 Dec;58(6):950-3.
Liebscher T, Schnell L, Schnell D, Scholl J, Schneider R, Gullo M, Fouad K, Mir A, Rausch M, Kindler D, Hamers FP, Schwab ME.
Nogo-A antibody improves regeneration and locomotion of spinal cord-injured rats.
ANNALS OF NEUROLOGY
2005 Nov;58(5):706-19.

EPILEPSY: Antiglial cell autoantibodies and childhood epilepsy

The role of autoimmunity in epilepsy is currently a focus of interest. The identification of syndromes which may present with seizures such as limbic encephalitis associated with voltage-gated potassium channel antibodies has increased interest in this group of disorders. However, these patients are usually unwell in other ways and do not usually just have seizures. The authors describe a child of 2 who developed refractory right focal motor epilepsy, suffering up to 100 seizures per day, associated with a right hemiparesis. An MRI showed an area of cortical abnormality in the left pericentral region and a presumptive diagnosis of Rasmussen's encephalitis was made, leading to treatment with immunosuppression. Epilepsy continued to be severe but neither the hemiparesis nor the MRI features progressed over the next 8 years. He underwent a biopsy of the abnormal region, which showed Taylor type cortical dysplasia with balloon cells but no evidence of an active inflammatory process. In recent years there has been a question of a relationship between antibodies to GluR3 to Rasmussen encephalitis and serum was taken from this child at 6, 11 and 20 months after diagnosis. Control sera were taken from other patients with RE, five patients with West Syndrome and two with Lennox Gastaut syndrome. The patient's serum appeared to increase calcium in glia in an in vitro model and the effect was not affected by Glu-R3, suggesting no major influence of this receptor on ion fluxes. In neurons, the affect of patient's serum was reduced by GluR3B suggesting competitive binding with patient's antibody and the changes in calcium were mediated via the Glu R3 receptor. The antibodies were present only in the early, very active phase of the disease. This patient had a developmental abnormality but early in the course of their illness expressed functioning antibodies – the first time this has been demonstrated. The relationship of these antibodies to pathogenesis is uncertain, and the same antibodies were not found in controls. It remains to be proven that the antibodies are not an epiphenomenon but their functional effect suggests a potentially more complex relationship between histopathology and immunology in the genesis of some epilepsy. Unfortunately the child's condition was not helped by steroid or IVIg early in the course of the disease. We await more evidence of immunological epilepsy with interest. - ***MRAM***

Rouberti A, Boukhaddaoui H, Sieso V, de Saint-Martin A, Lellouch-Tubiana A, Hirsch E, Echenne, B and Valmier J.
Antiglial cell autoantibodies and childhood epilepsy: a case report.
EPILEPSIA
2005; 46:1308-1312.

MIGRAINE: cortical hyperexcitability between episodes

It is known that visual processing between migraine attacks is abnormal, and we see this in some migraineurs who are constantly sensitive to light and certain patterns. (One of my colleagues owns a diagnostic patterned tie which migraineurs object to, and others simply tolerate). Whether this phenomenon is due to cortical hyper- or hypoexcitability was the subject of this interesting study. Twenty migraineurs and twenty controls were compared in their motion perception thresholds in two settings: responses to coherent moving dots presented in an incoherent and then a coherent environment. The results were that migraineurs performed better than controls in the coherent environment (with high signal to noise ratio) and worse in the incoherent environment. It is suggested that several neuronal encoding patterns in a defined cortical area in migraneurs may be activated during a noisy task, while a distraction free task allows a small focused area of activation. Excessive excitation due to abnormal release of excitatory neurotransmitters may be a factor in this and is supported by the finding of higher plasma levels of glutamate in migraineurs. It has also been suggested that repeated episodes of cortical spreading depression may result in suppression or damage to GABAergic inhibitory function. Alternatively it has been suggested that cortical hyperexcitability may cause migraineurs to be vulnerable to cortical spreading depression. It seems clear that the central factors in migraine are complex and as yet poorly understood. – ***HA-L***

Antal A, Temme J, Nitsche MA, Varga ET, Lang N, Paulus W.
Altered motion perception in migraineurs: evidence for interictal cortical hyperexcitability.
CEPHALALGIA
2005;25:788-94.

