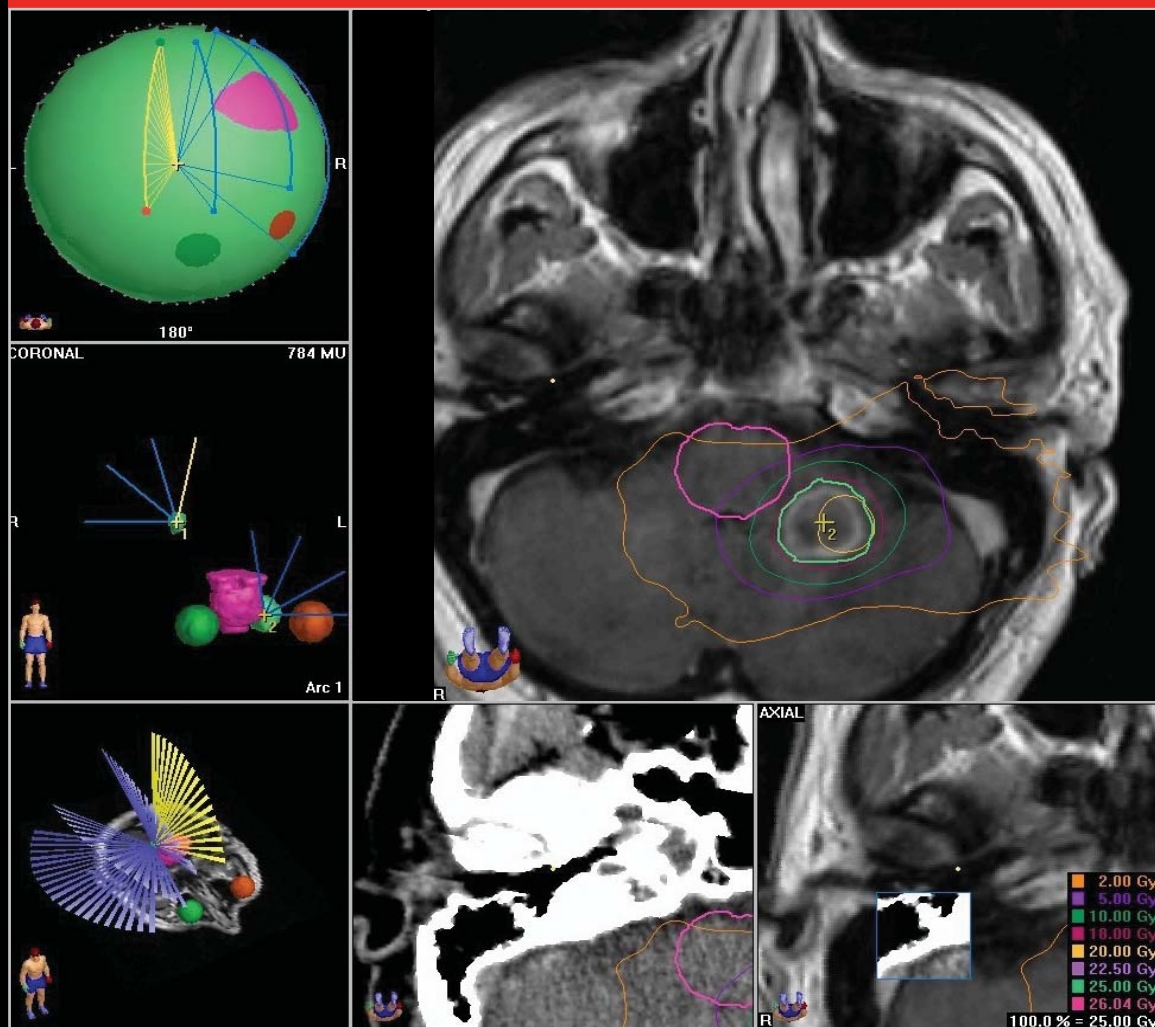


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Advances in Clinical Neuroscience & Rehabilitation



Ammar Al-Chalabi

Motor Neuron Disease

Nektarios K Mazarakis and Anthony J Hannan

Focusing on the Cerebral Cortex in Huntington's Disease:
Experience-Dependent Plasticity Deficits as the Cellular Basis of Dementia

Raymond D Adams

Central Pontine Myelinolysis

MIRAPEXIN: New indication for moderate to severe RESTLESS LEGS SYNDROME



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Prescribing Information RLS UK

Mirapexin™ (pramipexole) Presentation: Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing 0.125mg, 0.25mg and 1.0mg respectively of pramipexole dihydrochloride monohydrate. **Indications:** Symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS). **Dosage and Administration:** Adults and Elderly Patients: Administration: Give tablets orally with water 2-3 hours before bedtime. Start with 0.125mg salt (0.088mg base). This dose may be increased every 4-7 days to a maximum of 0.75mg salt (0.54mg base). Re-evaluate after 3 months. Renal impairment: Patients with creatinine clearance above 20mL/min require no reduction in daily dose. Hepatic impairment: Dose adjustment in hepatic failure is not required. Children: No data in patients under 18 years. **Contra-indications:** Hypersensitivity to pramipexole or any other constituent. **Warnings and Precautions:** Inform patients that hallucinations (mostly visual) can occur. Somnolence and, uncommonly, sudden sleep onset have been reported; patients who have experienced these must refrain from driving or operating machines. (A reduction of dosage or termination of therapy may be considered). 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. Literature indicates possibility of augmentation. **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

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Adverse events should be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). Information about adverse event reporting can be found at www.yellowcard.gov.uk

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“If the cell body were about thirty yards across the axon of a typical motor neuron would be about the size of a tube train tunnel connecting London and New York”. So writes Ammar Al-Chalabi of the motor neuron, the demise of which underlines motor neurone disease. In his short review Ammar lays out a logical, thorough, yet pragmatic approach to this condition highlighting recent advances as well as a range of useful statistics on its frequency and prognosis.

Neurodegenerative disorders of the CNS are viewed as conditions where the primary deficit is neuronal loss. Whilst there is no doubt that this is the case, this is a relatively late event with the early manifest problems being a consequence of more subtle abnormalities in the neuron at the level of neurotransmission and synaptic plasticity.

In this issue Tony Hannan and Nektarios Mezarakis explore this concept in murine transgenic models of Huntington’s disease highlighting the extent to which such an abnormality exists and can be modified by manipulation of the environment. This is a succinct account in an exciting area of neuroscience by acknowledged experts in this area who have done much to throw light on the significance of gene environment interactions in neurological disorders.

In a third review article, Thomas Bak takes us through the differing cognitive profiles of parkinsonian syndromes – an area to which he has made a substantial contribution. In this review, Thomas makes the point that documenting the profile of cognitive deficits in atypical parkinsonian syndromes is not only a useful exercise in its own right, but can be used to help define and refine the diagnosis. Indeed, as he writes, “with growing understanding of fronto-striatal connections it seems likely that at least some cognitive and motor symptoms are different manifestations of the same underlying pathology”.

Special care dentistry forms the topic for the Rehabilitation article. This “forgotten strand in rehabilitation” covers the dentistry needs of people with ‘special needs’ and the article by June Nunn provides a clear and informative narrative on how to prevent and recognise problems and their optimal management which will significantly impact on my practice with such patients.



The identification of intracranial metastases carries with it a poor prognosis and often it is not clear what treatment should be offered. In the Neurosurgery series, Peter Whitfield and oncologist Steve Kelly take us through the various different approaches and the evidence for their adoption or use in different clinical scenarios. This is a clear account based on a detailed analysis of the published literature and highlights the merits of surgery and whole brain irradiation in selected, affected, groups of individuals.

We are extremely privileged to have writing for us in this issue Professor Raymond Adams, still active at the age of 95! In his article Professor Adams lays out the vast number of neurological conditions to which he has made seminal contributions. Thus it was difficult to know what to ask Professor Adams to write about given this, but we settled on central pontine myelinolysis, and he

takes us through the original description of this case outlining how the syndrome came to be recognised in collaboration with his colleague Maurice Victor. This is an absolutely fascinating article which I am sure many will find of great intellectual interest as well as being of huge historical significance.

We also have a short article on a new initiative in MS, the Atlas of MS, organised by the Multiple Sclerosis International Federation (MSIF). This resource is designed to highlight and report on different aspects of MS across the globe and looks to be a very useful resource.

Finally it would not be right as we enter November 2006 not to have some mention of Alois Alzheimer – as it is now a 100 years since he described the first case of his disease, patient Auguste D, Andrew Larner delivers his usual scholarly account of this historical event and reassuringly tells us that his presentation “prompted no comments or reaction from the audience”.

We have our usual regular articles, including journal and book reviews, and as always we are keen to hear from you as to what we can do to improve and expand the journal that now has a circulation of over 4500.

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

ACNR Journal reviewers - reviews start on pg34

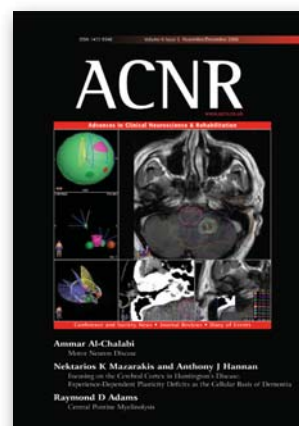
Heather Angus-Leppan, Royal Free & Barnet Hospitals;
Roger Barker, Cambridge Centre for Brain Repair;
Alasdair Coles, Cambridge University;
Andrew Larner, Walton Centre, Liverpool;

Mark Manford, Addenbrooke’s Hospital, Cambridge and Bedford Hospitals;
Wendy Phillips, Addenbrooke’s Hospital, Cambridge;
Robert Redfern, Morrision Hospital, Swansea;
Ailie Turton, University of Bristol.

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The cover picture shows the case of a 66-year-old patient who presented with a history of unsteadiness of gait. See page 18 for this neurosurgery article.

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Have your say about issues relating to your specialty, or in response to articles which appear in the magazine. Send your news and views to ACNR: Patriciamcdonnell@btinternet.com

Deadlines:

January/February	-	5 December
March/April	-	5 February
May/June	-	5 April
July/August	-	5 June
September/October	-	5 August
November/December	-	5 October





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new one at a different application site. Treatment is initiated with a single daily dose of 2 mg/24 h. Increase dose by 2 mg/24 h each week (e.g. 2 mg/24 h in Week 1, 4 mg/24 h in Week 2, 6 mg/24 h in Week 3 and 8 mg/24 h in Week 4), until an effective dose is reached. Maximal dose is 8 mg/24 h. **Contraindications:** Hypersensitivity to rotigotine or to any of the excipients. Neupro should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns. **Warnings and Precautions:** External heat should not be applied to the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of therapy. Rotate the site of patch application to minimise the risk of skin reactions. In case of generalised skin reaction associated with use of Neupro, discontinue treatment. Avoid exposure

to direct sunlight until the skin is healed. If treatment is to be withdrawn, it should be gradually reduced to avoid symptoms of neuroleptic malignant syndrome. Compulsive behaviours and hallucinations have been reported in patients treated with Neupro. Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients with severe hepatic impairment, and in patients taking sedating medicines or other depressants in combination with rotigotine. Switching to another dopamine agonist may be beneficial for those patients who are insufficiently controlled by rotigotine. **Undesirable Effects:** Very common side effects include nausea, vomiting, somnolence, dizziness and application site reactions. Common side effects include anorexia, hallucinations, sleep attacks, insomnia, abnormal dreams, headache, dyskinesia, lethargy, orthostatic hypotension, hypertension, hiccup, cough, constipation, diarrhoea, dry mouth, dyspepsia, hyperhidrosis, erythema, pruritus, asthenic

conditions and peripheral oedema. Uncommonly, syncope, loss of consciousness, visual disturbances, or hypotension may occur. Rarely, psychotic disorders, increased libido or convulsion may occur. **Basic NHS Cost:** Starter Pack: £110.34

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full information on side-effects, warnings and

precautions. Further information is available from

SCHWARZ PHARMA Limited, Schwarz House, East

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Date of Literature Preparation: March 2006.

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Adverse events should be reported to the Drug Safety department at SCHWARZ PHARMA Limited (UK) on 01494 797 500 or drugsafety@schwarzpharma.co.uk

References: 1. Neupro Summary of Product Characteristics. 2. Braun M et al. Poster presented at EFNS 2005. 3. Watts RL et al. Poster presented at MDS 2004. Abstract P737.



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Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg.
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agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures — in such patients the possibility of heart block or long sinus pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. 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:** November 2005.

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  NEUROLOGY

Date of preparation: November 2005.

A892e-ARI779i

Motor Neuron Disease

- Motor neuron disease (MND) is a greatly feared diagnosis leading some to seek euthanasia.
- It is the most common progressive condition to cause a combination of upper and lower motor neuron signs.
- MND is a disease of increasing age and is likely to become commoner as the population ages.
- The lifetime risk of MND is about 1 in 400, even though the prevalence is only about 5 per 100,000.
- The average GP sees one case per lifetime; the average neurologist sees one case per month.
- About 1 in 5 survives five years, and 1 in 10 survives more than ten years.
- Although the prognosis is generally poor, there are patterns of MND that generally predict a slower course and longer survival.
- About 1 in 10 people has a family history of MND and a fifth of these carry mutations in the SOD1 gene.
- Other genes for typical MND remain elusive, although some progress has been made.
- Causes for those with sporadic MND remain unknown, although there are many theories.
- Sub-clinical cognitive impairment is common; overt fronto-temporal dementia affects about 5%.
- Multidisciplinary clinics improve quality of life and lead to advances in treatment.
- Riluzole is a drug that has been shown to improve survival consistently in many different study designs.
- Advances in care such as non-invasive ventilation and gastrostomy lead to improved quality of life and extended survival, but may reduce quality of life for carers.

An introduction to MND

Motor neuron disease (MND), also known as amyotrophic lateral sclerosis (ALS), was first described by Charcot in 1869.¹ The classical picture is of progressive

wasting and weakness with brisk reflexes, in the absence of sensory signs and incoordination (Figure 1). The weakness starts in a limb or the bulbar region, and spreads, usually contiguously, over a period of months. Death occurs as a result of respiratory failure, typically within a few years of symptom onset. The dismal outlook of an inevitable progression to complete paralysis leads some to seek euthanasia.

The different types of MND

MND is a result of the degeneration of lower motor neurons in the anterior horn of the spinal cord and brainstem (amyotrophy), and degeneration of the corticospinal motor neurons (described as lateral sclerosis of the spinal cord by Charcot). The nuclei controlling eye movements, and Onuf's nucleus controlling bladder and anal sphincters, are spared.

The amyotrophy and lateral sclerosis components of MND do not always occur simultaneously, and as a result, other diagnostic categories exist. Progressive muscular atrophy describes the condition of pure lower motor neuron loss, and primary lateral sclerosis the condition of pure upper motor neuron loss. People with these patterns of MND do not always progress to classical amyotrophic lateral sclerosis, and it is more difficult to be certain that diagnostic mimics have been excluded. In some cases, the disease remains predominantly bulbar, in which case the label used is bulbar palsy (or pseudobulbar palsy if there are only upper motor neuron findings) (Table 1).

Clinical features outside the motor system

Emotional lability, often associated with pseudobulbar palsy, can be difficult for family members to deal with, and is also embarrassing and therefore socially isolating. Frontal lobe impairment is not uncommon. At its mildest this is detectable as word-finding difficulty,² but in about 5% of cases is severe enough to be a fron-



Ammar Al-Chalabi is a Senior Lecturer in Neurology and Complex Disease Genetics at King's College Hospital. He is also a Visiting Scientist in Neurology at Massachusetts General Hospital, and an Instructor in Genetics of Complex Human Diseases at Cold Spring Harbor Laboratory. He has been researching motor neuron disease since 1994, first as an MRC Clinical Training Fellow, and more recently as an MRC Clinician Scientist. He has a special interest in finding motor neuron disease genes using whole genome association.

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Table 1. The names given to different patterns of ALS

	Bulbar signs	Limb signs
<i>UMN</i>	<i>Pseudobulbar palsy</i>	<i>Primary lateral sclerosis (PLS)</i>
<i>LMN</i>	<i>Bulbar palsy</i>	<i>Progressive muscular atrophy (PMA)</i>
<i>Both</i>	<i>Amyotrophic lateral sclerosis (ALS)</i>	<i>Amyotrophic lateral sclerosis (ALS)</i>



Figure 1. Wasted hands with a typical clawed posture

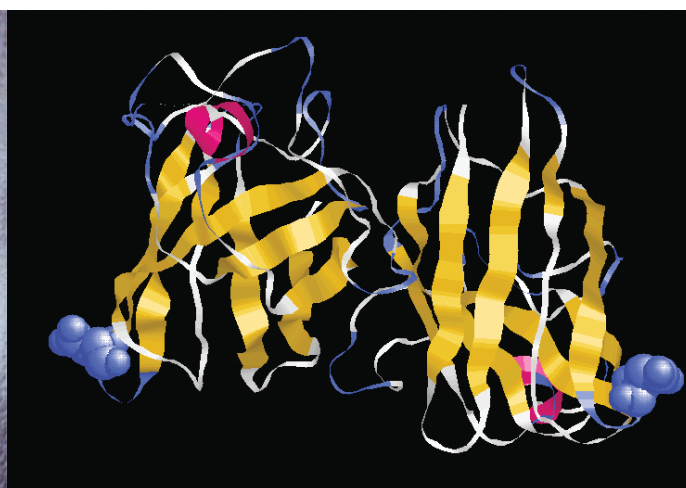


Figure 2. Mutation in the SOD1 molecule, the only known cause of ALS, showing the D90A mutation.

totemporal dementia. The overlap between MND and frontotemporal dementia is becoming increasingly recognised; for example, the two conditions may co-exist within families as a result of the same genetic defect.^{3,4}

Epidemiology, pathology and ideas about causation

MND has an incidence of about 1-2 per 100,000 person years and a prevalence of about 5 per 100,000. The lifetime risk is about 1 in 400, estimated either from death certificates Office of National Statistics⁵ or using population registers.⁶ Men are more at risk than women with a ratio of about 3:2. The peak age of onset is between 56 and 70, depending on the mode of ascertainment. There are no consistently shown environmental risk factors, although taking part in high level sports is probably the most widely accepted, and professional football is the most recent target of blame.⁷

It remains a mystery why motor neurons should bear the brunt of the disease process in MND. One possibility is their highly unusual shape. If the cell body were about 30 yards across, the axon of a typical motor neuron would be about the size of a tube train tunnel connecting London and New York. Pathologically, degenerating motor neurons contain inclusions that stain for ubiquitin, and also accumulations of neurofilaments. It is not clear whether the inclusions and accumulations protect the neuron, poison the neuron, or are simply markers like a gravestone. Neurofilament mutations have been found in MND, and other cytoskeletal defects are known to lead to motor neuron degeneration in both humans and animals. This may be because the cytoskeleton is essential for axonal transport, and the highly unusual shape of a motor neuron makes it vulnerable. Motor neurons also use excitatory pathways rather than the more widespread inhibitory pathways favoured by the rest of the nervous system. Excitotoxicity has therefore been proposed as a mechanism, and there is some evidence to support this idea. A closely related mechanism involving free radicals has also been suggested, and the finding of mutations in a free radical scavenging enzyme, SOD1, has lent support to this idea.⁸ Viruses too

have been implicated,⁹ particularly because another motor neuron disease, polio, is known to be virally mediated.

Genetics

Familial MND (10% of all cases) is usually autosomal dominant. Because it is indistinguishable from sporadic MND, it too shows an increasing risk with age, so some members of an affected family may be below the age of risk and unaffected despite carrying the risk gene. There are at least 12 loci for familial MND with four genes now identified, only one of which is for typical MND: SOD1. Mutations in SOD1 are responsible for about 20% of all familial cases as well as between 1 and 7% of sporadic cases^{8,10} (Figure 2). Genetics is recognised as playing an important part in susceptibility to sporadic disease too with a twin study reporting the genetic contribution to MND as being between 38 and 85%.¹¹ More than 40 candidate genes have been tested for association with sporadic MND, only a few of which have shown replicated association in more than one population: SOD1, NEFH, VEGF and ANG.^{12,13} With advances in genetic techniques, whole genome association studies are now underway and the next few years is likely to see the underlying genetic causes of MND revealed.

Making the diagnosis

There is no diagnostic test for MND, which remains a diagnosis of exclusion. In someone with classical features, progressive disease and EMG findings showing chronic partial denervation, there can be little doubt about the diagnosis once other possibilities have been excluded. In those with less typical features, or disease confined to one or two limbs, it can be more difficult, and it may be necessary to repeat tests a few months later.

