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Advances in Clinical Neuroscience & Rehabilitation



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Dr John C van Swieten, Dr Sonia M Rosso


Epidemiology of Frontotemporal Dementia

Dr Anish Bahra

Unusual Headache Disorders

Adnan Salman, et al

Noninvasive Conductivity Extraction for High-Resolution
EEG Source Localisation



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If using Follow On Pack, the dose for 5th week is 1.5 mg t.i.d., 6th week 2.0 mg t.i.d., 7th week 2.5 mg t.i.d., 8th week 3.0 mg t.i.d. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually by around 20%. When switching from another dopamine agonist follow manufacturer's guidance on discontinuation. Discontinue ropinirole by reducing doses over one week. **Renal or hepatic impairment:** No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. **Elderly:** Titrate dose in normal manner. **Children:** Parkinson's disease does not occur in children – do not give to children. **Contra-indications** Hypersensitivity to ropinirole, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Ropinirole has been associated with somnolence and episodes of sudden sleep onset. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction seen with other Parkinson's disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Adverse reactions** In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo, however, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see 'Precautions' and 'Effects on ability to drive and use machines'). **Effects on ability to drive and use machines** Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Overdosage** No incidences reported. Symptoms of overdose likely to be related to dopaminergic activity. **Marketing Authorisation Holder** SmithKline Beecham plc t/a GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. **Further information is available from:** Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; customercontactuk@gsk.com; Freephone 0800 221 441. **Date of preparation:** January 2005
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John van Swieten is well known in the field of dementia and it is his clear account on the epidemiology of fronto-temporal dementia (FTD) that forms one of our review articles in this issue. This condition - which encompasses semantic dementia and primary progressive aphasia - seems to be heterogeneous not only in its clinical presentation but its pathology and aetiology, including known genetic defects in tau and more recently in the ESCRT3 complex subunit CHMP2B. This review article clearly lays out the ambiguities of studies attempting to define the prevalence of FTD as well as delineating the heterogeneity and problems and challenges that this throws up.



For most of us (well for me, anyway) once outside the familiar ground of chronic tension type headaches, migraine and cluster headache, the diagnosis of different types of recurrent headaches becomes a little bit muzzy. What for example are hypnic headaches? In this article by Anish Bahra we are taken on a brief but thoroughly helpful review of unusual types of headache, many of which are especially responsive to indomethacin. This clearly written account by such an expert will now accompany me to clinic so that the next time I see someone with a walking headache I will know to refer them for an exercise tolerance test.

Our management series stays with headache. All in clinical practice are familiar with the headache following lumbar puncture, indeed in years gone by it was thought to be helped by not allowing the patient out of bed for several days. However, spontaneous intracranial hypotension as a cause of headache is much less common. In their article Imam and Weatherby explore the pathological basis of this condition, as well as all of its clinical features, investigations and management. This article highlights that it is CSF volume rather than pressure that is critical in the genesis of this condition which can be difficult to diagnose and treat.

Peter Tucker addresses a very interesting area of rehabilitation, namely one of the psychological sequelae and management of children/adolescents with acquired brain injury. As he comments, "a central difference between children and adults is that while the effects of the injury are immediately obvious in adults, children's development is disordered after injury and some deficits may take a considerable time to appear". This is explored through a series of informative tables, highlighting the differences in deficits in children and adults and their functional and educational impact. This is a stimulating review which discusses an often overlooked area of rehabilitation medicine.

Microarrays are now emerging as one of the most exciting new tools in biology as they allow one to look at thousands of genes in a single experiment. Jo Jones leads us through this new technique highlighting the principles that underpin it and the differences between spotted and oligonucleotide Affymetrix gene chips. This is a clear account of an important new technique which has been criticised on the grounds that

it promotes experiments which are non hypothesis-driven fishing expeditions. This is true, but fishing expeditions often identify new fishing grounds to harvest, and as such this is a powerful technique for doing just that. It does of course generate data that represents formidable bioinformatic challenges, as well as issues of which of the changes are of greatest biological significance.

The use of muscle biopsy in modern day neurological practice is explored by Dr Leslie Bridges and shown to be central in the diagnosis of many muscle disorders (see also Rakowicz www.acnr.co.uk/pdfs/volume2issue4/v2i4management.pdf). This account takes us through the practicalities of the biopsy procedure itself, through to its preparation, staining and interpretation. As with all articles in this series it boasts a plethora of wonderful illustrations.

In the visual series Stewart Shipp takes us through the complexities of the parallel visual pathways. The original scheme of organisation within the visual pathway devised by Hubel and Wiesel was conceived of as being serial-hierarchical processing, although in the mid 1960s different functional retinal ganglion cells (XYW system) were recognised, which led to the possibility that the visual system was composed of parallel pathways. This appears to have been verified over the years with three major pathways being recognised projecting from the retina to a number of targets both subcortically and cortically. Stewart Shipp takes us through this complex system highlighting what is known and not known and simplifying what is an immensely complex field into an easily digestible and illuminating article.

Don Tucker and colleagues from Oregon have also provided a very thought provoking article on the use of EEG to more accurately localise abnormalities in the CNS. This is a very technical article but nevertheless clearly written and provides insights into how old techniques can be developed and modified to provide even greater and more useful information in modern day neurological practice.

Andrew Larner takes us to one of literature's most famous epileptics, Fyodor Mikhailovich Dostoevsky. Andrew explores the origin of the epilepsy of this wonderful Russian writer, which encompasses aetiological causes ranging from psychogenic (Freud) to an onset from a left mesial temporal lobe focus (Rosetti & Bogousslavsky). This account is peppered with literary references and will hopefully enthuse you to read his novels - Dostoevsky that is, rather than Larner!!

Finally we have our usual wide range of journal, book and conference reviews. We hope you enjoy this new issue and do let us know if there aspects of neurobiology/neurology/rehabilitation that you would like to see in ACNR.

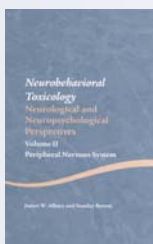
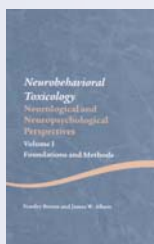
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Neurobehavioral Toxicology

Neurological and Neuropsychological Perspectives

Edited by **James W. Albers**
and **Stanley Berent**,
University of Michigan Medical School

Volume I: Foundations and Methods
ISBN: 1-84169-564-5
Volume II: Peripheral Nervous System
ISBN: 1-84169-565-3
Volume III: Central Nervous System
ISBN: 1-84169-636-6 (Coming in mid-2006)



This three-volume set provides a thorough background to the emerging field of neurobehavioral toxicology by looking at current clinical approaches and tests, and assessing current clinical research. The analysis of the impact of toxins on the human nervous system is particularly and increasingly pertinent given the ongoing expansion of pharmaceuticals, industrial hazards, biological warfare and global pollution. These books will become an essential reference and resource for practicing neurologists and neuropsychologists, occupational medicine physicians and medical toxicologists.

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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.

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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 by:** Orion Pharma (UK) Ltd., Oaklea Court, 22 Park Street, Newbury, Berkshire, RG14 1EA, UK. Full prescribing information is available on request. Stalevo is a registered trademark. **Date of Prescribing Information:** December 2005.

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Orion Pharma (UK) Ltd on 01635 520300.

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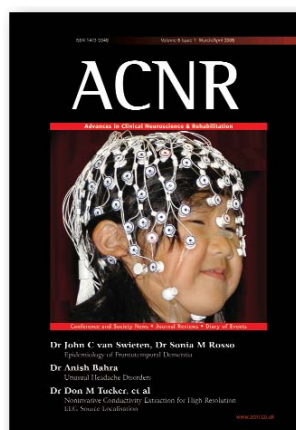
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Cover picture: The Geodesic Sensor Net arrays electrodes in a geometric pattern across the head to allow recording of the brain's electrical activity (the electroencephalogram). In addition, novel methods for assessing head tissue conductivity are being developed with this technology. See Salman et al, page 27.



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particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures — in such patients the possibility of heart block or long sinus pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia,

diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £63.54. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £89.06. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM. **Date of preparation:** December 2004.



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Epidemiology of Frontotemporal Dementia

Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disorder, characterised by progressive behavioural change and a disturbance of language and frontal functions. Memory problems are not prominent at the initial stage. The introduction of criteria according to the Lund-Manchester Groups has helped to distinguish FTD from Alzheimer's disease (AD) in clinical practice.¹ Semantic dementia (SD) and primary progressive aphasia (PPA) are clinical subtypes of FTD that present with prominent language disturbance; both show the same neuropathological characteristics as in typical FTD cases (although mainly restricted to the temporal lobe), suggesting a common aetiology. Therefore, in this chapter we will use the term FTD to describe all clinical variants of this neuropathological spectrum. The frequency of patients with respectively SD or PPA in cohorts of patients with FTD ranges between 10 and 25% in most studies.²⁻⁶ The demographic features of patients with SD and PPA (age at onset, duration of disease, gender distribution, and family history) do not differ in general from patients with FTD.

Patient characteristics

Most patients with FTD are of Caucasian origin.⁷ However, patients of African and Asian descent have also been reported.^{5,7} Most studies show an equal incidence of FTD in men and women (in the Dutch study 49% men, 51% women).⁷ The average age at onset is 50 to 60 years, with a broad range of 21 to 85 years. About twenty percent of patients are older than 65 years at onset of symptoms.⁷ Disease duration is on average 8 years, with a broad range of 2 to 20 years. Symptoms of motor neuron disease are associated with significantly shorter disease duration of 3 years on average. About forty percent of patients have at least one first-degree family member with dementia; half of these patients come from a family with a clear autosomal dominant pattern of inheritance of dementia. The age of onset in familial and sporadic cases does not differ significantly.

The aetiological and pathological heterogeneity of FTD has been the object of extensive research over the past decade. The pathological hallmark of FTD is circumscribed atrophy of the frontotemporal cortex, as described by Arnold Pick,⁸ with neuronal loss, gliosis and spongiosis of the superficial layers of the cortex in all cases. Upon immunohistochemical analysis however, FTD is pathologically heterogeneous with at least three different subtypes being recognised: tau pathology, ubiquitin pathology, and cases without distinctive histology. There is no correlation between the type of neuropathological substrate and clinical syndrome. The term Pick's disease is now exclusively designated for FTD with intraneuronal argyrophilic inclusions, so-called Pick bodies, which consist of abnormal tau protein. Only 10-30% of sporadic FTD cases show Pick bodies.⁹⁻¹⁰ In contrast, 30-60% of familial FTD is pathologically characterised by tau pathology.¹¹

Familial FTD

Although the exact figures vary somewhat between different populations, roughly about 20 to 25% of FTD patients have an autosomal dominant pattern of inheritance. Rare recessive forms have also been described,¹²⁻¹³ but the mode of inheritance is not obvious in the remaining families due to a lack of information on family history or the possibility of non-paternity.¹⁴ Furthermore, the phenomenon of incomplete penetrance has convincingly been demonstrated in one family, making it even more difficult to recognise the pattern of inheritance.¹⁵

In 1998, three research groups identified mutations in the

tau gene in eight families,¹⁶⁻¹⁸ and more than 35 different tau mutations have been recognised in families in Europe, North America, Japan, and Australia over the past years. The frequency of tau mutations varies considerably in different FTD populations, ranging from zero to 18%.¹⁹⁻²³ Mutations in the tau gene have been identified in most familial FTD cases with tau pathology.^{7,11,22} However, a considerable proportion (40-70%) of the total group of hereditary FTD cases shows neither tau mutations nor tau pathology, suggesting a different aetiology.¹¹ The pathological hallmark of a large number of these cases is the presence of ubiquitin-positive inclusions in the hippocampus and frontotemporal cortex. Some of these families have also shown linkage to chromosome 17q21-22 in the absence of tau mutations, suggesting that there may be a second gene involved located close to the tau gene.²⁴⁻²⁷ Furthermore, linkage to chromosome 3 has been reported in a Danish family and a mutation in the *CHMP2B* (charged multivesicular body protein 2B, also known as chromatin-modifying protein 2B) gene has recently been identified in this family.²⁸

Prevalence studies

Several population-based studies addressing the prevalence of FTD have been reported over the past few years. Although the prevalence estimates differ somewhat between studies, it is evident that FTD is much more common than previously suspected. There are two population-based studies from the United Kingdom (UK), one from Cambridge and one from London,²⁹⁻³⁰ one study from the province Zuid-Holland in the Netherlands,⁷ and one regarding the incidence of FTD from Rochester, Minnesota in the United States of America.³¹ Finally, a study in Gothenburg, Sweden estimated the prevalence of FTD in a population-based sample of 85 year olds.³²

The two UK studies are similar in design, investigating all patients with presenile dementia referred to a centre specialising in dementia; older patients were not included. They found an identical FTD prevalence of 15 per 100,000 inhabitants in the age group 45 to 64 years. However, there was a difference of more than factor two in the prevalence of patients with AD in these studies: 15 per 100,000 in Ratnavalli et al²⁹ and 35 per 100,000 in Harvey et al.³⁰ This difference may be due to incomparable rates of ascertainment and/or diagnostic methods between the two studies. The prevalence figures from the Cambridge study²⁹ suggest that FTD may be as common as AD before the age of 65 (both FTD and AD showed a prevalence of 15 per 100,000 inhabitants). However, clinical studies with post-mortem confirmation do not support this view. In a series of 158 consecutive dementia patients in Lund, Sweden only 13% had FTD, compared to 45% with AD, half with a presenile onset.³³ Similarly, in Japan a ratio of FTD to AD has been reported in presenile cases of about 1 to 4.5. In the Dutch study, the maximum prevalence estimate of FTD in patients aged 45 to 64 was 4.0 per 100,000, significantly lower than both UK studies.⁷ This difference may be partly explained by the fact that both UK studies examined all patients with presenile dementia in a defined population, in contrast to examination of only referred suspected FTD patients in the Dutch study.

In the Dutch study, the highest prevalence estimates of FTD were seen at ages 60 to 69, with prevalence estimates of 3.6 per 100,000 at age 50-59 years, rising to 9.4 per 100,000 at age 60-69 years and declining to 3.8 per 100,000 in the 70-79 year age group.⁷ A similar profile was seen in Rochester, Minnesota, where the incidence (new cases per 100,000 person-years) of FTD was shown to be 2.2 for ages 40 to 49, 3.3 for ages 50 to 59 and 8.9 for ages



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60 to 69; no older patients were found.³¹ However, a study in Gothenburg, Sweden estimated the prevalence of FTD in a population-based sample of 85 year olds to be 3.1 per 100 inhabitants.³² This is one of the first studies to address the presence of FTD in older patients and has revealed surprisingly high prevalence estimates. Drawbacks of the Swedish study are a lack of neuroimaging (CT-scanning was available in only 6 of 14 (43%) FTD patients) and neuropathological confirmation.

Conclusion

Epidemiological studies have shown that FTD is more common than previously suspected, but still relatively rare compared to AD, even at younger ages. The highest prevalence is found at ages 60 to 70, although patients older than 85 years have been reported. About 25% of patients have a hereditary form of FTD with autosomal dominant inheritance. Mutations in the tau gene are present in less than half of familial FTD cases. A mutation in the *CHMP2B* gene on chromosome 3 is probably even rarer. Therefore, it is very likely that more common disease-causing genes, one of them possibly located on chromosome 17q²¹⁻²² close to the tau gene, have still to be identified.

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Neutralising Anti-interferon-beta Antibodies in Multiple Sclerosis (NABINMS) – EU Grant

The European Commission Framework Programme 6 has recently awarded a specific grant to establish and validate neutralising anti-interferon-beta antibody (NAB) assays in the EU and to further study the impact of NABs on interferon-beta therapy (IFN β) in subjects with multiple sclerosis (MS). As part of this programme we have developed a novel NAB assay and are now in a position to test for NABs in subjects on IFN β therapy as part of our research programme. If over the next 6-12 months there is sufficient demand for this assay we will be able to provide it as part of our routine laboratory service. The evidence that NABs impacts negatively on the efficacy of IFN β is beyond doubt and has significant implications for the cost-effectiveness of IFN β therapy.¹ Subjects with MS treated with IFN-beta should be offered routine NAB testing within the first 24 months of starting treatment as standard clinical practice.² We would advise routine testing at

12 and 24 months. If subjects are NAB-ve at 24 months, repeat NAB testing is not indicated, unless a positive result is likely to affect a treatment decision. NAB testing should also be considered in subjects with clinical evidence of disease activity who have been on IFN β therapy for at least 6 months. It is recommended that in subjects who are persistently NAB+ve (≥ 100 NU on two consecutive occasions) IFN β therapy should be discontinued.² It is debatable about what to do with subjects who are persistently positive at lower titres (20-100 NU), as some subjects with low titres may still have evidence of in vivo IFN β bioactivity, eg induction of IFN β -specific genes, albeit at a lower level. In addition, there is greater tendency for subjects with low titres to spontaneously revert to NAB negative over the next 3-4 years; the chances of this occurring are up to 20% for subjects treated with IFN β -1a and up to 60% for subjects treated with IFN β -1b.³



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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. Co-administration 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 breastfeeding. **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

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Unusual Headache Disorders

Primary headache phenotypes continue to expand. This review will focus on some of the more uncommon primary headache disorders defined in chapter 4 of the International Headache Society (IHS) Classification for Primary Headaches: Primary stabbing headache, Primary cough headache, Primary exertional headache, Hypnic headache, and New persistent daily headache.¹ The aetiology remains speculative. There is increasing evidence for neurally driven mechanisms as integral to the development of the more common primary headaches. The same is likely to be true for the uncommon disorders. Most primary headache phenotypes may be precipitated by a secondary pathology. The appropriate context in which to investigate will be discussed.

Primary Stabbing Headache

Phenotype: The head pain occurs as single jabs or a series of jabs, predominantly in the distribution of the first division of the trigeminal nerve. The pain lasts for a few seconds. There are usually no additional features. Attacks occur with irregular frequency, from once to many times a day. In more than 50% of cases the disorder is associated with other primary headache disorders (migraine, cluster headache, paroxysmal hemicrania, hemicrania continua).

Management: The syndrome shows a complete or partial response to Indomethacin.²

Primary Cough Headache

Phenotype: The head pain is sudden onset, bilateral and precipitated (rather than aggravated) by coughing, straining or other Valsalva manoeuvres. The duration ranges from one second to 30 minutes. Typically the pain arises moments after coughing, reaches a peak almost instantaneously, then subsides over several seconds or minutes. Most patients are pain free between attacks but some may have a dull headache afterwards which persists for hours. Typically migrainous features, such as nausea, photophobia and phonophobia, are uncommon. Rarely the pain can be unilateral.³

Investigation: Symptomatic cough headache is reported for a number of pathologies which include Chiari I malformation, cerebrospinal fluid (CSF) volume depletion, basilar impression, medulloblastoma, middle and posterior fossa meningioma and pituitary adenoma.³ Although some reports of symptomatic cough headache show a clear association, the association in other cases is tentative. Clinical characteristics and treatment responses cannot differentiate between primary and secondary cough headache.⁴ Thus, until the literature becomes more clear, all patients with cough headache should have magnetic resonance imaging. A diagnosis of primary cough headache remains that of exclusion.

Management: The most consistently reported effective treatment is with indomethacin.⁵ Doses range between 25 and 250mg daily. Treatment should be withdrawn periodically as symptoms may naturally remit. Open-label trials, often case reports, of effective treatments are published for acetazolamide,⁶ methysergide,⁷ parenteral dihydroergotamine,⁸ naproxen,⁸ propranolol⁷ and lumbar puncture.⁹ The latter involves removal of 40ml of CSF. Constituents are normal. Responses can be dramatic and long-term.⁵

Primary Exertional Headache

Phenotype: Exertional headache is distinguished from exercise-induced migraine. The headache is brought on by and

occurs during or after physical exertion. The pain can be prevented by avoidance of physical exertion. The pain can be of thunderclap or gradual onset, bilateral, less commonly unilateral, throbbing in quality, and with or without migrainous features. Symptoms persist from 5 minutes to 48 hours.^{3,9,10}

Investigation: All patients with exertion-precipitated thunderclap headache must be investigated for symptomatic headache, most commonly subarachnoid haemorrhage (SAH).¹¹ Patients are more likely to have benign exertional headache if the headache is of gradual onset during exertion.

Management: In situations where exertion cannot be predicted, treatment is regular prophylaxis. If exertion can be predicted, pre-emptive therapy 30-60 minutes before exercise can be used. The most consistent responses have been reported for Indomethacin 25-250mg.¹² Aim to start at the lowest dose and titrate up as required and tolerated. Reports also exist for propranolol, naproxen and ergotamine derivatives.^{3,8}

Walk Headache

Walk headache is currently not defined by the IHS classification. The headache occurs with exertion, may be unilateral or bilateral and with or without additional features (eg nausea). There may be concomitant chest or left arm discomfort. The headache settles with rest and can be eased by anti-anginal treatment such as nitroglycerine spray. The diagnosis can be confirmed by an exercise electrocardiogram or thallium scan. The headache responds to treatment of the cardiac ischaemia. All reported cases except one have been over 50 years old (one 40 years). Older patients with a supportive history, particularly with cardiovascular risk factors, should be investigated accordingly.¹³

Primary Headache Associated With Sexual Activity

Phenotype: There are two clinical syndromes of headache associated with sexual excitement (coitus and masturbation): (1) Thunderclap headache just before or at orgasm. (2) Bilateral, often occipital, pressure-headache which gradually increases in severity towards orgasm. Sexual activity may be a precipitant for 'spontaneous' low CSF volume headache.¹⁴ This is presumed to be due to a ruptured developmental malformation eg perineural cyst or meningeal diverticulum. Sexual headaches are not experienced with every sexual encounter.^{3,10,14,15}

Investigation: As for exertional headache all patients with sexual excitement-precipitated thunderclap headache must be investigated for symptomatic headache.¹⁶ Patients are more likely to have benign sexual headache if the headache is of gradual onset and develops during excitement.