STROKE: A helping hand to help a hand

Can you pat your head and rub your tummy at the same time? Many people find this difficult and end up doing the same action with both hands. This is because the motor system has a strong tendency towards synchrony. There has been interest in exploiting this tendency in retraining arm movements in stroke patients. But the question is: Would the affected arm improve its movement in line with the non-paretic side or would its performance deteriorate? There have been a number of small n kinematic studies looking at stroke patients' movements using one arm or both at the same time. Results have been conflicting; some have found improved performance of the affected limb in bilateral movements while others have found its movement quality is degraded. Using a larger group of thirty-two chronic stroke patients with moderate hemiparesis, Harris-Love et al have analysed the kinematics of arm movements in bilateral and unilateral reaching movement conditions. They also investigated the effect of loading the non-paretic arm to see if the increased effort needed to move the non-paretic arm would trigger increased activation of the paretic arm. The patients were asked to reach forward across a table towards a box as fast as possible. The non-paretic limb was loaded with weights ranging from 5-20% of the maximum strength of the shoulder flexors. Kinematic data was captured using a magnetic tracking system and peak velocity, peak acceleration and total movement times were calculated. The paretic arm achieved higher peak velocity and acceleration in the bilateral condition, although movement time was not significantly different from when the reach was performed unilaterally. No further improvement was gained by weighting the non-paretic arm. It seems that performing the movement bilaterally at least improves activation of the ballistic phase of reaching. This makes sense since it is known from anatomical studies and from transcranial magnetic stimulation studies that the proximal muscles are strongly influenced by bilateral projections. Encouraging bilateral movements could be a useful strategy to facilitate early recovery of arm movements. There have been some encouraging results so far. It will be interesting to see if, when tested using a randomised controlled trial, these effects translate to long lasting improvements in function. – ***AJT***

Harris-love ML, McCombe Waller S, Whitall J.
Exploiting interlimb coupling to improve paretic arm reaching performance in people with chronic stroke.
ARCHIVES PHYSICAL MEDICINE AND REHABILITATION
2005; 86: 2131-7.

EPILEPSY: What difference does a neurologist make?

The authors contacted all patients with possible or definite epilepsy in the Wrexham catchment area, identifying them from GP records of diagnosis or anti-epileptic drug intake. In a population of 200,000, they excluded 183 children under 16 and 123 over 80. They also excluded 357 adults already attending an epilepsy clinic, leaving 275 patients. Only 53 (19%) had previously been seen by a neurologist. Each patient was seen and classified as definite or doubtful epilepsy. Prevalence of epilepsy was 0.69% - very similar to other studies. Overall remission rate was around 60%, similar for neurologists and non-specialists (Perhaps we should all go home). Misdiagnosis rate was 16%, similar to the one fifth of patients misdiagnosed in many hospital based studies in the last 20 years. For patients seen by neurologists, the misdiagnosis rate was 5.6% compared to 19.3% for patients diagnosed by non-specialists. For 87 patients (one third) they felt there were sufficient grounds to recommend specialist follow-up. In 17 patients a long-term remission was achieved by adjusting the dose of medication or changing the treatment. Ten of these were focal and 6 idiopathic generalised epilepsies, with one symptomatic generalised epilepsy. In this cohort, few of whom had previously seen a neurologist, a full clinical assessment led to a major change in diagnosis or treatment in about 20% of patients. So neurologists do seem to do better than non-neurologists and the study shows the size of the unmet need of patients in the community who suffer continuing seizures, and could either be re-diagnosed or treated better if they were seen by specialists. The challenge is to find ways of developing services to deal with this when neurologists are still quite thin on the ground. - ***MRAM***

Leach JP, Lauder R, Nicolson A, Smith DF.
Epilepsy in the UK: Misdiagnosis, mistreatment and undertreatment? The Wrexham area epilepsy project.
SEIZURE
2005;14:514-20.