Prognosis

The prognosis is generally very poor with survival measured in months to years. Death is from respiratory failure. Those with progressive muscular atrophy or primary lateral sclerosis in general have a slower disease progression. Other clinical features associated with a better than average survival include a younger age at onset of symptoms, disease confined to one or two limbs, and having the so-called

flail arm phenotype in which there is profound symmetrical weakness of the proximal upper limbs with relatively preserved strength elsewhere.¹⁴ The best predictor of a good outcome is however a long delay between symptom onset and review by a neurologist.¹⁵ This is probably because it reflects slowly progressive, milder disease that is as a result more difficult to diagnose. In general, MND continues at the same rate of progression or occasionally plateaus, and so a long referral delay implies a long duration to come. Despite this, even those with poor prognostic factors may still survive more than ten years, so there is hope for everyone.¹⁶

Treatment

Riluzole has been shown in several studies of prospective and retrospective design to be effective in prolonging survival, although the effect is modest and similar to some cancer therapies. Side effects include liver and bone marrow toxicity, dizziness and vertigo, which may interfere with skilled tasks such as driving. Nausea, lethargy and rash may also occur.

Other treatment involves active and aggressive symptom control using medication, for example quinine for cramps, anticholinergics for sialorrhoea, antidepressants for emotional lability, baclofen or tizanidine for spasticity and benzodiazepines and opiates for respiratory failure. These are combined with intervention from the multidisciplinary team with physiotherapy, occupational therapy, speech therapy, dietetic advice, counselling and palliative care. Respiratory failure can also be managed with non-invasive ventilation, which is not suitable for everyone but is effective at prolonging duration and improving quality of life. Similarly, for those with dysphagia, gastrostomy needs to be provided earlier rather than later, and may also improve survival.

Conclusion

The great advances in care and research, particularly over the last ten years, mean that we are chipping away at MND from the top with clinical trials, and from underneath with basic science. Soon a breakthrough in our understanding may lead to a highly effective treatment for this dreaded condition.

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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. Monitor weight in patients experiencing diarrhoea. Contains sucrose therefore should not be taken by patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency. **Undesirable effects:** **Levodopa / carbidopa** – Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, paranoid ideation and psychotic episodes, 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:** April 2006.

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Focusing on the Cerebral Cortex in Huntington's Disease: Experience-Dependent Plasticity Deficits as the Cellular Basis of Dementia

Huntington's disease (HD) belongs to an expanding family of devastating neurological disorders caused by abnormally elongated CAG trinucleotide repeats which encode extended polyglutamine tracts in the disease proteins.¹⁻⁶ HD is characterised by extensive neurodegeneration in the striatum and the cortex.^{7,8} The disease is classically known for its choreic and dystonic motor symptoms. However, cognitive deficits (dementia) and psychiatric manifestations (the most common of which is depression) represent major symptoms in HD, which usually precede the onset of motor abnormalities.⁹⁻¹²

This observation has led to an increased research effort concentrating in the examination of abnormal neurotransmission in areas involved in higher cognitive function such as the neocortex and the hippocampus. In accordance with the clinical picture, the genetic defect in HD could initially affect neurotransmission involved in higher cognitive function before any signs of neuronal loss in the striatum. So what is the evidence for abnormal neurotransmission in the HD neocortex and the hippocampus? Moreover, is there evidence of abnormal synaptic efficacy of neurotransmission in higher cognitive centres that could underlie dementia in HD?

Many studies using transgenic and knock-in mouse models of HD have shown that there is impaired synaptic transmission in corticostriatal and hippocampal circuitries.¹³⁻²² More recently, impaired synaptic transmission has been reported in HD mouse neocortical neurons even before the onset of motor symptoms.²³ Evidence of cortical neuronal dysfunction has also been reported in HD patients, for example using transcranial magnetic stimulation of the motor cortex.²⁴

Long-term changes in synaptic efficacy (synaptic plasticity) are thought to underlie higher cognitive functions such as learning and memory.²⁵ If cognitive function in HD is compromised before the onset of the motor symptoms then one could hypothesise that synaptic plasticity deficits may be the cellular basis of early symptomatology. Moreover, if higher cognitive functions are dependent on cortical functioning then a plausible hypothesis is that alterations in synaptic plasticity should be evident in the cerebral cortex of HD brains and correlate with the onset of dementia.

Initial evidence of abnormal synaptic plasticity in the hippocampus of R6/2 HD transgenic mice showed abnormalities in the form of long-term potentiation (LTP) and long-term depression (LTD) in the CA1 region of the hippocampus.²⁶ Interestingly, these synaptic plasticity deficits correlated with poor performance in a spatial memory task even before the onset of clear motor deficits. Similar impairment in hippocampal synaptic plasticity has also been reported in other HD mouse models.^{15,27} A key regulator of synaptic plasticity, brain-derived neurotrophic factor (BDNF), has been shown to be decreased in the hippocampus of R6/1 HD mice (a transgenic line with a shorter CAG repeat length and later onset of symptoms than R6/2 mice) and correlated with the onset of cognitive deficits.^{28,29} Furthermore, deficits of BDNF in the hippocampus and striatum are rescued by environmental enrichment, a form of cognitive and motor stimulation which

has been found to delay the onset and progression of HD in transgenic mice.^{28,30-32}

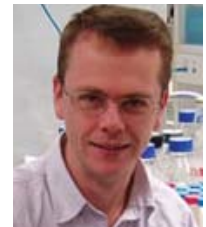
Interestingly, Cybulska-Klosowicz and colleagues showed that R6/1 HD mice show impaired functional cortical reorganisation – a form of experience-dependent plasticity – following a simple form of passive associative learning.³³ In normal rodents, a short period of classical conditioning causes cortical enlargement of the functional representation of the sensory modality (e.g. row of whiskers) that has been conditioned. However, in this study R6/1 HD mice showed a clear impairment to display an increase in the functional representation of the conditioned row of whiskers. Similarly, following a period of sensory deprivation, such as trimming a row of whiskers, the cortex displays a remarkable ability to reorganise as the functional representations of neighbouring intact whiskers take over the cortical region of those that have been deprived.³⁴ In this context, we showed, using 2-deoxyglucose metabolic labelling, that R6/1 HD mice which were sensory deprived failed to show cortical plasticity, in the form of map reorganisation, and that this cortical impairment correlated with a severe deficit to learn a sensory discrimination task.³⁵ It is interesting to note that the R6/1 mice used in the study were not yet displaying any motor symptoms, suggesting that cortical plasticity deficits and cognitive symptoms occur relatively early. More recently, Cummings and colleagues showed that cortical slices from R6/1 HD mice displayed abnormal short-term plasticity (exhibited as altered paired-pulse facilitation) and LTD.²⁷ Moreover, they showed a decrease in the cortical levels of both D1 and D2 dopamine receptors and found that *in vitro* administration of the D2 agonist, quinpirole, dramatically reversed the impairment in both short-term plasticity and LTD in the perirhinal cortex of R6/1 HD mice.

The above studies using transgenic mice that express the HD gene mutation suggest a functional impairment in cortical activity. Deficits in synaptic and structural plasticity could underlie the cognitive and psychiatric deficits observed in patients with HD. An interesting question is whether these cortical abnormalities are aetiologically involved in the striatal degeneration associated with the devastating motor symptoms characterising HD. One hypothesis is that cortical abnormalities, involving abnormal glutamatergic neurotransmission, might cause excitotoxic damage to striatal neurons via corticostriatal pathways. In other words, rather than medium spiny neurons dying via cell-autonomous 'suicide' they may be 'murdered' by corticostriatal afferents.³⁶ In this scenario, therapeutic interventions targeting the cortex could not only delay or ameliorate the cognitive and psychiatric abnormalities, but also the motor symptoms. Further evidence for the primary role of cortical pathology has been provided by the effect of environmental enrichment in salvaging cortical degeneration in HD mice,³⁰ as well as cortical transplantation experiments³⁷ and cortex-specific HD transgene expression in mice.³⁸

In any case, the observation of early cortical dysfunction and neural plasticity deficits could provide a very useful biological marker that would be particularly useful in terms of monitoring both the progress of the dis-



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ease and the effects of potential therapeutic interventions. An attempt to replicate the animal studies described above at the human level, such as reliably demonstrating cortical plasticity impairments in HD gene carriers with the use of fMRI, would be an excellent starting point in the clinical application of these research discoveries.

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Cognitive Profiles of Parkinsonian Syndromes

What the MMSE won't tell you and why

In the early 1970's a group of psychiatrists devised the Mini Mental State Examination (MMSE)¹ "for the serial testing of the cognitive mental state in patients on a neurogeriatric ward". The original sample of 69 patients included, apart from patients with affective illness, schizophrenia and neurosis, 29 patients with "dementia syndromes due to a variety of brain diseases", reflecting the concept of dementia as "a global deterioration of intellect". Thanks mainly to its brevity MMSE became the most widely used cognitive screening test, applied to a variety of neurological conditions for which it was not originally designed, among them Parkinson's Disease (PD) and related disorders.

There are two serious problems connected with the use of MMSE in this patient group. Firstly, MMSE has been demonstrated to be particularly insensitive to frontal-executive dysfunction, which, as will be shown below, constitutes the most common cognitive deficit in basal ganglia diseases. Secondly, based on the unitary concept of dementia, it does not examine different cognitive domains but confines itself to one global 'dementia score'. It is, therefore, unable to determine qualitative differences between diseases. Seen in historical perspective, these shortcomings of the MMSE are not surprising: frontal dysfunction and selective cognitive deficits in different types of dementia became the focus of scientific research many years after its publication. A test designed at the time in which the routine imaging procedure was pneumoencephalography can hardly be expected to be state-of-the-art 30 years later.

This does not mean, however, that cognitive assessment has to be long and laborious. The aim of this review is to demonstrate that brief and simple tests, which can be easily performed at the bedside, can distinguish the cognitive profiles of the individual diseases and detect deficits that would go unnoticed by the MMSE.

Motor and cognitive features of parkinsonian syndromes: two sides of the same coin?

Although a large number of diseases can present with 'parkinsonian features', such as tremor, rigidity or bradykinesia, we confine ourselves in this review to five diagnostic entities: PD, Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), Corticobasal Degeneration (CBD) and Dementia with Lewy Bodies (DLB). PSP, CBD and MSA (and to a much lesser degree DLB) share some common features which distinguish them from the classical PD and lead to their designation as Atypical Parkinsonian Syndromes (APS).² The borderline between PD and DLB is somewhat arbitrary: according to the current diagnostic criteria a patient presenting with parkinsonism followed by dementia is diagnosed as PD, if dementia precedes the parkinsonism the diagnosis is DLB.³

While all five diseases are associated with typical (or even pathognomonic) features (Table 1), none of them can be diagnosed on the basis of one single symptom. This applies in the same degree to motor as to the cognitive symptoms. Prominent tremor, for instance, is most often encountered in PD, apraxia in CBD, but both can also occur, albeit usually less pronounced, in other conditions, such as PSP. Interpreted in this way, the cognitive symptoms can be as useful in diagnosing the disease as their motor counterparts. In fact, with growing understanding of fronto-striatal connections it seems likely that at least some cognitive and motor symptoms are different manifestations of the same underlying pathology.⁴

The spectrum of cognitive symptoms in parkinsonian syndromes

In 1974, around the time of the publication of MMSE, Albert et al⁵ described characteristic cognitive and behavioural changes in 5 PSP patients (Table 2). They noted that the symptoms were different from those encountered in Alzheimer's disease (AD), but similar to those



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Table 1: Typical features of different parkinsonian syndromes:

PD	asymmetrical parkinsonism, including tremor, good L-Dopa response
PSP	vertical supranuclear gaze palsy, imbalance with falls backwards
MSA	dysautonomia, cerebellar dysfunction, imbalance with falls
CBD	apraxia, alien hand syndrome, cortical sensory dysfunction
DLB	fluctuating course with periods of disorientation, visual hallucinations

Table 2: The key symptoms of the Albert syndrome:

• slowing of thought processes
• impaired ability to manipulate knowledge
• forgetfulness
• behavioural and personality changes

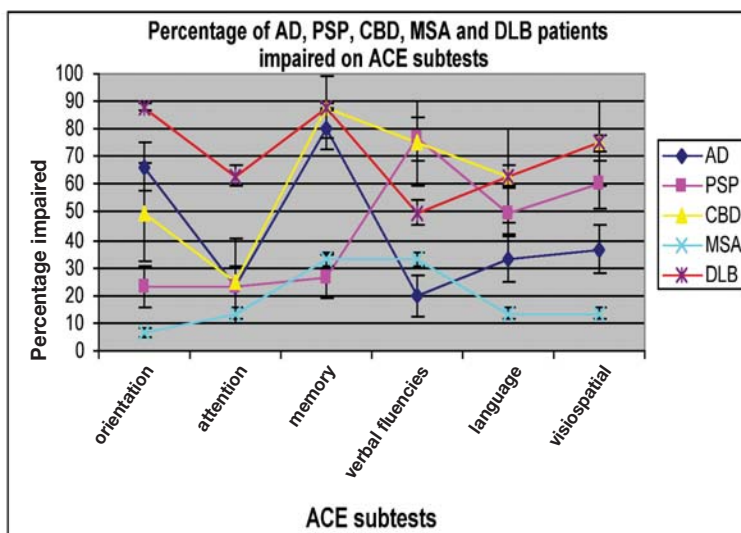


Figure 1: Cognitive profiles of AD, PSP, CBD, MSA, DLB and on the ACE.

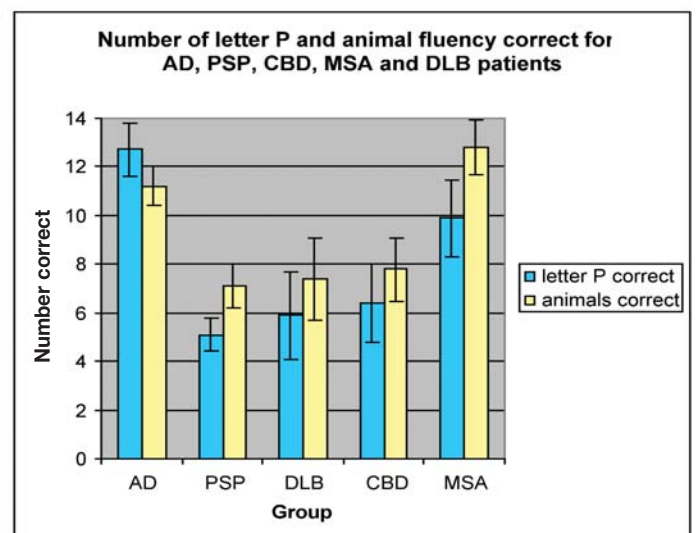


Figure 2: Letter and category fluency in AD, PSP, CBD, MSA and DLB.



My Granddad used to
shake and move funny.
It made him very sad
too.



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I think he's happier.

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Mirapexin™ (pramipexole) Presentation: Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing **0.125mg**, **0.25mg** and **1.0mg** respectively of pramipexole dihydrochloride monohydrate. **Indications:** The treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa. **Dosage and Administration:** Adults and Elderly Patients: Administration: Give tablets orally with water in equally divided doses three times per day. Initial treatment: 3 x 0.125mg salt (3 x 0.088mg base) per day for first 5-7 days. Then 3 x 0.25mg salt (3 x 0.18mg base) per day for 5-7 days, and then 3 x 0.5mg salt (3 x 0.35mg base) per day for 5-7 days. Increase the daily dose by 0.75mg salt (0.54mg base) at weekly intervals to a maximum dose of 4.5mg salt (3.3mg base) per day if necessary. Incidence of somnolence is increased at doses higher than 1.5mg salt (1.06mg base) per day. Maintenance treatment should be in the range of 0.375mg salt (0.264mg base) to a maximum of 4.5mg salt (3.3mg base) per day. Adjust dose based on clinical response and tolerability; reduce doses used in titration and maintenance phases if necessary. **Treatment discontinuation:** Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Reduce dose by 0.75mg salt (0.54mg base) per day to 0.75mg salt (0.54mg base) per day. Thereafter reduce dose by 0.375mg salt (0.264mg base) per day. Renal impairment: See SPC for revised dosage schedules. Hepatic impairment: Dose adjustment in hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings and Precautions:** Reduce dose in renal impairment. Inform patients that hallucinations (mostly visual) can occur. Somnolence and, uncommonly, sudden sleep onset have

been reported; patients who have experienced these must refrain from driving or operating machines. (A reduction of dosage or termination of therapy may be considered). If dyskinesias occur in combination with levodopa during initial titration of pramipexole in advanced Parkinson's disease, the dose of levodopa should be reduced. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. **Drug Interactions:** There is no pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules such as omeprazole and amantadine may interact with pramipexole resulting in reduced clearance of either or both drugs. Consider reducing pramipexole dose when these drugs are administered concomitantly. The dosage of levodopa should be reduced, and other Parkinsonian medication kept constant, while increasing the dosage of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. Coadministration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** Effects of pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used in pregnancy unless the benefit outweighs the potential risk to the foetus. Pramipexole should not be used during 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

therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin is titrated too fast. Mirapexin has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. Libido disorders (increase or decrease), pathological gambling, especially at high doses generally reversible upon treatment discontinuation. **Overdose:** There is no clinical experience with massive overdose. Expected adverse events include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive measures may be required, along with gastric lavage, intravenous fluids and electrocardiogram monitoring. **Basic NHS Cost:** 0.125mg (0.088mg) x 30 £9.25, 0.25mg (0.18mg) x 30 £18.50, 0.25mg (0.18mg) x 100 £61.67, 1.0mg (0.7mg) x 30 £58.89, 1.0mg (0.7mg) x 100 £196.32. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. **Marketing Authorisation Number:** Mirapexin 0.088mg (0.125mg) x 30 tablets EU/1/97/051/001; Mirapexin 0.18mg (0.25mg) x 30 tablets EU/1/97/051/003; Mirapexin 0.18mg (0.25mg) x 100 tablets EU/1/97/051/004; Mirapexin 0.7mg (1.0mg) x 30 tablets EU/1/97/051/005; Mirapexin 0.7mg (1.0mg) x 100 tablets EU/1/97/051/006. Further information is available from Boehringer Ingelheim Ltd., Eylesfield Avenue, Bracknell, Berkshire RG12 8YS. **Date of preparation:** June 2005.

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described in frontal lobe disorders. They called the clinical picture 'subcortical dementia', assuming that the deficits were caused by a disruption to fronto-striatal pathways. A similar pattern was later described in other basal ganglia diseases, including PD.⁶ However, the critics of the notion of 'subcortical dementia' stressed the anatomical inaccuracy of the term, as the advances in neuroscience called into question the neat distinction between 'subcortical' and 'cortical' pathology.⁷ We propose, therefore, to refer to this constellation of symptoms as 'Albert syndrome', stressing the descriptive accuracy of a clinical, rather than anatomical, entity. This term is also more precise than the broad notion of 'frontal-dysexecutive syndrome', since frontal lobes are extraordinarily complex in terms of their functional anatomy and the term 'frontal dysfunction' can be applied to very different clinical pictures.

The diseases which represent the 'Albert syndrome' in its purest form, are MSA and PSP. The difference between them is a more quantitative than qualitative nature. The cognitive dysfunction in MSA is often so mild that the patients are classified as unimpaired on most cognitive screening tests,² the only abnormality being a slight reduction in verbal fluency and free recall (Figure 1).⁷ We have seen only one patient with a clinical diagnosis of MSA and pronounced dementia; interestingly, his post-mortem showed a combination of alpha-synuclein and tau pathology. The cognitive dysfunction in PSP, although more pronounced, is similar in pattern, with a particular reduction in letter fluency (Figure 2).^{2,7}

In contrast, CBD and DLB have the widest range of cognitive abnormalities, extending well beyond the frontal-dysexecutive syndrome and in keeping with the widespread cortical involvement, as suggested by neuroimaging and neuropathology. Deficits in orientation, attention, memory and visuospatial function in DLB are well recognised, and have contributed to the designation of this disease as a 'dementia'.³ CBD was initially regarded as a purely motor syndrome, but recent studies documented a severe impairment in visuo-spatial functions⁸ and language,⁹ at times amounting to a full-blown non-fluent aphasia.¹⁰

Paradoxically, the situation is probably most complicated in the case of the classical PD. The traditional view, since the late 1970s, was that of a subcortical dementia.⁶ However, recent studies

Table 3: The FAB, DRS and ACE subtests in comparison:

FAB	DRS	ACE
Letter fluency	Initiation/Perseveration (inc. category fluency)	Orientation
Similarity judgement		Attention
Motor sequencing:	Conceptualisation	Letter & category fluency
- Luria 3-step examination	Construction (drawing)	Memory
- 'go-no go'	Attention	Language
- conflicting instructions	Memory	Visuospatial functions

documented significant memory impairment, related in severity to the degree of medial temporal atrophy,¹¹ while molecular studies linked together the pathologies of AD and PD.¹² It seems likely that a substantial number of PD patients present with a combination of Albert syndrome with mnemonic and semantic deficits characteristic of AD. Moreover, PD is increasingly recognised as a heterogeneous disorder, with subgroups showing different cognitive profiles.¹³

Practical considerations

Since the MMSE is likely to continue dominating the clinical cognitive assessment in the foreseeable future, the most realistic way to improve the evaluation of parkinsonian patients is to combine it with other tests. The first step would be to add tests sensitive to frontal dysfunction (or, more precisely, the 'Albert syndrome'), the second to evaluate other cognitive domains.