Management: The most effective therapies are propranolol (40-200mg) or Indomethacin (25-225mg) taken as regular prophylaxis or pre-emptively before sexual intercourse.³ There is a single successful report of Naratriptan 2.5mg taken 2 hours pre-emptively.¹⁷

A significant proportion of patients presenting with cough, exertional and sexual headaches have symptomatic headache (up to ~60%), thus the recommendation is to image all patients. Since the pain occurs in paroxysms and naturally remits, figures for symptomatic forms no doubt remain confounded by referral bias. Both primary and secondary forms of cough, sexual and exertional headache are more common in migraineurs.¹⁸ There does appear to be an association between exertional and sexual headache; this is



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Table: Summary of Unusual Headache Disorders

	Cough headache	Exertional headache	Sexual headache	Hypnic headache	Stabbing headache
Site of pain	Usually bilateral	Bilateral	Bilateral	Bilateral	Varying site – mainly V1 trigeminal
Character of pain	Sharp, stabbing	Throbbing	Thunderclap – before or at orgasm or bilateral pressure headache gradually increasing in severity towards orgasm.	Dull	Single jabs or series of jabs
Additional features	Nausea, photophobia and phonophobia uncommon	With or without nausea, photophobia and phonophobia	None	Usually featureless. Autonomic features, photophobia and phonophobia uncommon.	None
Duration	Seconds to 30 minutes	5 minutes to 48 hours	A minute to 3 hours	60 to 180 minutes	Seconds
Frequency	Sudden and precipitated by cough, straining or other types of Valsalva	Pain precipitated by and occurs during or after physical exertion	Associated with orgasm	Exclusively during sleep. Up to 6 times / night	Irregular frequency
Preventative Treatment	Indomethacin	Indomethacin, propranolol, ergotamine derivatives	Indomethacin, propranolol	Lithium, caffeine, indomethacin	Indomethacin

reported in 10–40% of patients.^{3,10,14} However a distinction between sexual excitement and exertion associated with sexual activity is not consistently made. Therefore the association may merely reflect the commonality of headache associated with exertion.¹⁵

Hypnic ('Alarm-clock') Headache

Phenotype: Attacks of head pain occur exclusively during sleep and wake the patient, often at consistent times during the night. The pain is typically moderately severe, generalised, dull and featureless. Attacks usually last an hour (range 15–180 minutes) and can occur up to 6 times per night.¹⁹ The pain can be unilateral, throbbing, with nausea and uncommonly autonomic features, photophobia and phonophobia can be present.

Investigation: Since all primary headache phenotypes can be precipitated by a secondary pathology, there remains an argument for imaging all patients with unusual headache disorders until there is adequate data to support doing otherwise.

Management: Treatment responses are from case reports which are few. Sumatriptan and oxygen do not seem to be effective. Aspirin is the most consistently reported effective abortive treatment. Preventative efficacy is reported for lithium, caffeine, indomethacin and flunarizine.

New Persistent Daily Headache (NPDH)

Phenotype: NPDH is a relatively newly recognised head pain disorder. The headache is daily and unremitting from onset (within 3 days at most), and lasts more than 3 months. The IHS classify the phenotype as that of tension-type headache but with new onset and chronic evolution; this is not supported by the literature. From a cohort of 56 patients, 80% could pin-point the exact date of headache onset.²⁰ In 30% onset was associated with a 'flu-like illness, in 12% extracranial surgery, and 12% a stressful life event.

Thirty-eight percent had a prior history of episodic headache, most commonly migraine. None had a prior history of chronic headache. The daily pain was continuous in 80% and bilateral in 64%. The prevalence of nausea was 68%, photophobia 66%, phonophobia 61%, throbbing pain 54% and visual aura 9%.

Investigations: The diagnosis of secondary NPDH is guided by additional neurological and systemic clinical features eg subarachnoid haemorrhage, meningitis, arterial dissection, head injury. Most of these patients present initially to the acute medical and surgical teams. The patient group who present to the neurologist is that represented by the cohort of Rozen,²⁰ often many months or years from the onset. Neurological examination pertinent to the headache and imaging (CT or MRI) are normal. One study found 85% of patients had evidence of active Epstein-Barr infection compared to 13% of controls. A treatable cause of NPDH is spontaneous low CSF volume headache. By the time the patient is seen postural features are often absent. Most patients do not have MRI with gadolinium to address pachymeningeal enhancement. This is the investigation of choice in patients presenting with NPDH.

Management: There are no randomised controlled trials of treatment in NPDH. Consistently clinical experience suggests these patients are refractory to abortive and preventative treatment. Despite withdrawal of all abortive medication, patients remain resistant to preventative treatment. Management usually involves minimisation of acute-relief medication, establishment of preventative treatment (often those used in the management of daily migraine), with or without local anaesthetic blockades such as greater occipital nerve injection. The initial series of 45 patients quoted 86% headaches had disappeared by 2 years, while many patients from the cohort of Rozen continued to suffer for more than 5 years.

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The Clinical Pathology of Muscle Disease

The role of muscle biopsy in the investigation of muscle disease has changed in recent times. Although some of the older indications are gone, new ones have arisen and the neuropathologist is now able to offer more than ever before, in the work-up of the patient with muscle disease.

How is a muscle biopsy done?

Muscle biopsy is done either as an open or percutaneous procedure.¹ Open muscle biopsy has the advantage of providing more tissue, and where the muscle is very fatty, allows selection of more muscular elements. Percutaneous procedures, such as needle biopsy and conchotome biopsy, have the advantage of being sideroom procedures with a smaller resulting scar and less disruption for the patient.

The choice of muscle for biopsy depends on clinical considerations. A mildly clinically affected muscle may show little change down the microscope whereas a severely affected muscle may show end-stage changes only. For these reasons, a moderately affected muscle is usually best. In many situations a good muscle for biopsy is quadriceps. Being a proximal muscle it is affected in most common disorders and being a large target it offers the best chance of a reasonable sized biopsy. It is also most familiar for the operator and the pathologist. From the histological point of view, quadriceps is a mixed muscle (containing approximately equal proportions of type 1, 2A and 2B fibres). Muscle diseases that bring about changes in these proportions can therefore readily be detected in quadriceps. Tibialis anterior, another muscle that is sometimes biopsied, comprises about 70% type 1 fibres, meaning that changes in fibre type profiles are less easy to detect. In either case, these differences mean that the origin of the muscle is an essential piece of information to provide to the pathologist.

Biopsy of a previously-needled muscle (eg one examined by electromyography) should be avoided for muscle biopsy, since it can show factitious changes due to the instrumentation.

What are the indications for muscle biopsy?

The decision to undertake a muscle biopsy is based on a number of clinical and practical considerations. Firstly, many diseases that affect muscle can be diagnosed without recourse to muscle biopsy. Patients presenting with fatigue may have myasthenia gravis, and diagnosis rests with serological tests for anti-acetylcholine receptor antibodies. Changes in the muscle are non-specific and muscle biopsy is unlikely to contribute to management. Similarly, in the work-up of suspected motor neuron disease, electrophysiological testing is usually sufficient for diagnosis.² Although in this case muscle biopsy shows highly characteristic and diagnostic features, it is simply not required once the diagnosis can be made by other means. In the early days, muscle biopsy had much to contribute in the diagnosis of muscular dystrophy, but with the advent of new genetic tests³ for a while biopsies went out of favour. Nevertheless, genetic tests are not always conclusive, and muscle biopsy has a very specific role along with the other modern tests available. For example, in the work-up of a limb-girdle dystrophy, the presence of so-called lobulated fibres in the biopsy may suggest a calpainopathy, thus narrowing the possible diagnoses so that genetic tests can be more targeted. In all of the above scenarios, muscle biopsy may not be the first line of diagnosis, but it often has much to offer in the difficult cases where other tests may fail to yield the expected results.

What happens in the laboratory?

Although this is widely known, it cannot be overemphasised that the muscle biopsy should be sent as fresh tissue (ie not formalin-fixed). This can be achieved by placing the tissue on a piece of well-squeezed, saline-dampened gauze in a universal container and sending immediately to the laboratory. If the biopsy is taken in an outside hospital it should be urgently couriered. The shorter the delay, the better. Some of the muscle enzymes, notably phosphorylase, begin to degrade outside of the body and may not be assessable if there is any appreciable delay before the muscle is frozen. The laboratory should be forewarned of the specimen coming to ensure that someone is available to deal with it on receipt. The clinical information on the request form should include the name and contact details of the referring physician, symptoms, signs, drug history (particularly statins and steroids), medical history (including diabetes and other hormonal conditions), family history, creatine kinase results, ultrasound⁴ and electromyogram² findings. The site of origin of the muscle (eg quadriceps) should be indicated.

Once the tissue arrives in the laboratory it should be handled by an experienced laboratory scientist. Correct freezing of the tissue is crucial to avoid damaging ice-crystal artefact. In our laboratory this is achieved by orientating the specimen, coating it in talcum powder and snap-freezing in liquid nitrogen. It can then be sectioned on a cryostat and various histochemical stains carried out.

Although histochemistry remains the mainstay of muscle biopsy diagnosis, immunohistochemical stains (most of which are also carried out on the frozen tissue) provide a growing armamentarium of alternative diagnostic options in a wide range of muscle diseases.

Analysis of frozen tissue is the first priority, but where tissue permits, muscle is also processed for paraffin sections and electron microscopy. Although paraffin sections are generally less valuable than frozen sections, certain of the immunohistochemical stains (notably those for subsets of lymphocytes) work best on paraffin sections. Electron microscopy continues to offer unique information, particularly in specific myopathies and metabolic disorders (eg mitochondrial myopathies and congenital myopathies).

As well as providing its own diagnostic work-up, the neuropathology laboratory also acts as an important staging post in the further referral of tissue to national or international specialist laboratories. For example, where the techniques are not done locally, tissue can be sent to specialist centres for Western blotting of proteins in cases of suspected muscular dystrophy, if immunohistochemistry has failed to give a definite diagnosis. Other referral centres offer biochemical assays on the muscle (eg in cases of suspected glycogen or lipid storage disorder) or genetic tests (eg for mitochondrial disorders). For these referrals, frozen tissue (either the remaining frozen tissue from the biopsy or tissue additionally put-by) are packaged on dry-ice and couriered with appropriate documentation and advanced notice to the specialist muscle laboratory.

Although frozen tissue is usually sufficient for the purposes of these specialist centres, it is worth remembering that for diagnosis of suspected malignant hyperthermia (the abnormal overheating response that some people show in response to certain anaesthetics) the patient themselves must attend the centre.⁵ In the testing for malignant hyperthermia, fresh muscle tissue direct from the patient is tested in a water bath to determine the direct effects of halothane and other agents on the physiological



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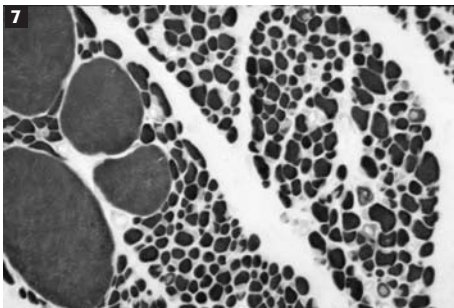
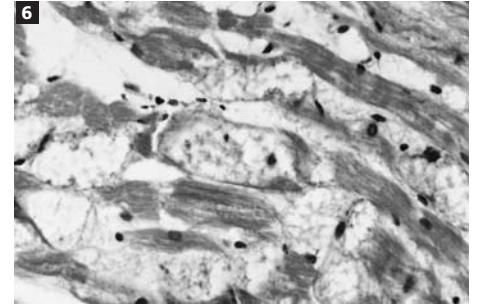
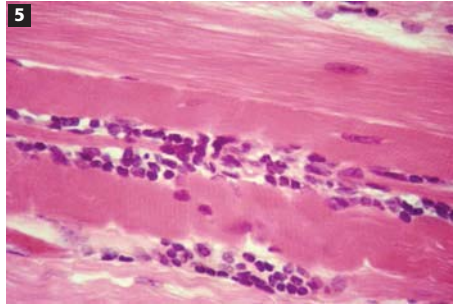
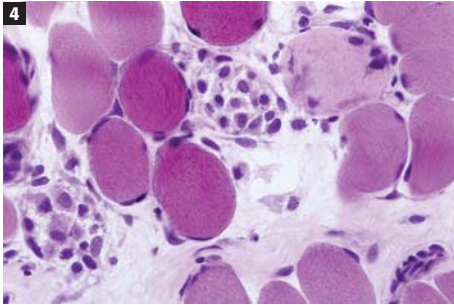
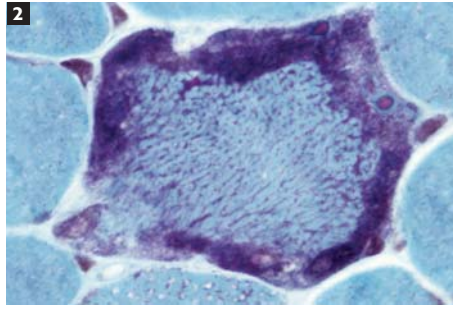
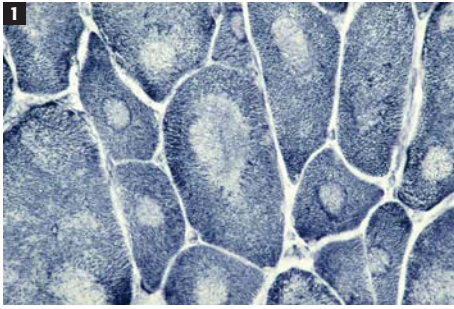


Figure 1: Well-defined areas of staining loss (central cores) in a case of central core disease. NADH-tetrazolium reductase stain. Medium-power magnification.

Figure 2: Ragged red fibre typical of mitochondrial myopathy. Gomori trichrome stain. High-power magnification. Photomicrograph courtesy of Prof RO Weller.

Figure 3: Fibre-type grouping typical of denervation and reinnervation. The type 1s (light) and type 2s (dark) are grouped together instead of forming the usual chequerboard pattern. Myosin ATPase (preincubated at pH 9.4). Low-power magnification. Photomicrograph courtesy of Prof RO Weller.

Figure 4: Duchenne muscular dystrophy. Note fibre necrosis and phagocytosis. Haematoxylin and eosin. Medium-power magnification.

Figure 5: Polymyositis showing interstitial infiltration by lymphocytes and macrophages. Haematoxylin and eosin. Medium-power magnification.

Figure 6: Infantile acid maltase deficiency (Pompe's disease). Note vacuoles due to abnormal glycogen accumulation. Haematoxylin and eosin. Medium-power magnification.

Figure 7: Spinal muscular atrophy showing hypertrophic type 1 fibres and groups of tiny type 1 and 2 fibres. Myosin ATPase (preincubated at pH 9.4). Low-power magnification.

characteristics of the muscle.⁶ Unfortunately, such testing cannot be carried out on archived frozen muscle.

How is a muscle biopsy assessed?

The muscle biopsy is assessed by the neuropathologist in a systematic way in the light of the clinical information provided. The maximum value from the biopsy is always achieved in the context of a dialogue between the physician and pathologist, ideally around the multi-headed microscope.

Despite the sophisticated panels of histochemical and immunohistochemical stains available, probably more than 50% of the value from a biopsy can be obtained from the haematoxylin and eosin stain (H&E). Using this one stain, the biopsy can be assessed for key features such as variation in fibre size, necrosis, phagocytosis, regeneration, vacuoles, inclusions, central nucleation, fibrosis, vascular abnormalities and inflammation.

Each of the histochemical stains has a specific role. Phosphorylase staining is absent in McArdle's disease. Oxidative stains (such as NADH-tetrazolium reductase and succinic dehydrogenase) stain the intermyofibrillar architecture, and show features such as moth-eaten and core-targetoid fibres (Figure 1). The Gomori trichrome technique shows the ragged red fibres of mitochondrial myopathies (Figure 2) (also shown as negatively-stained fibres in the cytochrome oxidase (COX) stain) and nemaline rods of nemaline myopathy. The myosin ATPase stains reveal the type 1, type 2A and type 2B fibres, the proportions and sizes of

which can be selectively altered in various diseases. Loss of the normal "chequerboard" pattern of fibre types (so-called fibre type grouping) occurs in denervation and reinnervation (Figure 3).

What are the common problems?

Even nowadays, despite many other types of test being available, certain muscle diseases regularly present in ways in which muscle biopsy is the only modality available for providing a definitive diagnosis.

Muscular dystrophies

Although Duchenne muscular dystrophy (DMD) is potentially diagnosable by genetic tests without recourse to muscle biopsy, certain situations still arise where muscle biopsy has much to offer. Firstly, not all mutations are detected with current genetic tests. In such cases, the demonstration of absent dystrophin protein by immunohistochemistry and/or Western blot on a muscle biopsy is able to provide an alternative means of diagnosis. Secondly, the clinical and genetic data are insufficient in some cases to distinguish between Duchenne and Becker muscular dystrophies (BMD). Muscle biopsy in DMD shows complete absence of dystrophin protein whereas in BMD there is patchy, incomplete loss of dystrophin staining.⁷ Thirdly, other less common forms of muscular dystrophy (eg sarcoglycanopathies, merosinopathies, dysferlinopathies) can be screened for by panels of reagent antibodies on muscle biopsy.

On H&E sections, muscular dystrophies are characterised by variation in fibre size, muscle fibre necrosis (Figure 4) and regeneration and replacement of muscle by fibroadipose tissue. To a large extent, similar appearances are seen regardless of the underlying dystrophy.⁸ This is because muscle has a limited repertoire of pathological response and the trigger for this response is similar in the various dystrophies.⁹⁻¹² Most of the muscular dystrophies are due to deficiencies of proteins with a role in maintaining muscle membrane integrity. Loss of membrane integrity causes muscle fibre necrosis by ingress of calcium and activation of cell proteases. The loss of specific proteins (such as dystrophin and sarcoglycans) from the sarcolemma can readily be demonstrated by immunohistochemistry and/or Western blot.

Inflammatory myopathies

Inflammatory myopathies, because of their severe effects and potential treatability, are amongst the commonest conditions queried in a muscle biopsy.^{13,14} Characteristic findings are variation in muscle fibre size, necrosis, regeneration and inflammation (Figure 5). The cellular infiltrate in polymyositis is predominantly T-lymphocytes and macrophages,¹⁵ whereas in dermatomyositis B-lymphocytes are also prominent.¹⁶ Dermatomyositis also shows a characteristic pattern of muscle fibre atrophy at the edge of fascicles, known as perifascicular atrophy. Inclusion body myositis (IBM) shows eosinophilic hyaline inclusions and vacuoles surrounded by granular basophilic material

(so-called rimmed vacuoles).

Difficulties in diagnosis arise when inflammation is absent. This can occur, due to sampling, in about 25% of biopsies from patients with polymyositis. In such cases, immunohistochemical staining for MHC-I and MHC-II can be useful, since staining with both of these reagents supports an inflammatory myopathy.¹⁷⁻¹⁹

Although distinction between polymyositis and inclusion body myositis should be easy, in practice problems can arise. Rimmed vacuoles and inclusions can be scanty in some cases of IBM, whereas the occasional rimmed vacuole and inclusion can be a feature of polymyositis. Following the clinical course of the patient, including the response or otherwise to steroid treatment, may be the only way of determining the true nature of the disease in such overlapping cases. Sometimes, it is worth considering a second biopsy, since rimmed vacuoles and inclusions can become more prominent with time in IBM.

Although the inflammatory element in muscular dystrophies is usually a minor secondary component, inflammation is sometimes severe and appearances overlap with myositis. Inflammation is particularly notable in facioscapulohumeral muscular dystrophy.

Statin myopathy

Statins are commonly-prescribed drugs and although the side-effects on muscle are well-recognised, they are sufficiently uncommon that uncertainty can exist as to whether the patient has a statin-induced myopathy or coincidental polymyositis. The typical toxic effect of statins on muscle is to induce muscle necrosis followed by regeneration.²⁰ The relative lack of inflammation usually allows distinction from polymyositis but overlap does occur. Immunohistochemical staining for MHC-I and MHC-II favours polymyositis over a statin effect. Electron microscopy is also useful. Polymyositis

is characterised by a T-cell attack on intact myofibres. Tubuloreticular inclusions are seen in endothelial cells in dermatomyositis (other vascular changes are usually also present). In statin-induced myopathy there is widespread dissolution of myofibrils.

Congenital myopathies

Like the muscular dystrophies, the congenital myopathies are hereditary diseases of muscle, but unlike the dystrophies they are not characterised by muscle necrosis.²¹⁻²³ Histological findings include central cores (areas of absent staining in oxidative stains seen in central core disease), nemaline rods (red-staining structures in the Gomori-trichrome stain seen in nemaline disease), myotubes (small centrally-nucleated fibres seen in myotubular myopathy) and fibre type disproportion (relative smallness of type 1 fibres compared to type 2 fibres in ATPase stains seen in congenital fibre type disproportion).

Metabolic myopathies

Carnitine deficiency is characterised by accumulation of lipid droplets in muscle fibres, readily demonstrated in lipid stains such as Sudan IV or oil red O. On the other hand, carnitine palmitoyl transferase deficiency may show normal muscle biopsy appearances, and diagnosis requires specific biochemical testing of the muscle in a specialist centre.

McArdle's disease is readily diagnosed in phosphorylase-stained sections by the absence of phosphorylase staining, although nowadays the diagnosis may be obtained by genetic testing on suspected cases, obviating the need for a muscle biopsy. Acid maltase deficiency results in a vacuolar change in muscle fibres (Figure 6) and accumulation of glycogen in lysosomes, seen in the glycogen stain (periodic acid Schiff, PAS), lysosome stain (acid phosphatase) and electron microscopy (EM). Interestingly, almost

identical appearances occur in chloroquine myopathy. Confirmation of acid maltase deficiency can be obtained by biochemical assay of the muscle (or simpler, by an enzyme test on the patient's blood).

Lipid and glycogen accumulation in muscle can also be a secondary effect of other muscle diseases, diabetes, other hormonal disturbances and steroid treatment.

Mitochondrial myopathies can also cause lipid and glycogen accumulation, as well as the diagnostic features of ragged red fibres and COX-negative fibres. By EM there is increased variation in the size and shape of mitochondria, and mitochondrial paracrystalline inclusions.²⁴

Floppy baby

Spinal muscular atrophy (SMA) is characterised by a biphasic distribution of fibre sizes. Hypertrophic type 1 fibres are seen against groups of tiny type 1 and 2 fibres (Figure 7). Sometimes muscle biopsy is essential for the diagnosis of SMA, because genetic testing does not detect all cases.

Other cause of floppy baby include nemaline myopathy, myotubular myopathy and mitochondrial myopathy as mentioned above, as well as forms of congenital muscular dystrophy.²⁵

Conclusion

Muscle biopsy has come a long way over the past 30 years, and despite many other modalities of investigation now being available, continues to add the final elucidating piece to the diagnostic jigsaw in many cases of muscle disease. Just as sophisticated imaging and genetic tests are unlikely to ever supplant a skillful evaluation of the symptoms and signs, it is likely that direct visualisation of the patient's muscle fibres down the microscope will continue to offer something uniquely important to the patient in the evaluation of their disease.

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**Reshaping the future
of Parkinson's disease.**

SCHWARZ

PHARMA

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Psychological Rehabilitation of Children and Adolescents with Acquired Brain Injury

As we are often told, the child is not just a small adult. In brain injury, a range of variables makes working with children and adolescents qualitatively different from working with adults for instance, developmental factors, functional plasticity, social and family factors.¹ After a brain injury, there are differences in the problems experienced by the child and family and in difficulties experienced by the clinician. Furthermore prognosis will be less clear in children than adults. All these differences have implications for service organisation. In order to provide valid assessment, comprehensive formulation, effective treatment, and accurate prognosis, services for children with brain injury should be provided by clinicians with specialist knowledge of these factors and with the skills to work with them.²

Developmental Factors and Prognosis

Younger people tend to recover more rapidly from brain injury than older people. Injury in preschool years is associated with a recovery curve that plateaus at 6 months whilst in older children the figure is more like 12 months.³ A more extensive 2-year recovery phase is quoted for adults with brain injury. This difference may reflect either faster neuronal recovery in the child or less recovery potential due to attenuated developmental processes in the child.