NEUROGENESIS: Forget Atkins, try CNTF

★★★ RECOMMENDED

Neurogenesis, as ACNR readers are probably now aware, occurs constitutively in the adult mammalian CNS in the subventricular zone (SVZ) and the dentate gyrus (DG) of the hippocampus. Constitutive neurogenesis may occur elsewhere in the brain but this is difficult to detect using current methods of labelling of newborn cells. Newborn cells are labelled using bromodeoxyuridine (BrdU), a thymidine analogue which binds to cells undergoing division. Kokoeva, Yin and Flier have infused BrdU continuously for 7 days into the ventricles of adult mice, and this labels more dividing cells than the normal, less frequent administration protocols. As a consequence, BrdU-positive cells were found in the hypothalamus, particularly in the arcuate nucleus, and the cells were unlikely to have migrated from the SVZ. Thus, neurogenesis may play a role in hypothalamic function. Ciliary neurotrophic factor (CNTF) is known to induce weight loss that is, unlike most other agents, sustained in the long term. An infusion of CNTF was found to increase the number of BrdU-positive cells in the hypothalamus, particularly in areas pertaining to feeding control. Newborn cells expressed CNTF receptors; around 50% expressed neuronal markers and around 20% oligodendrocyte markers. The newborn cells, after CNTF infusion, were also leptin responsive, as would be appropriate for such neurons. Mouse models of obesity, deficient in leptin or its receptor, also displayed a neurogenic response following CNTF but not sustained weight loss suggesting that the latter requires leptin signalling. CNTF-induced neurogenesis and sustained weight loss was abolished after anti-mitotic administration suggesting the two are causally related. This study shows that neurogenesis occurs in the hypothalamus, and this can be manipulated to produce weight changes. Thus, neurogenesis seems to be involved in other processes other than olfaction (SVZ neurogenesis) and memory (DG neurogenesis), with wide-ranging therapeutic implications. - ***WP***

Kokoeva MV, Yin H, Flier JS.
Neurogenesis in the Hypothalamus of Adult Mice: Potential Role in Energy Balance.
SCIENCE
2005:310(5748);679-83.

MIGRAINE: Size really matters

★★★ RECOMMENDED

The significance of patent foramen ovale (PFO) in migraine remains a troubled area. Studies show an increased incidence of PFO in migraineurs compared to controls. But a significant number of normals have a PFO, and as clinicians we have trouble knowing what PFOs mean in migraine and what to do about them. This is the first study examining the anatomy and size of these right-to-left shunts. 93 consecutive patients with migraine with aura and 93 healthy controls were studied with transoesophageal echo. A PFO was found in 47% of the migraine with aura group, significantly more than the 17% of controls. This is not a new finding. What is novel is the finding of a moderate to large shunt in 38% of the migraine group compared to only 8% in controls. In this study, the presence of a moderate to large shunt increased

the odds of having migraine with aura almost 8-fold. The echo findings in the two groups were otherwise identical. Unfortunately the study found no distinguishing clinical features of migraineurs with a shunt compared to those without, which could potentially help us to know who to focus our investigations on. It is good to have a study which details characteristics of shunts in migraineurs and this offers promise of untangling "benign" incidental PFOs from those which matter and require further action. – ***HA-L***

Schwerzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, Seiler C.
Prevalence and size of directly detected patent foramen ovale in migraine with aura.
NEUROLOGY
2005;65:1415-8.

PARKINSON'S DISEASE: Deep brain stimulation – is it really that good?

★★★ RECOMMENDED

In 1987 Alim-Louis Benabid developed a new therapeutic approach of using deep brain stimulation as a way of managing the more advanced motor complications of patients with advanced Parkinson's disease. It stemmed from the chance observation that thalamic high frequency stimulation in a patient with tremor alleviated their symptoms. As a result of this a large number of groups around the world slowly adopted this procedure and it is now one of the treatments of choice in patients entering this phase of the disease. Whilst there is no doubt that it is extremely effective the questions have always been what is the best site, how effective is the treatment and are there any significant side effects. Over the years the papers have rolled out reporting on various aspects of the procedure but of late there have been a flurry of papers looking at the long term efficacy of this treatment. The first major study of this sort was two years ago by Krack et al reporting in the New England Journal of Medicine. However in a recent issue of Brain, Rodriguez-Oroz and colleagues publish on a world wide multicentre study where 69 patients were assessed 3 – 4 years post operatively. The majority had subthalamic stimulation although about a third of the patients had pallidal stimulation. Overall the two sites seemed to be of equal efficacy with the main benefit being in reducing the off periods and dyskinesias, the axial symptoms responding less well and indeed complications of speech not being uncommon. Furthermore in terms of the underlying Parkinson's disease itself, the major benefits seem to be in tremor followed by rigidity, bradykinesia and gait. This study is very much corroborated by the study of Schupback et al reported in the JNNP in which they follow up for five years 37 patients who had bilateral subthalamic stimulation. The conclusion from this study was again that dyskinesias were greatly improved as were other features of the disease but they also report on cognitive decline and a series of other side effects all of which have been described before including disturbances of mood, dysarthria and weight gain. Thus overall deep brain stimulation clearly seems to offer advantages in the management of patients with relatively advanced Parkinson's disease. However the procedure is not without side effects which to some extent reflects pathology outside of the basal ganglia circuitry which is obviously not targeted by such interventions. The emerging publication of these long term series is clearly important and I suspect may impact upon recruitment of patients to such studies such that as the years go by the procedure will be reserved for more selected patients. Whatever the essential role of this treatment in the management of Parkinson's disease it is clear that the use of deep brain stimulation is here to stay (assuming that the economics of it in the UK can be resolved) and that when targeted to the right site, in the right patient has dramatic benefits at a stage of disease when medical therapies are often extremely difficult to use successfully. - ***RAB***

Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, Kulisevsky J, Albanese A, Volkmann J, Hariz MI, Quinn NP, Speelman JD, Guridi J, Zamarbide I, Gironell A, Molet J, Pascual-Sedano B, Pidoux B, Bonnet AM, Agid Y, Xie J, Benabid AL, Lozano AM, Saint-Cyr J, Romito L, Contarino MF, Scerrati M, Fraix V, Van Blercom N.
Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up.
BRAIN
2005;128:2240-9.

Schupbach WM, Chastan N, Welter ML, Houeto JL, Mesnage V, Bonnet AM, Czernecki V, Maltete D, Hartmann A, Mallet L, Pidoux B, Dormont D, Navarro S, Cornu P, Mallet A, Agid Y.
Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up.
JOURNAL OF NEUROLOGY NEUROSURGERY & PSYCHIATRY.
2005;76(12):1640-4.

ACNR's Editorial Board

Roger Barker is Co-editor and Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair.

Alasdair Coles is Co-editor and University Lecturer in Neuroimmunology at Cambridge University.

Stephen Kirker is Rehabilitation Editor and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge.

David J Burn is Conference News Editor and Consultant & Reader in Movement Disorder Neurology at the Regional Neurosciences Centre, Newcastle-upon-Tyne.

Andrew Larner is Book Review Editor and Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery, Liverpool.

Andrew Michell is Conference News Assistant and SpR in Neurophysiology, Queens Square, London.

Alastair Wilkins is Case Report Co-ordinator and Specialist Registrar in Neurology in Cambridge.

Roy O Weller is Neuropathology Editor and Emeritus Professor of Neuropathology, University of Southampton.

Masud Husain is Editor of the Visual Neuroscience series and Professor of Clinical Neurology at the Institutes of Neurology and Cognitive Neuroscience UCL, and the National Hospital for Neurology and Neurosurgery.

International Editorial Liaison Committee

Italy: **Professor Riccardo Soffietti**: Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni, Battista Hospital, Torino;

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

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

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

Journal reviewers this issue:

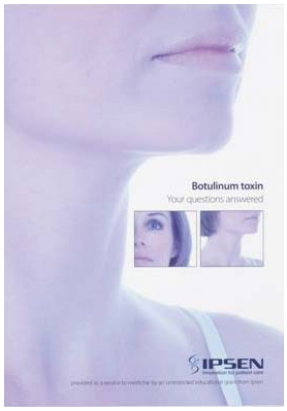
Roger Barker, Cambridge Centre for Brain Repair;
Alasdair Coles, Cambridge University;
Heather Angus-Leppan, Royal Free & Barnet Hospitals;
Mark Manford, Addenbrooke's Hospital, Cambridge & Bedford Hospital;
Wendy Phillips, Addenbrooke's Hospital, Cambridge;
Ailie Turton, Burden Neurological Institute, Bristol.

ACNR is published by Rachael Hansford, Whitehouse Publishing, 1 The Lynch, Mere, Wiltshire BA12 6DQ.
Tel/Fax: 01747 860168. Mobile: 07989 470278,
Email: Rachael@acnr.co.uk
Printed by: Warners Midlands Plc, Tel: 01778 391000.

Copyright: All rights reserved; no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without either the prior written permission of the publisher or a license permitting restricted photocopying issued in the UK by the Copyright Licensing Authority. Disclaimer: The publisher, the authors and editors accept no responsibility for loss incurred by any person acting or refraining from action as a result of material in or omitted from this magazine. Any new methods and techniques described involving drug usage should be followed only in conjunction with drug manufacturers' own published literature. This is an independent publication - none of those contributing are in any way supported or remunerated by any of the companies advertising in it, unless otherwise clearly stated. Comments expressed in editorial are those of the author(s) and are not necessarily endorsed by the editor, editorial board or publisher. The editor's decision is final and no correspondence will be entered into.