Probably the easiest, fastest (less than 5 minutes) and yet clinically meaningful test of frontal function is verbal fluency. It is believed to reflect one of the most central features of parkinsonian syndromes: the profound difficulty in generation of actions (verbal as well as motor). A reduction in verbal fluency has been documented in all five diseases,^{7,14} but is usually most pronounced in PSP, where it occurs as one of the earliest symptoms, often preceding the occurrence of motor abnormalities.⁷ Out of the ca. 30 pathologically confirmed PSP patients we have followed up over the last ten years in Cambridge all but one had reduced verbal fluency already at the initial exam. Verbal fluency is part of many cognitive batteries, such as Frontal Assessment Battery (FAB),¹⁵ Dementia Rating Scale (DRS)¹⁶ and Addenbrooke's Cognitive Examination (ACE)¹⁷ (Table 3) and became a kind of a 'cognitive equivalent of Erythrocyte Sedimentation Rate (ESR)': not specific, but useful to screen for abnormali-

ties, which will necessitate further investigation.

Two types of verbal fluency are widely used: letter/phonemic (e.g. words starting with the letters F, A, S or P) and category/semantic (eg animals or supermarket items) fluency. The first one is believed to relate more to frontal, the second to temporal dysfunction. Accordingly, one would expect a more pronounced reduction in letter fluency in parkinsonian, and in category fluency in AD patients. Indeed, such dissociation has been documented between APS and AD (Figure 2).⁷ However, a meta-analysis of 68 verbal fluency studies suggest that in PD patients semantic fluency might be even more impaired than phonemic, although the difference is less pronounced than in AD:¹⁴ a result in keeping with the interpretation of PD as consisting of a combination of features of Albert syndrome and AD.

While verbal fluency (and FAB) can be very useful in adding a 'frontal dimension' to the MMSE, determining a cognitive profile of a disease requires assessment of other cognitive domains such as language or visuo-spatial functions. One way of doing it is to select appropriate tests for each domain. This approach has the advantage of flexibility, but requires a good knowledge of different testing instruments. An alternative approach, much easier to implement in the clinical setting, is to use one of the standardised testing batteries, such as the DRS or ACE. The DRS¹⁶ is widely used in research, but has not enjoyed the same popularity in bedside assessment, due to its length (25-30 minutes) and the necessity for special testing materials (stimulus cards etc.). The ACE¹⁷ is shorter (15-20 minutes), does not require additional materials and incorporates the MMSE. It has been validated in PSP, CBD and MSA^{2,7} (Figure 1) and is currently being evaluated in PD and DLB. It can be obtained free from eneida.mioshi@mrc-cbu.cam.ac.uk.

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in clinical efficacy (time to clinically definite MS). Pancreatitis rarely observed, often with hypertriglyceridaemia. There is a potential risk of transmission of viral diseases due to the presence of human albumin. **Precautions:** Serious hypersensitivity reactions are rare, but bronchospasm, anaphylaxis and urticaria may occur. If reactions are severe, discontinue Betaferon and initiate appropriate medical intervention. Perform regular thyroid function tests if history of thyroid dysfunction or if clinically indicated. Monitor complete blood count, differential white blood count, platelet counts, AST, ALT and γ-GT estimations prior to, and regularly during, therapy. If significant increase occurs, or if jaundice suggested, consider withdrawal of Betaferon. Asymptomatic elevations of serum transaminases occur very commonly. Severe hepatic injury reported rarely, often in association with other hepatotoxic drugs or substances or comorbid medical conditions. Monitor for signs of hepatic injury. Monitor patients with significant pre-existing cardiac disease for worsening of their condition. Flu-like syndrome symptoms may prove stressful to such patients. Cardiomyopathy has been reported rarely. Discontinue treatment if a relationship to Betaferon is suspected. Contraceptive precautions are needed in women of childbearing potential. It is not known whether Betaferon is excreted in human milk, therefore a decision to stop breast feeding or stop therapy is needed. Monitor renal function carefully in patients with severe renal failure. CNS-related adverse events might affect ability to drive and use machines in susceptible patients. Injection site necrosis has been reported which may result in scar formation. Debridement or skin grafting required occasionally. If breaks in the skin occur advise patients to contact their physician before continuing with injections. With multiple lesions, stop therapy until healing occurs. With single lesions therapy may be continued. Advise patients to use an aseptic injection technique and rotate injection sites. Periodically review patients' self-injection procedures. Incidence of injection site reactions may be reduced by use of an autoinjector. **Drug interactions:** 28 days of corticosteroid or ACTH treatment has been well tolerated. Use of other immunomodulators is not recommended. A down regulation of hepatic cytochrome P450 has

been reported with interferons e.g. anti-epileptics. Exercise caution when administering with drugs that have a narrow therapeutic index and are dependent on the hepatic cytochrome P450 system for clearance. Caution with any drugs affecting the haematopoietic system. **Side effects:** The following adverse events collected as spontaneous reports are classified as: very common ≥ 1/10, common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000 to < 1/100, rare ≥ 1/10,000 to < 1/1,000, very rare < 1/10,000. **Very common:** flu-like symptom complex; chills; fever; injection site reaction, inflammation, or pain. **Common:** injection site necrosis. **Uncommon:** anaemia, thrombocytopenia, leucopenia, increase in ALT, AST, hypertension, depression, hypertension, nausea, vomiting, alopecia, urticaria, pruritus, rash, myalgia. **Rare:** thyroid dysfunction, convulsion, confusion, anxiety, cardiomyopathy, tachycardia, palpitation, bronchospasm, dyspnoea, pancreatitis, hepatitis, skin discoloration, suicide attempt, anaphylactic reactions, chest pain, increased blood bilirubin, γ-GT increased. 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/1/95/003/003, EU/1/95/003/004. **PL holder:** Schering Akteingessellschaft, D-13353 Berlin, Germany. Date of preparation: 12 June 2006

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Special Care Dentistry – A Forgotten Strand in Rehabilitation?

Special Care Dentistry is that branch of dentistry which provides comprehensive care for people with so-called 'special needs'. A contemporary definition, encompassing the World Health Organisation's ICF¹ principles¹ would be: 'People requiring special care dentistry are those with a disability or activity restriction that directly or indirectly affects their oral health, within the personal and environmental context of the individual'.²

Special Care Dentistry (SCD) as currently practiced in the UK is largely provided from services commissioned by Primary Care Trusts in community clinics and district general hospitals, mostly at a primary care level. In addition, secondary and tertiary care services are provided by a limited number of associate specialists and consultants in dental and other hospitals. Whilst there has been no formal, recognised training pathway in SCD, the General Dental Council agreed at the end of 2005 that it was timely to consider the recognition of the specialty and it is anticipated that by 2007 this will become a reality.

Special Care Dentistry and its patients

Some of the most frequently encountered patients in SCD are those with a learning disability. The challenges here for oral and dental health are in managing oral hygiene, coping with drug-induced dry mouths – which leads to rapid decay (Figure 1), as well as dental erosion (Figure 2). This happens for patients with seizures and those who have psychiatric disease. One of the challenges in rehabilitation is education and training for carers, especially given the level of basic qualification of such a group and their constant turnover.³ The use of mouth props (Figure 3) as well as triple sided toothbrushes (Figure 4) can help in patients who are resistant to brushing, mindful of the guidelines on the use of appropriate physical intervention.^{4,5}

Another significant group of patients who have learning disabilities are people with Down syndrome. This is a group of people who have distinctive oral and dental features: delayed shedding of primary teeth, absent successor teeth, anomalies of tooth shape, number and surface topography (Figure 5). Retention of primary teeth into third and fourth decades is not uncommon. The mid-face hypoplasia (Figure 6) means that teeth often do not meet in the normal relationship but orthodontic care to correct this relative prognathia may not be feasible because of cooperation problems and the very characteristic poor gum health. Tooth wear, as a consequence of grinding or gastro-oesophageal reflux disease (Figure 7) is also commoner in people with disabilities.⁶ In addition, severe gum disease means that early loss of teeth is more common in people with Down syndrome. Dental treatment may be compromised by congenital heart defects and the need for antibiotic prophylaxis, poor cooperation and the necessity to provide care under sedation or even general anaesthesia. As well, there are physical considerations such as steeply vaulted palates that act, unbeknown to carers, as a food trap – often an undiagnosed cause of halitosis. A large, fissured tongue, that seems large for the mouth but is a feature in part of the maxillary retrognathia (See Figure 6), may also trap plaque.

Another group of patients with disabilities that need regular dental care are people with cerebral palsy. Self-inflicted injuries can occur in young children with cerebral palsy when they are teething (Figure 8). This is known sometimes as Rige-fede disease when it principally affects the tongue.⁷ Management consists of fit-



Figure 1: Patient with a learning disability and psychiatric disease with a drug induced dry mouth and dental decay of the necks of the teeth as a consequence.



Figure 2: person with epilepsy - a dry mouth and gum overgrowth consequent on medication. The dry mouth encourages frequent ingestion of carbonated drinks resulting in extensive dental erosion in the front of his upper incisor teeth.



Figure 3: A mouth prop to aid in mouth opening and safe brushing for a carer.



Figure 4: A triple sided toothbrush that cleans three surfaces at a time; important when access to the mouth is restricted and time-limited by the patient's cooperation.



Figure 5: Congenitally absent teeth, microdontia and enamel hypoplasia in a person with Down syndrome.



Figure 6: Sagittal view of a patient with Down syndrome demonstrating the mid-face hypoplasia and relative prognathia.



Figure 7: Excessive tooth wear from grinding and gastro-oesophageal reflux in an adult with Down syndrome.



Figure 8: Ulceration of the ventral surface of the tongue as a result of tongue thrusting in a child with cerebral palsy, as lower primary incisors erupt into the mouth.



Figure 9: Patient with cerebral palsy with a (a) self-inflicted lip lesion and (b) after fabrication and placement of splints to prevent lip trauma.



Figure 10: Patient with a brain injury and lip trauma wearing a splint to prevent further trauma and permit soft tissue healing.



Figure 11: Excessive deposits of calculus in a child who has a PEG and who has an exaggerated gag reflex, making mouth cleaning difficult.



Figure 12: A commercial tooth brush with an integral aspirator to help clear debris and secretions while mouth cleaning.



Figure 13: An oral screen used actively to encourage lip closure by exercising the circum-oral musculature and thus preventing drooling.



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ting a splint, if impressions can safely be taken, but this will sometimes necessitate referral for a general anaesthetic (Figures 9a and b). This condition usually resolves but can recur on eruption of the permanent teeth as well. The alternative may be to remove the teeth that are traumatising the soft tissues, usually lips and cheeks, unless the physician can find a drug regime that reduces the degree of spasticity, without sedating the child to such an extent that their normal daily routine becomes impossible. An alternative, once children have permanent teeth, is to undertake orthodontic tooth movement so that the teeth do not trap the oral soft tissues.

Self-inflicted injuries occur as well in people with acquired brain injuries and can be intransigent to treatment.^{8,9} Again, fitting a splint can protect the oral soft tissues until better function is restored (Figure 10). Young children who, because of feeding difficulties are fitted with a PEG, and have nil by mouth, accumulate large quantities of calculus (Figure 11). This is impossible for carers to remove and they are not unnaturally worried that chunks will break off and be inhaled. Before resorting to a general anaesthetic to remove such deposits it is vital to ensure that, thereafter, carers will be able to prevent such deposits accumulating. Otherwise, you are committing the child to repeat general anaesthetics, an unacceptable practice. A helpful aid can be an oral suction device attached to a toothbrush (Figure 12). This enables carers to clear oral secretions whilst brushing. This is vital in such patients who often have a degree of dysphagia, a pronounced gag reflex as well as heightened circum-oral sensitivity, making mouth cleaning especially challenging.

Another habit that upsets families, carers, and sometimes peers, is drooling. This is not only a feature seen in cerebral palsy but also in Down syndrome and patients who have had a CVA. There are a number of treatment modalities to manage this distressing complaint.^{10,11} The general principle is to commence with the least invasive. This may simply be using an oral screen (Figure 13) in conjunction with behaviour management strategies, to encourage a lip seal in a compliant child. For other, less able patients, drug therapy, using scopolamine patches (Figure 14), botulinum toxin injections into the salivary glands, or even surgery to remove glands and/or re-route saliva



Figure 14: A Scopolamine patch is worn on the mastoid process and changed every 72 hours. The reaction experienced by some patients to scopolamine which necessitates removal of the patch.



Figure 15: Rampant caries of lower incisor teeth within 12 months of desalivation.



Figure 16: Placing concentrated fluoride varnish for a child with Down syndrome to prevent dental decay.

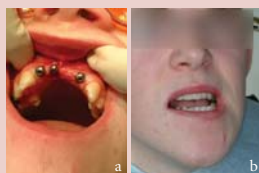


Figure 17: A patient with cerebral palsy, epilepsy and a learning disability with (a) implant fixtures, and (b) the finished bridge to replace traumatically avulsed upper anterior teeth.



Figure 18: A patient with Sturge-Weber syndrome who required cryotherapy to the (a) haemangioma of his palate to prevent trauma and thus bleeding from the opposing lower incisor teeth. (b) A splint has also been fitted to prevent a recurrence.



Figure 19: Drug induced overgrowth in a patient who needs gingival surgery to allow teeth to erupt.

ducts can be considered. The latter has a significant morbidity, especially for the teeth, deprived of protective saliva, which in a matter of months develop rampant decay (Figure 15) in lower incisor teeth, which are usually decay-resistant. Aggressive prevention with concentrated topical fluoride varnishes help but may not entirely halt the spread of the decay (Figure 16).

People with poorly controlled epilepsy often lose teeth as a result of trauma during a seizure. Replacement of lost anterior teeth can be a dilemma if the seizures are poorly controlled since teeth may also be lost from a prosthesis, and could be inhaled. In a patient where this is not the case, a bridge or a well-fitting denture can be fitted. For some patients with cerebral palsy, a lack of manual dexterity means that it is impossible to insert and remove a denture and implants can be

considered in such cases (Figures 17a + b)

Drug induced gingival overgrowth is a major management issue in dental care – it affects patients with seizure disorders, acquired and congenital (Figure 18) as well as a consequence of immunosuppression post-transplant. Alternative drug regimes may be a possibility but otherwise, oral hygiene, even eruption of teeth in the growing patient (Figure 19), can be an issue.

For all these patients, early diagnosis, good interdisciplinary care – so that the dental team, especially the hygienist – is involved in the planning and ongoing care with the medical team, can avert many of these problems that are known to impact significantly on quality of life for these patients.^{3,12} As well, much of the morbidity, and for some, mortality, associated with dental disease and its management, can be avoided altogether.¹³

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Evidence Based Management Options for Patients with Intracranial Metastases

Incidence

The incidence of cerebral metastases is variably reported with 14.3 per 100,000 per annum in a Scottish population study.¹ Overall, a third of patients with cancer develop intracranial metastases. The commonest primary tumours arise from the lung and breast. Melanomas, renal cell carcinomas and gastrointestinal tract malignancies account for most of the remainder (Table 1). MRI and post-mortem studies indicate that at least 50% of patients have multiple lesions. Around 80% of intracranial metastases are supratentorial and 20% occur in the posterior fossa.²

Table 1: Site of primary in patients with brain metastases. Plymouth data 1996-2004

Site of primary	Incidence (n=312)
Non small cell lung cancer	30%
Unknown primary	24%
Breast cancer	14%
Melanoma	8%
Small cell lung cancer	5%
Renal cell cancer	5%
Colorectal	4%
Others	10%

About 20% of intracranial metastases are precocious or synchronous presenting before or within two months of the primary tumour. Early presentation with intracranial metastases appears to be associated with poorer outcomes and frequently occurs in association with small cell carcinomas of the lung.³ The remaining 80% of patients present with metachronous tumours at least two months after the primary. This is commonly observed in patients with breast cancer and may occur several years after the primary presentation.²

Presentation

Patients with intracranial metastases have a spectrum of clinical presentations that can be classified as shown below.²

- Raised intracranial pressure – due to tumour, oedema or hydrocephalus (c25%)
- Focal neurological signs – these are dependent upon tumour location and include cognitive deficits (c50%)
- Focal or generalised seizures (c15%)
- Asymptomatic – detected on radiological screening investigations (c10%)

Imaging

Contrast enhanced T1 weighted MRI scanning is the clinical investigation of choice. Double or even triple contrast dosing has been recommended to increase the sensitivity of the investigation. Metastases usually appear as well-circumscribed enhancing intra-axial lesions with peri-tumoral oedema. Supratentorial metastases are frequently located at the grey-white matter interface in the distribution of the middle cerebral artery. They may appear as a homogeneous or heterogenous mass with areas of cyst formation. Occasionally intraventricular lesions are evident. The differential diagnosis includes a primary brain tumour and sometimes brain abscesses. Dural-based metastases can occur with a differential diagnosis including meningioma. SPECT and PET studies provide physiological evidence of a hypermetabolic focus characteristic of malignancy. This may be

helpful in distinguishing neoplasia from a cerebral abscess or radiation necrosis. MR spectroscopy and functional imaging techniques are not yet widely available but offer promise in establishing a non-invasive diagnosis and facilitating treatment approaches.

Management

Patients presenting with suspected intracranial metastases require a diagnostic work-up. MRI scanning is used to assess the number and location of intracranial metastases. If the patient has a known primary tumour, CT imaging is performed to assess the extent of local and extracranial metastatic disease. If the intracranial disease is precocious a full clinical examination and a CT thorax, abdomen and pelvis is performed to try to identify a primary lesion. A lung primary is often visible on chest radiograph. In the absence of a diagnosis, a biopsy of any extracranial disease is usually performed in preference to an intracranial procedure.

Given a diagnosis of intracranial metastatic disease a variety of therapeutic options are available. The use of steroids is widely practised whilst the relative roles of surgery, whole brain radiotherapy and stereotactic radiosurgery are complex. The evidence for these treatments is reviewed below.

Steroids and Whole Brain Radiotherapy (WBRT)

If no treatment is initiated the median survival of patients with brain metastases is approximately one month from the time of diagnosis. Non-randomised studies suggest that this can be increased to two months if steroids are used and three to six months if WBRT is also given.^{4,5,6} Steroids and WBRT have therefore been the mainstay palliative treatments for patients with cerebral metastases for more than 50 years.⁷ WBRT is usually delivered either as 20 Gy in five fractions over one week or 30 Gy in 10 fractions over two weeks. However, in the small group of patients with a relatively good prognosis (those in Class 1 in Figure 1), it may be appropriate to give a more prolonged fractionation schedule to reduce the risk of late neurocognitive dysfunction.

Surgical excision of a solitary intracranial metastasis

Hart et al have reviewed the addition of surgical resection to the armamentarium in treating patients with solitary intracranial metastases.⁸ Although there are a number of controlled trials, generally the number of patients recruited is small, and so significant differences in survival may be missed. Thus general applicability of these requires an



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Abbreviations:

KPS - Karnofsky Performance Score
WBRT - Whole brain radiotherapy
SRS - Stereotactic radiosurgery
Her - Herceptin

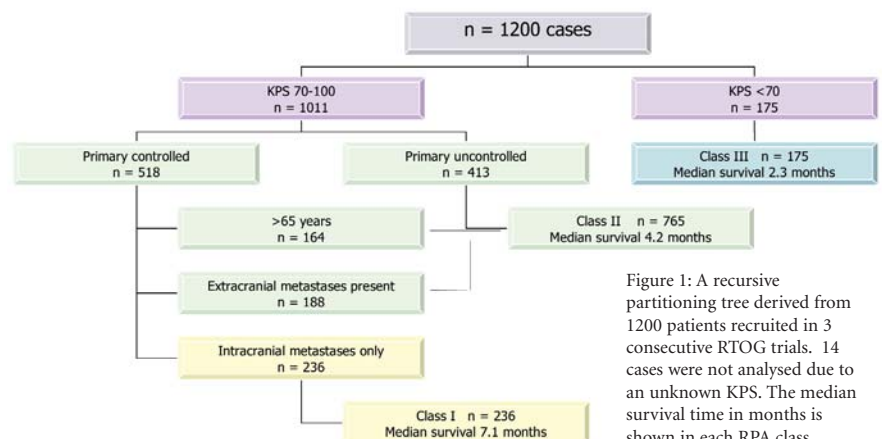


Figure 1: A recursive partitioning tree derived from 1200 patients recruited in 3 consecutive RTOG trials. 14 cases were not analysed due to an unknown KPS. The median survival time in months is shown in each RPA class.