The so-called Kennard Principle proposes that it is better to have a brain injury earlier than later in life. This is not necessarily the case, and disagreement on this issue is probably due to confusion in the meaning of 'outcome' or ignorance about the nature of brain plasticity.⁴ Although children and adolescents are more likely than adults to survive following brain injury, such an event will alter the entire subsequent developmental trajectory for a child. The relative contribution of plasticity and vulnerability in the developing nervous system has been discussed at length in the literature in an attempt to explain outcome. On one hand, the earlier the damage, the greater the potential for recovery due to plasticity.⁵ On the other hand, early disruption can cause vulnerability to severe and global maldevelopment.⁶ Developmental neuropsychology provides a synthesis of these views. It is likely that cognitive development involves a process of interaction between genetic determination and experience that effects a gradual modularisation of cognitive functions.⁷ In the young child, lack of early module development gives greater plasticity; hence modules can be relocated in early but not late lesions. Conversely this leads to vulnerability as there are no modules present in early lesions, so the system has to learn the whole function of the module from scratch with potentially impaired experience. Adults

might only lose some part of an already developed module. In short, neither vulnerability nor plasticity alone completely explains the range of consequences of childhood brain injury. Rather, a range of factors interacts to influence outcome (see Table 1).

Problems with cognition

The effects of a brain injury on cognitive processes are dependent on age at injury.⁸ A central difference between children and adults is that while the effects of the injury are immediately obvious in adults, children's development is disordered after injury and some deficits may take a considerable time to appear. Table 2 outlines differential cognitive effects of injury on the brain in children and adults.

The problem of interaction between cognition and environment

There is a dynamic development of cognitive resources in children as they grow up and adaptation to an increasingly complex world is a normal developmental task. For example, in transfer to secondary education, there is a greater requirement for abstract thinking, multi-tasking and organising. A child with a brain injury may cope adequately at primary school where the demand on independent ability is relatively low and the level of support is high. At secondary school, expectations of independent cognitive function increase and the level of assistance reduces. A consequence of the injury is a loss in the child's 'dynamic and relative interpretation of the environment',⁹ ie an inability to keep up with the increase in environmental demands so that the child will inevitably struggle to keep up with his peers.

Problems with behaviour & emotion

Across the age range, brain injury is associated with behavioural difficulty:

- Hyperactivity, bedwetting, oppositional and antisocial behaviour have been reported in injured children
- Disinhibition and social inappropriateness, cheekiness, embarrassing remarks may be aversive to others thus isolating the child
- Agitated or aggressive behaviour commonly occurs within the sub-acute phase of a brain injury for any age
- Executive and intellectual deficits may be associated with a failure to adapt to environmental or social rules at home, school or work
- Impulsivity and sexual disinhibition may leave the child or adult vulnerable.



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Table 1. Injury characteristics and recovery from early brain insult*

	Plasticity	Vulnerability
Severity of lesion	Bimodal effect such that small lesions and very large lesions may lead to interhemispheric reorganisation	More severe insults result in greater vulnerability
Nature of lesion	Focal lesions, eg stroke, tumour	Generalised trauma, eg traumatic brain injury, infections
Age at onset	Greatest in initial 12 months of life and decreasing through childhood	Greatest for prenatal insults and decreasing through childhood
Gender	More common in females, especially for left hemisphere	More common in males, greater for right hemisphere
Psychosocial context	High socioeconomic status, access to rehabilitation, early intervention	Low socioeconomic status, limited resources

Table 2. Effects of brain injury on cognition in children and adults¹⁸

	Children	Adults
Processing Speed	<i>Decrement in processing speed which can be mistakenly attributed to lack of concentration This impairment will have a pervasive effect on education as the pace of learning required in school increases</i>	<i>Decrement in processing speed Strategies will be needed to allow extra time</i>
Intelligence	<i>Fluid intelligence is impaired Fewer crystallised resources Longer term severe and global deficits in intellect and social cognition are associated with early injury</i>	<i>The loss of fluid and sparing of crystallised resources is dependent on location and type of lesion</i>
Attention	<i>Deficits in the focus, division and ability to sustain attention may mean distractibility from play, study or road safety Child may have difficulty developing attentional control</i>	<i>Attention problems are common post head injury, especially after diffuse damage Difficulty regaining control of attention</i>
Language	<i>Language is central to the child's socio-cultural and intellectual development Children losing language due to left hemisphere damage before 6 years are likely to regain these skills due to plasticity Complete recovery is less likely with injury after the critical period of language development</i>	<i>Presence of expressive and / or receptive language problems is dependent on location of lesion After the acute phase a stable picture of language is revealed</i>
Memory	<i>Young children are unlikely to spontaneously report a difficulty The younger child has less knowledge acquired previously New learning deficits can have a cumulative effect as the child fails to keep up – a minor problem can develop into a major difficulty The task is to acquire skills</i>	<i>Previously may have acquired strategies for remembering Retrograde memory largely intact Anterograde memory impaired Prospective memory impaired Implicit memory is more resilient to injury than explicit memory The task is to regain skills</i>
Perceptual and motor skill	<i>Problems are common in the acute stages Psychomotor slowness and dyspraxia persist after a mild injury, which can adversely affect social and scholastic functioning</i>	<i>Problems common in acute stages Persistence dependent on severity Has implications for activities of daily living</i>
Executive Function	<i>Longer term difficulty with executive skill development Frontal lobes are still developing late into the second decade Apparent recovery from injury Difficulties may become apparent in later childhood and be 'grown into'</i>	<i>Impairments usually evident in the post-acute phase Lack of insight may prevent adaptation to change in condition</i>

Emotional consequences are usually an interaction between organic and psychological factors, which can be difficult to differentiate:

- In children, symptoms may resemble those found in mental health disorders: somatic complaints, impaired control of affect or anxiety resulting in compulsive behaviour
- In adults, common emotional changes are agitation, heightened or flattened affect, mood swings and depression. This may represent frustration with the slow rate of recovery and a negative view about the future due to loss of skills
- In both groups, anxiety, fear or post-traumatic stress disorder is not unusual if a traumatic incident has occurred.

Socio-cultural problems

The child's place in the family structure is different from that of the adult's, which can be an advantage or disadvantage. Children's social networks are complex, comprising family, education system and cultural community. This potentially makes them more difficult than adults to work with, but presents wider possibilities for intervention. The mutually gratifying teaching-learning process between child and adult is abruptly interrupted by head injury, which makes the acute post-injury phase a stressful period for the family.¹⁰ If this can be successfully negotiated, having a supportive family to bring newly-learned rehabilitation techniques home pro-

vides opportunities for continued adaptation. Conversely, children from disadvantaged social backgrounds and those with limited support show greater impairment and slower recovery than those who are rich in social resources. Reduced access to services, special education and significant psychiatric problems may all impact on future recovery.⁸

Service Organisation: Assessment

There are methodological differences in psychological assessment between adults and children with brain injuries. Although the child is involved in the interview, parents or teachers are primary informants too. A developmental history is fundamental and, along with information about nature of injury, provides the basis for hypotheses of the assessment. Age-normed tests are specifically designed to suit developmental stages and sometimes require greater flexibility in administration than with adults. Therefore, assessment tends to gather information from more sources and attempts to account for changes in dynamic factors.

Service Organisation: Rehabilitation

Combined with assessment the fundamental components of interventions for child brain injury are rehabilitation and education.² In rehabilitation, principles that are employed across the age range are restoration of function (eg regaining physical or speech ability with therapy), functional adaptation (eg self-instructional training for a behavioural prob-

lem) and environmental modification (eg use of mobile phone for memory impairments).⁸ Inpatient rehabilitation is far more commonly provided for adults than children. Holistic rehabilitation, which aims for psychosocial adjustment and compensation for cognitive disorders in a therapeutic environment, is the most theoretically developed and studied. Evidence supporting its efficacy is tentative yet positive.¹¹

With paediatric rehabilitation, there is greater emphasis on providing services in the community. Access to specialist services is more likely when neurosurgery or intensive care is necessary or when complex difficulties and transitions are part of the formulation. Once medically stable many children will receive little systematic rehabilitation and there is a tendency to return home as soon as possible. Few trials with robust methodology have been published in paediatric brain injury rehabilitation,¹² but there is evidence to suggest Cognitive Behavioural Therapy for brain injury is effective in reducing emotional distress and improving cognitive function in adults.¹³ Interventions combining patient and family work appear to be more effective than purely patient focused therapy.¹⁴

Service Organisation: Education

Unlike in the adult world, compulsory education is required for children with brain injury from age five to age 16. It is therefore important to work out the educational trajectory of the child, assess whether return to school is possible

and whether additional support is required. It is the responsibility of the health service to highlight special educational needs of a child after a brain injury. There is increasing responsibility on schools for meeting the special educational needs of pupils. A statutory assessment, which outlines provision needed on returning to school, should include assessment results from a multidisciplinary team. As recovery progresses, rehabilitation is best integrated with educational content. For this reason a paediatric neuropsychologist will continue with follow-up appointments to monitor developmental progress and liaison with schools to recommend therapeutic intervention. As special edu-

cational provision has not been systematically provided to children with brain injury there is limited evidence regarding its efficacy.¹² However, an intervention aimed at empowering parents in their interaction with teachers and other professionals involved in their child's care has been favourable.¹⁵

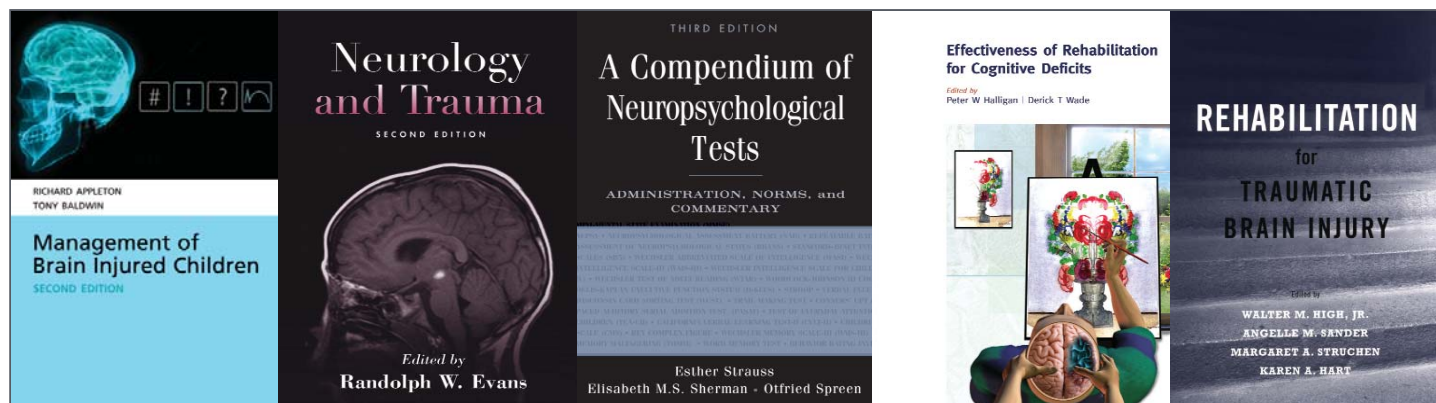
Conclusion

There are qualitative and quantitative differences between children and adults in presentation and management of psychological aspects of brain injury. Outcome is more difficult to predict in children than in adults and prognosis for children will be unclear until adult-

hood. For this reason it is important to provide ongoing neuropsychological assessment for children. Children's services are more systemic in nature and work with the family as a whole. Rehabilitation services for adults have greater inpatient involvement whereas support for children's recovery moves rapidly from health to education sectors. There is growing evidence for the use of rehabilitation and special educational support for children with brain injury. Advances in technology of psychological interventions in health and education provide exciting possibilities for clinical work and research with children and adolescents with brain injury.

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Parallel Visual Pathways

A plethora of parallel visual pathways

Combined anatomical and physiological studies have demonstrated many sets of parallel pathway (PP) in the visual system. For example, there are PP from retina to superior colliculus and cortex; PP within the thalamocortical projections; and at a higher level, the mosaic of PP that emerge from modular subunits of V1 (primary visual cortex), or later still the supposedly binary PP that course toward the parietal and temporal lobes – the ‘dorsal’ and ‘ventral’ pathways (Figure 1). Each PP, taken separately, has an elemental subdivision of visual function to match its anatomical compartmentalisation. In other words, PP have been taken to be markers of functional specialisation in the visual system.

However, taking a global view, the functional labelling of the integrated PP circuit-diagrams tends to become rather more taxing, as their components mix together in a rather indiscriminate (and disconcerting) fashion. As we shall see, the root of the problem is that the discrete PP that have been identified at one level generally fail to dovetail neatly with those at the next. Nevertheless, complex as it is, growing knowledge of visual PP organisation should help point the way toward unravelling many other brain pathways and systems.

It's the exception that proves the rule...

The visual subsystem of the primate brain with the finest pedigree is probably the ‘motion pathway’. Human cortical area V5 (or MT) is selectively activated in motion processing tasks, and in macaques we know that the same area is selectively innervated by the M (magnocellular) retinogeniculate channel.^{1,2} This is good engineering, since the M channel's transient response and preservation of timing information make it a logical source of signals to subservise motion analysis. Figure 2 shows how this pathway reaches V5 via a discrete internal relay within area V1, the output layer (layer 4B) being a stronghold of directionally-selective neurons within V1.³ Even the ‘spiny stellate’ cells from which this output originates are unique: essentially pyramidal cells shorn of their apical dendrite, as if to preclude any chance contamination by dendrites straying outside the layer.^{4,5} Up to this level, the motion pathway ticks all the boxes for a segregated, specialised subsystem, almost spectacularly so. Unfortunately, if we examine the total outflow from the LGN (lateral geniculate nucleus), it begins to look atypical.

...and the rule is to re-mix

The LGN has three channels altogether, the other two P (parvocellular) and K (koniocellular) containing progressively smaller neurons than those in the M channel. Although the P channel overlaps the spatiotemporal sensitivity of the M channel, it has roughly tenfold more neurons and its specialisation is very different. It carries information about the fine spatial details of a static scene, with

red/green cone opponency for added colour vision. By contrast, the K channel is more of a miscellany; its only identified role is to harness B-cone signals, to provide the blue-yellow dimension of colour vision.⁶ Like the M channel, the P and K channels initially retain their integrity by terminating in separate strata of V1 (Figure 2). But they then encounter a host of cross-fertilising intrinsic relays, as a new modular system is generated within the cortex.

Cytochrome oxidase modules in V1 and V2

The metabolic capacity of brain tissue (revealed by a histological stain for the mitochondrial enzyme cytochrome oxidase) provides a serendipitous marker for modular sub-compartments in early cortical visual areas. These are the so-called ‘blobs’ (or ‘patches’) in V1 and ‘stripes’ in V2.^{3,7} M, P and K channels converge on these structures, whose specialised functions are not dictated by the composition of their input so much as by the nature of their own intrinsic processing. For instance the P system feeds both blobs, and the regions between them – the ‘interblobs’ – but while blobs are specialised to extract low acuity spectral information, the interblobs sacrifice much of the spectral content and synthesise higher resolution orientation specificity.

Not surprisingly the blobs, being the root of cortical colour analysis, also receive direct input from the K channel.⁶ But luminance signals from the M channel also reach both these modules. Thus blobs are ‘mongrel’ modules in that they represent a fusion of all three M/P/K channels – presumably because such a composite input is required to signal all the spectral and nonspectral intensity variations on which colour vision (including seeing shades of grey) depends.

The majority of the output from V1 relays through area V2, via specific blob-stripe connections (Figure 2). In fact there are three V2 modules, one of which (thin-stripes) are fed by blobs, the other pair (thick- and interstripes) by interblobs.⁸ The V2 stripes target very different areas of prestriate cortex: V5, predictably, is fed only by thick-stripes, as these are the main repository of direction-selectivity in V2; all other areas seem to be fed by selective combinations of stripe input.^{9,10} The general role of V1 and V2 is to initiate colour, form and motion analysis, and to distribute the initial products to separate prestriate areas for further specialised processing – but the parallel outputs of V2 are rather better categorised by cytochrome module than by the retino-geniculate M/P/K channels.

Dorsal/ventral dichotomies

In recent years, one major distinction has been made between a ‘dorsal’ set of pathways – from V1 to parietal areas – and a ‘ventral’ pathway – which channels visual information from V1 to the temporal lobe. It was first proposed that the dorsal system is specialised for spatial localisation (a ‘where’ function), whereas the ventral pathway is critical for object recognition (a ‘what’ function). More recently, a challenge to this view has considered the



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Up to this level, the ‘motion pathway’ ticks all the boxes for a segregated, specialised subsystem, almost spectacularly so. Unfortunately, if we examine the total outflow from the LGN (lateral geniculate nucleus), it begins to look atypical.

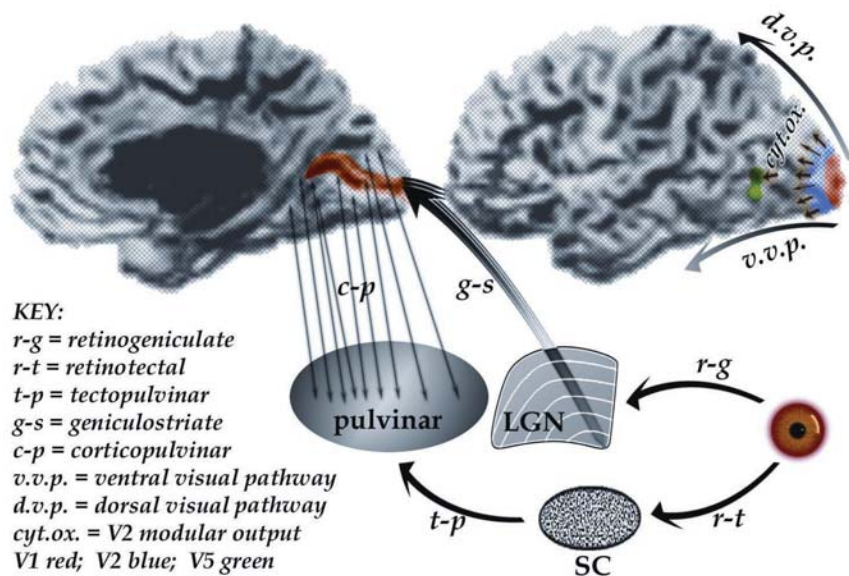


Figure 1: A plethora of parallel pathways. Retinal outputs can be categorised by their immediate destination (thalamus/LGN or midbrain/SC), or by their physiological class, which also correlates with the layer of termination within the LGN (ie M/P/K channels, indicated by the triplet arrowhead leading to area V1). Both the geniculate and tecto-pulvinar pathways distribute to a broad expanse of visual cortex, although the former is much more concentrated upon area V1. V1 and V2 generate a fresh subdivision of function from M/P/K input, as expressed in their cytochrome oxidase modules, and relays of these modular outputs can be traced through a number of nearby areas. The division of cortical visual pathways into dorsal and ventral streams represents compartmentation of function on a larger scale, effectively in terms of the source of visual input to the parietal and temporal lobes respectively. In contrast to retinal and tecto-pulvinar outputs, which are unidirectional, all cortical and cortico-thalamic connections are reciprocal, and utilise extensive feedback in their operations.

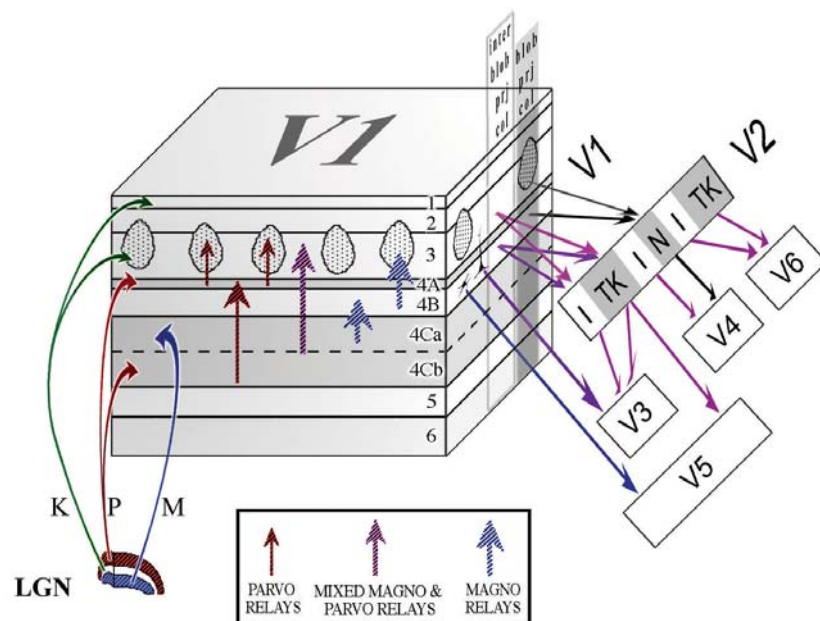
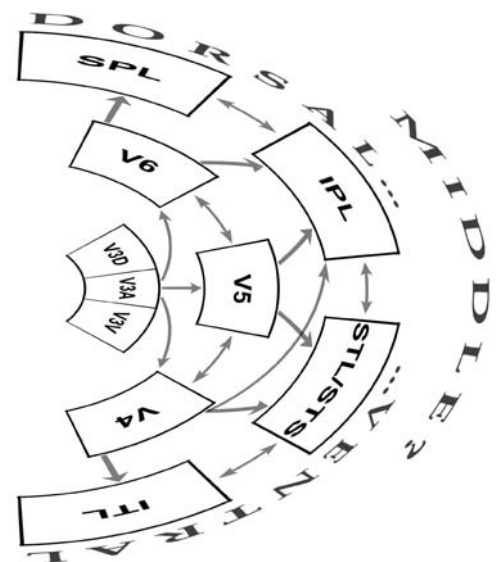


Figure 2: Parallel inputs and outputs of V1. The M/P/K channels relayed via the LGN terminate in separate layers of V1, but are then mixed together by cortical intrinsic relays and interlaminar connections; hence the outputs of V1 represent various composites of the geniculate channels – as coded by the colour key. Layer 4B is dominated by M input, and hence the ‘stellate’ cells of this layer provide a relatively clean M signal (blue). Pyramidal cells of layer 4B pick up additional signals via their apical dendrites in higher layers (purple). The two cell types appear to have different patterns of distribution to prestriate areas, such as V3 and V5. The output to V2 arises from layers 2 & 3, as well as 4B, and the pattern of these projections is better categorised by cytochrome oxidase module. Basically, the output from V1 is bi-partite, with neurons in projection columns (‘prj col’) that align either with a blob, or an interblob, connecting with different modules in V2 (I = interstripe, N = thin stripe, TK = thick stripe). In turn, the stripes of V2 target different sets of prestriate areas (including many more than areas V3-V6 shown here). The exact M/P/K compositions (shown as magenta/purple for varying P/M mixes and black for all three), are not well known. For all its apparent complexity, this is a much simplified depiction of our database of known circuitry (that, itself, is far from complete).