Would you like to join ACNR's reviewer's panel?
For more information, email Rachael@acnr.co.uk or tel: 01747 860168

New Leaflet Addresses Key Questions about Botulinum Toxin



'Botulinum toxin: your questions answered' is a new leaflet for people with dystonias available from Ipsen Limited. The leaflet was developed initially to help The Dystonia Society, the organisation dedicated to the support of people affected by dystonia, answer questions from members about the use of botulinum toxin type A (Dysport®).

Dystonia is a term used to describe a group of conditions characterised by uncontrollable muscle spasms that can affect one or several parts of the body, causing abnormal movements and postures. The condition is thought to affect over 40,000 people in the UK, making it ten times more common than motor neurone disease. It is estimated that there could be thousands more dystonia sufferers, many of whom do not realise that they have the condition. Dysport® is not a new medicine for the treatment of dystonia – it has been used successfully for over 15 years.

The leaflet addresses a wide range of questions ranging from 'how does it work?' to 'do I have to come to hospital for my treatment?' and 'how many injections will I need?'. The questions are answered simply and concisely.

Copies of the leaflet can be obtained from Medical Information Department, Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE. Tel: 01753 627777, Email: medical.information.uk@ipsen.com

New Sonara Digital Transcranial Doppler System

Pulse Medical Limited have introduced the Sonara digital Transcranial Doppler system from Biobeat Medical, available with 2, 4, 8Mhz probes and monitoring Head-frame.

Operating the Sonara is simple and intuitive with its large 15" integrated touch screen display. The user-friendly remote control can be used in one hand to control all of the main features.

The Sonara has many features including M-Mode display, Monitoring, Multi-gating, Velocity Profiles, Emboli Detection, and many unique features such as Summary Screen, Risk factor and Trends.

The Sonara is also ideal for research with complete statistical analysis of your patient database, with colourful graphs. The data can even be exported as a Bmp, Excel format, or as raw data.

For further information please contact Pulse Medical Limited, 3000 Cathedral Hill, Guildford, Surrey GU2 7YB. Tel: 01483 243573 Fax: 01483 243501. Email: sales@pulsemedical.co.uk Web: www.pulsemedical.co.uk

Botulinum Toxin in the Treatment of Cerebral Palsy

'The role of botulinum toxin in the treatment of cerebral palsy. Frequently asked questions and answers for parents and children' is a new booklet available from Ipsen Limited. The booklet was developed together with Scope, the disability organisation in England and Wales.

Cerebral palsy is caused by damage to the brain that takes place before, during or in the early days after birth. When the brain is damaged in this way, many children have 'spasticity', where their arms and legs feel stiff and are difficult to move. Some movement may be possible, but tends to be quite limited and prevents them from independently joining many of the activities in which children participate. Botulinum toxin type A (Dysport®) can be used to treat this spasticity in children of two years of age and older.

The booklet will help parents and children understand why botulinum toxin injections have been recommended. It explains what botulinum toxin is, how it is used, how it works and what effects it has. At the end of the booklet there are some frequently asked questions.

Copies of the leaflet can be obtained from Medical Information Department, Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE. Tel: 01753 627777. Email: medical.information.uk@ipsen.com and from Scope's website: www.scope.org.uk

Annual National Dementia Conference

MA Healthcare are once again staging their Annual National Dementia Conference. Held on the 23-24 February 2006 in London, this conference attracts key speakers within the field of dementia and delegates from around the UK. Now in its 8th year places at this fully CPD accredited conference sell out quickly so secure your place today by going online at www.mahealthcareevents.co.uk, or by calling the booking hotline on 01425 481464.

Free SpO2 Pulse Oximeter Sensor Audit from the Electrode Company

The Electrode Company Ltd specialises in non-invasive monitoring, optical sensors and high performance pulse oximetry. It produces a portable microspectrometer, which, in an independent UK wide survey of pulse oximeter sensor accuracy in over 30 hospitals discovered that over 30% were a cause for concern.

To help hospitals establish their own quality control, the company is offering a free audit to test up to 50 SpO2 sensors in individual NHS Trusts; this offer is available now and up to March 31st 2006. The results of each individual trial will be sent in a confidential written report to each Trust.

The use of pulse oximeters is becoming more widespread, and increasingly patients are being SpO2 monitored intermittently on the wards. Their accuracy is important because it has clinical ramifications if faulty. For example, a sensor with a positive error will lead clinicians to believe that the patient is better oxygenated than is the case.