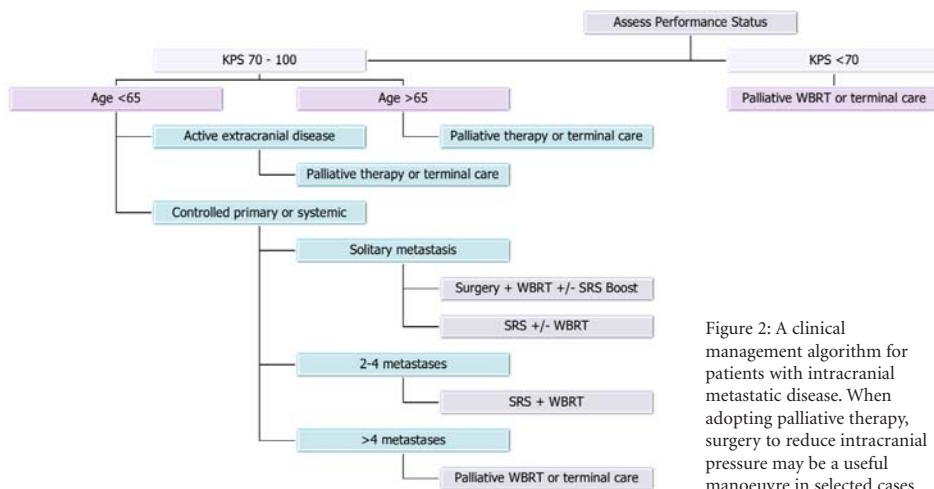


Figure 2: A clinical management algorithm for patients with intracranial metastatic disease. When adopting palliative therapy, surgery to reduce intracranial pressure may be a useful manoeuvre in selected cases.

informed, thoughtful approach.

Patchell et al randomised 48 patients with solitary metastases in a single centre.³ Twenty-five underwent surgery + WBRT and 23 had WBRT alone. The survival hazards ratio (HR) 0.50 [95% CI:0.26, 0.95] favoured the surgical group with median survivals of 40 weeks in the surgery + WBRT group and 15 weeks in the WBRT alone group. In addition, functional independence was much better preserved in the surgical group (38 weeks versus 8 weeks $P<0.005$). Local or distant intracranial recurrence occurred in 20% of the surgical group and 52% of the WBRT alone group ($P<0.02$). Overall 71% of the surgery + WBRT cases who died (15/21) and 50% (11/22) of the WBRT alone cases died from systemic causes. It should be noted that the primary tumour was a non-small cell carcinoma of the lung in 37/48 (77%) cases and the high prevalence of this radioresistant tumour may bias the results in favour of surgery.

A Dutch trial ($n=63$) also showed a trend toward improvement in outcome in the surgery + WBRT group (10 months median survival) compared with WBRT alone (6 months median survival) although this did not reach statistical significance; survival HR 0.57 [95% CI:0.30, 1.06].⁹

The Canadian multicentre trial recruited 84 out of an eligible 145 cases to a trial comparing surgery + WBRT with WBRT alone. In contrast to the other RCTs, a non-significant trend toward improved outcome with WBRT alone ($n=43$) rather than surgery + WBRT ($n=41$) was reported; survival HR 1.39 [95% CI:0.76, 2.55].¹⁰ These different findings compared with the reports of Patchell et al and Vecht et al may be due to different inclusion/exclusion criteria. Twenty-one percent of patients had a KPS of 50-60 and would have been excluded by Patchell et al and probably by Vecht et al. A higher proportion of patients had extracranial metastatic disease at the time of randomisation compared with the Patchell et al and Vecht et al studies (45% vs. 37.5% and 31.7% respectively). Fewer patients had non-small cell lung carcinoma (53.6%) compared with 77% in the Patchell study. The inclusion of such patients may have conferred a bias favouring WBRT. In addition the exclusion of 59 eligible cases questions the widespread applicability of the findings.

In summary, the evidence base appears to support the role of surgery in treating patients with accessible solitary metastases who have a relative-

ly good performance status ($KPS>70$) with no or controlled extracranial disease.

Over the past decade frameless stereotactic neuronavigation has developed and provides the surgeon with the confidence to perform an accurately located minicraniotomy (3cm diameter) directed at tumour excision. A microscope assisted trans-sulcal or trans-gyral approach can then be performed to locate the tumour. A clear plane of dissection is usually achieved permitting removal of the lesion. For larger metastases, the cavitating ultrasonic aspirator can help debulk the lesion in parallel with progressive circumferential dissection at the tumour/ brain interface. Stereotactic biopsy is only performed where the tumour is considered inaccessible or the clinical status does not warrant craniotomy.

WBRT after surgical resection of a solitary metastasis

Evidence to support the use of adjuvant WBRT after resection of a solitary metastasis was reported in a further study by Patchell et al.¹¹ Forty-six patients were randomised to surgery and 49 to surgery + WBRT. The dose of WBRT was high, at 50.4 Gy in 28 fractions, in an attempt to reduce the risk of neurological sequelae. Recurrence of intracranial disease occurred in 70% of those not receiving postoperative WBRT versus 18% in the surgery + WBRT group ($P<0.001$) indicating that the addition of WBRT seemed to afford efficacious intracranial tumour control. On an intention to treat analysis WBRT did not confer a significant survival benefit (43 vs. 48 weeks; $P=0.39$; RR of death 0.91, 95% CI 0.59-1.40). However, the survival data are confounded by the fact that some patients crossed over and received WBRT on disease recurrence. Additionally, in the surgery alone group, 44% of patients were deemed to have died as a result of neurological disease compared with 14% in the combined treatment arm. Although it may be considered that this study provides Class I evidence to support the use of WBRT as an adjunct to surgical resection, others have argued that WBRT may not be necessary in all patients as this did not significantly improve overall survival, and duration of functional independence.¹²

WBRT + SRS boost

1. Patients with unresectable intracranial metastases

Most patients with intracranial metastases are

not suitable candidates for surgical resection due to the multiplicity of lesions, active extracranial disease and poor performance status. The majority of such patients with good performance status receive WBRT. Andrews et al reported a large RCT ($n=331$) addressing whether a SRS boost (Gamma knife or LINAC) improved outcome in patients with 1 to 3 intracranial metastases and a $KPS\geq 70$.¹³ For patients with solitary lesions, WBRT + SRS boost ($n=92$) increased survival from 4.9 months to 6.5 months ($P=0.0393$) compared with WBRT alone ($n=94$). A difference in survival was not identified for patients with multiple intracranial metastases. However, WBRT + SRS boost significantly enhanced or stabilised KPS status, enabled reduced steroid use and improved local control at follow-up across both the solitary and multiple metastases groups. The addition of an SRS boost to WBRT is therefore worthy of consideration in patients with up to 3 metastases and functional independence.

2. Patients who have undergone surgical resection

The rationale to treat patients who have undergone resection of a solitary metastasis with WBRT + SRS boost seems a logical application of the evidence from patients with unresectable metastases.¹³ However, class I evidence to compare the outcome between patients who have received surgery + WBRT and surgery + WBRT + SRS boost does not exist.

Is SRS an effective alternative to surgical resection?

The literature is replete with case studies showing that SRS can provide local control of cerebral metastases that rivals the outcome of surgery + WBRT +/- tumour bed boost.^{14,15} Such studies provide evidence to support the use of SRS but do not relegate surgery as a front-line therapy. For metastatic tumours in inaccessible and radiosensitive locations such as the brainstem, SRS does seem to confer significant survival and quality of life benefit.¹⁶ However, class I evidence is lacking since a RCT comparing SRS versus surgical excision as the initial treatment for solitary intracranial metastases has not been performed. A clinical example of SRS treatment is provided in Box 1.

The role of SRS without WBRT for intracranial metastases

Recently debate has arisen regarding the use of SRS without adjuvant WBRT as a primary treatment for cerebral metastases. In a non-randomised comparative study 268 patients received SRS alone and 301 had SRS + WBRT. The median survivals between different paired prognostic groups were similar. However, 24% of the SRS alone group had salvage WBRT at disease relapse diluting the potential to demonstrate that WBRT confers outcome advantage.¹⁷ A prospective randomised Japanese study has reported in abstract form that up-front WBRT ($n=59$) conferred significant benefit compared with SRS alone ($n=61$) in terms of local control and lowering the risk of developing further intracranial lesions although the median sur-

vival times between the treatment arms was similar.¹⁸ If SRS alone is used, judicious post-treatment follow-up is required to detect new metastases or local failure enabling further SRS (to a new lesion) and/or WBRT to be administered.

Tumour Histology: Radiosensitivity

Melanoma, renal cell and non-small cell lung cancer metastases are relatively resistant to conventional fractionated radiotherapy. However, prospective and retrospective studies do indicate that SRS appears to be effective in achieving local control for these tumour types. It is feasible that a boost of SRS after WBRT has a more significant effect on increasing local control in this group than in patients with more radiosensitive tumours e.g. small cell cancer of lung, breast cancer.

Prognostic factors: Recursive Partitioning Analysis (RPA)

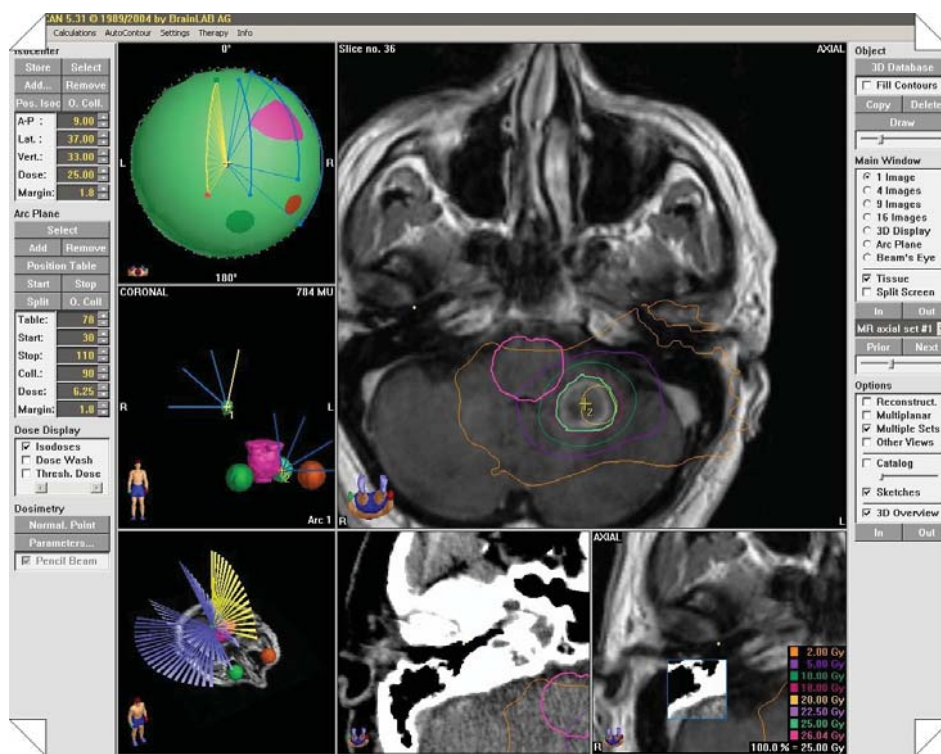
Recursive partitioning analysis is a regression tree analysis tool that has been used to define prognostic factors in patients with metastatic disease. In a cumulative series of 1200 RTOG trial recruits, Gaspar et al tested 21 variables for prognostic predictive value. The most effective discriminators of survival were the performance status (KPS 70 or greater vs. < 70); age (<65 vs. 65 or greater) and absence of systemic metastases. Using these nodal partitions the patients were categorised into three classes which correlated well with median survival times as shown in Figure 1.¹⁹

Chemotherapy and hormonal therapy in the management of patients with intracranial metastatic disease

Due to the differing sensitivity of tumour types and the complex combinations of surgery, WBRT and SRS, effective chemotherapeutic trials are difficult to conduct. At present mono or combination chemotherapy has not been shown to improve survival in patients with intracranial metastases. However, for tumours that are sensitive to chemotherapy and hormonal therapy, particularly breast cancer, these treatments are likely to maintain disease control outside the brain making effective control of intracranial disease important. Chemotherapy is sometimes adopted as a salvage treatment in a young patient with disease relapse. It appears that patients with small cell lung cancer and breast cancer may gain benefit from treatment regimes at this stage. In addition, evidence that 'up front', pre-irradiation chemotherapy may be an effective approach has been published. Randomised controlled trials are warranted in this area.

Newer treatments

Historically, most chemotherapeutic agents do not cross the blood brain barrier. However with the development of small molecules eg lapatinib (which is active against HER1 and HER2), this problem is likely to be overcome. Early trials suggest that treatment with lapatinib reduces the likelihood of patients with metastatic breast cancer developing cerebral metastases.²⁰



Box 1: This 66-year-old patient presented with a history of unsteadiness of gait. Imaging investigations revealed lesions in the left cerebellar hemisphere and right temporoparietal region. A CT of the abdomen showed a mass in the right kidney. The chest CT examination was normal. The intracranial metastases were treated on a day case basis with frame-localised stereotactic radiosurgery using 4 dynamic arcs to each lesion. Unfortunately the patient then developed bone pain leading to a diagnosis of bone metastases. Palliative care was therefore implemented in lieu of any resection of the presumed renal primary.

Clinical algorithm

With improvements in systemic cancer treatment it is probable that increasing numbers of patients with intracranial metastases will warrant treatment by the neuro-oncology team. Best management requires a multidisciplinary approach with access to all treatment modalities including surgery, WBRT and SRS. The use of an evidence based recursive partitioning analysis guided clinical algorithm (see figure 2) is of value in guiding individual patient therapy.

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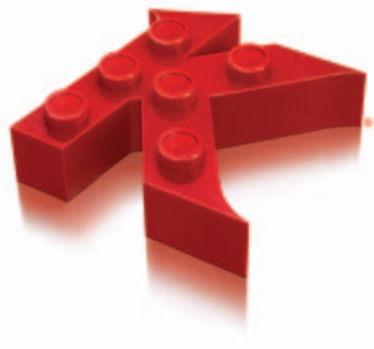
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Central Pontine Myelinolysis

In a decade of service in Neuropathology at the Boston City Hospital and 27 years as Bullard Professor of Neuropathology and Chief of the Neurology Service at the Massachusetts General Hospital, I was afforded the opportunity to discover a number of neurological diseases and clarify neurological phenomena. The best known are: asterixis, intention myoclonus (Lance-Adams Syndrome), the primacy of brain embolism as the leading cause of stroke, the vanishing embolus allergic uremic, and myeloma polyneuritis, the details of the clinico-pathologic relationships of basilar artery occlusion, the histopathology of acute and subacute bacterial meningitis, the neurology of brain death, the clinical aspects of normal pressure hydrocephalus, congenital muscular dystrophy, the pathology of B12, pyridoxine and pantothenic acid deficiencies, hepatic encephalopathy, acquired subacute hepatocerebral degeneration, human Eck fistula (porto-caval shunt), haemosiderosis of meninges, histopathology of ammonia intoxication, pituitary apoplexy, the primary lesions of diphtheritic polyneuropathy, the complete anatomy of Wernicke-Korsakoff disease, thiamine deficiency and its relationship to Wernicke-Korsakoff disease, the thalamic basis of global amnesia, striato-nigral degeneration, and transient global amnesia. All were observed and reported for the first time with various collaborators in our department. Central pontine myelinolysis (CPM), about which I was asked to write, was one of these. The following notation describes its discovery and current status.

Maurice Victor, then a Fellow in the Neurological Unit of the Boston City Hospital, was at the time assisting me in a broad study of the neurological effects of alcoholism. He had been asked to examine a stalwart middle-aged man with delirium tremens. A few days later he asked me to accompany him on a second visit, occasioned by an abrupt worsening of the patient's condition. When we examined him in detail it was noted that he was apparently quadriplegic, unable to chew, swallow or speak but with retained tendon reflexes and Babinski signs. He could move his eyes and his pupils reacted to light. He seemed to respond slightly to painful stimuli over his body and face. We thought the clinical picture corresponded to what I had earlier described with W Watson as 'pseudo-coma' (and others later, as the 'locked-in' syndrome). We suspected occlusion of the basilar artery. No further tests were made.

The patient died of pneumonia a few days later and I had the opportunity to examine his brain. The basilar artery was patent and there was no evidence of atherosclerosis. Particularly wide open was the territory of the upper extension of the basilar and posterior cerebral arteries which probably ruled out brain embolism. Horizontal sections through the mid-pons showed the entire basis pontis to be relatively firm but granular and grayish in appearance. Only the myelin in the peripheral rim of the pons and the tegmentum (except possibly the medial lemniscus) was intact. The Research Fellows in my laboratory had called the lesion an infarct, despite the absence of vascular causation. But when sections stained for cells, myelin and axis cylinders became available, I observed the nerve cells and axis cylinders throughout the lesion were intact. Only the myelin sheaths were destroyed and myelin products were in the early stages of phagocytosis. Some of the oligodendrocytes had degenerated. There were no infiltrates of inflammatory cells and the blood vessels were patent. Clearly the lesion was not an infarct.

In order to distinguish the pathology of this lesion from other known forms of myelin destruction, I introduced the term central pontine myelinolysis, thinking it would denote both the nature of the lesion and its topography. The initial

report appeared under the names of Victor, Adams and Mancall in 1959.¹ During the next few years, once the disease had come to medical attention, other specimens of the same type began to appear in the medical literature. Both males and females, mostly adults, were affected. Alcoholics predominated. As to its overall frequency, Victor and Laureno at the Cleveland Municipal Hospital found 9 cases amongst 3,548 successive autopsies (0.25%). Karp and Laureno² at Emory University in Atlanta called attention to its frequent association with severe hyponatremia; and Laureno, collaborating with Victor,³ reproduced this lesion in dogs by inducing hyponatraemia and rapidly restoring sodium levels with intravenous 3% saline solution.

When reviewed in terms of its pathology, the pontine lesion could vary in size from a few millimeters to almost the entire basis pontis and part of the medial lemniscus. Rarely it extended to the lower part of the midbrain. The medulla was spared. In exceptional cases, lesions of similar type have been found outside the pons – in the thalamus, subthalamus, cerebellar or cerebral white matter and elsewhere. With respect to the extra-pontine cases, one may be tempted to draw an analogy to Marchiafava-Bignami disease. However, the latter clearly destroys axons as well as myelin with cavitation and atrophy of layer III of the frontal cortex.

The diagnosis has been facilitated by recognition of the circumstances with which it is most often conjoined i.e. severe hyponatraemia with alcoholism, renal failure, liver failure or any condition leading to hyponatraemia such as chronic cachexia, bacterial infections and neoplasms. In children, it complicates severe burns. T2 weighted MRI scans reveal the pontine lesions with fidelity. By this technique one can see small 2-3mm lesions that may be asymptomatic as well as larger symptomatic but non-fatal ones. A few of the latter with substantial MRI-visible pontine myelinolysis have recovered after 6-12 months. MRI also has exposed some of the extrapontine lesions which may be unaccompanied by CPM.

As regards other aetiologies, there is no evidence of multiple sclerosis, post-infectious encephalomyelitis, acute necrotizing encephalomyelitis, any form of Marchiafava-Bignami disease, or any one of the genetic-determined encephalopathies. Sporadic cases have been, seemingly by chance, associated with Wernicke disease and various forms of alcoholic encephalopathies (acute delirium tremens, acute auditory hallucinosis, chronic auditory hallucinosis) as described by the author and colleagues.⁴

Regarding the hyponatraemic associations of CPM in adults, more than half are chronic alcoholics who have developed critical levels of low serum sodium from salt wasting of inappropriate antidiuretic hormone (SIADH) secretion. If serum sodium falls rapidly below 120 meq/L the patients become drowsy, confused, stuporous and comatose. The sodium level may reach 100 meq/L. The real danger comes with the rapid correction of the hyponatraemia by intravenous NaCl, at which time CPM develops. When the level of serum sodium is slowly restored (<10meq/24 hours), CPM does not develop. However, the rapid correction of serum sodium as the only factor in causation has been questioned by McKee and colleagues who demonstrated typical lesions postmortem in 10 of 139 severely burned children who had been subjected to severe hyperosmolality some days before death but not in the terminal phase.⁵ They were never hyponatraemic. Some factor other than hyposmolality must be operative, perhaps a rapid change in electrolyte environment of the myelin sheaths in certain regions of the brain. Thus aetiology still needs further study. Nevertheless, we now know of at least one means of prevention.



Dr Raymond D Adams is the Bullard Professor of Neuropathology (Emeritus) at Harvard Medical School and was Chairman of the Neurology Department at Massachusetts General Hospital from 1951-1978. Born in Oregon in 1911, he received his MD from Duke University and trained in neurology and neuropathology at MGH and Harvard. He has received numerous honorary MD and DSc degrees from institutions worldwide in recognition of his contributions to neurology. He is known for his expertise in the diagnosis and treatment of disorders of the human nervous system and was the discoverer of a number of new syndromes and diseases. He has written over 250 scientific articles and 13 books on the neurosciences. His textbook, *Principles of Neurology*, is the definitive general neurology reference used by generations of neurologists.