Figure 3: A highly schematic summary of connections from prestriate visual areas to regions of the parietal and temporal lobes of primate cortex. Each block may be taken to represent a cluster of nearby areas (eg as shown explicitly for the block marked V3d/V3A/V3v). The exact demarcation of the classical dorsal and ventral systems raises problems. Firstly, the afferent pathways do not form two clearly segregated ‘streams’, as the presence of cross connections sets up an interlinked network. Secondly, the relative territory of ‘dorsal’ and ‘ventral’ in the region of the temporo-parietal junction is not clear cut – and the addition of a third, ‘middle’ system might offer an equally valid, if equally indeterminate model of brain organisation. SPL & IPL = superior & inferior parietal lobe; STL/STS = superior temporal lobe/sulcus; ITL = inferior temporal lobe (or ventral occipital / fusiform cortex in human brain).



dorsal/ventral distinction to relate to functions of visuomotor control versus visual perception.^{11,12} However, the anatomical basis of this dorsal/ventral segregation has never been satisfactory, since the overall visual circuit diagram resembles a network as much as two linear pathways, with early areas V1, V2 and V3 belonging to neither in particular.^{9,13} A ‘third’ pathway, leading to the temporo-parietal junction,

and a ‘third’ function, that of attentional control, could be added¹⁴ – but neither has much dented the popular dogma of a functional dichotomy.

Figure 3 details some of the cross-talk inherent in this circuitry. The ventral system is fed largely by V4, and is thus an extension of V2 thin- and interstripes. But there is also a contribution from thick-stripes via V3. The net effect

is that M and P signals are about equally weighted (with the relative K contribution unknown). The dorsal system receives strong input from V5. In consequence it is generally portrayed as disproportionately driven by M input, with theoretical relevance to the magno-cellular hypothesis for the basis of dyslexia.^{15,16} However there are many additional inputs to superior and inferior parietal areas, mediated

by prestriate areas such as V3A and V6, that in turn are fed by interstripes as well as thick stripes. Hence, in terms of circuitry, the dorsal stream is better characterised by the relatively minor contribution it receives from blob/thin stripe relays. Yet it is by no means totally colour-blind. V5, for instance, can process chromatic motion signals, a direct K input from the LGN being one likely source.^{17,18} If the M-channel/motion pathway is not such a purely magnocellular affair, does this signify any dilution of its functional role? Arguably not, if the job description is to detect when a coloured pattern (eg camouflage) moves, without necessarily identifying the component colours.

Subcortical sidelines?

The 'second visual system' is traditionally the pathway from retina to extrastriate cortex via colliculus and pulvinar. It is frequently invoked to explain residual vision in cases of V1 loss (engagingly termed 'blindsight' – where the subject correctly guesses the location of a stimulus in the blind field, despite denying any conscious experience of seeing it). In fact, as V1 is also by-passed by K-channel broadcasts from the LGN, to area V5 and elsewhere, 'blindsight' unmasks the direct visual capacities of the total 'bypass circuitry'.¹⁹ Even so, blindsight phenomenology fails to provide a full functional profile of the second visual system because this system is not merely an alternative route for retinal signals to access the cortex. Its normal function

depends on the interplay of ascending retinal and descending cortical pathways – eg in bottom-up and top-down modes of spatial attention being jointly exercised through colliculo-pulvinar circuits.²⁰ In other words, far from being an unconscious pipeline, the second visual system seems an important subsidiary of conscious awareness.

This much condensed review reveals some of the complexity of visual circuitry – and it is only the beginning. Brain anatomy is not a topic that has simplified as it has matured over the course of the last century, so we can only expect to look forward to more of the same.

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Common: necrosis. **Uncommon:** anaemia, thrombocytopenia, leucopenia, increase in ALT, AST, hypertonia, depression, hypertension, nausea, vomiting, alopecia, urticaria, pruritus, rash, myalgia. **Rare:** lymphadenopathy, thyroid dysfunction, γ -GT and triglyceride increase, convulsion, confusion, anxiety, emotional lability, cardiomyopathy, tachycardia, palpitation, bronchospasm, dyspnoea, pancreatitis, hepatitis, skin discoloration, sweating, menstrual disorder, suicide attempt, anaphylactic reactions, malaise, chest pain. **Very rare:** hypocalcaemia, hypercalcaemia, depersonalisation. Other adverse events reported during clinical trials are: lymphopenia, neutropenia, altered laboratory tests for glucose and urinary proteins, peripheral oedema, dizziness, insomnia, conjunctivitis, ear pain, migraine, vasodilatation, sinusitis, increased cough, diarrhoea, constipation, skin disorder, myasthenia, urinary disorders, impotence, pain in various sites, asthenia, infection, abscess. The incidence rate of injection site reactions decreases over time. If breaks in the skin

occur advise patients to contact their physician before continuing with injections. For further information please refer to the SmPC. **Legal category:** POM **Basic NHS price:** £596.63 for 15 x 3ml Betaferon vials with diluent. **PL numbers:** EU/1/95/003/001, EU/1/95/003/002 **PL holder:** Schering Aktiengesellschaft, D-13353 Berlin, Germany. **Date of preparation:** 24 January / 03. **@Betaferon is a registered trademark of Schering AG.**

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Dostoevsky and Epilepsy

Although their influence did not reach western Europe until some years after his death, the works of the Russian novelist Fyodor Mikhailovich Dostoevsky (1821-1881) have intrigued writers, philosophers and theologians ever since. For example, Dostoevsky is "a significant presence in the margins of much that has been written" in the Archbishop of Canterbury's 2005 Clark Lectures delivered at Trinity College, Cambridge.¹ Likewise, neurologists have taken Dostoevsky as a subject for study, because of his epilepsy, and that ascribed to a number of his characters.

Perhaps the first neurologist to write on Dostoevsky's epilepsy was Sigmund Freud (1856-1939); he had trained under Charcot before turning to psychiatry. In an article entitled *Dostoevsky and parricide*, first published in 1928, Freud stated that:

Dostoevsky called himself an epileptic. ... it is highly probable that this so-called epilepsy was only a symptom of his neurosis and must accordingly be classified as hystero-epilepsy – that is, as severe hysteria.

Freud's reasoning for thinking Dostoevsky's seizures psychogenic was based on the timing of their inception:

The most probable assumption is that the attacks went back far into his childhood, that their place was taken to begin with by milder symptoms and that they did not assume an epileptic form until after the shattering experience of his eighteenth year – the murder of his father. It would be very much to the point if it could be established that they ceased completely during his exile in Siberia ...²

In the biography by Dostoevsky's daughter, it was "according to family traditions" that the onset of epilepsy occurred on learning of the death of his father, Mikhail Andreyevich (sometime head physician at the Malinsky Hospital for the Poor in Moscow), but Dostoevsky's own letters contradict this.

Ingenious though the psychoanalytical formulation was, it was vigorously challenged shortly after its translation into English (in the *Realist* of July 1929) by the historian EH Carr (1892-1982), then preparing a biography of Dostoevsky³ (and some years away from commencing his monumental fourteen-volume *History of Soviet Russia* for which he is chiefly remembered). His analysis of the extant sources suggested that, quite contrary to Freud's belief, Dostoevsky's seizures did not start until during his imprisonment in exile in Omsk, ie not earlier than 1849, some years after his father's death in 1839, and indeed was not unequivocally diagnosed as epilepsy until 1857, shortly after his first marriage.⁴

If not pseudoseizures, then from what type of epilepsy did Dostoevsky suffer? A number of neurologists have examined the issue. Alajouanine, one of the successors to Charcot's chair, believed Dostoevsky had partial and secondarily generalised seizures with ecstatic auras,⁵ but Gastaut initially plumped for idiopathic generalised seizures.⁶ Voskuil felt that the seizures began in 1846 (Carr had examined, and discounted, the evidence for this⁴) and suggested complex partial seizures with secondarily generalised nocturnal seizures and ecstatic auras.⁷ Gastaut, returning to the subject, acknowledged the possibility of a silent temporal lesion but such as permitted "almost immediately secondary generalization to each seizure".⁸ DeToledo suggested, on the basis of Smerdyakov's admission of feigning a seizure to provide himself with an alibi for the murder of

his father Old Karamazov in *The Brothers Karamazov* (an episode perhaps recapitulating Dostoevsky's experience of his own father's death), that Dostoevsky was well acquainted with the possible secondary gain of seizures, but he stopped short of bringing the historical wheel full circle back to Freud by suggesting that Dostoevsky had pseudo-seizures.⁹ Most recently, Rosetti & Bogousslavsky entered the lists: they suggested seizure onset in 1846 and that Dostoevsky's father was not in fact murdered, en route to their conclusion that Dostoevsky suffered from temporal lobe epilepsy, most likely left mesiotemporal (this lateralisation based on Dostoevsky's postictal aphasia, since ecstatic auras are thought to be non-lateralising), with complex partial and secondarily generalised seizures, with a relatively benign course.¹⁰

Whatever its particular nature, what impact did this seizure disorder have on Dostoevsky's art? Siegel & Dorn¹¹ have traced six characters with epilepsy in Dostoevsky's oeuvre, of which the most notable are Prince Myshkin in *The Idiot* (1868) and Smerdyakov in *The Brothers Karamazov* (1881). Certainly the former has an experience of mystical ecstasy akin to Dostoevsky's ecstatic auras, whereas Smerdyakov's epilepsy, as related above, is "a piece of machinery necessary to the plot, and appears to have no other artistic or spiritual significance".⁴

Ecstatic auras, a feeling of absolute harmony and happiness, a sense of spiritual exaltation and triumph, a feeling of power to transcend the limits of the material world, comparable with Mahomet's vision of Paradise, were first recorded by Dostoevsky in 1865. Such ecstatic auras have sometimes been labelled as "Dostoyevsky's epilepsy," although this terminology does not appear in the various ILAE classifications of seizures; they have been associated with focal right temporal abnormalities.^{12,13} In one case, ecstatic auras have been reported to be induced by watching television – not as implausible as it may at first appear, since such episodes were independent of the content of the television programme – but these were associated with generalised rather than focal epileptiform activity.¹⁴

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I thank my colleague Dr Ivan Iniesta, a genuine Dostoevsky scholar, for drawing my attention to another recent article on this subject by Baummann et al. (Seizure 2005;14:324-330).

Noninvasive Conductivity Extraction for High-Resolution EEG Source Localisation

Electroencephalography (EEG) is an indispensable neurological diagnostic tool in terms of the fast time scale, portability and cost efficiency. Improved spatial resolution of EEG measures would greatly benefit multiple clinical and research applications, including stroke, epilepsy and cognitive studies. The recent advances in dense arrays electrode application have made feasible EEG brain imaging for both rapid application and long-term monitoring.¹ It has been shown that reliable inverse solutions can be obtained and dense array sampling (128, 256 and 512 channels) on the scalp can be projected back to the cortex providing a unique opportunity for monitoring brain activity both in space and time (Figure 1). However, the spatial accuracy of EEG will remain limited because i) mostly simplistic models of the human head (like multi-shell spheres) are commonly used in the inverse procedure of back-to-cortex projection, and ii) the regional conductivities of the human head tissues are largely unknown. This is true not only in each measurement case but in general. Several imaging modalities have been proposed so far to quantitatively measure the electrical conductivity of tissue noninvasively, but none of them is free from some limitations and shortcomings. Magnetoacoustic Hall effect imaging² relies on propagation of

ultrasound into the tissue, and is not quantitative. Magnetic resonance current density imaging³ requires applying rather high level of external currents to make produced magnetic field contrast visible by MRI. The electrical conductivity tensor of tissue can be quantitatively inferred from the water self-diffusion tensor as measured by diffusion tensor magnetic resonance imaging (DTI).⁴ It can be successful in extracting anisotropic conductivities of the brain tissue, but more problematic regards bone (skull) tissues where the water content is much smaller.

The lack of accurate skull conductivity (most resistive tissue) is particularly problematic given the developmental variations in the human skull from infancy through adolescence. Without an accurate forward model of the skull (specifying the volume conduction from cortex to scalp) even advanced inverse efforts cannot achieve precision with EEG data as the error of source localisation due to conductivity uncertainty may reach a few centimetres.⁵ Several authors addressed this problem by using the noninvasive electrical impedance tomography (EIT) approach. A similar approach was used by Hoekema et al⁶ in the semi in-vivo conductivity measurements of the skull parts temporarily removed during epilepsy surgery, - fitting for only one



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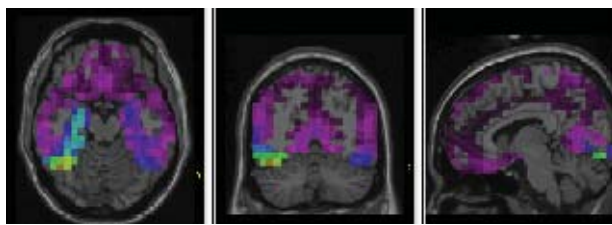


Figure 1: The coloured voxels represent the magnitude of brain activation at the onset of the seizure activity, superimposed on a typical MR image for visualisation.

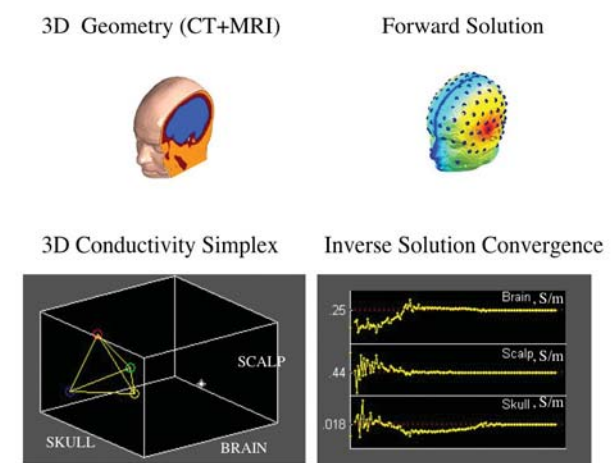


Figure 2: The parameterised EIT procedure: top - 3D subject geometry, CT registered with MRI (left), the forward solution for a particular set of tissues conductivities on the head surface and registered electrodes with EGI Photogrammetry System (right), bottom - initial simplex in the conductivity space (left) and conductivity convergence in the inverse solution (right).

Table 1. Initial and estimated tissues parameters in 4-compartment realistically shaped FD model			
Tissue type	$\sigma(\Omega^i m^j)$ (assumed)	$\sigma(\Omega^i m^j)$ (estimated)	$\Delta\sigma(\Omega^i m^j)$ (estim. error)
Brain	0.25	0.2491	0.0099
CSF	1.79	1.7933	0.0311
Skull	0.018	0.0180	0.00017
Scalp	0.44	0.4400	0.00024

unknown parameter was performed, though. Goncalves et al.⁸ applied spherical and a three-layer boundary element (BEM) models to fit their EIT measurements for six subjects.⁹ However, since in such models skull thickness and conductivity are interchangeable to some extent, more accurate geometry representation is needed. Recently we have shown in our group^{10,11} that using the parameterised EIT measurements procedure and realistically shaped high-resolution finite difference models (FDM) of the human head based on the subject specific co-registered CT and MRI scans, as is shown in Figure 2, it was possible to extract three and four tissues conductivities (Table 1) both in simulations with synthetic and real experimental data with good accuracy using the multi-start downhill simplex algorithm.¹²

Our current focus is to further improve conductivity information for the benefit of high-resolution EEG source localisation. We are conducting measurements repeatedly on individual subjects to prove the method's robustness and show individual variability of head tissues conductivity across individuals. Electrical Geodesics, Inc. (EGI) has developed a data acquisition system that provides current injection between selected electrode pairs (at very safe current levels) and simultaneous acquisition of return potentials from the dense sensor array of the Geodesic Sensor Net. Our current work will further refine a methodology for constructing accurate forward models of electrical conductance for the human head through incorporating the high-resolution structural details of the human head from MRI/CT scans and providing the non-invasive procedure

for estimation of the major tissues conductivity parameters. The latter is based on parameterised EIT inverse solution for the data collected at EGI. In the next stage of the project, a refined forward solver will incorporate anisotropies of the head tissues, in particular skull and white matter. The advanced simulation annealing algorithm has been proved to show better performance in the inverse procedure in terms of finding the global minima of the cost function with larger number of unknowns. This will allow us to extend the procedure to a parcellated skull (10-12 anatomically relevant bone plates) and include the skull conductivity inhomogeneities information into the forward solver for the EEG inverse problem. These tasks require extensive computational resources. At Neuroinformatics Center, University of Oregon we have access to a multi-cluster (SGI, Dell, IBM p650; IBM p690; IBM BladeServer) high performance parallel computing system dedicated to analysis of human EEG and MEG data. The first and primary application of these computing resources is to solve the conductivity problem of the human head.

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The Basics of Microarrays

Since its emergence 10 years ago¹ DNA chip technology has transformed biomedical research. Born out of advances in genome sequencing and microchip technology it is now a widely used and accepted technique, reflected by the exponential increase in the number of citations appearing yearly in the published literature; but what are microarrays and why are they so important?

Expression profiling – the original array

To date the most important application for microarrays has been the monitoring of gene expression. Only a fraction of a cell's genes are transcribed from genomic DNA to produce messenger RNA (mRNA) at any one time. These genes are sometimes referred to as the expression profile or 'transcriptome' of a cell. The transcriptome is a major determinant of cell function, conferring unique properties to each cell type. Unlike the genome the transcriptome is dynamic; changing in response to normal cellular processes, environmental stimuli, and in disease states. In the pre-genomic era expression analysis was performed in a low-throughput, 'one gene – one experiment' fashion, typically by northern blot analysis. Microarrays have revolutionised this, allowing experimenters to interrogate thousands of genes and entire genomes in a single experiment.

Microarrays exploit a key characteristic of nucleic acids; that is the principle of base pairing, adenine to thymine, and guanine to cytosine, leading to the hybridisation, or joining, of complementary strands of nucleic acid. Each microarray is made up of many single-stranded nucleic acid fragments or 'probes' immobilised at fixed locations onto solid supports. The supports themselves are typically glass microscope slides, approximately 1.5cm square, but can also be silicon chips or nylon membranes. Crucially each single stranded nucleic acid probe, representing a particular gene of interest, has its own unique location on the chip. Although protocols vary, the basic technique involves initial isolation of messenger RNA from the sample of interest. The RNA is then copied, while incorporating either fluorescent nucleotides or a tag that is later stained with fluorescence. The labelled RNA or 'target' is then applied to the array. If a complementary sequence is present both on the array and in the sample they will hybridise. After a period of time the excess is washed off, and a laser light scanner is used to measure the level of fluorescence at each location. The degree of fluorescence corresponds to the level of hybridisation that has occurred and, therefore, to the abundance of the gene transcript in the sample. The fixed layout is 'decoded' and abundance is determined for each gene of interest.

Basically two types of expression arrays have developed so far; the spotted array and the high density, in situ synthesised, oligonucleotide array.

Spotted arrays

Spotted arrays employ a delivery approach. Complementary DNA (cDNA), ie DNA synthesised from mRNA by reverse transcriptase, or oligonucleotides corresponding to specific genes are synthesised 'off line' and then printed or 'spotted' onto the microarray support material using pins, ink-jets and other dispensers; each 'spot' representing a particular gene. These kinds of arrays are usually hybridised with labelled cDNA and allow for two colour hybridisation experiments: two cDNA samples are labelled with two different fluorescent tags (eg Cy3 and Cy5), the labelled samples are mixed together and hybridised to the same chip. After washing, the chip is scanned to generate images from two channels, thus allowing the measurement of two expression profiles in one run. The two expression

profiles can be directly compared by merging the images, allowing up and down regulated genes to be visualised. Typically the control or reference sample is labelled green and the test sample red. Genes up-regulated in the test sample appear red, down regulated genes appear green. Yellow spots indicate equal expression in both samples (Figure 1).

Spotted arrays have two major advantages: cost and flexibility. Microarrays containing a few hundred to a few thousand probes of interest can be printed at a relatively low cost. Custom arrays containing gene sets of interest allow multiple experimental conditions to be examined, which would be prohibitively expensive using commercially available arrays. Disadvantages include: the labour intensive process of synthesising and purifying the cDNA prior to array fabrication and the limitations on density dictated by spot size. Limited spot density means fewer spots and therefore fewer genes per slide, with many fewer controls. In addition spotted arrays are more prone to reproducibility problems. For these reasons spotted arrays are predominantly used in academic laboratories.

Oligonucleotide arrays

High density oligonucleotide arrays employ a synthesis approach – ie oligonucleotides are synthesised directly onto the surface of the array at pre-selected positions. The technology is based on in situ chemical synthesis techniques pioneered by Fodor et al in 1991,² and has been



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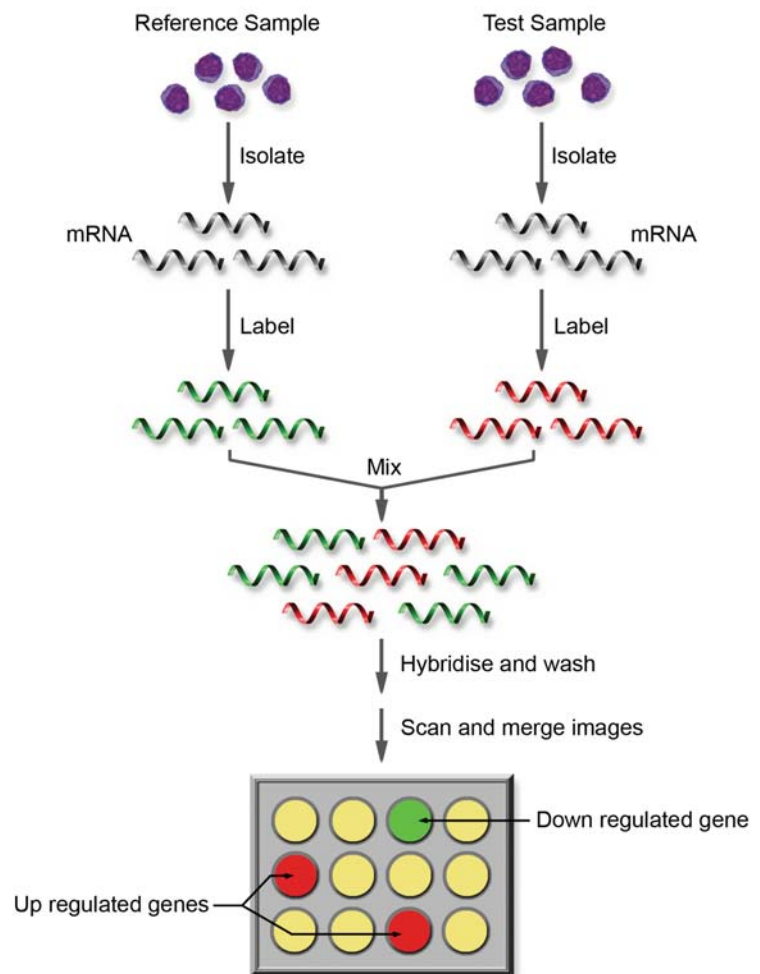


Figure 1: Spotted array. Using two different fluorescent labels (green and red) and a single chip the expression profiles of two samples can be directly compared. Genes up-regulated in the test sample appear red, down regulated genes appear green. Yellow spots indicate equal expression in both samples. Image courtesy of Hayden Jones.