For information on this free audit, please contact the Electrode Company on audit@electro.co.uk or Tel. 01633 861772.

Axio Imager.A1 with LED Illumination for Routine Microscopy

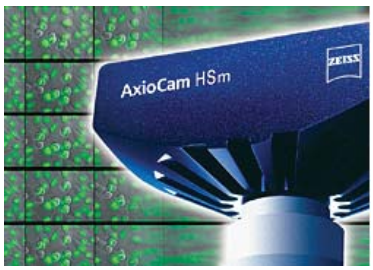
An entry-level version of the Zeiss Axio Imager microscope specially optimised for routine microscopy in pathology, histology, cytology and anatomy is now available. Retaining the optical and ergonomic benefits of the Axio Imager family, the Axio Imager.A1 incorporates an LED illumination system to significantly boost the price/performance ratio.

A powerful LED light source beneath the condenser offers 'Fixed-Köhler illumination' for all contrasting techniques while eliminating the complexity of a transmitted-light beam path. The optical arrangement also ensures homogeneous illumination throughout a range of condenser lens magnifications between 2.5x and 100x. The result is convenient observation and documentation of histological sections in brightfield, phase contrast, darkfield and simple polarisation contrast at an economical price.

LED illumination is now a credible alternative to conventional halogen light sources, offering users simpler and economical operation without sacrificing performance. The intensity-independent colour temperature makes observation and documentation simpler. The LED component is significantly more energy efficient than a halogen lamp whilst the service life is 200 times longer.

For more information Tel: Carl Zeiss UK on 01707 871233.

Zeiss Launches Digital Camera for Live Cell Imaging



Carl Zeiss has launched a vibration-free, digital camera specially optimised for high-speed imaging. Capable of capturing up to 200 high resolution images per second, the Zeiss AxioCam HS offers researchers the opportunity to record in fine detail fast processes in living objects.

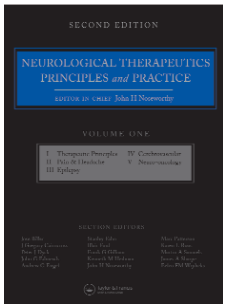
The combination of high speed and high resolution is ideal for experimental work in the fields of neurobiology and developmental biology, amongst others. It opens up new fields, permitting fine intensity graduations to be differentiated even at high speed, the analysis of transport processes in cells at the molecular level and the analysis of motion processes.

The AxioCam HS is available in two versions, monochrome only or colour, both offering 12-bit digitisation. The camera's application software enables compressionless storage of these 12-bit images direct to the computer hard drive with the maximum recording time limited only by the disk capacity. In this way, AxioCam HS records image sequences as digital film clips in scientific image quality. Set-up like this, the new camera is the perfect digital replacement for microscope video cameras, replacing the video's low resolution, low sensitivity, fixed image rate, and limited control with a fully computer-controllable digital video recorder.

For further information, Tel. 01707 871233.

Neurological Therapeutics: Principles and Practice, Second Edition

Editor-in-Chief: John Noseworthy



Building upon the success of its predecessor, this important new edition in 3 volumes continues to address the need for a comprehensive textbook focused primarily on therapeutics.

Providing a reference that is both authoritative and accessible for daily use, key features of this evidence-based, highly acclaimed work include: more than 275 major topics covering the vast patient mix; the most current definitive medical citations; section editors who are all internationally recognised leaders in their fields; new chapters addressing the important issues of stem cell therapy, pharmacogenomics, palliative care, the management of the organ donor, metabolic myelopathy, superficial siderosis and ADHD; focus on the issues underlying treatment decisions; comprehensive summary tables and informative figures.

For more information contact Taylor & Francis on Tel: 0207 017 6184, Email: info.medicine@tandf.co.uk or visit the website: www.tandf.co.uk/medicine

New Dysport® Packaging

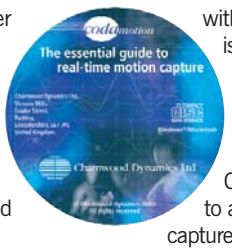
Ipsen Limited has launched new liveried packaging for Dysport® (botulinum toxin type A), following improvements suggested by customers.

The new carton is easier to open and contains the new product logo and branding. It is significantly smaller, taking up less shelf space in the refrigerator. The new pack introduction also coincides with an extension of the shelf life of Dysport® to 24 months.