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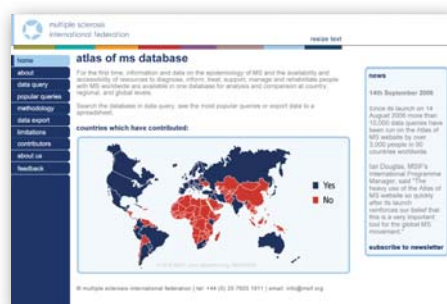
MSIF Atlas of MS Website Compares MS Data Worldwide

On August 14, 2006, the Multiple Sclerosis International Federation (MSIF) launched the Atlas of MS, a major interactive website presenting data gathered by MSIF and the World Health Organization (WHO). It illustrates the epidemiology of multiple sclerosis (MS) and the availability of resources to diagnose, treat, support, care and campaign for people with MS in different countries around the world. The data, which can be analysed and compared at a country, regional, or global level for 62 countries, is available at www.atlasofms.org.

Data was gathered via a questionnaire created by the Atlas of MS Work Group, comprising of international experts and people affected by MS. The responses are organised into themes and presented in maps and graphs (with the facility to download the underlying data). Themes covered are:

- epidemiology of MS
- services and support for people with MS
- the diagnosis of MS
- management of MS
- treatment of MS
- quality of life of people with MS

Within each theme, users can search for and compare data on a number of variables and regions. For example, under epidemiology, prevalence of MS or the ratio of males to females with MS can be viewed by country, region or



worldwide. Or, for the management of MS, data for the number of neurologists or nurses per 100,000 people can be viewed. To date, more than 30,000 data queries have been run by over 5,100 people in 98 countries.

Paul Rompani, MSIF's Deputy Chief Executive, said "We are thrilled with the Atlas of MS website and the opportunities it offers to improve the quality of life of people with MS worldwide. The information presented confirms that resources for MS diagnosis, treatment, care and support vary widely between countries. Furthermore, MSIF aims to expand the breadth of the Atlas of MS replacing impressions and opinions with facts and figures. We hope that the realities uncovered by the Atlas will motivate patient organisations and other campaigners to press governments and healthcare providers to improve MS treatment and care worldwide."

The Atlas of MS is a growing and evolving project, and data will be updated on an ongoing basis. This will include securing representation from countries that have not yet submitted data, and updating existing entries with the most up-to-date information incorporated as it is received. Furthermore, we aim to expand the breadth of the Atlas, with data being gathered for new categories and sub categories as and when necessary (for example when a new treatment becomes available). In addition, a 'snapshot' of the database will be taken at the end of each year to allow medium-term analysis of developments in the themes covered.

The survey results will also be used to produce a combined MSIF/WHO publication, authored by members of the Atlas of MS Work Group. As well as presenting data, the publication will include brief reviews of selected topics which summarise medical, lifestyle, social and economic issues affecting people with MS. The Atlas of MS publication will be available in April 2007.

For more information on the MSIF Atlas of MS website and/or the development of the MSIF/WHO Atlas of MS publication, please contact Lucy Hurst, Information and Communications Manager, on lucy@msif.org

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Alzheimer 100

At the 37th Conference of the South-West German Psychiatrists in Tübingen on 3rd-4th November 1906, Dr Alois Alzheimer presented his clinical and neuropathological findings in the case of a patient, Auguste D, who suffered cognitive decline and behavioural changes in the presenium. The presentation, entitled 'On a peculiar disease process of the cerebral cortex', apparently prompted no comments or reaction from the audience. The first case of 'Alzheimer's disease' had been reported, although the condition was not to bear this eponym until Emil Kraepelin used it in the 8th edition of his psychiatry textbook published in 1910.¹²

Alzheimer's lecture was published in the following year in the *Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtlich Medizin*³ (English translations are available⁴⁻⁶). It detailed the clinical observations Alzheimer and his colleagues in Frankfurt had made on Auguste D from the time of her admission in 1901, aged 51, until her death in 1906, and also Alzheimer's neuropathological findings (by this time he had moved to Munich, via Heidelberg), including peculiar changes in the neuronal neurofibrils visualised with the Bielschowsky silver stain, later to be called neurofibrillary tangles, and miliary foci of extracellular material, corresponding to senile plaques. Both the case file⁷ and the pathological slides⁸ of Auguste D have been rediscovered



and re-reported, confirming that Auguste D did indeed have Alzheimer's disease as we now understand it.

In a later contribution⁹ (also available in English¹⁰), Alzheimer described a further personally examined case, Johann F, and three other pathological cases, and linked the neuropathological substrate of neurofibrillary pathology to the clinical correlate of dementia. The pathology of this second patient has also been re-examined:¹¹ apparently it showed numerous senile plaques but no neurofibrillary tangles in the cerebral cortex. More recently, the kindred of Johann F has been extensively investigated through the historical records, suggesting an autosomal dominant disorder with variable penetrance and with age of onset between the 30s and mid 60s.¹² The index case was negative for amyloid precursor protein (APP) gene mutations,¹¹ but was not investigated for presenilin-1 mutations.

The 100th anniversary of the first description of Alzheimer's disease has been marked by a publication documenting some of the clinical and scientific progress which has been made over the ensuing century, the vast majority of it within the last 40 years.¹³ Although much has been learned about disease aetiology and pathogenesis, the ultimate goal of disease-modifying treatment for AD remains elusive, although it does not seem unreasonable to hope for new therapeutic developments in the foreseeable future.



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European Federation of Neurological Societies

Glasgow, UK, 2-5 September, 2006.



Apparently, when Glasgow was awarded the 10th EFNS Congress back in 2001, Professor Ian Bone, the Chairperson of the Local Arrangements Committee, guaranteed that it would not rain for the duration of the conference. In the event, this prediction failed, perhaps unsurprisingly, to come to fruition, but the intermittent wet weather failed to dampen delegates' enthusiasm for a meeting, based at the Scottish Exhibition and Conference Centre (SECC), which delivered in so many other ways (the exhibition even featured a stand devoted to ACNRI!).

It all started with the EFNS President, Dr Jacques de Reuck, speaking on the medical intervention which has saved most lives – the condom – followed by Professor Graham Teasdale, current President of the Royal College of Physicians and Surgeons of Glasgow (RCPSG) speaking on the Glasgow Coma Scale, first published by himself and Bryan Jennett in 1974. He drew the important distinction between use of the Scale in monitoring individual patients over time, and the use of the Score (range 3-15) in summarising series of patients and for use in protocols and guidelines. The assembled delegates were then led by a pipe band out of the SECC to cross the River Clyde via Bell's Bridge to the Glasgow Science Centre for the welcome reception.

Of the many communications presented over the subsequent three days, items attended to by the current reviewer and judged of note included the following (with apologies in advance to those whose particular interests encompass multiple sclerosis, headache, stroke, neuro-oncology, etc):

Movement Disorders: a satellite symposium examined the place of dopamine agonists in the treatment of Parkinson's disease. In response to concerns about gambling behaviour associated with dopamine agonists, Professor Warren Olanow (New York) stated that since 3% of Americans have a gambling addiction, the small numbers of PD patients reported in published case series may simply reflect population prevalence and not be specifically treatment related. However, a poster from Professor Donald Grosset (Glasgow) reported that around 10% of patients prescribed dopamine agonists in West Scotland have problematic gambling. Professor Niall Quinn (London) delivered a clear and clinically useful account of atypical parkinsonian disorders: suggested red (or pink) flags for a diagnosis other than idiopathic Parkinson's disease included absence of tremor or rigidity, young onset, symmetrical onset, early freezing or falls, rapid progression, poor L-dopa response, and early dysautonomia, speech and swallowing difficulties, and dementia.

In a main topic session devoted to gait disorders, Professor Jose Masdeu (Pamplona, Spain) presented some fascinating clinico-radiological correlations, including lesions of the thalamus (thalamic astasia), thalamocortical white mat-

ter, and mesial frontal lobe, all of which affect physiological gait control systems (the 'automatic pilot'). Professor Thomas Brandt's lecture on vestibular gait disorders was, as ever, challenging for those less than au fait with the extensive ramifications of the vestibular system, but it was interesting to see the role his dog, Tessa, played in showing that running can be better than walking with unilateral vestibular failure. The possibility that walking may slow cognitive decline (N Giladi, Tel-Aviv, Israel) heartened those of us allergic to running.

Epilepsy: the provocative title 'Can genetics help us to understand and manage common neurological diseases?' was sufficient to draw some delegates from their beds early on Sunday morning. For those not initiated in the art of genetics, it was reassuring to learn that 'careful phenotyping is the key to any genetic study' but it was less reassuring to hear that a wide phenotype may be seen with the same gene mutation in a single kindred (SM Sisodiya, London). Nonetheless, the ability to identify genetic polymorphisms which determine responsiveness to certain anticonvulsants may be of practical relevance in the clinic (NW Wood, London). In a satellite symposium, I heard for the first time the term "pseudointractable" used to describe patients not responding to certain anti-epileptic drugs which do not work well in idiopathic generalised epilepsies (S Benbadis, Tampa, USA).

Sleep disorders: in a satellite symposium entitled 'Sleeping with CNS Disorders', Professor Colin Espie (Glasgow) declared that "Sleep is of the brain and for the brain". The frequency of sleep disturbance in fibromyalgia was discussed, along with the possible therapeutic use of pregabalin. Its effect on sleep may be independent of an analgesic effect (D Rowbotham, Leicester). Restless legs syndrome also merited a satellite symposium, and 'Movement disorders and sleep' was the title of a lecture accompanied by some startling and amusing videos of polysomnographic studies (C Trenkwalder, Kassel, Germany).

Dementia/neuromuscular disease: a very well attended focused workshop examined the emerging field of encephalopathies associated with voltage-gated potassium channel (VGKC) antibodies, co-chaired by Professors Angela Vincent and Martin Rossor. Since VKGC antibody-mediated non-paraneoplastic limbic encephalitis (NPLE) may easily be misdiagnosed as dementia, and most patients are over 50, the condition may well be underdiagnosed. Marked recovery from NPLE may be seen after immunotherapy, although spontaneous improvement has been recorded. Patients may be left with a retrograde amnesia extending prior to the acute illness, prompting a suggestion from the floor that the rare syndrome of focal retrograde amnesia might possibly be



causally related to missed VKGC antibody-mediated NPLE in some cases. Angela Vincent also chaired a satellite symposium on targeted immunomodulatory therapy in the management of myasthenia gravis, which included a clear exposition on the various subtypes of MG (Ian Hart, Liverpool) and a masterful account of the deficiencies of the evidence on which to base therapeutic decisions in MG by Renato Mantegazza (Milan).

Neurohistory: Delegates not only had the opportunity to hear of the work of Sir Robert Carswell (Rachel Thomas, Glasgow), but also to see it on display: the Neurohistory Tour included a visit to the Special Collections Department at Glasgow University Library where Carswell's Pathological Anatomy of 1838 was on view, including the celebrated Plate IV Figure 4, thought to be the first illustration of the lesions of multiple sclerosis. Also to be seen were copies of such celebrated works as Vesalius' *De Fabrica* of 1543 and Willis's *Cerebri anatome* of 1664; a copy of the latter was also on display at the RCPSG, the final stop on the history tour, as was an operating table used by the celebrated neurosurgical pioneer Sir William McEwen who worked in Glasgow. Another of his operating tables was seen at the Hunterian Museum, where the tour commenced, along with some of his and William Hunter's gruesome surgical specimens.

Neurology and Art: Richard Briers co-hosted a special session entitled 'The Good Life' which included: a piano recital from a lady with Parkinson's disease whose condition had been transformed by deep brain stimulation; the small bagpipes played by a man with finger dystonia; and songs from a lady with multiple sclerosis. Their fortitude and skill in the face of these disabling conditions was truly inspirational for all those whose aim is to understand and ameliorate neurological disease.

AJ Larner, Walton Centre for Neurology and Neurosurgery, Liverpool, UK.

7th European Congress on Epileptology

Helsinki, Finland, 2-6 July 2006.

A banquet of epileptology was served up in a sun-bronzed Helsinki in early July, in the ILAE 7th European Congress on Epileptology. Sessions ranged from the highly clinical to fundamental basic science, and included symposia with a local Baltic flavour, notably one dedicated to Unverricht-Lundborg disease (commonest in Finland, where the incidence exceeds 1 in 20,000).

With approximately 30% of patients resistant to currently available anti-epileptic drugs, novel pharmaceutical approaches are being sought. H Potschka (Hanover) discussed efflux-transporter mediated pharmacoresistance, and how efflux across the blood brain barrier might be reduced. Could drug delivery be targeted to the epileptogenic zone, so avoiding systemic drug side effects? This intriguing subject was elegantly addressed both by H Cock (London) and P Boon (Ghent), while A Vezzani (Milan) and D Boison (Portland) discussed respectively, focal gene therapy for epilepsy and techniques for

local augmentation of (anti-epileptic) cortical adenosine levels.

While new therapeutic methodologies are of future interest, the lack of evidence to guide current prescribing practice was highlighted. P Ryvlin (Lyon) explored selection of the first AED in partial epilepsy. According to recent ILAE criteria for robust evidence in epilepsy monotherapy, there are only four class 1 and two class 2 trials published to date! The problem of rational drug choice in IGE is even worse given the paucity of IGE drug trials (B Schmitz, Berlin). Attempts to fill this evidence vacuum were discussed, notably by A Marson (Liverpool) who described the findings of SANAD, the largest ever randomised trial in epilepsy, with 2443 patients.

What of the noble goal of preventing acquired epilepsies from developing in the first place? In her inspirational talk A Pitkanen (Kuopio) dissected past failings and current prospects for drugs to modulate the neuronal reorganisation underpinning epileptogenesis

following acquired brain insults. G Holmes (Dartmouth, New Hampshire) emphasised the need for surrogate markers of epileptogenesis (particularly MRI or EEG changes), to make antiepileptogenesis trials in humans more feasible.

Other highlights were insightful discussions of ictal and interictal autonomic dysfunction and its links to SUDEP, recent developments in epilepsy genetics, imaging and pre-surgical evaluation including the vexed question of whether low IQ is a contraindication to epilepsy surgery (consensus: it isn't).

With more than 1000 presentations, one can only convey a flavour of the feast, so my apologies for numerous distinguished omissions. I left refreshed by the event, the Finnish hospitality, and swims in the sea, which I was delighted to find was warm rather than – well – Baltic.

*Doug Crompton, SpR in Neurology,
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28th International Congress of Clinical Neurophysiology

Edinburgh, UK, 10-14 September 2006.

One day all conferences will be like this! Comfortable chairs with masses of legroom, plentiful coffee and lunch without queues, seamless presentations because of the IT support...it all makes a difference. Well over 1000 delegates from across the world were treated to a superb scientific programme in the excellent facilities of the Edinburgh International Conference Centre. With up to six parallel sessions over four days it was impossible to attend more than a fraction of the presentations, so I shall share a couple of highlights.

Keynote lectures were almost uniformly superb, with the flashiest presentation going, somewhat predictably, to Evan Snyder (La Jolla, USA) for his overview entitled 'What Can Stem Cells Do Now?', starting with a spoof (I think) video advertising 'stem cell lager' – repairs your

liver while you drink! He took great pains to remind us that stem cell treatment is not all about replacing neurons, and that some promising results suggest that they can reduce host scarring and inflammation in the CNS, allowing the process of self repair.

Mary Reilly (London, UK) gave a useful overview of how to think about inherited neuropathies – a terrifying and confusing subject for most of us. It seems we're back to calling them CMT's, not HMSN, for now. First, work out the inheritance if possible (AD, AR, X-linked or sporadic). Next, use neurophysiology to determine whether they are primarily axonal or demyelinating (upper limb motor conduction <38m/s suggests CMT1, >38m/s CMT2, and remember the intermediate form with, for example, connexion 32 mutations and patchy conduction 25-45 m/s). Third, and finally, go

for the gene: for autosomal dominant CMT1 go first for PMP-22 then P0, whereas if autosomal recessive there are lots of genes, and you'll be lucky to find the culprit. The problem is that one gene can cause lots of phenotypes, and one phenotype can be caused by a number of genes (that's my excuse).

Eric Stålberg (Uppsala, Sweden) talked about jitter measurements when performing SFEMG, reminding us that it is best measured between two single unit potentials (ideally with interpotential interval over 300s). If, in fact, one is a compound motor unit potential, comprising say 2-10 single units, the jitter will be underestimated by a factor of up to $\sqrt{2}$. Furthermore, he pointed out that disposable concentric needles (commonly used in the UK with fears of CJD) will slightly under-detect jitter compared to single fibre needles.



Prof Jonathan Cole President BSCN presenting Prof Tony Barker (BSCN Geoffrey Parr Lecturer) with a gift after his lecture.



L-R - Robin Kennett, Ian Smith - Treasurer, Jonathan Cole - Convenor and Chair of the ICCN, Nick Murray, Kerry Mills - Chair of the Scientific Committee and Roberto Guiloff.

Shawn Bird (Philadelphia, USA) gave an excellent talk about the use of direct muscle stimulation and conduction studies in patients on the intensive care unit. It is common not to be able to record voluntary activity on routine EMG in patients with suspected ITU neuropathy/myopathy, and the presence of spontaneous activity is not really helpful in distinguishing the two. Furthermore, sensory potentials are frequently absent due to oedema, or are unrecordable due to artefact. In this situation, if a neuropathy dominates then the response to nerve stimulation (recording with a needle in the muscle) will be poor, but direct muscle stimulation much better (by a factor of 2+). On the other hand, if a myopathy dominates then the muscle potential, although small, will be equal (approximately) in response to both nerve and direct muscle stimulation.



There were many excellent 'CNS' presentations on epilepsy, MEG and so on. In a useful workshop on focal epilepsy Alois Ebner (Bielefeld, Germany) reminded us of recent work suggesting that patients with temporal lobe seizures may not require pre-operative video telemetry provided their inter-ictal EEG, clinical seizure semiology

and MRI findings all correspond, and there are no psychiatric contraindications. This theme was echoed in a poster presented by Catherine Scott from the Queen Square group.

So, overall an excellent meeting held during a Scottish 'Indian summer' (plus a day of monsoon of course) – so hot in fact that during the Scottish Evening Dinner and Ceilidh, held in the stunning surroundings of the Royal Museum of Scotland, I seriously considered a swim in the ornamental carp ponds. The miniature and huge Ron Mueck sculptures on display ten minutes walk from the conference centre provided another excellent lunchtime distraction. I look forward to the next ICCN – four years from now, in Japan.

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6th Annual Brain Injury Legal Seminar

London, UK, September 2006.

This annual event developed from a partnership between the Brain Injury Social Work Group and Stewarts Solicitors Personal Injury division.

The seminar attracted a diverse audience and a range of eminent speakers. Those planning the day succeeded in focusing on the topical issues that challenge the provision and delivery of support services to brain injured people and their families. The presentations shared by the speakers updated our knowledge, guiding us through the complex legal framework of personal injury law, public law and case law.

In terms of day-to-day practice and problem solving the session about 'Who Pays' dealt with the complexities of health and community care law and charges for services. Disclosure of records for legal proceedings was relevant for employees of NHS Trusts, social services and other public servic-



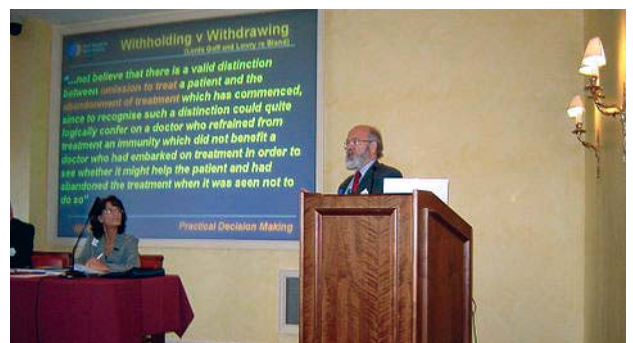
es, providers of rehabilitation and providers of care.

An experienced case manager described her role, supported by a legal opinion, about the value of case managers in personal injury claims.

Two of the sessions covered contrasting and controversial subject currently gaining extensive media exposure: Following the case of Tony Bland, the speaker shared considerations in practical decision making before withholding and withdrawal of treatment for people in a persistent vegetative state, issues for both relatives and members of the multidisciplinary team. Compensation for victims of 7/7, victims of terrorism and crime rounded off this interesting day.

Patti Simonson,
Tel: 0208 780 4530,
Fax: 0208 780 4530,
Email: psimonson@rhn.org.uk

Brain Injury Social Work Group



Patti Simonson, Chair BISWG (left) and Professor Keith Andrews, Director of the Institute of Neuropalliative Rehabilitation, Royal Hospital for Neuro-disability, London.



Paul Paxton Partner, Stewarts Solicitors (left) and Patti Simonson, Chair BISWG.

Association of British Neurologists Autumn Scientific Meeting

London, UK, 4-6 October, 2006.

In contrast to the backdrop of 'fairy lights and the faint bark of seagulls' experienced at the Spring Scientific Meeting of the Association of British Neurologists (ABN) (see ACNR 2006;6(3):35), the bright lights of the capital and the faint bark of the London cabbie set the scene as delegates assembled at the Royal College of Physicians of London for the Autumn Scientific Meeting of the ABN. As always, the main focus of the start of the meeting was to catch up with old

friends and colleagues from across the country over lunch resulting in a friendly and lively atmosphere and animated conversation.