Figure 2: GeneChip® Array in hand. Affymetrix GeneChip® probe array. Image courtesy of Affymetrix.

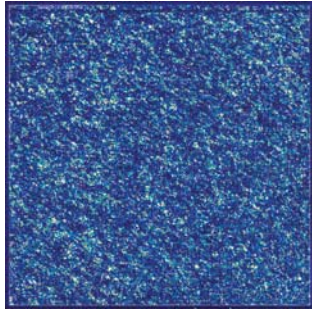


Figure 3: GeneChip® Array Output. Data from an experiment showing the expression of thousands of genes on a single GeneChip® probe array. Image courtesy of Affymetrix.

advanced by Affymetrix, the industry leader in this field.

The basic principle of manufacturing Affymetrix's GeneChips (Figure 2) is the use of photolithography (a process in which light and a series of masks are used to direct light dependent chemical reactions) and combinatorial chemistry to build short single stranded DNA sequences (25-mers) directly onto the microarray support by sequentially adding nucleotides. Key to Affymetrix's approach is probe redundancy; ie multiple probes of different sequences designed to hybridise to different regions of the same mRNA. The use of multiple, independent detectors for the same gene greatly improves the accuracy of quantitation and reduces the rate of false positives and miscalls.³ Accuracy is further enhanced by the use of mismatch (MM) control probes. MM probes are identical to their perfect match (PM) partners, except for a single base difference in a central position. The MM probes provide a measure of non-specific hybridisation aiding discrimination between 'real signal' and noise. Each square, or chip feature, contains millions of copies of the same probe. This sequence mismatch strategy, along with the use of multiple sequences for each gene, increases specificity and helps to identify and minimise the effects of non-specific hybridisation and background signal. Each chip is hybridised with one sample, washed and scanned to produce a single image (Figure 3). Samples are compared by comparing individual images.

In contrast to spotted arrays, oligonucleotide sequences are designed and synthesised based on sequence information alone. They are advantageous in that they eliminate the need for physical intermediates such as clones, PCR products and cDNAs.⁴ High density oligonucleotide arrays are fast, accurate and reproducible; the main disadvantage being cost.

An array of applications

The power of array technology lies, not only in the volume of data produced, but in its ability to provide an integrated 'snapshot' of the transcriptome. Expression arrays can be utilised to answer fundamental biological questions; knowing when, where and to what extent a gene is expressed is central to understanding the biological role of its encoded protein, and changes in the expression pattern of groups of genes can provide clues regarding integrated cellular pathways and regulatory mechanisms.

Microarrays also have medical applications. By comparing the expression profile of diseased and healthy cells arrays can help determine the cause and consequence of disease.⁵ In addition, expression profiles can aid diagnosis and disease classification; in a paper published in 1999 in the journal *Science*, Lander's group was the first to show that gene expression arrays could be used to distinguish between two types of leukaemia, acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML).⁶ In addition to classifying disease states and predicting outcomes, expression arrays can be used to analyse the effect of treatment and to predict patient response to therapy.⁷ Expression arrays aid the development of new treatments; by understanding how drugs work in cells⁸ and by identifying potential therapeutic targets.

Microarrays are versatile tools. This article has focused on expression arrays, but using conceptually similar approaches other array formats exist; eg single nucleotide polymorphism (SNP) chips can be used to measure genomic variation between individuals, and comparative genomic hybridisation (CGH) arrays to investigate genomic gains, losses and gene amplifications associated with disease. Protein arrays can be used to monitor protein expression and also to glean insights into the function of individual proteins by looking at the array of proteins they bind to.

Conclusions

Microarrays have revolutionised molecular biology. Only a decade ago the possibility of measuring the abundance of every transcript in a cell, at a given moment in time, in a single experiment was almost inconceivable. Microarray experiments are not strictly hypothesis led and have, therefore, been subject to criticism being described as 'fishing exercises'. Microarray experiments are 'question-led' and the lack of a rigid hypothesis is a fundamental strength of the technique, allowing the generation of un-biased data that is not constrained by previous assumptions. Lack of a strict hypothesis does not equate to lack of experimental design; indeed the large financial and intellectual burden of an array experiment demands a rigorous study design, perhaps greater than that required in a conventional experiment where a trial and error approach can be more easily tolerated.

Combined with computational tools for rigorous data analysis, integrated bioinformatics databases and the traditional approaches of genetics, biology and mathematics, microarrays increase the possibility that one day we will understand the function and regulation of all genes and proteins.

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The Neurology Short Case, 2nd Edition

Few circles are harder to square than that of the short neurology textbook. There is a view that such books are invariably useless, and that their only effect is to encourage the reader to carry his ignorance with a little more groundless confidence. Nowadays, of course, that is not seen as such a bad thing, confidence being the chief skill medical schools aim to develop in their students in the few hours of neurological training before they are unleashed on the public. But this is not good enough for the MRCP exam - not even in its newly emasculated, idiot-friendly, PACES format - and it is certainly not good enough for anyone who wishes to acquire a modicum of neurological competence.

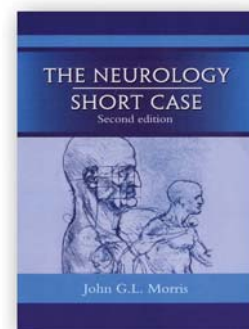
I mention PACES because it is the process of inferring the localisation of the lesion from the clinical signs and symptoms that novices find especially difficult. This ought to be surprising since clinical localisation is not an open-ended problem, but simply a reasoned choice from a finite set of possibilities. And since for clinical purposes the neuroanatomy need only be resolved at a fairly coarse granularity, this set ought to be small enough for anyone to deal with. Unfortunately, reasoning from facts takes more effort than just recalling them, and as a result both students and teachers shy away from it.

The principal merit of Professor Morris's book, then, is in lucidly demonstrating the clinical thinking on which neurological localisation depends. This is presented in the setting of the neurological short case - once one of the more feared components of the MRCP exam - but the coverage is not biased towards the esoteric, as is usual in exam books. Each chapter (of 13 in total) takes a common clinical prob-

lem or constellation of signs (the wasted hand, ptosis, gait disturbance, etc) and systematically outlines in each case which are the critical features to look for, and how each feature successively constrains the set of possible loci of the lesion. The text is nicely illustrated with clear diagrams that are refreshingly stripped of all inessentials, including any anatomical fidelity that is not relevant to their purpose. Somewhat incongruously, most chapters include a box briefly summarising the management of the relevant syndrome or a common condition which it exemplifies.

The book suffers in places from alarming oversimplification. For example, a naive reader may conclude that fasciculations always imply a diagnosis of motor neurone disease - this is dangerous clinically, and potentially fatal in the membership exam. Professor Morris would probably retort that no reader would be quite that naive, and perhaps that is the main problem with his exposition: too much of his obvious clinical ease has crept into pages intended for those who have very little. The structure of the inference is there but it is not displayed emphatically enough. Indeed, there is a loose-limbed, casual air to the proceedings, as if Professor Morris spent a few afternoons casting clinical pearls of variable size and quality in the direction of his assistant who then strung them up into something rather less tiered and more variegated than he originally intended. The total effect is certainly more High Street than Bond Street.

But if the book is not quite bling enough, the accompanying CD of illustrative video clips is enough to redeem it. It is a pleasing collection of clinical material and on its own justifies the very reasonable price.



John GL Morris
Published by: Hodder Arnold
Price: £16.99, Book + CD
ISBN: 0340549238

Reviewed by:
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Atlas of Neuromuscular Diseases: A Practical Guideline

The introduction of this book states it is "designed to help in the diagnosis of neuromuscular diseases at all levels of the peripheral nervous system" and is "for students, residents, physicians and neurologists who do not specialise in neuromuscular diseases". Justification for the book reflects the fact that the authors "found no other book which provides a complete overview in a structured and easily comprehensible pattern supported by figures and pictures". So that's the "what", "who for", and "why" covered then! But does it "do what is says on the tin"?

Well as overviews go this Atlas provides 51 pages on Cranial Nerves, 19 pages on plexopathies, 20 on radiculopathies, 70 on mononeuropathies (29 of which are on the trunk), 83 on polyneuropathies, 19 on neuromuscular transmission defects, 79 on muscle, and 12 on Motor Neuron Diseases. A final 12 page chapter called General disease finder, lists neuromuscular diseases seen in certain clinical settings (cancer, circulatory disorders, anaesthesia) which is a helpful entity to ponder as one troops off to yet another consult on the (oncology/ cardiothoracic/ Intensive Care) wards.

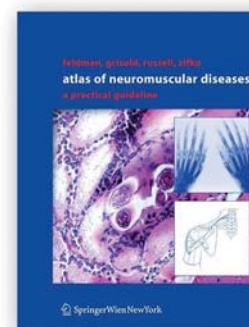
The chapters are presented in a standardised format: quality (what it does, in case you were wondering), neuroanatomy, symptoms, signs, pathogenesis, diagnosis plus differential, therapy, +/- prognosis, and references. All standard fare and perfectly acceptable with a few minor gripes such as - why change the surgical sieves for each cranial nerve and how about a steer on what of a long list of aetiological possibilities you will actually see and what you won't (diagnosing neuroaxonal dystrophy - late infantile(of course!) as a cause of deafness, for example).

I liked the plexopathy chapters with the odd colour photo and scan reproduction brightening up the Atlas geography considerably. What about the polyneuropathy section? Well, inevitably a balance has been struck between inclusivity and detail.

Two pages on chronic inflammatory demyelinating polyneuropathy may be quite enough for a medical student but even the most general of neurologists would I suspect feel a touch short-changed. What of Guillain-Barre Syndrome? Well, again a little under 2 pages with a suggested treatment regime for intravenous immunoglobulin that I have never seen or used. Myasthenia fares better with 8 pages plus a big list of drugs to beware. Attractive photographs of clinical and histological slides also add visual impact to the muscle section.

Those involved in teaching trainees about motor neuronopathies may question whether genetic studies, imaging, and laboratory studies should be given equal weight to neurophysiological examination in the diagnosis of ALS but this too is a relatively minor whinge.

The fundamental problem in trying to cover an area so vast in a single text remains. Depth competes with mass. Striking the balance between a detailed source of information versus an expensive test of neuromuscular integrity (in picking the thing up) is tricky. This Atlas tends to the informative end and has value as a single volume for those visiting the landscape of neuromuscular disease or en route to other neurological destinations. For those practitioners intent on staying the Atlas is a good place to start.



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Spontaneous Intracranial Hypotension – Diagnosis and Management

Introduction

Spontaneous intracranial hypotension (SIH) produces a headache similar to a post lumbar puncture headache. Although the terms 'hypotension', 'low CSF pressure' and 'low CSF volume' are often used interchangeably, the syndrome can occur in the setting of 'normal' CSF pressures. Loss of CSF volume rather than pressure better explains the clinical features and imaging abnormalities.¹

Classification of low volume headaches

The international classification of headache disorders recognises three subsets of low CSF volume headache.² These are post-dural (post-lumbar) puncture headache, CSF fistula headache and headache attributed to spontaneous low CSF volume/spontaneous intracranial hypotension. Criteria needed for these diagnoses are summarised in Table 1. The cardinal feature indicating low CSF volume headache is aggravation of symptoms within 15 minutes of sitting or standing. In post-dural puncture headache symptoms should improve within 15 minutes of lying down.

Aetiology and risk factors

SIH has been associated with abnormalities of the cervical spine and chiropractic manoeuvres. Although there may be a clear trigger such as a Valsalva manoeuvre or trauma, SIH may occur without a clear precipitant. The cause is thought to relate to a breach of dural diverticulae, or tearing of nerve root sheaths. Connective tissue disorders have been suggested as possible predisposing factors, as SIH has been reported in patients with Marfan's and Ehlers-Danlos syndromes.

Not all patients with spontaneous intracranial hypotension have low CSF pressures when measured at lumbar puncture. This implies that there may be significant individual variation in CSF pressures, and also that the rate of CSF loss may be more important in producing the syndrome than the residual CSF pressure or volume. CSF leaks are not identified in every case of apparent SIH. In part this may relate to the limitation of investigations. However patients with a typical history, without clear evidence of a leak, and who have failed 'blind' blood patches, often prove very difficult to treat. It is possible in such cases that a CSF leak may have occurred, with a residual effect on CSF dynamics (eg lowered pressure setting in the choroid plexus, and sensitisation of meningeal afferents).

Based on similarities between post lumbar puncture headache (PLPH) and SIH, a number of inferences can be made. PLPH is less common at the extremes of age and this has been attributed to reduced epidural distensibility in the very old and very young.³ A higher risk has been reported in young females with a low body mass index.⁴ Patients with dementia appear to have a very low risk of PLPH⁵ and this has been attributed to low pain sensitivity, rigid dural fibres, arteriosclerotic vessels, and large CSF spaces due to cerebral atrophy. PLPH occurs less frequently in those with higher CSF opening pressures.⁶ These factors may also be of relevance in SIH.

Pathophysiology

Two main theories have been proposed to explain the cause of headache in patients with low CSF volume headache. They have been outlined in greater detail by Paldino et al.⁷

1) Traction on pain sensitive structures

Under normal conditions, CSF supports the brain reducing its weight from 1500g to only 48g within the cranium. This remaining weight is supported by suspension from several pain-sensitive structures. These include the meninges, cerebral and cerebellar veins (tributaries of the sagittal and transverse sinuses, respectively) as well as the fifth, ninth, and tenth cranial nerves and the superior three cervical nerves. Descent of the brain and traction on these structures, explains the orthostatic nature of the headache.

However tonsillar descent is not found in all patients with SIH. This may be because displacement of the brain is underestimated (because the patient lies supine during brain imaging). It may also be because there are additional pathophysiological mechanisms.

2) Dilation of pain sensitive intracranial vascular structures

The mean recumbent CSF pressure is approximately 150mm of water at all levels. In the erect posture, a pressure gradient occurs; highest in the lumbar sac, about 0 at the level of the cisterna magna, and around -85mm H₂O in the ventricles. Venous engorgement in both brain and spine occurs in SIH. According to the Monro-Kellie doctrine, the upright posture should be associated with further dilation of pain-sensitive intracranial venous structures. In support of this theory is the finding that coughing or Valsalva manoeuvres (that decrease the venous return to the heart and therefore increase intracranial venous volume) can reproduce headache in a patient with SIH even when supine.

Clinical Features

The onset of headache following SIH may be gradual or subacute but a thunderclap form is also well recognised in about 14% of cases.⁸ Associated clinical features are neck stiffness, tinnitus, hyperacusis, photophobia, nausea, interscapular and radicular upper limb pain, vertigo, visual field defects, and cranial nerve palsies.

As SIH becomes chronic, the postural aspect of the headache may become much less apparent, and an index event may not be recalled. SIH should therefore be considered in the differential diagnosis of new onset persistent daily headache.⁹

Rare presentations of SIH include sudden deafness, orthostatic tinnitus, rapid onset encephalopathy and coma (attributed to diencephalic compression resulting from brain descent), Parkinsonism, and chronic behavioural features suggestive of frontotemporal dementia.¹⁰⁻¹² Radiculopathy due to cervical epidural venous engorgement has also been associated with SIH.¹³

It is also important to note that orthostatic headaches have been described without CSF leakage as the major clinical manifestation of postural tachycardia syndrome (a disorder characterised by chronic orthostatic symptoms and a dramatic increase in heart rate on standing, but that does not involve orthostatic hypotension).¹⁴

Investigations

Investigation of patients with suspected SIH may help corroborate the diagnosis and identify the site of CSF leakage.

Magnetic Resonance Imaging (MRI)

MRI brain with contrast is the initial investigation of choice in suspected SIH. Meningeal enhancement is the earliest and most frequent feature, occurring in more than 80% of subjects; tonsillar descent is seen in more than



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Table 1: Diagnostic criteria for headaches attributed to low cerebrospinal fluid volume (from the International Classification of Headache Disorders³)

Post-dural (post-lumbar) puncture headache

Headache that worsens within 15 minutes after sitting or standing and improves within 15 minutes after lying

One of neck stiffness, tinnitus, hyperacusis, photophobia or nausea

Dural puncture has been performed

Headache develops within 5 days after dural puncture

Headache resolves spontaneously within 1 week or within 48 hours after effective treatment

CSF fistula headache

Headache that worsens within 15 minutes after sitting or standing and improves within 15 minutes after lying

One of neck stiffness, tinnitus, hyperacusis, photophobia, nausea

A known procedure or trauma has caused persistent CSF leakage with at least one of the following: low CSF pressure evidence on MRI, evidence of CSF leakage on conventional myelography, CT myelography or cisternography and CSF opening pressure <60 mm H₂O in sitting position

Headache develops in close temporal relation to CSF leakage

Headache resolves within 7 days of sealing the CSF leak

Headache attributed to spontaneous (or idiopathic) low CSF pressure

Diffuse and/or dull headache that worsens within 15 minutes after sitting or standing, with at least one of the following

One of neck stiffness, tinnitus, hyperacusis, photophobia or nausea

A known procedure or trauma has caused persistent CSF leakage with at least one of the following: low CSF pressure evidence on MRI, evidence of CSF leakage on conventional myelography, CT myelography or cisternography and CSF opening pressure <60 mm H₂O in sitting position

Headache develops in close temporal relation to CSF leakage

Headache resolves within 7 days of sealing the CSF leak

40% and subdural hygromas/haematomas in about 17%.¹⁵ The subdural effusions result from transudation from engorged venous plexuses. Such changes range from very striking to quite subtle. Engorgement of venous sinuses may also cause enlargement of the pituitary gland.¹⁶

It is important to note that a normal MRI brain is compatible with the diagnosis of SIH,¹⁷ and also that pachymeningeal enhancement can occur in the setting of significant and proven CSF leaks in patients who are headache free.¹⁸ A normal initial brain MRI in symptomatic patients however is predictive of poor outcome.¹⁹

Cervical MRI scans may show meningeal enhancement and a dilated internal vertebral venous plexus in 85% and spinal hygromas in up to 70% of cases.²⁰ The utility of spinal MRI for detecting the site of CSF leakage relative to other modalities (see below) is not clear.

Doppler Flow Imaging

This is predicated on the basis that the superior ophthalmic vein is a tributary of the cavernous sinus and it might therefore reflect the engorgement of the intracranial venous sinuses that occurs in this condition. Increased diameter and maximum flow velocity of the superior ophthalmic veins has been demonstrated in patients with SIH using transorbital colourflow Doppler imaging. One study suggests this technique has very high specificity and sensitivity, though clearly does not assist in identifying the site of leakage.²¹

Radionuclide Cisternography

Radionuclide cisternography frequently demonstrates 'surrogate' markers of a low volume CSF state. These include limited ascent of the tracer to the cerebral convexity in 91% of cases, early appearance of the

radioisotope in the bladder in 65%, and early soft tissue uptake of radioisotope in 43%.²² Actual leakage of CSF has been identified in 52% of cases,²² most commonly at the cervico-thoracic junction or in the thoracic spine. Intermittent leaks may go undetected and the technique may be insufficiently sensitive to identify small leaks.

CT Myelography

CT myelography has been found to demonstrate the level of a CSF leak in 67% of patients overall, compared with only 50 and 55% for spinal MR imaging and radionuclide cisternography.²³ In no case did radionuclide cisternography reveal the leak when CT myelography did not. Unfortunately CT myelography can be very time consuming, as it requires CT slices be obtained through the skull base and the entire spinal axis. Spinal imaging and radionuclide cisternography may perhaps be helpful as guides for focusing on particular areas with CT myelography.

Lumbar Puncture

Lumbar puncture should be considered only if the features are equivocal and should be avoided before MRI with contrast as this can interfere with interpretation of the results. CSF opening pressure is typically low (usually 0–5cm CSF).⁵ It may however be normal in up to 17% of cases.²⁴ CSF constituents are usually normal although high protein concentration and lymphocytic pleocytosis may be seen.²⁵

Treatment

Medical

Conservative measures like bed rest are the first line treatment for low intracranial pressure headache. If not effective, intravenous caffeine at a dose of 500mg in 500ml saline over two hours (repeated once or twice) is often used although the evidence base is limited.⁹ Cardiac monitoring is necessary as caffeine can induce arrhythmias. There is also some evidence to suggest that theophyllines may be efficacious. It has been proposed that methylxanthines produce arterial constriction through the blockade of adenosine receptors.²⁶ Consequently, intracranial blood flow and, presumably, venous engorgement are decreased. Abdominal binding with a surgical corset may help, while glucocorticoids or mineralocorticoids have been used in some studies but are of questionable effect.

Interventional

i) Autologous epidural blood patch

The technique was initially based on the observation that PLPH was less severe after a 'bloody tap' compared with a 'clear tap'. The mode of action is not clear but may be due to a tamponade effect. It is performed by slowly injecting autologous blood into the same interspace or the interspace below the site of leak.

In contrast to PLPH the site of CSF leakage may not be certain in SIH. It may not be critical to identify the site of leakage. There is some evidence that lumbar epidural blood patching may be effective over nine spinal segments when the patient's head is lowered to 30°. A recent report suggests that early 'blind' epidural blood patching within one week of onset is effective; demonstrating complete cure in 77% of 30 patients (with or without typical MRI changes) after one (57%) or two (20%) blood patches. These patients did not have lumbar punctures, nor was the site of CSF leakage identified.²⁷

ii) Other treatment modalities

Epidural saline injection has been reported to give immediate relief for headache. This is thought to be by reduction in the distensibility of the epidural space. This manoeuvre could also be life saving in obtunded patients with SIH.²⁸

A small group of patients with a typical history but no clear evidence of a leak, may fail 'blind' blood patches. These patients often prove very difficult to treat. It is possible in such cases that a CSF leak may have occurred, with a residual effect on CSF dynamics (eg lowered pressure setting in the choroid plexus, and sensitisation of meningeal afferents).

Conclusion

Loss of CSF volume best explains the syndrome often designated 'low-pressure headache'. CSF pressures may not always be low.

Patients with chronic symptoms of SIH may not volunteer or recall a

definite ictus and over time the postural aspect of the headache may become less clear. SIH may thus present as new onset persistent daily headache rather than as an orthostatic headache. MRI brain with contrast is the first line investigation of SIH. Patients with a normal contrast enhanced MRI brain appear to have a worse prognosis. Radionuclide cisternography generally shows abnormalities in SIH although it is relatively poor at locating the site of a CSF leak. CT myelography of the spine is arguably the most sensitive test to identify the site of a leak. However it is time consuming if there are no clues as to where to focus the study.