Dysport® is indicated for focal spasticity including the treatment of arm symptoms associated with focal spasticity in conjunction with physiotherapy, and dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older, only in hospital specialist centres with appropriately trained personnel. It is also indicated for the treatment of spasmodic torticollis, blepharospasm and hemifacial spasm in adults.

For more information contact Customer Services on 01753 627627.

Revised Codamotion CD-ROM



Developer and manufacturer of the world's only truly portable real-time motion capture system, Charnwood Dynamics, has published a revised CD-ROM demonstrating the benefits of the advanced Codamotion CODA CX-1.

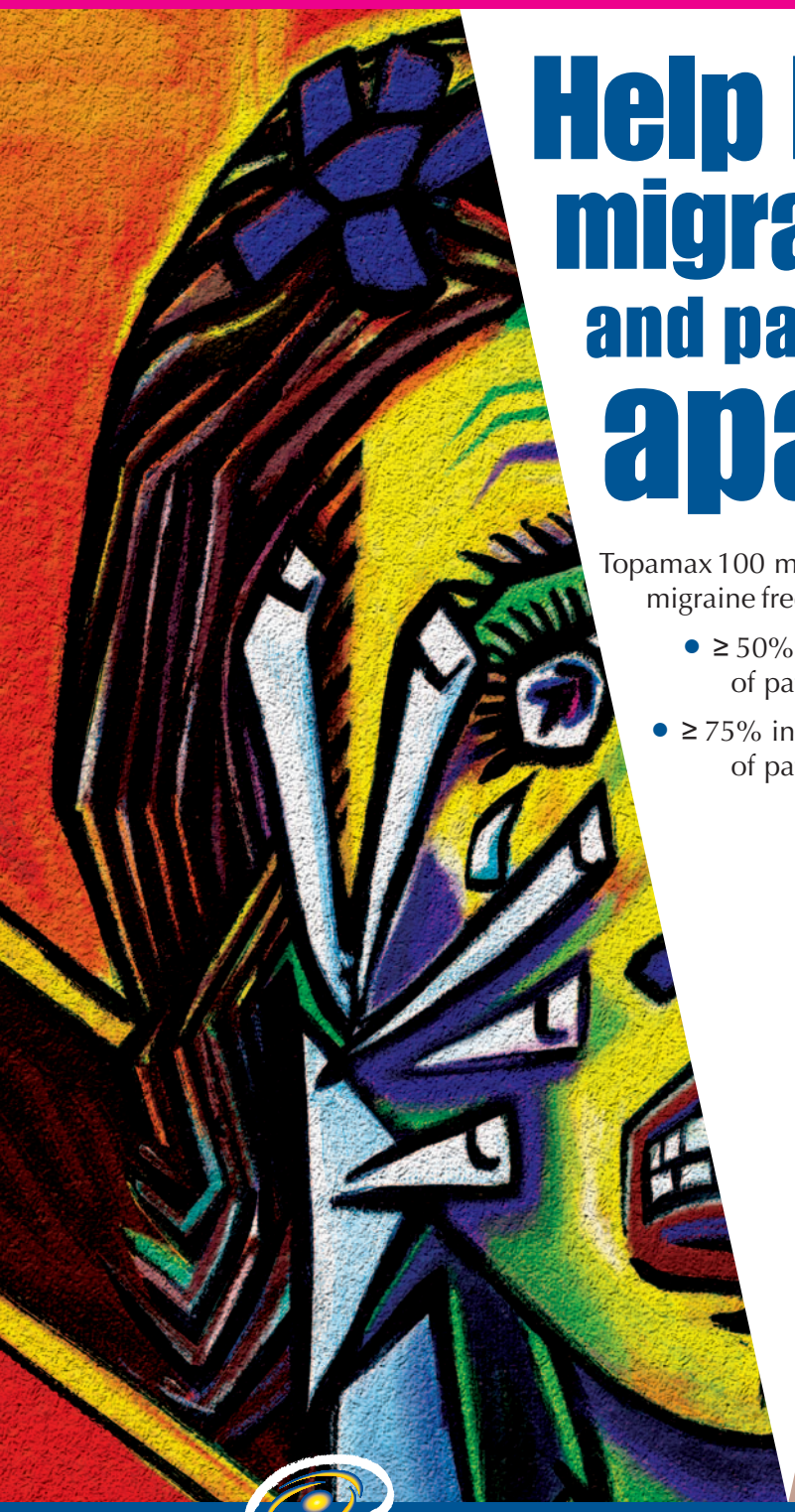
The system offers a remarkable level of real-time 3-D motion capture. It only takes 0.5 milliseconds for data to be output; so multi-channel, tightly coupled, control of external devices is now possible at this same low latency - a performance feature that is closer to real-time than any other system available.