The first scientific session opened with a stimulating series of presentations on neurodegeneration including a description of the use of ¹¹C-PIB positron emission tomography demonstrating increased amyloid deposition in the brains of subjects with amnesic mild cognitive impairment associated with a higher risk of converting to

Alzheimer's disease (Dr Okello). Dr Merrison gave a fascinating presentation on the myogenic potential of bone marrow derived stem cells and the implications this may have for cellular therapies in the future. Dr Pal concluded the session by revealing that the MRC Prion Unit has developed a monoclonal antibody demonstrating strong immunoreactivity to post-mortem brain tissue from variant CJD with the tantalising possibility of a future screening test for vCJD. The ensuing

symposium examined the mechanisms of neurodegeneration with stimulating presentations from Profs. Shaw, Lovestone, Perry and Brooks.

The evening symposium on Movement Disorders chaired by Prof Quinn and Dr K.R. Chaudhuri comprised an overview on restless legs syndrome, an update on dystonia eruditely delivered by Prof Bhatia and a series of video cases of unusual movement disorders. After an inspiring first day, delegates then repaired to the welcome reception for a restorative glass or so of wine and what seemed like an endless supply of canapés.

The following day the Epilepsy and Multiple Sclerosis scientific session told us of a functional MRI paradigm that may help predict the degree of memory loss after epilepsy surgery (Dr Powell) and an update in the use of Campath 1-h (Dr Hirst) and natalizumab (Dr Giovannoni) in MS. We then moved into the 'Top Scoring Papers' session which comprised an outstanding series of presentations, including a discussion of the syndrome of transient epileptic amnesia (see also ACNR 2006;6(4):13-14), an update on the Scottish Neurological Symptoms Study from Dr Stone and an outline of the clinical features of dysferlinopathy. Prof Wiles gave us data on the outcome of MiniCEX and DOPS assessments for trainees in neurology emphasising the importance of multiple assessments carried out by multiple assessors and highlighting the value of observation and feedback in improving the evaluation of a trainee's performance.

Dr Tengah provided feedback from the pilot Knowledge-Based Neurology Exam and revealed the uncomfortable news for consultants that they had not quite matched the 100% pass rate achieved by the year 5 SpRs. The value of protecting the integrity of consultants' supporting professional activity sessions therefore seems proven!

One of the highlights of the meeting was the presentation of the ABN medal to Professor



Above: Meeting in progress in the Wolfson Lecture Theatre, and below: our President, Professor David Chadwick at the dinner in Middle Temple.



Richard Hughes for his prolific work on peripheral neuropathy, including a citation by Dr Michael O' Brien. Prof Hughes gave a comprehensive and stimulating outline of our previous and current knowledge of diseases of peripheral nerves and a glimpse into the future about where we might be in 2037.

The meeting continued with a lecture from Prof Wessely on Gulf War Syndrome and as always the clinicopathological conference was well attended and stimulating. The conference dinner at Middle Temple was outstanding but led to a few fatigued faces on the final day of the con-

ference. The closing sessions were an eclectic mix of interesting case presentations, (with the presentation prize passing to Dr MS Jones for an unusual case of rat lungworm meningitis), followed by a discussion of what the future holds for the world of neurology in terms of medical politics, imaging and an increased knowledge of the genome. The meeting concluded with a debate in which 'This house believes that common and chronic neurological conditions are best managed by general practitioners' which perhaps unsurprisingly was overwhelmingly voted against by the ABN both before and after the debate. Encouragingly, however, most felt that way forward was increased collaborative working between primary and secondary care.

The organisers of the Autumn meeting, Prof Christopher Shaw and Dr Robert Weeks, are to be congratulated on an outstanding achievement. As always the ABN meeting was a superb mix of high quality scientific papers, outstanding lectures from keynote speakers, the opportunity for discussion at the CPC and debate, the chance to conduct some of the business of neurology with the ABNT and Programme Directors meetings, interaction with our colleagues in the pharmaceutical industry and importantly to socialise with old and new friends within our field. It was also heartening to see so many new consultants and trainee neurologists attending (including senior house officers) showing their enthusiasm for what has to be the most fascinating of medical specialities. The support of our junior colleagues is crucial to the ongoing survival of the Association of which we are all so justly proud and we look forward to welcoming more of them at future meetings.

*Dr Andrea Lindahl,
Consultant Neurologist, University Hospitals
Coventry and Warwickshire, UK.*

Events Diary

To list your event in this diary, email brief details to Patricia McDonnell at patriciamcdonnell@btinternet.com by November 22nd, 2006

2006

November

Birmingham Neuro-Ophthalmology Conference

1 November, 2006; Birmingham, UK
Hilary Baggott
T. 0121 507 6785

Neuro-Ophthalmology Seminar

1 November, 2006; London, UK
Nicky Briggs
T. 0207 935 0702
E. Events@Rcophth.Ac.UK

West of England Seminar in Advanced Neurology

2-3 November, 2006; Devon, UK
E. cgardnerthorpe@doctors.org.uk

10th MS Trust Annual Conference

2-4 November, 2006; Bournemouth, UK
T. 01462 744045
W. www.mstrust.org.uk/conference

Current Trends in Epilepsy: An International Symposium by AIIMS

3-5 November, 2006; New Delhi, India
W. www.aiims.edu/aiims/events/
Neurology/currenttrends.htm

3rd International Symposium on Microneurosurgical Anatomy (3rd ISMA)

5-8 November, 2006; Kemer, Antalya-Turkey
Prof. Erdener Timurkaynak MD
E. etimurkaynak@yahoo.com
W. www.isma2006.org

BSRM Winter Meeting & AGM

6-7 November, 2006; Loughborough, UK
Sandy Weatherhead
T. 01992 638865
E. 01992 638905

Neurology Symposium

9 November, 2006; Edinburgh, UK
T. 0131 247 3636
E. m.farquhar@rcpe.ac.uk
W. www.rcpe.ac.uk/education/events/index.php

International Psychogeriatric Association Latin American Regional Meeting

16-18 November, 2006; Mexico City, Mexico
E. 2006mexico@ipa-online.org

ESNA Conference

22-24 November, 2006; Solihull, UK
Sally Collins E. SallyAnn.Collins@rothgen.nhs.uk

Joint World Congress on Stroke

22-25 November, 2006; Cape Town, South Africa
T. +41 22 9080488
E. stroke2006@kenes.com

NEW

10th International Congress of Parkinson's Disease and Movement Disorders

26-29 November, 2006; Kyoto, Japan
E. info@movementdisorders.org
W. www.movementdisorders.org

XVI Meeting of the International Neuro-ophthalmology Society

29 November - 2 December, 2006; Tokyo, Japan
Info: <http://www.inos2006.jp/>

5th International Congress on Autoimmunity

29 November - 3 December, 2006; Sorrento, Italy
W. www.kenes.com/autoim2006/

NEW

17th International Symposium on Amyotrophic Lateral Sclerosis/Motor Neurone Disease

30 November - 2 December, 2006; Yokohama, Japan
E. symposium@mndassociation.org
W. www.mndassociation.org

December

BISWG Brain Injury and Mental Health -UK Study Day

1 December, 2006; Edinburgh, UK
Fen Parry
T. 0131 537 6853
E. fen.parry@edinburgh.gov.uk or
mhairi.campbell@pct.scot.nhs.uk

MS Trust General Study Days

5 December, 2006; Lincolnshire, UK
T. 01462 476704

W. www.mstrust.org.uk/education.jsp

Cochrane Systematic Reviews in Practice: Stroke

5-6 December, 2006; Perugia, Italy
E. cochrane.neuronet@unimi.it

NEW

1st UK Stoke Forum Conference

7-8 December, 2006; London, UK
W. www.ukstrokeforum.org

NEW

Attention and Driving: a cognitive neuropsychological approach

8-9 December, 2006; Wurzburg, Germany
W. www.koenigundmueller.de/pdf/kurs/FB061208A.pdf

Advanced cognitive rehabilitation workshop: Attention and Information Processing, following brain injury

8-9 December, 2006; London, UK
W. www.brainretraining.co.uk
E. enquiries@brainretraining.co.uk

RSM Bench to Bedside- Neuroprotection, Regeneration and Restoration of Function in the Nervous System

12 December, 2006; London, UK
Tina Lanzara

T. +44(0)20 7290 3844

F. +44(0)20 7290 2977

E. tina.lanzara@rsm.ac.uk

W. www.rsm.ac.uk/academ/c10-nprot.htm

'Neurocon 2006' 55th Annual meeting of the Neurological Society of India.

14-17 December, 2006; Madurai, Tamil Nadu State, India.

D. Kailai Rajan M.Ch(Neuro)
T. +91 452 2640044 +91 452 2526364
F. +91 452 2641424
E. kailairajan@eth.net kailairajan@sancharnet.in
W. www.neurocon2006.com

2007**January****NEW****BISWG South Wales and the West Country Regional Meeting**

18 January, 2007; Cardiff
Kate Coles
T. 02920 224871
E. kate.coles@hughjames.com

NEW**35th National Conference Indian Association of PMR Specialists**

19-21 January 2007; Patna, India
Email: pmrenquiry@yahoo.com
ajitvarma592@yahoo.com

February**Think Ahead Think Success - OT Support Workers 2nd Biennial National Conference**

6 February, 2007; York, UK
Julie Hawkins
T. 020 7450 2337
F. 020 7450 2349
E. julie.hawkins@cot.co.uk

35th Annual INS Meeting

7-10 February, 2007; Portland, Oregon, USA
International Neuropsychological Society
T. + (614) 263-4200
F. + (614) 263-4366
E. ins@osu.edu

The Society for Research in Rehabilitation Winter Meeting

8 February, 2007; Sheffield, UK
W. www.srr.org.uk
E. m.marshall@sheffield.ac.uk

NEW**Global Conference on Neuroprotection & Neuroregeneration**

14-16 February, 2007; Garmisch-Partenkirchen, Germany
W: www.gcnprn.org

London Fashion Week Design Workshop - Inclusive clothing and materials for different needs: alternative solutions for the high street

16 February, 2007; London, UK
Aileen Toal
T. 020 7450 2300
F. 020 7450 2349
E. aileen.toal@cot.co.uk

3rd Annual Update Symposium on Clinical Neurology and Neurophysiology

19-21 February; 2007, Tel Aviv, Israel
W. www.neurophysiology-symposium.com

1st East Meditteran Epilepsy Congress

21-24 February, 2007; Luxor, Egypt
T. +353 1 205 6720
F. +353 1 205 6156
E. info@epilepsycongress.org

British Neuropsychiatry Association 2007 Meeting - Parkinson's Disease, Epilepsy, Mind and Brain: The next 20 years

22-23 February 2007; London, UK
T/F. 01621 843334
E. gwen.cutmore@lineone.net
W. www.bnpa.org.uk

March**1st Congress on Epilepsy, Mind & Brain**

2-4 March, 2007; Prague, Czech Republic
W. www.kenes.com/epilepsy

International Congress on Neurology and Rehabilitation (ICNR)

9-11 March, 2007; New Delhi, India
E. icnr2007@gmail.com W. www.iamst.com
23rd Annual Pacific Rim Conference on Disabilities
12-13 March, 2007; Waikiki, Hawaii
E. prinfo@hawaii.edu
W. www.pacrim.hawaii.edu

4th Annual Meeting of the Global College of Neuroprotection & Neuroregeneration

14-16 March, 2007; Garmisch-Partenkirchen, Germany

E. info@gcnprn.org
W. www.gcnprn.org
T. +44 115 969 2016
F. +44 115 969 2017

8th International Conference AD/PD 2007

14-18 March, 2007; Salzburg, Austria
W: www.kenes.com/adpd/

1st International Congress on Epilepsy, Mind & Brain

29-31 March, 2007; Prague, Czech Republic
T. +41 22 908 0488
F. +41 22 732 2850
E. epilepsy@kenes.com

April**Certificate Course in Neurological Rehabilitation**

10-27 April, 2007; Newcastle upon Tyne, UK
E. traceymole@wfnr.co.uk

ABN Spring Scientific Meeting

11-13 April, 2007; Cambridge, UK
E. info@theabn.org

Alzheimer's Disease: Update on Research, Treatment, and Care

12-13 April, 2007; San Diego, California, USA
W. http://cme.ucsd.edu

The Challenges of Commissioning for Brain Injury Services-A National Conference

25 April, 2007; London, UK
Patti Simonson
T. 0208 780 4530
F. 0208 780 4530
E. psimonson@rhn.org.uk

59th Annual Meeting of the American Academy of Neurology

28 April-5 May, 2007; Boston, USA
W. www.aan.com

American Academy of Neuroscience Nursing (AANN) Annual Meeting

29 April - 2 May, 2007; Orlando, USA
E. info@aann.org

May**2nd Biennial Vocational Outcomes in Traumatic Brain Injury Conference**

24-26 May, 2007; Vancouver, BC Canada
E. sljproductions@telus.net
W. www.tbicvancouver.com

8th European Neuro-Ophthalmology Society Meeting

26-29 May, 2007; Istanbul
Pinar Aydin O'dwyer
E. aydinp@eunos2007.org
W. www.eunos2007.org

XVI European Stroke Congress

29 May - 1 June, 2007; Glasgow, UK
E. info@stroke.org.uk

Consortium of Multiple Sclerosis Centers (CMSC)

30 May - 3 June, 2007; Washington DC, USA
E. info@mcsare.org

June**39th International Danube Symposium for Neurological Sciences and Continuing Education in conjunction with the 1st International Congress on ADHD**

2-5 June, 2007; Wurzburg, Germany
W. www.danube-wuerzburg.de or
www.adhd-wuerzburg.de

1st International Congress on ADHD: From Childhood to Adult Disease

3-7 June, 2007; Wuerzburg, Germany
E. peter.riederer@mail.uni-wuerzburg.de

11th International Congress of Parkinson's Disease and Movement Disorders

3-7 June, 2007; Istanbul, Turkey
W. www.movementdisorders.org/meetings/index.shtml

Kuopio Stroke Symposium

6-8 June, 2007; Kuopio, Finland
E. jukka.jolkkonen@uku.fi
W. www.uku.fi/stroke2007

2nd International Congress on Neuropathic Pain

7-10 June 2007; Berlin, Germany
T. +41 22 908 0488

F. +41 22 732 2850
E. neuropain@kenes.com
W. www.kenes.com/neuropain

4th World Congress of the International Society of Physical Medicine and Rehabilitation

10-14 June, 2007; Seoul, Korea
E: isprm2007@intercom.co.kr
W: www.isprm2007.org

Workshop: Prediction of Outcome

15-16 June, 2007; Erlangen, Germany
Prof. Dr. Hermann Stefan
E. Hermann.stefan@neuro.imed.uni-erlangen.de

17th Meeting of the European Neurological Society

16-20 June, 2007; Rhodes, Greece
W: www.ensinfo.com
T. +41 61 686 77 11
F. +41 61 686 77 88
E. info@akm.ch

Advances in Neurorehabilitation Part of The Festival of International Conferences on Caregiving, Disability, Aging and Technology (FICCDAT)

16-19 June, 2007; Toronto, Canada
E. catherine@smartmove.ca
W. www.ficdat.ca

International Society for Stem Cell Research Meeting

17 -22 June, 2007; Cairns
International Society for Stem Cell Research
T. +847-509-1944
F. +F: 847-480-9282
E. isscr@isscr.org

2nd Neurorehabilitation Panamerican Congress

18-20 June, 2007; Buenos Aires, Argentina
E. dfelder@ineba.net
W. www.ineba.net

Canadian Neurological Sciences Federation (CNSF) 42nd Annual Scientific Meeting

19-22 June, 2007; Alberta, Canada
W. www.ccnsc.org

Joint Meeting of WFNR and EMN

22-24 June, 2007; Fiuggi, Italy
E. fservade@ausl-cesena.emr.it
W. www.emn.cc

ISVR Balance Beginners Course

25-27 June, 2007; Southampton, UK
Lyndsay Oliver
T. 023 8059 2287
E. lo@isvr.soton.ac.uk

July**27th International Epilepsy Congress**

8-12 July, 2007; Singapore
T. +353 1 205 6720
F. +353 1 205 6156
E. Singapore@epilepsycongress.org
W. www.epilepsycongress2007.com

7th IBRO World Congress of Neuroscience

12-17 July, 2007; Melbourne, Australia
W. www.ans.org.au/anshome.htm

August**Eureka Distance learning course on Genetics of epilepsy (III.) (Autumn 2006 to Spring 2007)**

15 August, 2007; Application Deadline
Verena Hézser-v. Wehrs
T. +49 521 144 - 4310
F. +49 521 144 - 4311
E. office@epilepsy-academy.org
W. www.epilepsy-academy.org

Baltic Sea Summer School on Epilepsy

19-23 August, 2007; Lithuania
W. www.epilepsy-academy.org
E. ruta.mameniskiene@yahoo.com

11th Congress of the European Federation of Neurological Societies

25-28 August, 2007; Brussels, Belgium
T. +43 1 889 05 03
F. +43 1 889 05 03 13
E. headoffice@efns.org

September**World Federation of Sleep Research Societies World Congress**

1-8 September, 2007; Cairns, Australia
W. www.icmsaust.com.au/wfsrs2007

3rd World Congress on Huntington Disease followed by the Congress of the International Huntington Association

8-12 September, 2007; Dresden, Germany
W. www.huntington-disease.org

NEUROTOX '07 In association with The Royal Entomological Society

9-13 September, 2007; Portsmouth, UK
Nicole Honeyghan
T. +44 (0) 20 7598 1566
F. +44 (0) 20 7235 7743
E. nicole.honeyghan@soci.org

British Aphasiology Society Biennial International Conference

10-12 September, 2007; Edinburgh, UK
E. info@stroke.org.uk

Congress of Neurological Surgeons Annual Meeting

15-20 September, 2007; San Diego, USA.
Congress of Neurological Surgeons
T. +847 240 2500
F. +847 240 0804
E. info@CNS.org
W. www.neurosurgcongress.org

4th World Congress of the World Institute of Pain

25-28 September, 2007; Budapest, Hungary.
W. www.kenes.com/wip

2nd International Conference: Looking Ahead: Innovations in Brain Injury Rehabilitation

26 - 27 September, 2007; Leeds, UK
Frances Pitwell
T. 01924 89610
E. director@birt.co.uk

October**ABN Joint Meeting with Indian Academy of Neurology**

4-7 October, 2007; Mumbai, India
Info: info@theabn.org

132nd Annual Meeting of the American Neurological Association

7-10 October, 2007; Washington DC, USA
W. www.aneuroa.org
E. lorijanderson@msn.com

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

10-12 October, 2007; Southampton
W. www.conference2k.com

4th ISPRM World Congress, Seoul, Korea

8-12, October 2007; Seoul, Korea

E. traceymole@wfnr.co.uk

Parkinson's Disease Foundation's 50th Anniversary Conference: Frontiers of Science & Clinical Concerns in Parkinson's Disease

11-12 October, 2007; New York, NY, USA
W. www.pdf.org

International Psychogeriatric Association 13th Congress

14-19 October, 2007; Osaka, Japan
E. ipa@ipa-online.org

AAANEM Annual Scientific Meetings

17-20 October, 2007; Phoenix, Arizona, USA
AAANEM
T. + (507) 288-0100
F. + (507) 288-1225
E. aanem@aanem.org

November**5th International Congress on Vascular Dementia**

8-11 November, 2007; Budapest, Hungary
W. www.kenes.com/vascular

ABN Joint Meeting with Norwegian Neurological Society

14-16 November, 2007; London, UK
E. info@theabn.org

June 16-20, 2007 – Rhodes/Greece

A yellow starburst graphic with a white outline, consisting of multiple points radiating from a central point.

Neurologists in training offer Deadline January 18, 2007

Young neurologists programme 2007

Following the great demand in 2006, ENS is pleased to offer once again a limited number of grants providing free accommodation from Saturday to Wednesday, including registration and admission to teaching courses at the ENS 2007 meeting in Rhodes to European Neurologists in training, born on or after January 1, 1972. This programme is **not** dependent on submitting an abstract.

Applications should provide a letter from chairman of their department to certify that they are in training as well as a copy of their passport.

The applicants must also select the 3 courses they want to attend. Application is only available **online** at www.akm.ch/ens2007.

Attendance to courses is compulsory and no-shows will be excluded from this offer in the future and will be charged for their attendance.

Deadline for applications: **18 January 2007**. Applications without passport copy or arriving after this date will not be considered.

Good quality accommodation has been reserved this year and will be on a double room occupancy basis. We invite applicants to mention on their registration form the name of another young neurologist they would wish to share the room with.

For further information please check our regularly updated website: **www.ensinfo.com**

Please apply online on **www.ensinfo.com** – ENS 2007 the online application will be available from October onwards.

Separately to this offer, young colleagues who have an abstract accepted for presentation at the ENS meeting may also apply for a travel grant. Please see further details on the congress website.