It is usual practice to try and focus a blood patch on the site of the CSF leak (the most common site is cervico-thoracic). However this may incur a delay to treatment while imaging investigations are arranged. Recent studies suggest that 'blind' blood patching at an early stage may be very effective.

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Department of Clinical Neurosciences

**Joint meeting of
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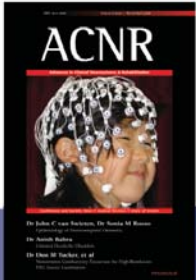
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The Guarantors of Brain have offered a bursary to UK clinically qualified delegates which will fund all but £50 of the meeting fee. **Registration deadline 10th March, 2006.**

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**Deadline for May/June issue:
7th April, 2006**

American Epilepsy Society Annual Meeting

Washington, USA, 2-6 December, 2005.

The 2005 meeting of the American Epilepsy Society, usually the highlight of the epilepsy year, was like its venue in Washington DC, big but uninspiring. The meeting was at least congenial, whereas the city planners were given the remit to make DC intimidating to visitors. The area around the White House and the Capitol contains a plethora of neoclassical federal department buildings, each of which takes several minutes to walk past, which are imposing but unattractive; the park they surround is enormous and its best features a small lake and the Washington monument, the tallest free-standing stone structure in the world, elegant and needle-like from a distance, it has walls that are 15 feet thick at their base. In Georgetown one sees another side of the city. Site of the race riots of the late 1960s, it has out-Islingtoned Islington in upper middle class renaissance and antiques shops. The national museums of Washington are the highlight and are free, from the National Gallery of Art to the Space Museum.

What about the meeting? The 25th annual Merritt Putnam symposium was about the issue of pharmacoresistance, which though interesting remains speculative and the next few years will hopefully establish its clinical importance. Expression of drug transporters such as P-glycoprotein, important in phenytoin disposition, may be different in epileptic and normal brains and can be influenced by verapamil, a P-gp inhibitor. In other models there may be changes in the targets of AEDs such as sodium channels or GABA_A reducing the effectiveness of medications and underlying this changes in mRNA may be detectable. In the meantime new drugs continue to be developed and there was a call from Marc Dichter of Pennsylvania for new ways of evaluating efficacy and new types of study which would allow us to evaluate new medication more speedily.

The annual course was a pragmatic one for clinicians, covering a number of issues including diagnosis and the value of EEG, long term cognitive outcome of epilepsy and women's issues. The format was varied and stimulating, using case studies, formal presentations and debates to highlight the issues, but much of the content was revision rather than revolution. Lawrence Hirsch from Columbia argued entertainingly and cogently that there is no evidence to support the aggressive management of anaesthetising

patients with non-convulsive status epilepticus to EEG burst-suppression. On this issue I came away with a clear feeling of uncertainty, which is probably intellectually healthy if not clinically useful.

The MESS study, published in the Lancet last Summer,¹ looked at 1443 patients with early epilepsy or single seizures who were randomised to immediate or deferred treatment. In essence, early treatment improved seizure outcome at 1-2 years but not at 3-5 years and there was no difference in major morbidity or mortality. In his platform presentation, David Chadwick presented an algorithm developed from this study which can be used to quantify the risk of recurrence and help decide whether to treat straight away (Table 1).

His study on behalf of the MRC of drug withdrawal is now 15 years old but remains a standard and has also given rise to a more complex algorithm (Table 2) for the risk of recurrence. If these algorithms are reliable in clinical practice then they will be helpful for clinicians and patients in planning when to start and stop medication. I await a pharmaceutical company initiative for a handy pen/seizure recurrence calculator/built in USB memory stick and laser pointer.

There were a variety of evening symposia, one on consciousness in epilepsy, which at 7.30pm was variably reflected in the consciousness of the audience. David McCormick (Yale) reviewed thalamocortical mechanisms in the generation of generalised spike-wave discharges and showed how the short loop between thalamus and thalamic reticular nucleus is responsible for normal sleep spindles, whereas the long loop from thalamus to cortex creates abnormal spike and wave discharges. Inhibitory cells are implicated with the spindle discharges, but blocking them with bicuculline seems to release an abnormal 2-3Hz discharge.

Neuropsychological assessment reflects clinical experience that absence is a variable phenomenon with different degrees of altered awareness in complex partial seizures versus 3Hz spike-wave

absences. In addition, the idea that spike wave causes loss of awareness is simplistic as the alteration in awareness starts before a spike-wave burst and increases towards a spike wave burst in association with the development of harmonics of the burst on the EEG. In addition there are genetic effects on awareness with female probands and relatives, being differently affected from males. This area has been ripe for fMRI study suggesting, amongst other things that complex partial seizures may propagate from mesial temporal structures to inhibit arousal mechanisms.

There was a vast number of poster information nuggets to view. Donepezil does not help memory in epilepsy – surprised? Patients who suffer cognitive decline from their epilepsy tend to be those with lower IQ, longer duration of epilepsy, more abnormal hippocampal volume and more cerebral atrophy. Temporal lobe drop attacks, which sometimes develop later in the course of the illness may be ictal asystole. Four patients were reported with severe unilateral hippocampal sclerosis whose seizure onset was in the opposite hippocampus. Presumably the atrophy was so severe that there were not the neuronal circuits needed for seizure generation. Postictal whispering or feeble speech rather than aphasia is a sign of non-epileptic seizures. One episode of ictal aggression was described in a patient with a right temporal lobe tumour. He got out of bed turned towards his wife and motioned as to shoot her with a bow and arrow, whilst making a shooting noise and then briefly tried to strangle her. The EEG confirmed a right temporal seizure discharge – honest m'lud! The Columbia University group described 6 critically ill patients with encephalopathy who suffered focal motor seizures when exposed to alerting stimuli; something to be remembered when nursing patients on ITU. Subtle white matter lines on MRI may be a marker for tuberose sclerosis. If teachers know that a student has epilepsy then they tend to rate their performance lower on teacher assessment

Simplified model	Score
One seizure prior to presentation	0
Two seizures prior to presentation	1
>2 seizures prior to presentation	2
Neurological disorder / deficit, learning disability or developmental delay	+1
Abnormal EEG	+1
	Final score
Low risk	0
Medium risk	1
High risk	2-4

Factor	
1. Starting score for all patients	-175
Age >16	45
Taking more than 1 AED	50
Seizures occurring after start of treatment	35
Any TCS	35
Myoclonus	50
EEG while in remission	
Not done	15
Abnormal	20
Duration of seizure-free period =D	200/D
2. Total score	T
3. Exponentiate $Z=e^{T/100}$	Z

	Probability of seizure recurrence	
	By 1 year	By 2 years
On continued treatment	1-0.89 ^Z	1-0.79 ^Z
On slow withdrawal of treatment	1-0.69 ^Z	1-0.60 ^Z

than they achieve on objective academic assessments, whereas this is not the case if they do not know that they have epilepsy. Ethosuximide (now only one preparation available in the UK) is traditionally only used in absence epilepsy. One study reported its efficacy in epileptic negative myoclonus in 10 patients. A reminder that topiramate can cause hypohydrosis and hyperthermia. Two studies looked at the effect of cooling the cortex, one using a thermoelectric device in animals and the other using a cooling helmet in

humans. In one man, this reduced core temperature by 0.24°C and scalp temperature by 14.3°C for 1 hour each week. He had no seizures during the 4 week trial period compared to 0.75 per week in the rest of the study.

My most unforgettable time in DC was in the Holocaust Museum, which leaves you at once traumatised through the depiction of horror and uplifted by stories of resilience and selfless acts of heroism. A most potent reminder of vital personal, religious and political freedoms. I disapprove

of what you say but I will defend to the death your right to say it – Voltaire.

Mark Manford,
Consultant Neurologist, Norwich.

1. Marson A, Jacoby A, Johnson A, Kim L et al. *Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial.* Lancet 2005;365:2007-13.

British Society For Immunology Annual Meeting

Harrogate, UK, 6-9 December, 2005.

Cleanliness causes depression

The "hygiene hypothesis" explains why allergy and autoimmunity are on the increase. The increasing cleanliness of industrialised society reduces the opportunities to encounter trivial or harmless infections. So we have fewer chronic infections. Yet the immune system has evolved to live with, or even depend upon, such infections. For they induce release of cytokines such as IL-10 which promote regulatory T cells that suppress allergic and autoimmune responses. Without commensals, the immune system is tipped towards a pro-inflammatory and pro-allergic state. So far, so good.

Graham Rook, from UCL, has taken this further. He hypothesised that the hygiene hypothesis might also explain depression. Experimentally, he demonstrated that mice infected with *Mycobacterium vaccae*, which induces regulatory T cells and suppresses allergic responses, had increased serotonergic staining in localised CNS pathways and swim for longer in the "forced swim test" of depression. He argues that perhaps depression is an abnormally prolonged form of the "sickness behaviour" that accompanies the release of pro-inflammatory cytokines. Now I know why cleaning the kitchen makes me so unhappy.

Reverse vaccinology for meningitis

The revolution in the management of meningitis passed me by. Did you realise that meningococcus A, C, Y and W are no longer? Since the UK introduced a vaccination policy in 1999 for everyone under the age of 18 (and we were the first country to do it), the number of cases has fallen precipitously. The scientist behind those vaccines was R Rappuloi, from Chiron Vaccines in Siena. Now the hunt is on to develop a vaccine against meningococcus B. It is proving difficult. By traditional vaccine technology, only one antigen can be detected on the surface of meningococcus B, of which there are many thousands of variants. Where only one strain exists (such as New Zealand) a vaccine is easy to create and it works. But for the rest of the world a "one fits all" vaccine is required... to find this, Rappuloi has developed the technique of "reverse vaccinology". He persuaded the scientific community to sequence the genome of meningococcus B and 18 months later he had identified 90 novel proteins expressed on the surface of meningococcus B, which he has whittled down to 5 vaccines now entering clinical trials. Pasteur would have been proud.

Controlling pathogenic CNS – reactive T-cells: death and regulation

An effective immune system must be able to respond to all possible pathogens whilst maintaining tolerance to self. These twin requirements are finely balanced, with increased T-cell receptor (TCR) diversity resulting in an increased risk of autoaggression. Steve Anderton (Edinburgh) has demonstrated some of the niceties of this balance using EAE induced by the Ac1-9 peptide of myelin basic protein (MBP) in mice expressing a transgenic Ac1-9-reactive TCR. The peptide was subtly altered (single amino acid changes at key positions) to make a series of altered peptide ligands (APLs) with varying binding affinities to the TCR. Interestingly, EAE could only be induced by immunisation with the wild type peptide. Sub-agonist and surprisingly super-agonist APLs failed to induce disease. Super-agonists are defined by the ability to stimulate T-cells in vitro at significantly lower concentrations than the wild type peptide. Immunisation with the super-agonist led to the apoptotic elimination of super-activated cells in a Fas dependent manner. Only T-cells with very low affinity TCRs survived apoptotic cell death. These cells were unable to respond to wild type antigen at the concentration found in vivo, and were, therefore, unable to induce disease. In addition, immunisation with the sub-agonist activated T-regulatory cells thus preventing disease induction.

The search for an endogenous agonist for Toll like receptor 3 (TLR), a repair mediator in the CNS

It would be extremely useful to be able to exploit repair mechanisms in the CNS to treat MS, but how could these repair mechanisms work? Jan van Noort (Netherlands) discussed TLR3 and its possible role. Activation of TLRs upregulates pro-inflammatory cytokines, some of which are relevant for tissue repair. In the MS lesion, TLR3 expression increases early in microglia and later on the surface of astrocytes; and in vitro TLR3 ligation causes astrocytes to release neurotrophic factors, anti-inflammatory cytokines and other factors important in repair. The only known agonist for human TLR3 is dsRNA. Van Noort and colleagues have found another ligand, preferentially expressed in the CNS, by screening tumour cell lines. High expression levels of this agonist were found in foetal development at axonal growth regions and developing dendrites and lev-

els decreased with age. Inflammation seemed to increase production of this agonist in neurones and oligodendrocytes. We will not get to know the identity of this agonist until the patent lawyers have had their say, but it sounds promising...

TIM and galectins: Role in T cell differentiation, autoimmunity and tolerance

The T cell immunoglobulin mucin (Tim) proteins are type 1 membrane glycoproteins expressed on T cells. Tim-3 was first identified in VJ Kuchroo's Boston laboratory, and is expressed on terminally differentiated TH1 cells, which produce IFN-g and IL-2, and at low levels by TH1IL-17 cells. Kuchroo described how Tim-3 is an inhibitory molecule. Blocking Tim-3 with an immunoglobulin fusion protein resulted in hyperproliferation of TH1 cells and an increase in levels of IFN-g, and the abrogation of antigen-specific tolerance. This suggests that Tim-3 and its ligand are important regulators in peripheral tolerance and expansion of effector TH1 cells. Kuchroo's laboratory has also identified the ligand for Tim-3: galectin-9.

Galectins are carbohydrate-binding proteins, which act as controllers, silencers and tuners of the immune system, and have a vital role in immune cell homeostasis. Galectin-9 inhibits IFN-g production by Tim-3 expressing TH1 cells in vivo and induces TH1 cell apoptosis in vitro. TH1 cells incubated with recombinant galectin-9 clumped together and underwent rapid cell death, however, when Tim-3 deficient TH1 cells were incubated with recombinant galectin-9, cell death was partially impaired suggesting that galectin-9-mediated cell death is both Tim-3 and contact dependent. C57BL/6J mice, immunised with myelin oligodendrocyte glycoprotein (MOG) to induce EAE, and injected with galectin-9 had a 50% decrease in IFN-g production by antigen specific IFN-g producing CD4+ T cells, indicating that galectin-9 targeted antigen-specific TH1 cells in vivo, but not other peripheral T cells. These mice had reduced disease severity and mortality. Kuchroo proposes that Tim-3 and its respective ligand, galectin-9 may be involved in regulating the fine balance between maintaining tolerance to self and defending the body from pathogens.

Alasdair Coles, Joanne Jones,
Vicki Robertson, Sara Thompson, Cambridge.

16th International Symposium on ALS/MND

Dublin, UK, 8-10 December, 2005.

Pre-Christmas Dublin was the lively venue for the 16th International Symposium on ALS/MND organised by the Motor Neurone Disease Association in co-operation with the International Alliance of ALS/MND Associations. Over 850 clinicians, researchers and health care professionals along with patients and representatives attended the 3 day meeting. The sparkling Burlington Hotel could just about cope with the numbers with many of the parallel sessions full to capacity. The programme committee, chaired by Professor Pamela Shaw (Sheffield), managed to pack in sessions ranging from basic science and clinical research through to clinical care and support. The review below highlights some of the sessions I attended.

Alternative medicine

The Opening Session began with a talk on 'Alternative medicine – hope or hype'. This was delivered, somewhat dryly and without visual aids, by Dr Steven Barrett (Pennsylvania, USA) who has established the website Quackwatch (www.quackwatch.org). From his opening salvo – “‘Quackery’ is a nasty term, and so is ‘complementary medicine’” – his choice of hype over hope was clear. He took issue with denoting the field as ‘complementary’ or ‘alternative’ saying that these terms give quackery a credibility and legitimacy it hasn't earned. He emphasised that ‘alternative’ therapies are not necessarily harmless, giving false hope and having negative effects on wider public health issues, even if not often physically detrimental. Whilst not agreeing with all he said, I found his talk challenging. We are so keen not to offend nor dash hope in our dealings with people with MND that it is all too easy to say that certain complementary therapies are unlikely to do physical harm and if patients report that such treatments make them feel better suggest they continue them. Is this really the best advice we can give?

In the second talk of this plenary session Nigel Leigh (King's, London) gave a clear overview of variation in ALS/MND, emphasising the heterogeneity of the disorder in terms of phenotype and prognosis. A take home message was that a one-mechanism, one-prescription-for-all type of approach may not be appropriate.

Lessons from other motor neuron disorders

I thought this was one of the best sessions of the meeting. A comprehensive talk on recent advances in the genetic understanding of distal hereditary motor neuropathies by Peter de Jonghe (Antwerp) was followed by a review of spinal muscular atrophy by Michael Sendtner (Wuerzburg). He detailed research suggesting that this is not caused by a primary defect in cell survival but rather with a defect in axonal growth and maintenance. He outlined various therapeutic possibilities including up-regulation of axonal mRNA transport and local protein synthesis at the presynapse. Martin Schwab (Zurich) gave an elegant account of axonal regeneration and functional recovery in adult injured mammalian spinal cord. He outlined the role of neurite

inhibitory growth factors and reviewed results of experiments administering neutralising antibodies to Nogo-A in rats and monkeys following acute cord injury. It's not yet clear if any of this work on treatment following acute cord injury will be relevant to ALS/MND, a disease where there is still no good early marker of disease.

Protein folding and degradation defects

Heather Durham (Montreal) gave an overview of the proteasome and its role in cell regulation and neuromuscular disease. I hope that she will write the talk up as a review, as she presented much complex data in a very accessible way. Avijit Chakrabarty's short talk outlining the use of an antibody that specifically binds to misfolded SOD1 generated much interest. About 20% of autosomal dominant familial ALS cases are due to mutations in SOD1, an enzyme that normally functions as a homodimer. Mutant SOD1 is more aggregation prone than wild-type SOD1 in vitro and prior to aggregation SOD1 goes through a monomeric intermediate. The newly developed SEDI (SOD1 exposed dimer interface) antibody specifically recognises an epitope that is only exposed in monomeric SOD1, and lovely data was presented showing that the antibody binds to misfolded SOD1 in spinal cords of transgenic G93A and G37R SOD1 mice, binding not seen in non-transgenic littermates. It was also suggested that the antibody staining around vacuoles in motor neurones represented misfolded SOD1 in mitochondria, which fits well with the proposed pathogenic role for mitochondria in ALS/MND. Results on staining of only one surviving motor neurone in the spinal cord of a single ALS patient were presented. After the session many groups with human tissue offered to collaborate and future reports of the results in ALS/MND tissue are awaited.

Preclinical therapeutic trials

A highlight here was the work presented by D Kieran (Dublin) on angiogenin. Work in recent years has shown that the hypoxia-inducible factors VEGF and IGF-1 are neuroprotective to motor neurons. At the ALS/MND Symposium in 2004 Orla Hardiman's Dublin group presented data showing that mutations in the gene encoding the hypoxia-responsive peptide angiogenin are associated with ALS. The paper in the current symposium built on this, showing that angio-

genin is expressed in cultured motor neurons, this expression increases during hypoxia and that co-treatment with angiogenin significantly increases motor neuron survival in cultures exposed to hypoxia or excitotoxicity. The role of hypoxia inducible factors in motor neuron degeneration and their potential as therapies is clearly a 'hot' research area in ALS/MND at present.

Clinical trials

The session of the meeting that I'm most asked about by people with MND and their carers is that on clinical trials. "Was there anything new from the meeting that's going to help me now?" Sadly, no new positive clinical trial data was presented at the meeting. The negative results of the Phase II/III clinical trial of TCH 346, an anti-apoptotic agent, were presented by Bob Miller (San Francisco). The negative results of (another) study of creatine 5g once daily were presented by Dr Rosenfeld (Charlotte, USA). I was surprised that Dr Rosenfeld concluded his talk by saying that perhaps another study of creatine should be performed, using higher doses of the agent and looking at its effect combined with exercise. My take on the presentation of his data was that, despite the promising results in the SOD1 mouse model, creatine is not of benefit in human ALS/MND.

Elsewhere in the symposium safety data was presented from Phase I and II trials of compounds such as the manganoporphyrin AEOL10150, glatiramer acetate, tamoxifen and thalidomide. Novel trial designs such as futility trials, which allow smaller patient and control numbers, or trials based on selecting rapidly progressing patients were also discussed.

Genetics sessions

Points I noted from the genetics sessions included: more families with ALS and frontotemporal dementia linked to chromosome 9p21 have been identified, but no gene has as yet been reported; spastin mutations are not found in primary lateral sclerosis; spastin mutations are occasionally found in both adult and juvenile onset ALS; mutations in VAPB, a protein that interacts with synaptobrevin to aid vesicular packaging and transfer have been found in about 2% of ALS patients (both familial and sporadic) and occasionally in controls.

Conclusions

Although no 'big breakthroughs' were presented at the meeting, there was much to be encouraged by and I certainly left feeling upbeat about the prospects for ALS/MND care and research. Oh yes, I forgot to mention the social side of the proceedings. The Irish MND Association really do know how to host a meeting. Many thanks to Dr Hardiman and all the local MND workers for creating an excellent atmosphere throughout the meeting and for staging a great conference dinner, complete with Irish dancing. I don't think Riverdance has to fear from an influx of MND researchers just yet.

Professor Karen E Morrison, Professor of Neurology, University of Birmingham.



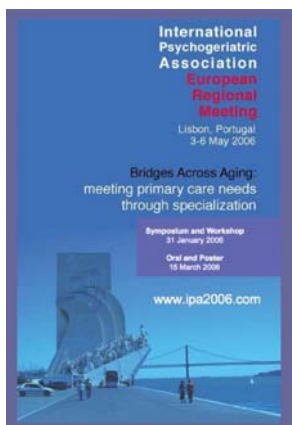
An MND patient using a nasal mask for assisted ventilation.

An MND patient using a communication device strapped to her foot.

CONFERENCE PREVIEW: Bridges across Ageing: meeting primary care needs through specialisation. International Psychogeriatric Association European Regional Meeting

Lisbon, Portugal, 3-6 May, 2006.

A programme of plenary sessions, symposia and workshops, poster presentations, as well as themed oral sessions for new research and satellite symposia supported by industry, will be the structure for this meeting, focused on bridging primary care with specialties to most effectively meet the mental health needs of the elderly. International speakers will bring knowledge and data appropriate to an audience of professionals including psychiatrists, primary care physicians, neurologists, internal medicine physicians, psychologists, social workers, nurses, occupational therapists and other colleagues with interests in geriatric mental health.



Topics include: Delivery of psychogeriatric services; Dementia; Depression and suicide; Medical aspects associated with AD; Mental health services in nursing homes; Mild cognitive impairment; Psychosis; Psychotherapies and cognitive training.

Recent advances in the field of Psychogeriatrics will be presented, especially in the areas of understanding basic neurobiology, diagnostics, therapeutics, and service development and delivery. Symposia will also be presented by the World Psychiatric Association, European Association for Geriatric Psychiatry and on the EDCON project.

Visit www.ipa-online.org to see the latest programme, speaker information and submission and registration details.

Horácio Firmino, Meeting Chair.

Portugal is a beautiful country known for its contrasts – from its outstanding landscapes of beaches and mountains to its rich history and exciting contemporary development. The same is true in its diverse ageing population. The distribution of the elderly population in Portugal is not homogeneous, reflecting the socio-economic diversities of each region. At this time, 17% of the Portuguese population lives beyond 65 years of age. The largest percentage of population over 65 resides in the central and southern regions of the country. According to a study of the National Institute of Statistics (2002), the population in Portugal over 65 years of age has doubled in the last 40 years, so that in about 30% of families, there is at least one elderly person and around half of these families are composed of elders.