The compact and self-contained system can be operated virtually anywhere with just a laptop computer. It is now easier to transport to remote areas, and can be transported from one hospital laboratory to another.

The revised Codamotion CD-ROM guide is essential to anyone involved in motion capture, especially those application areas where its portable, real time capabilities deliver instant response/simulation, accurate results and real time integration. The CD combines text, graphics, video and sound to help explain the system and how it applies to the many application areas.

The complimentary CD is available from Charnwood Dynamics Ltd, Tel: 0116 230 1060, or see www.codamotion.com

NOW LICENSED AS A NEW SPECIALIST OPTION IN MIGRAINE PROPHYLAXIS



Help keep migraines and patients apart

Topamax 100 mg/day reduced migraine frequency by:

- ≥ 50% in 46% of patients[1]
- ≥ 75% in over 25% of patients[1]

TOPAMAX® (topiramate)

Every migraine-free day is a good day

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. **Uses: Epilepsy**: Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. **Migraine prophylaxis** when 3 or more attacks/month; attacks significantly interfere with daily routine. Six monthly review. Use in acute treatment not studied. Initiation: specialist care. Treatment: specialist supervision/shared care. **Dosage and Administration**: Oral. Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. **Epilepsy**: Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3-6 mg/kg/day (two divided doses). Initiate at 0.5-1 mg/kg nightly with weekly or fortnightly increments of 0.5–1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5-9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1-3 mg/kg. **Migraine**: Over 16 years: Usually 100 mg/day (in two divided doses). Initiate at 25 mg nightly with weekly increments of 25 mg. Longer intervals can be used between dose adjustments. Children under 16 years: Not studied. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. **Contra-indications**: Hypersensitivity to any component. **Precautions and Warnings**: Withdraw gradually. Renal impairment delays achievement of steady-state. Caution with hepatic impairment. May cause sedation; so caution if driving or operating machinery. Depression/mood alterations have been reported. Monitor for signs of depression; refer for treatment, if appropriate. Suicidal thoughts: Patients/caregivers to seek immediate medical advice. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and require discontinuation of Topamax and treatment. Increased risk of renal stones. Adequate hydration is very important. Bicarbonate level may be decreased so monitor patients with conditions/drugs that predispose to metabolic acidosis and reduce dose/discontinue Topamax if acidosis persists. Galactose intolerant, Lapp lactase deficiency, glucose-galactose malabsorption: do not take. **Migraine**: Reduce dose gradually over at least 2 weeks before discontinuation to minimise rebound headaches. Significant weight loss may occur during long-term treatment. Regularly weigh and monitor for continuing weight loss. Food supplement may be required. **Interactions**: Possible with phenytoin, carbamazepine, digoxin, hydrochlorothiazide, pioglitazone, oral contraceptives, haloperidol and metformin. Caution with alcohol/CNS depressants. **Pregnancy**: If benefits outweigh risks. Discuss possible effects/risks with patient. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). **Lactation**: Avoid. **Side Effects**: Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diarrhoea, diplopia, dry mouth, dyspepsia, headache, hypoaesthesia, fatigue, mood problems, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis reported rarely. Suicidal ideation or attempts reported uncommonly. Bullous skin and mucosal reactions reported very rarely. **Pharmaceutical Precautions:** Tablets and Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed. **Legal Category:** POM **Package Quantities and Prices**: Bottles of 60 tablets. 25 mg (PL0242/0301) = £20.92, 50 mg (PL0242/0302) = £34.36; 100 mg (PL0242/0303) = £61.56; 200 mg (PL0242/0304) = £119.54. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.04, 25 mg (PL0242/0349) = £24.05, 50 mg (PL0242/0350) = £39.52 **Product licence holder**: JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ. UK. **Date of text revision**: August 2005. **APIVER150805**.

Reference: 1. Bussone G, Diener H-C, Pfeil J *et al.* Topiramate 100mg/day in migraine prevention: a pooled analysis of double blind randomized controlled trials. Int J Clin Pract 2005; 59(8): 961-968.

JANSSEN-CILAG Ltd

00005127