Visit the ENS 2007 website featuring:

- Continuously updated scientific programme
- **Online abstract submission (deadline February 7, 2007)**
- Online registration as well as hotel & tour reservations
- Option to compose your personal congress programme
- Details about the industrial exhibition
- Information on the congress venue and the island of Rhodes

For further information please contact:

Administrative Secretariat: 17th ENS 2007, c/o AKM Congress Service
P.O. Box, CH-4005 Basel / Switzerland

Phone +41 61 686 77 11 Fax +41 61 686 77 88 E-mail info@akm.ch

www.ensinfo.com

ENCEPHALITIS SOCIETY



Professional Seminar

Neurosupport Centre, Liverpool

Tuesday 16 January 2007 1pm – 7pm

Keynote speakers

Professor Barbara A Wilson OBE and Professor Michael Kopelman

Presentations will include an update of contemporary treatment and research in Acquired Brain Injury and Encephalitis. The programme will conclude with a networking event over wine and canapés, and a piece of theatre exploring the scientific and personal perspectives of Acquired Brain Injury.

There is a charge of £35 for the event, please email elaine@encephalitis.info for a programme and booking form.

Encephalitis Society, 7B Saville Street, MALTON, North Yorkshire, YO17 7LL
Phone: 01653 692 583 • Fax: 01653 604 369
Email: mail@encephalitis.info • Website: www.encephalitis.info



The Royal College of Surgeons of England

Intracranial and Spinal Anatomy for Neurosurgeons

19-23 February 2007

Convenors: Mr Francis Johnston (Neurological Anatomy), Consultant Neurosurgeon, Atkinson Morley's Hospital, London
Dr Paul Butler, Consultant Neuroradiologist, The Royal London Hospital, London
Mr Ian Sabin, Consultant Neurosurgeon, The Royal London Hospital, London

Aimed at	• HSTs in neurosurgery
Content	• Five days of pure and applied neuroanatomy comprising three modules that can be taken separately or together.
Programme	• Neurological Anatomy 19 February - 21 February 2006 A hands-on cadaveric dissection and lecture bases course on the neuroanatomy of the brain and spinal cord with emphasis on tract and vascular anatomy. • Neuroradiology 22 February 2006 Lectures and tutorials covering radiological anatomy of the brain and spine illustrated by MR and CT scans demonstrating a range of pathological processes • Approaches for Intracranial Surgery 23 February 2006 A lecture and demonstration course, with cadaveric dissections, reinforcing anatomical knowledge and covering eight common neurosurgical approaches using prosected cadaveric specimens
Fees:	£1050 Neurological Anatomy £325 Neuroradiology £400 Approaches for Intracranial Surgery - 20 places £1390...SPECIAL PRICE FOR WEEK

For further details please contact us on:
Neurosurgery Administrator
Raven Department of Education
The Royal College of Surgeons of England
35-43 Lincoln's Inn Fields, London, WC2A 3PE
T: 020 7869 6332
F: 020 7869 6329
E: neurosurgery@rcseng.ac.uk

The 3rd Annual Update Symposium on

Clinical Neurology and Neurophysiology

February 19-21, 2007
Tel Aviv, Israel

Secretariat: ISAS International Seminars
PO Box 574, Jerusalem, Israel
Tel: 972-2-6520574, Fax: 972-2-6520558
Email: meetings@isas.co.il

Sessions on:

- Parkinson's Disease
- Chronic Pain and Headache
- CNS Neoplasms

Workshops on:

Localized Treatment of Pain
Botulinum Toxin Injection

Deadline for Abstracts: November 15, 2006

<http://www.neurophysiology-symposium.com>



First London Colloquium on Status Epilepticus

Registration is invited for this conference and post-conference workshop, to be held in London on April 12-15 2007. Attendance is open to any clinician or scientist. Details of the conference and registration are available on: www.conference2k.com/statusconf.asp.

The colloquium will be a landmark meeting in the field of status epilepticus, following in direct lineage the Marseilles Colloquium held in 1962, and the two Santa Monica meetings on this topic held in 1980 and 1997. The colloquium is the first of two planned meetings, the second of which will be held in Innsbruck in 2009.

The purpose of the conference is:

- To summarise current knowledge in key clinical and basic science areas
- To define optimal clinical practice
- To debate controversial issues
- To point to future clinical and scientific research areas

The faculty members are major clinical and scientific figures in the field of status epilepticus from around the world, and a global perspective is being taken.

The programme is divided into three sections:

- Molecular nature of status epilepticus
- Clinical aspects of status epilepticus
- Outcomes of status epilepticus

Poster presentations are invited from any registrant (details and application forms are available on www.conference2k.com/statusconf.asp). Applications can be submitted on any clinical or scientific subject in the field of status epilepticus. The closing date for submission is December 31st 2006.

The post-conference workshop is open to clinicians from European ILAE chapters. The purpose of the workshop is to establish recommendations for the treatment of status epilepticus in Europe.

Registration is now open and is restricted to 250 persons, so please register quickly to avoid disappointment. In addition an attractive social programme is offered.

The conference is being held under the patronage of the ILAE Commission on European Affairs, the ILAE Commission on Therapeutic Strategies, the British and Austrian national ILAE chapters, University College London (Institutes of Neurology and Child Health) and the Medical University Innsbruck.

This meeting is supported by the ILAE Commission on European Affairs and by an educational grant from UCB

Further information from Denise Hickman, Director, Conference 2k, Capstan House, Western Road, Pevensey Bay, East Sussex, BN24 6HG
email: denise@conference2k.com • Tel: 01323 740612/01691 650290 • Fax: 01691 670302

11th CONGRESS OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

BRUSSELS, BELGIUM, AUGUST 25-28, 2007



President of EFNS Management Committee: **Jacques L. De Reuck**, Belgium
Chairperson of the Congress Programme Committee: **Gian Luigi Lenzi**, Italy
Chairperson of the Local Arrangements Committee: **Jean Schoenen**, Belgium

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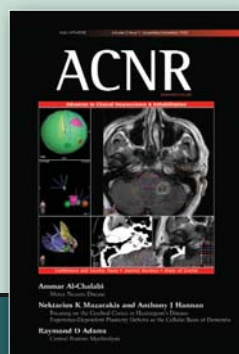


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EDITOR'S CHOICE

MULTIPLE SCLEROSIS: Is BENEFIT of any benefit?

Is there any point to taking interferon-beta from the very first episode of demyelination, before a diagnosis of multiple sclerosis can be made? An important question but sadly, three trials later, the answer is... "maybe not, but not sure." An ideal group to test this question on are those people who present with a clinically isolated demyelinating syndrome and have three or more lesions on MRI: the Queen Square group has shown that, fourteen years later, nearly 90% of these will have developed MS, in contrast to less than 20% of those with normal scans (Brex PA. *NEJM* 2002;346:158). The BENEFIT trial, reported recently in *Neurology* has treated just that group with placebo or Betaferon, a 'me-too' study to follow that of Avonex (CHAMPS. *NEJM* 2000;34:898) and Rebif (Comi G. *Lancet* 2001;357:1576). The bottom line is that over two or three years, interferon reduces the proportion of people developing a second attack of demyelination, and thus converting to MS, by about one third (placebo arm conversion rates: CHAMPS 0.50, ETOMS 0.45, BENEFIT 0.45 versus treated arms: CHAMPS 0.35, ETOMS 0.34, BENEFIT 0.28). A similar effect size was seen in the BENEFIT trial on those diagnosed as having MS by the more sensitive 'McDonald criteria', in which new MRI lesions can substitute for a second clinical episode (0.85 versus 0.69). All very good. The key question, though, is does treatment with interferon-beta reduce the accumulation of disability? Extraordinarily, this data is deliberately omitted, despite having been collected, from the BENEFIT and the original CHAMPS papers. Forgive a cynical question, but would the data have gone unreported if it had been positive? In ETOMS, where the investigators were more open, interferon-beta had no significant effect on the accumulation of disability. And a similar lack of effect on disability was seen in the 5 year open-label extension study of the CHAMPS cohort (Kinkel RP. *Neurology* 2006; 66:678). (A similar 5-year extension study of the BENEFIT trial is planned.) This is not to say that interferon treatment of the clinically isolated syndrome is useless in the long-term. But it may be. And the current lack of rigour in editorial offices like *Neurology*, where trials like BENEFIT can be published with the most important data omitted, is not going to encourage sponsoring companies to bite the bullet and design big and long enough trials to answer the questions that patients ask. -AJC

Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Bauer L, Jakobs P, Pohl C, Sandbrink R. *Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes.*

NEUROLOGY
2006;10;67(7):1242-9.

ADULT NEUROGENESIS: Is my brain growing larger?

There is no doubt that neurogenesis takes place in the adult brain, including in humans, at least in the dentate gyrus of the hippocampus and the subventricular zone, although its significance and importance to normal behaviour is debated. Of late one area of great contention has been whether neurogenesis takes place at other sites in the adult human brain, including the cerebral cortex, with conflicting experimental data between rodents and non-human primates. In a recent paper in *PNAS*, this issue has been investigated in a cunning way using two different strategies in separate groups of individuals. One builds on an earlier BrdU study in patients with neck and head malignancies and the others relates to the testing of nuclear bombs 40+ years ago! In the first approach patients with certain types of non-CNS malignancy were given BrdU as part of their management. At death, four months to four years later, the number of BrdU positive cells which were labelled with NeuN (a neuronal marker) within the cortex were counted, in the same way as had been done previously for the hippocampus (Ericsson PS et al *Nature Med* 1998;4:1313-17). The result was clearcut - there were none. In the second approach, five individual brains were examined to ascertain the birth date of cortical neurones using ¹⁴C incorporated into DNA. This strategy relied on the facts that between 1955 and 1963 there was greatly increased levels of ¹⁴CO₂ in the atmosphere because of above-ground nuclear bomb testing, and that this would be incorporated into plants and then through the food chain into dividing cells. They then analysed post mortem cortical DNA through a process of accelerator mass spectrometry and compared its expression in

NeuN (neuronal and non NeuN populations of cells) and found that essentially all cortical neurons were born by birth and did not arise during adulthood. Thus these two approaches show that no new neurons are generated in adulthood in the normal human neocortex, although it should be stressed that new cells were seen but they were not neurons. Furthermore, it is unclear whether this is also true for the damaged and degenerating cortex. Thus whilst these elegant experiments seem to have laid to rest one bone of contention in the field of adult neurogenesis it does not mean that adult neurogenesis is not possible in the cortex under some circumstances which could be of reparative significance. - RAB

Bhardwaj RD, Curtis MA, Spalding KL et al.

Neocortical neurogenesis in humans is restricted to development.
PROCEEDINGS OF THE NATURAL ACADEMY OF SCIENCES
2006;103(33):12564-8.

HEADACHE: Cluster headache presentation

Cluster headache remains underdiagnosed and undertreated. This paper examined clinical features of cluster headache, as defined by International Headache Society criteria, between April 2002 to March 2004. 257 patients were recruited prospectively from the Headache Clinic at the University Hospital in Essen in Germany, as well as nation-wide from self-help groups, and internet advertising on a clinic webpage. This design was both the strength and weakness of the study. It allowed a pragmatic study of the differences between patients seen in a super-specialised setting and those in a general population. The weakness of course was failure to define the overall population, negating any estimation of prevalence; and the introduction of a selection bias in those self-referred. The study confirmed the typical features of cluster headache, but there were features usually associated with migraine in many (nausea and vomiting in 27.8%, photophobia and phonophobia in 61.2%), sometimes confusing the diagnosis. A considerable number of patients (17.8-59.8%) had used acute and prophylactic medications, such as opioids, with no proven efficacy in cluster headache. Neurologists in the United Kingdom face a huge challenge to work to improve triaging and management of common neurological conditions in primary care (hopefully allowing us to focus more at the acute end of neurology where our impact is potentially greatest). This study highlights one area where there is scope for improved education, diagnosis and management of headache patients by all treating doctors. - HAL

Schurks M, Kurth T, de Jesus J, Jonjic M, Roskopf D, Diener H-C.

Cluster headache: clinical presentation, lifestyle features, and medical treatment.

HEADACHE
2006;46:1246-54.

HEAD INJURY: holds out in the long-term

When Charles Warlow received his Gold Medal from the ABN, he gave a lecture which emphasised the value of long-term studies of neurological conditions. A title in a recent *JNNP* paper would have pleased him: a 16 year follow-up of head injury from Swansea. The basic issue was: do people with head injury have accelerated decline in cognition as they get older? And the headline result was: no. There was no real difference between psychometric scores at 16 (10-32) years compared to 1 year (1 week to 5 years) after a head injury. So far so good. The small print throws up some wobbles though. Firstly, from a pool of 351 cases with an initial assessment, only 133 replied to the letter inviting them to take part in the research, of whom only 74 (24%) were eventually studied. It is very likely that those omitted from this small cohort would be over-represented by people whose cognition had deteriorated in the long-term. And secondly, only 15/74 patients had their initial assessment at least two years from the injury. For the others, it remains possible that their cognition improved in the medium term, and then declined. - AJC

Wood RL, Rutterford NA.

Long-term effect of head trauma on intellectual abilities: a 16-year outcome study.

J NEUROL NEUROSURG PSYCHIATRY
2006;77(10):1180-4.

HEADACHE: Three cases of nummular headache

This article describes three patients with a distinct primary headache, previously proposed in 2002 by Pajera as a separate entity. The headache is mild to moderate, chronic with exacerbations, and crucially, in a circumscribed rounded or elliptical area of 2-6cm. The area of pain is not tender and sensation is normal. One patient had a minor head injury three months prior, one patient had some migrainous features with the headache, none had struc-

tural lesions. The headache was chronic, often present for decades. The authors propose that these headaches do not fit in with any other headache category and that the term nummular headache is useful. None of the treatments tried were successful. It is always helpful to provide patients with an accurate diagnostic label, and the curious headache distribution is very distinctive. This report is likely to increase awareness of this headache type, and having seen people who have described this curious shape, I will be on the lookout. If SUNCT is anything to go by, it is likely that over time, successful treatments will be reported. - *HAL*

Dach F, Speciali J, Eckeli A, Rodrigues GG, Bordini CA.

Nummular headache: three new cases.

CEPHALALGIA

2006;26:1234-7.

STROKE: Living with mental slowness

Stroke has many physical and cognitive effects and as clinicians we can predict fairly well how poor mobility or hand function will affect a person's independence in self care or social participation. Similarly we can guess how cognitive impairments such as memory, language or unilateral inattention will impinge on function. However we are inclined to compartmentalise the effects and this leads to a rather narrow forecast of how people will cope in daily life. There is a tendency to forget that difficulties in one area of function can impinge on other functions, for example if a task is slightly difficult adding the load of another simultaneous task requiring more attention can lead to impoverished performance of both. Some studies have measured reduced performance in dual task scenarios such as walking and doing simple calculations, others have picked up on a general mental slowness evident from prolonged reaction times; however studies exploring the real world consequences of mental slowness have been rare. Now a group in the Netherlands have reported the results of a study in which patients with stroke who suffer from mental slowness were interviewed about its effect on their lives. The patients were interviewed serially until saturation of the data was reached. In total thirteen patients were interviewed and the group comprised of a mixture of hemispheres affected, types of stroke, ages, genders, times since stroke and education. Most of the sample complained that they weren't able to process information quickly enough or adequately. For example they found it difficult to follow conversation on the phone or in meetings or even when listening to the radio. They complained of problems in decision making. Storing and retrieving information from memory required more time and effort than before their stroke. All the participants reported problems in dividing attention and many were easily distracted and could no longer perform tasks automatically. These problems all increase difficulty in everyday life and many of the patients reported psychological or somatic complaints as a result. For example, they reported feeling agitated, tired, dizzy or having headaches. The study also shed light on the strategies that the patients use to compensate for their mental slowness. They either avoided or withdrew from difficult situations or they tried to control their activities, for example by doing things in a quiet environment or preparing for events ahead of time. Of course some of these complaints may have been due to depression or more introspection following stroke, but this study paves the way for the development of new tools for measuring mental slowness after stroke and highlights the need for continuing rehabilitation to try to improve people's mental acuity after stroke. Brain speed training exercises are available on games players and PC now. Perhaps these might be useful for continuing rehabilitation at home. - *AT*

Winkens I, van Heugten CM, Fasotti L, Duits A, Wade DT.

Manifestations of mental slowness in the daily life of patients with stroke: a qualitative study.

CLINICAL REHABILITATION

2006;20:827-34.

MULTIPLE SCLEROSIS: Nose and IL-10 required

David Wraith, an immunologist in Bristol, spends a great deal of time thinking about antigen-specific therapies for autoimmune and allergic disease. He has shown that it is possible to re-educate the immune system not to attack the brain in an animal model of cerebral autoimmunity, Experimental Allergic Encephalomyelitis (EAE). He does this by administering a key peptide from the CNS myelin molecule, myelin oligodendrocyte protein, intranasally. For good reasons, but by unclear mechanisms, the immune system becomes tolerant to peptides administered to a mucosal surface, either nasally or orally. This observation led to a North American trial of eating bovine myelin basic protein (thankfully not sourced from UK cattle!) as a treatment of multiple sclerosis. It did not work. But there is still some hope that the nasal route will be more effective. In this study Wraith's group attempted to

induce tolerance to EAE with nasal peptide in mice knocked out for the IL-10 cytokine. They could not. The fact that nasal tolerance requires IL-10 is provocative for it is this cytokine that is key to a group of regulatory T cells, called Tr1 cells, which are found in humans as well as mice. The nose may well be the answer to multiple sclerosis. First, the nose could be inoculated to induce nasal tolerance and suppress disease activity... And then nose-derived ensheathing cells could be used to repair areas of demyelination (Barnett S. Brain 2000; 123: 1581)! - *AJC*

O'Neill EJ, Day MJ, Wraith DC.

IL-10 is essential for disease protection following intranasal peptide administration in the C57BL/6 model of EAE.

J NEUROIMMUNOL

2006;178(1-2):1-8.

EPILEPSY: How bad is epilepsy?

From 1981-2001, 890 patients were seen at the Western General Hospital in Edinburgh with newly diagnosed epilepsy. Over the same period 2,689 patients were referred with uncontrolled epilepsy from elsewhere. Mortality was calculated in relation to actuarial risk as defined by UK government data for each individual and the predicted and actual survivals were plotted on Kaplan-Meier curves. Causes of death including post-mortem confirmed SUDEP and unconfirmed (probable SUDEP) were analysed. In the newly diagnosed cohort, about half achieved seizure-freedom for at least one year and about a third were refractory. The mortality rate in this group was 10.4%, significantly higher than the expected 7.4%, giving an SMR of 1.42. In the refractory group the SMR was 2.54. There was no increase in mortality amongst those patients who entered remission. Amongst those patients with chronic epilepsy the crude death rate was 11.7% with an expected mortality of 5.7%. Symptomatic epilepsy did worse than other groups but idiopathic epilepsy was no worse than expected for an age-matched population. In the newly diagnosed group the SMR was higher than expected for self-harm, respiratory disorders and accidents. In the chronic group, deaths due to SUDEP, status epilepticus, accidents, suicide and cerebrovascular disease were also increased. Probable SUDEP affected seven patients (1.08 per 1000 patient years) and six of these were in patients who did not respond to treatment. In the chronic cohort there were 55 probable SUDEP deaths (2.46 per 1000 patient years). This study supports data that has been published previously. It has the usual flaws of not being population-based or prospective but is valuable nevertheless. It relates to the patients we all see in our clinics (except mine eat fewer deep-fried Mars bars) and enables us to give them information on their prognosis. Some of this is moderately reassuring; SUDEP rates were about half the figure of 0.5% annually, which is widely quoted for a refractory group and even better for a newly diagnosed group. Some we can try to prevent, by identifying and treating depression early and by being more fastidious in dispensing advice about avoiding accidents. The data are also very reassuring for those young patients with idiopathic generalised epilepsy. - *MRAM*

Mohanraj R, Norrie J, Stephen LJ, Hitiris N, Brodie MJ.

Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study.

LANCET NEUROL

2006;5:481-7.

HEADACHE: Does acupuncture work?

Acupuncture has a number of potential advantages as a treatment of migraine and other headaches, including the perception that it is 'natural', acceptability to many patients who do not like to take tablets, and no interactions with medications. This small study examined the response of 28 patients randomised to actual or sham acupuncture, and treated with 16 sessions in 12 weeks. There was no difference in the response rate between the two groups in terms of headache reduction and associated symptoms. This is a well designed study, but it is unfortunate that the numbers are small. A larger study along the same lines could resolve the doubts left after the Cochrane review of acupuncture for idiopathic headache (last updated in 2001). This concluded that existing evidence supports the value of acupuncture for idiopathic headache, but that the quality and amount of evidence was not fully convincing. Unfortunately the need for a large-scale study to assess the effectiveness of acupuncture for migraine and other headache remains. - *HAL*

Alecrim-Andrade J, Maciel-Junior JA, Cladellas XC, Correa-Filho HR, Machado HC.

Acupuncture in migraine prophylaxis: a randomized, sham-controlled trial.

CEPHALALGIA

2006;26:520-9.