The increase of this elderly population has led to the development of social policies to guarantee an ageing with quality of life. New solutions of home support and day centres help to maintain the elderly in their own residences, and provide options beyond nursing home placement. Portugal is a country with handicap access both socially and politically thus offering a peaceful and quality environment for the elderly.

CONFERENCE PREVIEW: Brain Injury Social Work Group AGM (BISWG)

Birmingham, UK, 16 May, 2006.

The Annual General Meeting and case discussions take place at the British Association of Social Workers Head Office, 16 Kent Street, Birmingham B5 6RD.

BISWG exists to raise awareness and standards for the provision of resources to those people with a brain injury and their families and carers. The organisation aims



Patti Simonson, Chair, Brain Injury Social Work Group.

to bring together interested professionals who seek both to offer and to receive knowledge, education and skills in this specialised area.

Case Discussions will focus on the following areas – transition of young people to adult services and adults to older people's services, capacity, direct payments, supporting people and/or continuing health care fund-

ing, medico-legal cases where statutory assessments/services are being requested.

If you have any case summaries you feel would provide pertinent discussion in these areas, please send details to Guy Soulsby. This will not be an event where a panel provides expert guidance but one where we will share ideas/information amongst the group.

Contact: Guy Soulsby;
Tel. 0151 250 6247,
Email: guy.soulsby@merseycare.nhs.uk



CONFERENCE PREVIEW: Primary Care Neurology Society 2006 Conferences

Primary Care Neurology 2006 will take place on the 11th May, at One Great George Street, Westminster, London and also in the North of England on the 12th October, at Cutler's Hall, Sheffield. The P-CNS are extremely grateful for all the excellent feedback they received from last year's conference, and have found it very helpful when formulating this year's programme. Topics include:

- Primary Care Neurology in the Psychiatrists Chair

- Fits Faints and Funny Turns
- Access to MS Services
- Development of Neurological Rehabilitation Services

It offers a programme of keynote lectures, an Interactive Question Time and clinical workshops which will focus on:

- Issues in Primary Care Dementias
- Diagnosis and Long-term Management Issues in Parkinson's Disease

- Establishing a Primary Care Epilepsy Service
- Identifying and managing mental health issue in neurology

Speakers include:

Dr Mark Ashworth, Dr Alan Carson, Dr Andy Dowson, Dr Mike Footitt, Dr Helen Hosker, Dr Steve Iliffe, Marianne Peachey, Dr Greg Rogers, Amanda Scutt, Dr Chris Ward,

A booking form is available from the P-CNS website, www.p-cns.org.uk



11th Wye College



Advanced Neurosciences Symposium

5-7 July 2006

The British Neuropathological Society is pleased to announce a 3 day residential symposium to be hosted at Wye College, in the heart of the Kent countryside. The aim of the symposium is to bring together trainees in neuropathology, neurology, neurosurgery and young neuroscientists with international leaders in neuroscience research to allow exchange of ideas in an informal setting. Active participation of delegates will be strongly encouraged. The sessions are intended to range from basic neuroscience, through the application of neuroscience to understanding pathogenesis, to disease phenotypes and opportunities for intervention. The topics to be covered this year will be:

- Tau and neurodegeneration
- Stem cell biology
- Update on prion diseases
- Cerebrovasculature
- Pituitary
- Disorders of peripheral nerve

Cost will be £295 per delegate and will cover accommodation and meals (limited places available). Full details of the programme, the venue and registration forms will be available on the British Neuropathological Society website at:

<http://www.bns.org.uk>

Association of British Neurologists
Spring Meeting
19-21 April 2006
The Grand Hotel, Brighton



Full details and booking at www.abn.org.uk

Or contact: Confab Consulting Ltd,
Tel: 020 8906 7778, Fax: 020 8906 7790,
E-mail: ABNSpring06@confab-consulting.co.uk



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

The 3rd Joint National
Brain Injury Conference
'Brain Injury - The Quality Agenda'
24 & 25 May 2006
The Moat House Hotel, York

Organised by the Brain Injury Rehabilitation Trust, Partnerships in Care - Brain Injury Services and Kemsley, National Centre for Brain Injury Rehabilitation at St. Andrew's Hospital.

Topics include issues relating to the rehabilitation pathway, outcomes and the legal and regulatory framework. Areas of unmet need such as services for adolescents, profound brain injury and brain injury within prisons will also be addressed.

For a copy of the conference programme and booking form, visit the conference website at www.qualityagenda.co.uk

Alternatively please contact Martyn Smythe-Hudson on 01604 616454 or Fiona Winder on 01763 255609, or email kemsley@standrew.co.uk or Fwinder@partnershipsincare.co.uk

To list your event in this diary, email brief details to Patricia McDonnell at events@acnr.co.uk by March 31st, 2006

2006

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
Info. <http://www.gcnpr.org/2006/gcn2006.html>

NEW

'Acquired Brain Injury-Designing a Virtual Rehabilitation Team'
2 March, 2006; London, UK
Patti Simonson
T. 0208 780 4530 E. psimonson@rhn.org.uk

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
Info. <http://www.asnweb.org/>

International Symposium on Clinical Neurology and Neurophysiology
6-8 March, 2006; Tel Aviv, Israel
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

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

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

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

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

XVIII Symposium Neuroradiologicum
19-24 March, 2006; Adelaide, Australia
Info. <http://www.snr2006.sa.gov.au/>

NEW

International Conference on CJD: "Decade past - Decade to come"
20 March, 2006; London, UK
E. gturner@cjdsupport.net T. 01630 673993

NEW

NCYPE Introduction to Epilepsy Training
21 March 2006, Lingfield, Surrey, UK
Ruth Norman T. 01342 832 243
W. www.ncype.org.uk

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

British Neuropsychological Society Spring Meeting
22-23 March, 2006; Cambridge, UK
E. georgina.jackson@nottingham.ac.uk
W. <http://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
Simon Timmis T. 0207 290 3844
E. simon.timmis@rsm.ac.uk

Neural Networks ICNN 2006
24-26 March, 2006; Wien, Austria
Info. <http://www.ijci.org/icnn2006/>

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

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

NEW

Europe Blended Learning course on EEG in the diagnosis and management of epilepsy
31 March, 2006; Application Deadline
Verena Hézsér-v. Wehrs T. +49 521 144 – 4310
E. +49 521 144 – 4311
E. office@epilepsy-academy.org,
W. <http://www.epilepsy-academy.org>

April

European Congress of Endocrinology 2006
1-6 April, 2006; Glasgow, UK
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

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

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

NEW

BAAP Annual Conference
April 6-8, 2006; Southampton, UK
Dr Wanda Neary
E. wandaneary@hotmail.com

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

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
www.cognitivesciencesociety.org/content/meeting

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

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

AAANS 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

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

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

NEW

Towards an understanding of Parkinson's disease
24 April, 2006; Devon, UK
T. 01392 405171

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; Göteborg, Sweden
E. stroke2006@gbg.congrex.se
W. www.congrex.se/stroke2006

American Society of Neuroradiology (ASNR) - 44th Annual Meeting
29 April-4 May, 2006; San Diego, USA
Lora Tannehill, E. tannehill@asnr.org

May

4th International Symposium on Neuroprotection and Neurorepair: Cerebral Ischemia and Stroke
3-6 May, 2006; Magdeburg, Germany
Info. <http://www.neurorepair-2006.de/nr/>
European Regional Meeting of the International Psychogeriatric Association
3-6 May, 2006; Lisbon, Portugal
Info. <http://www.ipa-online.org/ipaonlinev3/meetings/meetingannouncements/...>
E. 2006lisbon@ipa-online.org

NEW

RSM Neurological Disorders in Pregnancy
4 May, 2006; London, UK
Laura Matthews T. +44 (0)20 7290 3848
E. sponsorship@rsm.ac.uk

Jahrestagung der Deutschen Gesellschaft für Epileptologie
4-6 May, 2006; Strasbourg, France
Info. <http://www.dgfe.info>

Cochrane Systematic Reviews in Practice: Parkinson's Disease
5-6 May, 2006; Lisbon, Portugal
E. cochrane.neuronet@unimi.it

1st Mediterranean Epilepsy Congress
10-14 May, 2006; Sharm El Sheikh, Egypt
Info. <http://www.epilepsyscharm2006.com/>

NEW

Primary Care Neurology 2006
11 May, 2006; London, UK
P-CNS website, www.p-cns.org.uk

NEW

NCYPE Managing Epilepsy
11 May 2006, Lingfield, Surrey, UK
Ruth Norman T. 01342 832 243
W. www.ncype.org.uk

BISWG Annual General Meeting and Case Discussions
16 May, 2006; Birmingham, UK
Guy Soulsby T. 0151 250 6247
E. guy.soulsby@merseycare.nhs.uk

15th European Congress of Physical and Rehabilitation Medicine
16-20 May, 2006; Madrid, Spain
Congress Office, Diputación 401 Bajo O8013, Barcelona. T. +34 93 2463566, F. +34 93 2317972
Targeting Adenosine A2A Receptors in Parkinson's Disease. Boston
17-19 May, 2006; MA, USA
Galina Slezinger, MassGeneral Institute for Neurodegenerative Disease,
T. +1 617-724-9611,
E. michaels@helix.mgh.harvard.edu
W. www.A2APD.org

NEW

3rd Joint National Brain Injury Conference (Brain Injury – The Quality Agenda)
24 - 25 May, 2006; York, UK
E. fwinder@partnershipsincare.co.uk or
Kemsley@standrew.co.uk W. www.qualityagenda.co.uk

16th Meeting of the European Neurological Society
27-31 May, 2006; Lausanne, Switzerland
Info. <http://www.akm.ch/ens2006/>

International conference on Monitoring sleep and sleepiness - from physiology to new sensors
29-30 May, 2006; Basel, Switzerland
E. enquiries@sleeping.org.uk

6th Congress of the Federation of European Psychophysiology Societies
31 May-3 June, 2006; Budapest, Hungary
www.feps2006.com

Consortium of Multiple Sclerosis Centers (CMSC)
31 May – 4 June, 2006; Phoenix, USA
E. info@mscare.org

June

8th Annual Neurology SpR Study Weekend June 2006
E. lucie@medivents.co.uk

NEW

RSM HIV-AIDS Neurology
1 June, 2006; London, UK
Laura Matthews T. +44 (0)20 7290 3848
E. sponsorship@rsm.ac.uk

NEW

Advances in the Diagnosis and Management of Early-Stage Parkinson's Disease
6-22 June, 2006; a series of UK meetings
6 June, 2006; Manchester, UK
8 June, 2006; Edinburgh, UK
14 June, 2006; London, UK
15 June, 2006; Bristol, UK
22 June, 2006; Birmingham, UK
T. 020 8326 3135 E. events@chameleon-uk.com

10th International Child Neurology Congress
11-16 June, 2006; Montreal, Canada
www.icnc2006.com, E. info@eventsintl.com

NEW

5th International Congress on Mental Dysfunction in Parkinson's Disease
12-14 June, 2006; Amsterdam, The Netherlands
J. Desel-Willems, SCEM Conference Services
T. +1 31-345-57-66-42; F. 1-31-345-57-17-81;
E. scem@scem.nl; W. www.mdpdamsterdam.nl

European Pain School 2006. Pain and Central Nervous System
12-18 June, 2006; Siena, Italy
Prof. Anna Maria Aloisi, T. +39 0577234103,
E. +39 0577234037,
E. uropainpainschool@unisi.it,
W. www.unisi.it/pain-school/

41st Annual Scientific Meeting of the Canadian Congress of Neurological Sciences
13-17 June, 2006; Montreal, Quebec, Canada
CCNS Secretariat Office by E. brains@ccns.org,
W. www.ccns.org, T. 1+(403) 229-9544,
F. 1+(403) 229-1661

6th International Congress of Neuroendocrinology
19-22 June, 2006; Pittsburgh, USA
T. 001 412 6478232, E. CCEHS@upmc.edu,
W. www.upmc.edu/CCEHS/cme/formal_courses.asp

International Communication Association
19-23 June, 2006; Dresden, Germany
W. www.icahdq.org

RCN Neuroscience Nursing Forum conference Neuroscience nursing: moving ahead 2006
24 June, 2006; London, UK
E. pat.anslow@rcn.org.uk

Cognitive Rehabilitation for Physiotherapists, following brain injury
24 June, 2006; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

Updates in Neuro-Oncology
24-26 June, 2005; Arezzo, Italy
E. ctartaglia@cscongressi.com,
W. www.cscongressi.com

Neurotology Symposium
25-30 June, 2006; Antalya, Turkey
F. 02 123 610 507, T. 02 123 610 504.

MS Care - International Perspectives



multiple sclerosis
international federation

21st April 2006

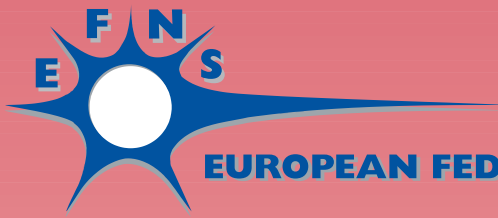
Manchester International Convention Centre, England

Speakers include:

- ***Professor Alan Thompson, National Hospital for Neurology and Neurosurgery, London***
- ***Nancy Law, National MS Society, USA***
- ***Professor Alastair Compston, Addenbrookes Hospital, Cambridge***
- ***Dr Gianvito Martino, San Raffaele Hospital, Italy***
- ***Dr Lee Dunster, MS Society***
- ***Professor Reinhard Hohlfeld, Max Planck Institute of Neurobiology, Martinsried, Germany***
- ***Marva Serotkin, Chief Executive Officer, The Boston Home, Boston USA***
- ***John Temme, MS Society of Canada***

For Booking Information:-

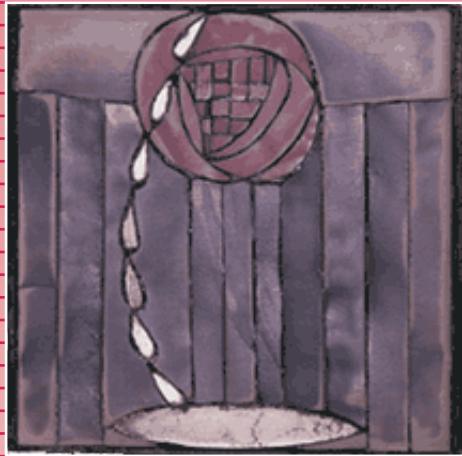
Telephone Liane Wimhurst on 020 8438 0837 or email: lwimhurst@mssociety.org.uk



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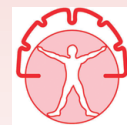
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www.efns.org



Co-Sponsored by the European Section of
the Movement Disorder Society (MDS – ES)

EDITOR'S CHOICE

Specific verb deficit in a familial neurodegenerative disease

There is accumulating evidence that language is an integrated cognitive function, rather than being distinct from other cognitive domains; and that different neural networks underlie specific word categories, such as nouns and verbs. For example, the motor cortex is activated somatotopically upon hearing relevant verbs; selective verb deficits have been observed in motor disorders such as MND and PSP; and motor deficits have been observed in patients with 'specific' language impairments. Thomas Bak and colleagues, from Cambridge, have described two patients (father and son) and presented pathological, genetic, functional imaging and psycholinguistic data to shed light on the relationship between language and motor function. Both father and son developed a movement disorder resembling PSP, but with a prominent and more global dementia than would be expected in PSP. Naming, comprehension and semantic knowledge of verbs (using the kissing and dancing test, a verb-specific equivalent of the pyramids and palm tree test) were selectively impaired in both father and son; and this selective verb impairment persisted despite a global cognitive decline. Left-sided frontal hypometabolism was observed (using FDG-PET) in the son, and in a similar distribution, ubiquitin-positive inclusions were found in the father. The left frontal cortex is believed to be involved in verb processing. Ubiquitin-positive inclusions are unusual in PSP, and are more often associated with motor-related neurodegenerative disease like MND and semantic-related neurodegenerative disease like semantic dementia. PSP is a tauopathy, but there were very few tau-positive inclusions or tangles observed in the post-mortem brain; and no mutations in the tau gene in either patient. This study describes an unusual familial PSP-like disorder and suggests that there may be a genetic influence linking the abstract representation of movements (verbs), and the movements themselves, furthering our understanding of neurodegenerative disease, genetics, linguistics and cognitive science. - WAP

Bak TH, Yancopoulos D, Nestor PJ, Xuereb JH, Spillantini MG, Pulvermuller F, Hodges JR.

Clinical, imaging and pathological correlates of a hereditary deficit in verb and action processing.

BRAIN

2006;129:321-32.

PARKINSON'S DISEASE: Pride and Prejudice and GDNF

*** RECOMMENDED

The discovery of GDNF in 1993 led to great expectations that this trophic factor might have a positive effect in the clinical course of Parkinson's disease by rescuing the dopaminergic neurons and their projection to the striatum. Steve Gill and colleagues in Bristol embarked on a trial some years ago in which they directly delivered GDNF into the putamen of five patients with Parkinson's disease. This followed an unsuccessful trial where the factor was delivered into the ventricular system. The delivery of GDNF directly into the brain by implanted catheters, in a small open label study, clearly showed that it was a safe and efficacious procedure. Indeed in one case that was reported last year dopaminergic fibre sprouting was seen around the site of catheter implantation at post-mortem, which sat well with the previously reported increased dopaminergic signal on PET scanning at the site of GDNF delivery to the posterior putamen. It is on this background that we have to view the recent paper by Lang et al on the Amgen sponsored GDNF study in PD. This study involved 34 patients who were randomised to either receive placebo or GDNF infusion and the primary end point was changes in their UPDRS motor scores at six months. There was no significant effect of the growth factor. There were other concerns. Three patients developed antibodies to GDNF (although remained asymptomatic from this) and there were problems of catheter migration and infection in three other patients. At first glance, this negative study would lead one to believe that GDNF has no place in the future management of Parkinson's disease. This study has been criticised on a number of levels. The first relates to the delivery of the growth factor, in terms of concentration, rate and mode of delivery (size of catheter etc. were different) such that there were real concerns that the growth factor did not diffuse across the striatum but simply refluxed up the catheter tract

thereby, suggesting this study might be a false negative. In addition the patients chosen for treatment were very young and the end point was relatively short. This trial has caused a great deal of controversy not least because many of the patients on active treatment felt they were improving yet the negative outcome of the trial led Amgen to withdraw treatment. Several patients are taking court action to try and obtain further supplies of the medication. Overall this study is disappointing, but I think there are a number of methodological issues which means that it has to be interpreted with a great deal of caution. Furthermore on a broader issue, it would seem that, as with the neural transplantation double blind placebo controlled trials for PD, these trials are being performed before the therapeutic technique has been fully developed. Whilst open label studies will always be criticised because of placebo effects, it is nevertheless the only way to work out the best parameters and the optimal way to deliver that new agent. Only once that has been achieved can double blind placebo controlled trials take place. Therefore my own feeling is that GDNF definitely does have a role to play in Parkinson's disease and that this trial has not shown any efficacy for methodological, rather than scientific reasons. - RAB

Lang AE, Gill S, Patel NK, Lozano A, Nutt JG, Penn R, Brooks DJ, Hotton G, Moro E, Heywood P, Brodsky MA, Burchiel K, Kelly P, Dalvi A, Scott B, Stacy M, Turner D, Wooten VG, Elias WJ, Laws ER, Dhawan V, Stoessl AJ, Matcham J, Coffey RJ, Traub M.

Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease.

ANNALS OF NEUROLOGY

2006 Jan 20; [Epub ahead of print].

Other relevant references

Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws ER Jr, Lozano AM, Penn RD, Simpson RK Jr, Stacy M, Wooten GF; ICV GDNF Study Group. **Implanted intracerebroventricular. Glial cell line-derived neurotrophic factor. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD.**

NEUROLOGY

2003;60:69-73.

Love S, Plaha P, Patel NK, Hotton GR, Brooks DJ, Gill SS.

Glial cell line-derived neurotrophic factor induces neuronal sprouting in human brain.

NATURE MEDICINE

2005;11:703-4.

Gill SS, Patel NK, Hotton GR, O'Sullivan K, McCarter R, Bunnage M, Brooks DJ, Svendsen CN, Heywood P.

Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease.

NATURE MEDICINE

2003;9:589-95.

VENTRICULAR DRAINS: Dogma gone to the dogs

*** RECOMMENDED

It feels somewhat awkward to have an established practice not only called into question but actually undermined so that I must confess to having experienced certain unease whilst reading this paper. Like many other clinicians I have maintained, without justification it would now appear, that daily examination of CSF from an external ventricular or lumbar drain is an important measure in predicting the onset of meningitis. Tales of woe have been passed on to a succession of resident staff about the necessity for daily documentation of CSF glucose, protein, and cell count and to all of these doctors I now offer my apologies. In an extensive prospective study of patients undergoing external CSF drainage the authors demonstrated no statistical difference in the CSF concentrations of glucose and protein, or cell count, or interleukin-6 (IL-6) between patients developing external drain-related bacterial meningitis (ED-BM) [22 patients out of 230] and a control group [patients without ED-BM] in any of the 3 days prior to onset of meningitis or in the first three days following its onset, nor any predictive value in these tests, either individually or longitudinally (ie following daily trends for individual patients - another of my obsessions!). ED-BM was defined as "a positive culture on 1 or more consecutive days in combination with one or more clinical signs of bacterial meningitis (fever, headache, nuchal rigidity, and/or altered mental status) and was considered to have commenced on the first day on which a positive culture was obtained. Whilst IL-6 was significantly higher in patients with active meningitis no predictive value for this test could be established. On the other hand evidence was presented to suggest that a gram stain may be useful in suspected ED-BM. Their conclusion was that a diagnosis of ED-

BM could only be made from microbiological culture. Furthermore, in view of the low risk of meningitis in the first few days after establishing external CSF drainage they recommend sampling only twice during the first week and then daily sampling for culture thereafter and requesting gram stain only in those in whom meningitis is suspected clinically. – RR

Schade RP, Schinkel J, Roelandse FWC, Geskus RB, Visser LG, van Dijk MC, Voormolen JHC, van Pelt H, and Kuijper EJ.

Lack of value of routine analysis of cerebrospinal fluid for prediction and diagnosis of external drainage-related meningitis.

JOURNAL OF NEUROSURGERY

2006;104:101-8.

HEADACHE: in teenagers

As a junior doctor working in a renal unit in Australia, I looked after many people with end-stage renal failure due to analgesic nephropathy. Almost all were women with chronic daily headache and compound analgesic use, often dating back to their teens. Fortunately analgesic nephropathy is now very rare. But the findings of Dyb and colleagues suggest analgesia use and daily headaches in teenagers are not. In this Norwegian cross-sectional population based study of 5,471 people aged from 13 to 18 years, the prevalence of daily headache associated with analgesia use was 0.5%. The rate was higher for females (0.8%) than males (0.2%). The study found a linear relationship between analgesia use and headache frequency. This does not allow us to untangle the extent to which medication overuse exacerbated headache, but there is cause for concern at the degree of analgesia use. The extent to which early intervention and treatment of migraine in teenagers could prevent the establishment of daily headache and analgesics is an important area of future work. - HAL

Dyb G, Holman TL, Zwart J-A.

Analgesia overuse among adolescents with headache.

NEUROLOGY

2006;66:198-201.

DYSTONIA: Left or right hand? Motor planning decisions in Writer's Cramp

*** RECOMMENDED

Have you ever put a shoe on the wrong foot or a glove on the wrong hand? These everyday tasks require mental rotation, or the ability to match orientation of garment with body part in your mind's eye. Mental rotation of body parts has been used experimentally as an ingenious cognitive analogue for motor planning. Imaging studies have shown that mental rotation involves the posterior parietal and visual cortex, motor cortical areas and basal ganglia. These are the same areas that are involved in the performance of real perceptual motor tasks. This suggests that planning movements might involve a speedy cognitive run through involving an image of the body part that will be used in the action; most typically the hand. Fiorio et al have used a task involving mental rotation of hands and feet to explore the breakdown in motor control in people with Writer's Cramp. Using images of hands and feet presented at six different angles and in four different planes on a computer screen, they tested the ability of 15 patients and 15 age-matched unimpaired subjects, to identify whether the images were of right or left hands and feet. Reaction times from the presentation of the image to the onset of the verbal response were measured. Both groups had more difficulty determining their responses when the hand or foot was presented at an angle that was physically difficult to achieve. This finding supports the idea that to decide, "left or right?" subjects imagined the position by mentally simulating from the perspective of their own hands and feet. In keeping with their focal condition, the patients were slower than the normal subjects in mentally rotating hands but not feet; however their reaction times were slower than normal irrespective of whether the image corresponded to the hand affected by Writer's Cramp or to the unaffected hand. This last finding is puzzling but is in keeping with neuroimaging and electrophysiological studies showing that sensorimotor structures may be affected bilaterally in the brain despite unilateral clinical manifestations. The authors surmise that central processing abnormalities could be present before the manifestation of the condition, rather than be caused by it. Could these motor planning impairments be predictive of a susceptibility to dystonia or other peripheral sensorimotor deficits? – AJT

Fiorio M, Tinazzi M, Aglioti SM.

Selective impairment of hand mental rotation in patients with focal hand dystonia.

BRAIN

2006; 129: 47-54.

VARIANT CRETZFELD JACOB DISEASE: Beef and chicken, but not tonsillectomy

Bob Will's group in Edinburgh identified the first case of new variant CJD in the UK in 1996 and has followed the emergence of the 135 other cases since then. It is widely accepted that the disease was caught by eating beef from cows infected with BSE. Particular suspects have been neural contaminants of head meat and meat mechanically recovered from vertebral columns (a practice that ceased in 1995), which end up in low-cost meat products. This paper summarises the low-tech end of the group's enterprise: the results of interviews of the patients and their families and 922 controls (and their relatives as well!). Cases were more likely to have consumed beef, pies and burgers than controls. This seems to support the dogma. However there was evidence that these results might reflect recall bias; similar eating behaviour was reported in the 33 cases who had been labelled as having vCJD, yet turned out to have other illnesses. And eating chicken also associated with vCJD! Sausage, haggis, pork, lamb and venison consumption was no more likely amongst cases and brain itself was eaten by slightly more controls! There was no evidence that being a farmer, butcher or abattoir worker predisposed to vCJD. And, thank goodness, no association was found with surgical operations or blood transfusions (despite the one proven case of transfusion-associated vCJD which occurred in 2003). Interestingly a tonsillectomy after 1980 seemed to protect somewhat against vCJD, perhaps reflecting the role of an intact lymphoreticular system in the pathogenesis of the illness. This paper is the product of laborious, and probably rather tedious, work and has produced no real surprises. But what it lacks in charisma, it easily makes up in importance.... We are surely beholden to study closely the consequences of a terrible mistake in our food processing industry. - AJC

Ward HJ, Everington D, Cousens SN, Smith-Bathgate B, Leitch M, Cooper S, Heath C, Knight RS, Smith PG, Will RG.

Risk factors for variant Creutzfeldt-Jakob disease: A case-control study.

ANNALS OF NEUROLOGY

2006 Jan;59(1):111-20.

MENINGITIS: Cognitive outcome of bacterial and viral meningitis

In this study from Göttingen, Germany, survivors of bacterial and viral meningitis aged between 16-70 years admitted to one centre over a 12-year period were given an extensive (3 hour) neuropsychological test battery focusing particularly on the domains of attention, memory and executive function rather than general intelligence measures. Prior history of alcoholism or substance abuse, recognised predisposing factors for bacterial meningitis, were amongst the exclusion criteria. 59 cases each of bacterial and viral meningitis were tested; of the former group, the commonest organisms identified were *S. pneumoniae* and *N. meningitidis* (16 each), in 18 cases no organism was identified. 30 healthy controls were also tested. With the exception of attention, patients were worse than controls in all domains. Bacterial meningitis patients were generally worse in their cognitive performance than viral meningitis patients, with short-term and working memory and executive tasks being the most frequently and severely affected domains, but with additional difficulties with language and visuoconstructive function. There was no obvious difference in outcome between infections with *S. pneumoniae* and *N. meningitidis*, contrary to a previous study which did not control for comorbidity such as alcoholism. Neuroradiologically, bacterial meningitis survivors had reduced brain volume and greater ventricular volume compared to viral meningitis patients, and white matter lesions correlated negatively with short-term and working memory performance. The findings largely conform to what one might expect on the basis of clinical practice. They demonstrate that complaints of memory disturbance in meningitis survivors should be taken seriously and highlight the fact that viral meningitis is not necessarily benign or self-limiting. These cognitive sequelae may therefore become outcome measures in studies of the treatment of meningitis. Whether they are remediable once established, however, must be doubtful. - AJL

Schmidt H, Heimann B, Djukic M et al.

Neuropsychological sequelae of bacterial and viral meningitis.

BRAIN

2006;129(2):333-345.

EPILEPSY: the scientific basis of paternalism

Don't stay out too late or drink too much. It certainly gets us on the right side of the parents of kids with juvenile myoclonic epilepsy, although perhaps is not appreciated so much by the patients themselves. This study used TMS to measure cortical excitability in 10 patients with JME and 10 controls in the morn-

ing, the day before and the morning after sleep deprivation. In JME, sleep deprivation caused a loss of short latency intracortical inhibition and an increase in short latency intracortical facilitation, which was not seen in controls. This was seen without any change in EEG spike activity. It is thought that these changes relate to alteration of GABAergic activity. So now in true TV commercial-speak we can say it's scientifically proven that late nights affect JME brains. - **MRAM Montagnotti P, Bongiovanni LG, Fugetta G, Zanette G, Fiaschi A.** Effects of sleep deprivation on cortical excitability in patients affected by juvenile myoclonic epilepsy: a combined transcranial magnetic stimulation and EEG study.

JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2006;77:56-60.

HEADACHE: Migraine and analgesia-overuse headache

*** RECOMMENDED

There have been several clinical studies this year on the prevalence of analgesia overuse headache. The clinical scenario is familiar – episodic migraine changing to chronic daily headache associated with analgesia overuse. But there is little understanding of the mechanisms underlying this. In this study, Schoenen and colleagues studied metabolic changes using 18-FDG PET in 16 chronic migraineurs with analgesia overuse before and 3 weeks after medication withdrawal compared with a control population of 68 people. While analgesics were taken, there was reduced metabolism in several areas (thalamus, anterior cingulate gyrus, insula/ventral striatum, right inferior parietal lobule and orbitofrontal cortex). There was increased metabolism in the cerebellar vermis. After cessation of medication, all changes were reversed except for persistent orbitofrontal hypofunctioning. This same area shows persistent hypometabolism in drug dependence. The authors suggest this could predispose migraineurs to recurrent analgesic overuse, but there are a number of alternative explanations. This study begins to address the pathophysiology of an important clinical problem, and raises interesting possibilities. - **HAL Fumal A, Laureys S, Di Clemente L, Boly M, Bohotin V, Vandenheede M, Coppola G, Salmon E, Kupers R, Schoenen J.**

Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine.

BRAIN
2006;129: 543-50.

EPILEPSY: It's not just the fits!

Canada has two systems of validated door-to-door health surveys which gives valuable information on medical issues at a general population level. Some areas were excluded, especially military bases and Indian reserves but also some more remote areas in Quebec and Ontario were not reached. Overall ascertainment was just under 90%. Interviewers sought 20 chronic conditions including epilepsy. All 20 conditions were commoner in those with epilepsy but the following diseases were more than twice as common amongst patients with epilepsy compared to the rest of the population: peptic ulcer; stroke; urinary incontinence; chronic fatigue; migraine; chronic bronchitis; emphysema and heart disease. Confidence intervals for all these conditions did not cross unity and cancer was also significantly commoner in one of the two studies. The findings were similar in both men and women. Some of these data – stroke and migraine for example – hardly come as a surprise. It is also not clear whether the study includes data regarding smoking rates, generally higher in those with epilepsy or social class. Unemployment is common in epilepsy and associated social disadvantage may explain some of the findings but it nevertheless remains very clear that the consequences of epilepsy extend outside the obvious effects of fits and the immediate pathophysiological associations with psychiatric and other neurological diseases, which are familiar to us. - **MRAM JF Téllez-Zenteno S Matjevic and S Wiebe.**

Somatic comorbidity of epilepsy in the General Population in Canada.

EPILEPSIA
2005;46:1955-62.

MULTIPLE SCLEROSIS: the diagnostic criteria shift again

Diagnosing multiple sclerosis has never been easy, but in recent years has come the added incentive to diagnose the condition earlier on the unproven basis that early treatment reduces future disability later. So, in 2000, a committee of the great and good met to redefine the illness and the “McDonald criteria” were defined. The novelty of these criteria was that they allowed defined MRI changes to take the place of clinical relapses, and so “multiple” sclerosis could be diagnosed after only one clinical attack, provided there was MRI evidence of disease activity greater than three months later. I suspect that the average jobbing UK neurologist rarely diagnoses multiple sclerosis in this way, and most neuroradi-

ologists I know look pretty blank when asked if the MRI McDonald criteria are met in this or that case. So it is likely that only the MS research community are going to be interested in a proposed revision to these criteria, which appear in the Annals. The most important change is a proposal to shorten still the time to diagnose multiple sclerosis.... by using two MRI scans. If the first scan is done at least 30 days after the onset of a clinical event, then it can be used as a “reference scan”. The second scan can be done at any point after that (even the following day!) and if it shows a new T2 lesion, multiple sclerosis can be diagnosed. Hoorah!?! Other changes are increased weight given to spinal cord MRI lesions and downgrading the role of CSF oligoclonal bands in the diagnosis of primary progressive multiple sclerosis. Diagnosing multiple sclerosis as rapidly as a month after a single demyelinating clinical event may sound good, but it also increases the burden of the illness on the patient and doctor. Conversations in clinic about treatment can be awkward as the role of disease-modifying drugs in such a situation is very unclear. And also the traumatic experience of being diagnosed with multiple sclerosis is compressed into an uncomfortably short time span. I doubt these criteria will make an impact on routine care of people with multiple sclerosis for some time yet, at least in the UK. - **AJC**

Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS.

Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”.

ANNALS OF NEUROLOGY
2005 Dec;58(6):840-6.

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS.

Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis.

ANNALS OF NEUROLOGY
2001 Jul;50(1):121-7.

EPILEPSY: Biting the bullet in non-epileptic seizures

No matter how often you stop the drugs, they come back on them – why? Part of the problem is that the literature contains a confusing statistic that 20% of patients have both epilepsy and non-epileptic seizures and doctors lose their nerve. The trouble is that the literature asks the wrong question. To quote John Cleese: “in my opinion, which I admit is only spot on” there are three main groups. Firstly, patient A who has new onset epileptic seizures, secondly patient B who has new onset non-epileptic seizures and thirdly patient C who has a longstanding and intractable problem. I would argue that patients A and B almost always have a single diagnosis and patient C is responsible for all the confusion. This study gives support to taking confident steps for those patients who have non-epileptic seizures. The authors had the luxury of defining their cases with video-EEG-telemetry and ensuring that their patients historically had no other seizure types. Of 99 patients, one refused to withdraw medication, and another 20 were not followed up completely for various reasons. Amongst the 78 completing withdrawal, the seizure frequency fell from 22 to 9 per month by one year and admissions for pseudostatus fell from 23 to 4. There were no major complications. This study shows us that it is safe to act decisively early in the course of their illness and withdraw the medication, which reinforces the illness behaviour, before the social consequences of their illness become intractable. - **MRAM**

Oto M, Espie C, Selkirk M, Duncan R.

The safety of drug-withdrawal in patients with non-epileptic seizures.

JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2005;76:1682-5.

Journal reviewers this issue:

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New TaqMan, Assays for Detection and Quantitation of Human MicroRNA

Applied Biosystems has launched its TaqMan, MicroRNA Assays for the detection and quantitation of mature human microRNA (miRNA) expression levels, a promising new area of genomic research. miRNAs are a recently discovered class of small RNA molecules that represent a new layer of post-transcriptional gene regulation that is not yet fully characterised.

These novel assays eliminate major challenges in detecting and quantifying miRNAs and are expected to stimulate research in areas such as cancer, stem cell research, and developmental biology. Based on the industry-standard TaqMan reagent-based chemistry, Applied Biosystems' proprietary stem-loop reverse transcriptase assay technology, and real-time PCR, the assays provide highly sensitive and reproducible data through a simple two-step process.



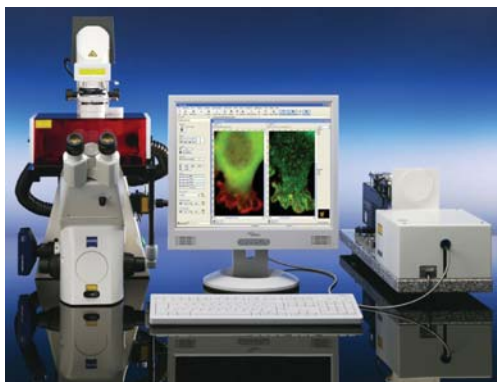
Unlike other conventional methods such as hybridisation arrays, the TaqMan MicroRNA Assays allow researchers to discriminate between mature miRNA and its precursor form. The assays require very small starting samples (1-10 nanograms of RNA or equivalent) allowing researchers to conserve valuable samples and simplify the analytical process.

For more information about the TaqMan MicroRNA Assays see <http://mirna.appliedbiosystems.com>

Laser TIRF Imaging System

A microscope capable of routinely visualising molecular level dynamic processes at the cell membrane while maintaining optimum specimen incubation conditions has been introduced by Carl Zeiss. The Laser TIRF Imaging System is the only system to combine specimen incubation over the long time periods required in many of these live cell experiments with multi-colour TIRF, epi-fluorescence and transmitted-light contrasting techniques under laser safety conditions. Each of the four stage options (fixed, heating, mechanical and scanning) is available with incubation.

The new microscope is the first to offer the combination of TIRF and transmitted-light contrasting techniques, such as DIC and brightfield, which enables sequential recording of two image pairs per second. By selectively exciting cellular fluorophores adsorbed, adhered, or bound to the surface and combining it with con-



ventional epi-fluorescence, researchers can relate surface effects to internal cellular structures.

The Laser TIRF is also said to be the first TIRF system to offer rapid laser line changes, and its unique geometry ensures that TIRF is maintained while switching wavelengths.

For further information contact: *Aubrey Lambert, Carl Zeiss UK, Tel. 01707 871233, E. a.lambert@zeiss.co.uk*

UCL Launches New Institute of Behavioural Neuroscience

University College London is about to celebrate the launch of its new Institute of Behavioural Neuroscience, the IBN.



The IBN is currently a virtual gathering of scientists, but a new suite of laboratories to be built in the coming year in the Bedford Way Psychology building will turn the virtual institute into a real one. The suite will house a cluster of research groups whose collective focus is on trying to unravel the neural circuits and processes that underlie behaviour. The launch is to take place in May, will consist of a workshop, and a plenary lecture by the renowned behavioural neuroscientist and author Joseph LeDoux, with a champagne event and poster session afterwards. Interested parties should visit the website for further details.

For further information on the IBN and its launch, see www.ibn.ucl.ac.uk

Neurodegenerative Diseases

Neurodegenerative Diseases is a bimonthly, multidisciplinary journal for the publication of advances in the understanding of neurodegenerative diseases, including Alzheimer disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington disease and related neurological and psychiatric disorders. Neurodegenerative Diseases publishes results from basic and clinical scientific research programmes designed to better understand the normal functions of genes and proteins involved in neurodegenerative diseases, to characterise their role in pathogenic disease mechanisms, to model their functions in animals and to explore their roles in the diagnosis, treatment and prevention of neurodegenerative diseases. It is Karger's firm belief that successful strategies for novel treatments of neurodegenerative diseases will emerge from the intelligent integration of basic neurobiology with clinical sciences. Therefore, Neurodegenerative Diseases will accept high-quality papers from a broad spectrum of scientific research areas ranging from molecular and cell biology to neuroscience, pharmacology, genetics and the clinical sciences.



For more information see www.karger.com/ndd

Join people affected by MS from across the UK

At MS Life (21st April, Manchester) you can find out about the latest in scientific research and alternative therapies. You can talk to other people about juggling a social life with the symptoms of MS or patients can talk to an MS nurse about the best care options for their circumstances.

MS Life can help patients through the maze of MS information giving the opportunity to get

relevant information. It is also a chance for them to share their experiences with others who understand what living with MS is like.

At the event 100 exhibitors will be separated into 6 zones: research, support, interactive, employment, leisure and mobili-



ty. Within these zones there will be everything from cooking demonstrations to Reiki sessions, a web café and a smoothie bar as well as all the information and advice that is currently available for people affected by MS.

To book your place go to www.msconvention.org.uk

Gateway to the Network of MS Services – Practical Advice for Maximising the Wealth of MS Resources

Biogen Idec have developed an educational programme on Multiple Sclerosis, Disease Modifying Therapies, national policy and guidelines related to MS.

A ready-made CD-ROM resource is designed to: Provide essential information about MS, including diagnosis, management, treatments and guidelines; Facilitate improved communication and efficient referrals between primary and secondary care; Prompt primary and secondary

care to map out local services and referral pathways in order to identify barriers and appropriate solutions; Ensure all Healthcare Providers are aware of the available local services and points of contact; Aid both primary and secondary care and NHS managers to implement the National Service Framework for Long Term Conditions; Be adapted to local requirements by individual Healthcare Professionals.

The material for this resource was developed from advisory forums conducted among Healthcare Professionals, from both primary and secondary care, with an interest in MS.

Copies of the CD ROM can be obtained from Medical Information at Biogen Idec, Foundation Park, Maidenhead, Berkshire, SL6 3UD or Tel. 01628 501000.

This resource is supported by the Primary Care Neurology Society.



Kings College Hospital NHS Trust Installs Two Siemens Arcadis Varic Systems

Kings College Hospital NHS Trust has improved workflow in its Day Surgery Unit and its Neuroradiology department following the installation of the Arcadis Varic. From patient registration to image documentation, it significantly reducing the operating room preparation time. As syngo is DICOM compliant, the Arcadis Varic systems have enabled Kings College Hospital NHS Trust to integrate with PACS, allowing both departments to operate in a completely filmless environment.

As Kings College Hospital already uses Siemens syngo based equipment, the Arcadis Varic system enabled staff to transfer their working knowledge of existing equipment to the new system – reducing training time. The Varic offers superb user-friendliness, with its compact, lightweight and ergonomic design providing staff with maximum



Pictured with the ARCADIS Varic C-arm at The Kings College Hospital, are (L to R), Steve Bibby, Neuro-radiographer, Lorna Thomson, General Radiographer, Tej Bangay, PACS Manager, Geraint Evans, Neuro-radiographer, Tim Aseervatham, Neuro-radiographer and Gail Neame, General Radiographer.

manoeuvrability in tight environments during surgical procedures, while its use of intelligent colour encodings ensures fast and efficient user orientation.

The Neuroradiology Department has added the Varic as a third imaging system to increase patient throughput and reduce waiting lists.

For more information contact Mike Bell, Siemens, Tel. 01344 396317.

Headway Challenges for 2006

Why not challenge yourself in 2006 and take part in one of these exciting Headway events? Take part in a once in a lifetime trek or cycle ride or perhaps run a marathon whilst at the same time raising money for Headway – the brain injury association.



Dates for 2006:

- 13 - 21 March - Sahara Trek
- 21 - 25 June - London to Paris Cycle Ride
- 18 - 26 August - Iceland Trek
- 10 September - Experian Robin Hood Marathon and Half Marathon
- 14 - 23 September - Peru Trek
- 29 - 10 November - Vietnam Cycle Ride

Skydiving with the Red Devils!

Skydiving with the Red Devils was extremely popular last year and Headway now has dates between March through until October 2006 at sites in Nottinghamshire, Gloucestershire and Fife.

Headway also arranges white water rafting, parachuting and Outward Bound weekends as well. If you are interested in taking part in one of these events and would like more information please call Genna or Rachel at Headway on 0115 924 0800.

Laser Scanning Module Doubles Experimental Versatility



The Zeiss LSM DuoScan combines speed, accuracy, sensitivity, specimen penetration and flexibility with minimal specimen damage. The module adds a second laser scanner to

the award-winning LSM 510 META or LSM 5 LIVE laser scanning microscopes. The dual-output, independently-adjustable lasers allow simultaneous stimulation and confocal observation while optional multi-photon microscopy preserves living tissue allowing observation without photodamage.

“Capturing fast cellular reactions occurring during or immediately after photomanipulation without a time lag will open up applications such as FRAP, FLIP, FLAP, photoactivation, photoconversion and uncaging to further development,” says Aubrey Lambert, Zeiss UK marketing manager. “All rely on flexible sample photomanipulation to push back the frontiers of biomedical science and LSM DuoScan is the perfect partner.”

The LSM DuoScan’s point scanner offers a

high degree of flexibility in photobleaching and can define multiple regions of interest (ROI) with pixel accuracy in all photomanipulation applications. This ensures that areas outside the area chosen for photobleaching are not damaged. High speed FRAP and FLIP experiments can be conducted at a variety of wavelengths, even when used with fast, parallel, multi-channel image acquisition. Accurate ROI micromanipulation also ensures excellent precision and flexibility in photoactivation, photoconversion and uncaging experiments. Selective activation of fluorescent proteins is a further experimental possibility opened up by the LSM DuoScan photomanipulation unit.

For further information contact: Aubrey Lambert, Carl Zeiss UK, Tel. 01707 871233, E. a.lambert@zeiss.co.uk

Help keep migraines and patients apart

Topamax 100 mg/day reduced
migraine frequency by:

- $\geq 50\%$ in 46%
of patients¹
- $\geq 75\%$ in over 25%
of patients¹



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 meformin. 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, hypoesthesia, 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:** PL0242 **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.

Information about adverse event reporting can be found at www.yellowcard.gov.uk and adverse events should also be reported to Janssen-Cilag Ltd.