Head Injury, Pathophysiology and Management - Second Edition

Reilly and Bullock, doyens in the field of neurotraumatology, have compiled a substantially revised second edition of this textbook. The book is divided into three sections, with contributions from many authors, mainly from the United States of America, the UK and Australia. The chapters are of a consistently high quality.

Section 1 comprises six chapters, detailing our current understanding of the pathophysiology of head injury. The colour neuropathology plates, illustrating macroscopic and microscopic changes are outstanding, making this chapter readily accessible. Overall, this section of the book provides a well-referenced background in neurotraumatology.

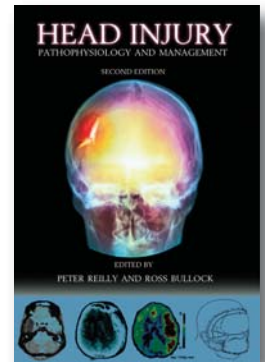
In Section 2, the clinical grading systems are evaluated with clarity. The chapter describing the imaging of head injury contains over one hundred scans, which illustrate the numerous radiological consequences of traumatic brain injury. The description of bedside monitoring techniques from the Cambridge team is clear and comprehensive.

The remaining eleven chapters in the book describe the treatment of patients with traumatic brain injury. These chapters are scribed with attention to the link between basic science and clinical application. Where available,

published evidence is critically appraised. The pharmacological section on frequently used drugs, such as mannitol, frusemide, barbiturates and hypertonic saline is particularly useful. Less widely used protocols such as the Lund system are discussed. The descriptions of surgical techniques are clear. In particular the chapter on ballistics is elegantly illustrated. Andrew Maas has compiled a well-referenced chapter, which reviews neuro-protective strategies in considerable detail. Brian Jennett's authoritative account of the outcome after severe head injury is a gem. Delayed complications, including epilepsy and psychological sequelae are covered.

In summary, I recommend this book to all neurosurgical and neuro-intensivist trainees. In addition, others working in the field including rehabilitation will find a wealth of useful background and clinical information to guide practice. The editors are to be commended on producing a fine volume.

*Peter C Whitfield, Consultant Neurosurgeon and
Honorary University Fellow, South West Neurosurgery
Centre, Plymouth, UK.*



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Ross Bullock
Published by: Hodder Arnold
2005
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Price: £155.00

Asperger's Syndrome and High Achievement: Some Very Remarkable People

Different like me. My book of autism heroes

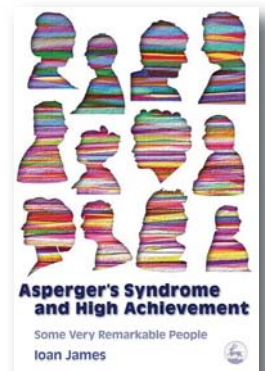
These two books tackle similar subject matter, but with different prospective audiences. Ioan James is a mathematician who has previously published books on remarkable mathematicians and physicists. Now he tackles the topical subject of Asperger's syndrome (AS), assembling twenty 'possibles' (M:F = 18:2) dating from the 16th to the 20th century, a task in which he has been encouraged by such experts as Uta Frith and Simon Baron-Cohen. The book is a series of brief vignettes, emphasizing the Asperger-like features of each individual, rounded off with a concluding chapter synthesizing the various key features of AS: social impairments, all-absorbing narrow interests, repetitive routines, speech and language peculiarities, problems of non-verbal communication, and motor clumsiness (which of us could not lay claim to some of these?). The book subscribes to what might be called the William Hague approach, following his biography of William Pitt, namely drawing on others' accounts of each subject to produce a narrative, without indulging in the tedium of consulting primary sources or doing original research.

It is a highly readable text, not least of course because the chosen characters are of great interest, including composers and musicians (Satie, Bartok, Gould), authors (Swift, Highsmith), artists (Michelangelo, van Gogh, Warhol) and scientists (Newton, Einstein, Bertrand Russell, Turing). Since AS is a disorder with, to my knowledge, no biomarkers, I would have liked more on differential diagnosis: the possibility of personality disorder is mentioned for Ramanujan (p125) and Wittgenstein (p133), and this has also been suggested for van Gogh although not mentioned here, but the possibility of obsessive compulsive disorder is not raised. This may simply reflect the author's lack of clinical training. A few typographical errors intrude: 'Alfred' Einstein (p12) alarmed me a little, and only a mathematician could miscalculate van Gogh's age at death as 47 (p 86) rather than 37!

Jennifer Elder's book is aimed at children between 8-12 years of age. Like James, she has 20 who 'don't fit in' (M:F = 15:5), and there is some overlap (Einstein, Warhol, Turing, Newton, Gould). These are one-page, thumbnail, sketches with no medical jargon. I don't know if this catalogue will build self-esteem in children who are different, but I wish it every success.

More serious, for me, is the unquestioned notion, in both these works, of the autistic spectrum itself. Is it possible that this nomenclature serves to medicalize, or pathologize, a variant of human personality which is normally distributed in the population? Could one not posit a personality type – let us call it 'hetero-ism' – characterised by the converse features? 'Sufferers' have highly developed social skills, 'team workers' who are good at motivating other people to work for them, able in claiming credit when things go well and apportioning blame to others when not; they have broad but passing interests, with a tendency to flit from one to another, but nonetheless are vocative and willing to express opinions, often forcefully, however little knowledge they actually have, opinions which they can alter dramatically dependent upon the needs of the situation; they have excessive interest in other people's business, to the point of presumption in knowing others' mind states ('hypermentalising?'), reflective of a general lack of mental resources for solitude; and lack of routine or punctuality. Could one not then identify twenty famous people in whom these features were evident: probably business types, entrepreneurs, managers, artists (actors, singers); many with some of these features but not achieving renown (hospital managers, perhaps?); and some in whom such traits are so extreme as to be dysfunctional, such that their lives are so chaotic that they cannot operate effectively in society, and hence attract medical/social input?

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



Author: I James
Published by:
Jessica Kingsley 2006
ISBN: 1-84310-388-5
Price: £13.99



Author: J Elder
Published by:
Jessica Kingsley 2005
ISBN: 1-84310-815-1
Price: \$16.95

1. Van Meekeren E. *Starry starry night. Life and psychiatric history of Vincent van Gogh.* Amsterdam: Benecke 2003.

Brain Injury & Returning to Employment - A Guide for Practitioners

The author, who is well known in the field of vocational rehabilitation, has written a well laid out book with clear objectives. These are to 'provide an overview of the cognitive and psychological issues associated with brain injury and return to work' and this is achieved. It aims to offer occupational techniques to address cognitive and psychological barriers to work, and addresses these in a limited fashion by providing basic information on these. The target audience is broad and includes employment related professionals working with this client group and therein lays the reason why the book might not provide the depth of information required for any one professional group.

The book offers a good emotive description of the issues surrounding brain injury and employment, which makes for easy reading. The author presents complex information on cognition in easily digestible chunks without being patronising. The chapters on vocational assessment and vocational rehabilitation are educative. However it understates/separates the physical aspects of brain injury, the practical aspects of returning to work, the rights of the client, and duties of the employer, all of which affect return

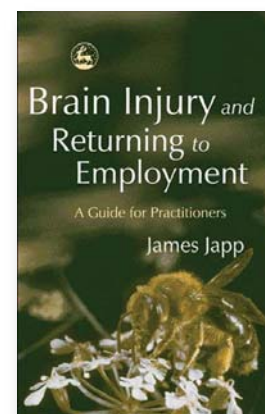
to employment. The case studies are primarily descriptive, which is stated in the chapter introduction but to me present a missed chance to provide an interactive learning opportunity.

It would have been an opportunity to highlight ways various disciplines (target audience) could work together in returning a client to employment at various stages of the client's journey – acute, post acute/rehabilitative medical phase and late vocational/social phase.

So in summary, interesting emotive reading, a good, general source of information that raises awareness about the issues (particularly cognitive and psychological) surrounding brain injury but might disappoint if expecting a comprehensive guide to help practitioners return their clients to work.

It is a good starting point for vocational and rehabilitation professionals, especially if it generates further learning, keeping in mind the paucity of literature available in vocational rehabilitation.

*Maya DeSouza, Spinal Cord Injury Centre
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Author: James Japp
Published by: Jessica Kingsley Publishers
ISBN-10: 1-84310-292-7
Price: £15.95

Handbook on Cerebral Artery Dissection

This is Volume 20 of a series of "Frontiers of Neurology and Neuroscience" edited by Dr Bougousslavsky. It is an excellent little book on cerebral artery dissections and I would recommend it not only to neurologists with an interest in vascular disease and stroke physicians, but also any neurologist seeing acute neurology.

Cerebral artery dissection has joined cerebral venous sinus thrombosis as a diagnosis that no longer remains the preserve of the neurologist. Twenty years ago it was thought to be rare and carry a poor prognosis, mainly because it was discovered late in very selected cases and/or at post-mortem. With increasing awareness and more advanced diagnostic technologies, the disease has become recognised far more often, and its spectrum is ever increasing. For a few years now, I have found clever-dick medical registrars suggesting the diagnosis in ward referrals, and most recently even spotty SHOs and house physicians have joined in. Whilst this may reflect local teaching success, it also may leave the neurologist a bit frustrated. However, physicians tend to get nervous about doing more than including it in their differential diagnosis, but some do start to investigate and treat it themselves. However, the unappreciated expanding clinical spectrum and pitfalls in investigation are rarely realised by the non-neurologist, and larger numbers of cases may not only be missed, but unfortunately no longer even referred for neurological opinion.

This is where this excellent little book comes into its own. It hopes to "contribute to efforts linking clinical and basic science", but I think its more practical value to neurologists is that it provides succinct and largely well written chapters on those aspects most important to the clinician. Herein lie the details which are way beyond the knowledge of physicians (at least at present). The epidemiology is dealt with by Schievink (excellent as always) and the many clinical manifestations are well set out. I will guarantee you will learn something new: the range of clinical symptoms and signs extends well beyond the classical descriptions, occurring in isolation or unusual combinations.

Of course none of these clinical features is specific to a dissection. It therefore follows that these lesions should enter the differential diagnosis in much of acute cranial neurology (and if you read the book, also that of the cervi-

cal cord and root!) and that confirmatory tests are required. The next few chapters discuss these in the form of ultrasound, MR studies, and CT and catheter angiography. Some of these can get a bit technical, but it is clear that a neurologist needs to have a reasonable understanding of them, particularly if the patient is being seen outwith a specialist neurosciences centre.

Subsequent chapters deal with prognosis and treatment, and it becomes strikingly clear that a randomised trial is required, which will obviously require multi-centre organisation. One may start in the UK shortly (see www.dissection.co.uk); British neurology should do this well.

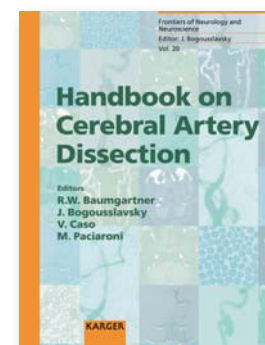
Intracranial arterial dissection is probably at the stage of knowledge where extra-cranial dissections were ten or fifteen years ago. One suspects that a similar evolution of knowledge will emerge in this subject, and Caplan's chapter is well worth a read. Much of the literature on this has been neurosurgical, but I suspect most intracranial dissections are missed unless they cause sub-arachnoid haemorrhage and that most neurologists seeing acute neurological patients should be considering this diagnosis more often in the future.

As for the science, there are chapters on connective tissue abnormalities found in skin biopsies, and the histological abnormalities within not only the dissected but systemic arteries in such patients, and these and the genetic approach have provided some insight into the question of why such lesions occur. These chapters are less easily digestible for the clinician, though even I managed to understand them. The undoubted influences of environmental factors, both non-traumatic and traumatic, are also well covered.

In general I can find little to fault the book. Of course there are the usual problems which may arise with multiple authorship and with some repetition between chapters, but I did not spot any major contradictions between them. The writing styles naturally vary between the excellent and the turgid, and the latter sometimes makes the reading an effort, particularly in the non-clinical parts. Nevertheless I think this is a book which contains what you need to know, in a brief and largely clear style, and I would recommend it.

Now, where is that spotty house physician.....?

TP Enevoldson, WCNN, Liverpool.



Editors: RW Baumgartner, J Bougousslavsky, V Caso, M Paciaroni
Publisher: Karger
ISBN-10: 3-8055-7986-1
Price: CHF 198.00

BENEFIT study shows Betaferon reduces risk of developing multiple sclerosis

Schering announced results from the subgroup analysis of the BENEFIT* study which showed that Betaferon® (interferon beta-1b) 250mcg treatment



reduced the risk of developing clinically definite MS (CDMS) consistently across all subgroups regardless of age, gender, steroid treatment or symptoms at onset of disease.

These data were part of the BENEFIT results, which showed that Betaferon 250mcg treatment reduced the risk of developing clinically definite MS (CDMS) by 50% compared with placebo. The BENEFIT trial tested patients presenting with one clinical episode suggestive of MS for a period of up to 24 months.

"In the BENEFIT study, we found that

Betaferon reduced the risk of developing MS consistently throughout the study population. Additionally, we found that certain patient subgroups had an even

better response to early treatment with Betaferon," said Dr. Chris Polman, Professor of Neurology, VU Medical Center, Amsterdam. Betaferon was very well accepted in the BENEFIT study, with 93% of patients completing the two-year study period. More than 95% of all patients completing the study have elected to continue with Betaferon as part of an open-label follow-up study.

For further information
Tel: +44 (0)845 609 6767,
Email: customer.care@schering.co.uk

Ipsen launches the access programme

Ipsen Ltd, the UK subsidiary of the Ipsen Group, has launched the access programme, a new, innovative and flexible medical education service. The key objectives of access are:

- to provide health professionals with 'access' to botulinum toxin training and clinical expertise
- to provide health professionals with 'access' to information resources and support for conditions where botulinum toxin is used
- to provide 'access' to information for people



with conditions that are treated with botulinum toxin. The access programme encompasses a portfolio of support services, blending existing resources with various new elements that will become available in the future, including training courses and education tools.

For further information about the access programme, please contact: access
Co-ordinator, Ipsen Ltd, 190 Bath Road, Slough, Berkshire SL1 3XE.
Email: access.coordinator@ipsen.com

Guideline to improve care of Parkinson's patients

The National Institute for Health and Clinical Excellence (NICE) and the National Collaborating Centre for Chronic Conditions based at the Royal College of Physicians have launched a guideline on the diagnosis and management of Parkinson's disease. Parkinson's disease is estimated to affect 100–180 people per 100,000 of the population.



Recommendations include:

- People with suspected Parkinson's disease should be referred quickly and untreated to a specialist.
- The diagnosis of Parkinson's disease should be reviewed regularly and reconsidered if atypical clinical features develop.
- People with Parkinson's disease should have access to specialist nursing care.

Dr Carl Clarke, Clinical Advisor on the Guideline Development Group, said, "The NICE guidance will help to ensure that all patients with Parkinson's disease are seen by an expert. It will also provide support for all patients and carers from Parkinson's Disease Nurse Specialists and allow better access to rehabilitation services. It will ensure that expert clinicians have access to the latest tests to diagnose Parkinson's disease, and all appropriate drugs."

Price £28.00 (UK) £30.00 (overseas)
ISBN 1860162835
To order your copy call 020 7935 1174 ext 358 or visit http://www.rcplondon.ac.uk/pubs/brochures/pub_print_PD.htm

New booklet about botulinum toxin and spasticity



'Helping you to understand spasticity and the role of botulinum toxin' is a new booklet available from Ipsen Limited, the UK subsidiary of the Ipsen Group, for people with spasticity who have been prescribed botulinum toxin.

The booklet has been produced to help the patient learn more about their condition and also to understand how botulinum toxin can help their spasticity. It addresses what spasticity is and how it is treated, the use of botulinum toxin, and provides a list of some of the organisations that can provide further help and support, such as Different Strokes, HemiHelp, Scope and the Stroke Association.

Botulinum toxin type A (Dysport®) is indicated for focal spasticity including the treatment of arm symptoms associated with focal spasticity in conjunction with physiotherapy, but only in hospital specialist centres with appropriately trained personnel.

Copies of the booklet can be obtained from: Medical Information Department, Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE. Tel: +44 (0)1753 627777, Email: medical.information.uk@ipsen.com

Living With Fatigue

The MS Trust has recently published a book to help people with MS who are affected by fatigue.



Fatigue is one of the commonest symptoms of MS and yet as an 'invisible' symptom, it is often misinterpreted or misunderstood by family, friends or colleagues. The book examines the many factors that can add to fatigue and provides practical ideas and suggestions to help people manage their own fatigue. 'Living With Fatigue' was written in conjunction with Michelle Ennis, an MS specialist occupational therapist, and is illustrated with comments by people with MS who know what it is like to live with fatigue.

Living With Fatigue is free. If you think this book would help any of your patients, they can order copies by sending their postal address to info@mstrust.org.uk or Tel: +44 (0)1462 476700.

BioStation IM combines incubator and inverted microscope in one compact bench-top unit

Nikon Instruments has launched a completely integrated 'hands-off' system for managing, observing and recording the growth of cells in culture. Biostation IM combines the precise environmental control capabilities of a high-performance CO2 incubator with the advanced optics needed for drift-free, live-cell imaging.

BioStation IM constantly maintains an optimum environment by avoiding fluctuations in temperature, humidity and gas concentration associated with the movement of cell cultures from an incubator to a microscope, which should improve the consistency of cell growth and reduce the variability of experimental data. Furthermore, the hands-off approach reduces the scope for contamination.



It has an optical system with a special anti-drift design that ensures images are always kept in sharp focus, enabling accurate time-lapse readings to be taken over a period of days.

Cultures can be imaged at both the macro and the micro 10x to 80x under phase contrast, using special lenses that provide the highest possible contrast with the least amount of 'halo'. It is also possible to observe the cells under epi-fluorescence illumination. Biostation IM comes in two versions with different lenses for work with plastic or thin bottom glass petri dishes. Viewing is via an integrated, digital camera, with images being made available via an external computer linked to the IM.

For more information contact
Nikon Instruments Europe:
Tel: +44 (0)208 247 1718,
Email: info@nikon-instruments.com
Web: www.nikon-instruments.com

What does freedom from seizures mean to you...?

The International Bureau for Epilepsy's Freedom in Mind Experience, supported by an education grant from UCB, encourages people with epilepsy to express what freedom from seizures would mean to them using pictures and to communicate their hopes and aspirations for a seizure-free



Epilepsy, said: "This graphically demonstrates

the impact of epileptic seizures on lives and gives a glimpse of how these lives would be transformed if their epilepsy was controlled"

Healthcare professionals are urged to encourage anyone with epilepsy to get involved and to consider their own hopes and feelings about epilepsy in a way they may not have explored before.
Further information and entry forms can be requested by emailing: info@freedominmind.com

Solutions for your every EEG and Sleep Lab needs...



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Compumedics Siesta Revolutionary Diagnostics for a Wireless World

Its revolutionary wireless data transmission will change the way you perform diagnostic testing. Its revolutionary size, flexibility and power make this universal data recorder a truly versatile system. Don't just imagine what you could do. It is reality with the Siesta system.



Compumedics ProFusion EEG 4 Next Generation Clinical LTM Software

Compumedics ProFusion EEG 4 is a true next generation clinical LTM software package that offers unprecedented ease of use in the EEG lab, and in post-recording analysis and review. Developed from the beginning in close consultation with EEG clinicians and neurologists it is an attractive and easy to use GUI designed to streamline all aspects of EEG work.

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ProFusion NeXus is designed to optimize the workflow of busy diagnostic and research laboratories. ProFusion NeXus is our core infrastructure and operates as a common interface for all for Compumedics' sleep and neurology clinical assessment software packages. ProFusion NeXus works to manage patients, data and decisions in the modern clinical diagnostic laboratory.

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AC335 Issue 1

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 metformin. Caution with alcohol/CNS depressants. **Pregnancy:** If benefits outweigh risks. Discuss possible effects/risks with patient. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 μ g oestrogen). **Lactation:** Avoid. **Side Effects:** Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diarrhoea, diplopia, dry mouth, dyspepsia, headache, hypoaesthesia, fatigue, mood problems, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary angle-closure glaucoma, reduced sweating (mainly in children), metabolic acidosis reported rarely. Suicidal ideation or attempts reported uncommonly. Bullous skin and mucosal reactions reported very rarely. **Pharmaceutical Precautions:** Tablets and Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed. **Legal Category:** [POM] **Package Quantities and Prices:** Bottles of 60 tablets. 25 mg (PL0242/0301) = £19.08, 50 mg (PL0242/0302) = £32.12; 100 mg (PL0242/0303) = £55.31; 200 mg (PL0242/0304) = £102.80. Containers of 60 capsules. 15 mg (PL0242/0348) = £15.70, 25 mg (PL0242/0349) = £23.55, 50 mg (PL0242/0350) = £35.57 **Product licence holder:** JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ UK. **Date of text revision:** 8th June 2006. **APIVER080606** **Date of preparation:** June 2006. **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. Adverse events should also be reported to Janssen-Cilag Ltd.