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Management Topic: Parkinsonism at a glance
Rehabilitation Article: Catastrophic Injuries - towards early intervention and rehabilitation

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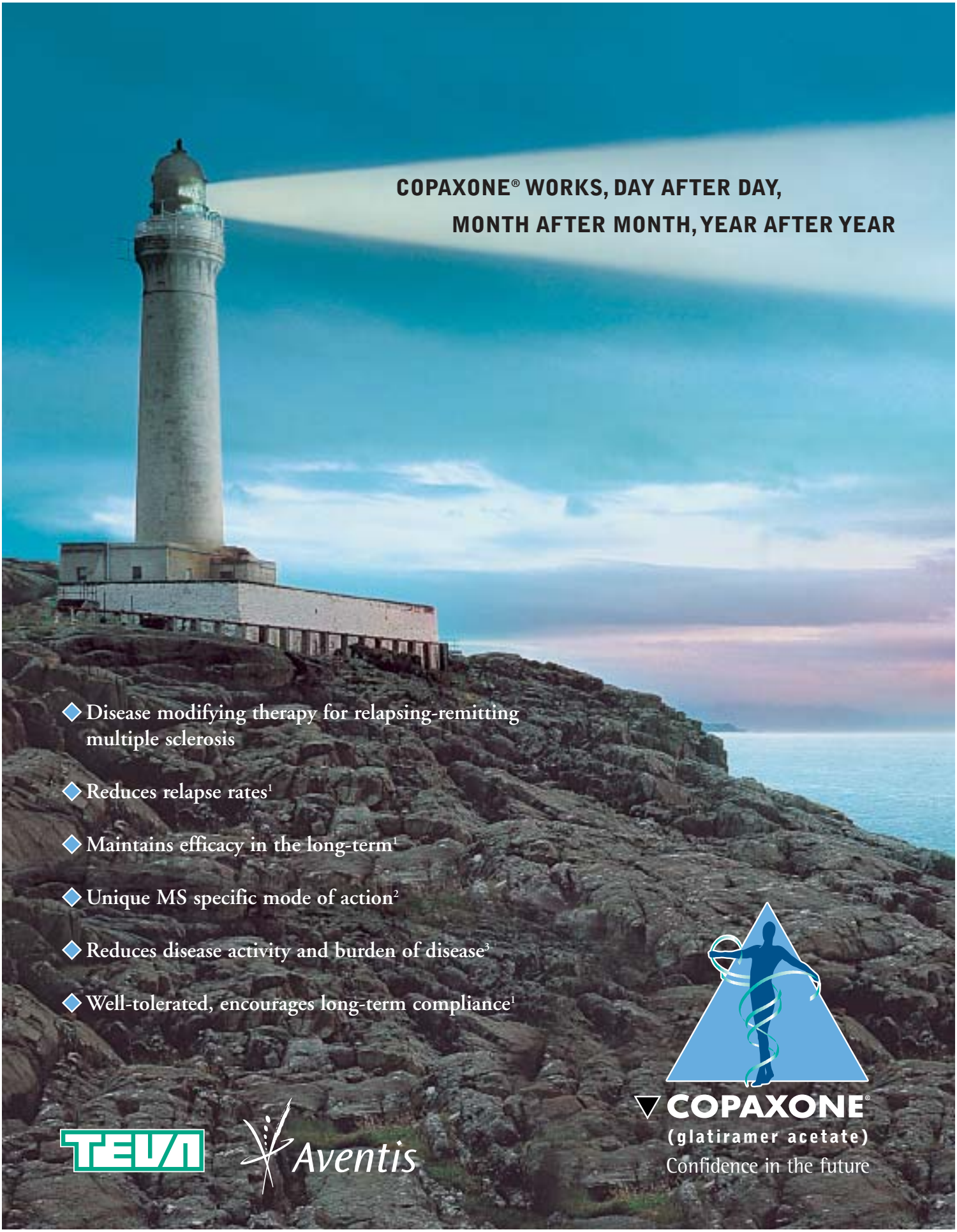

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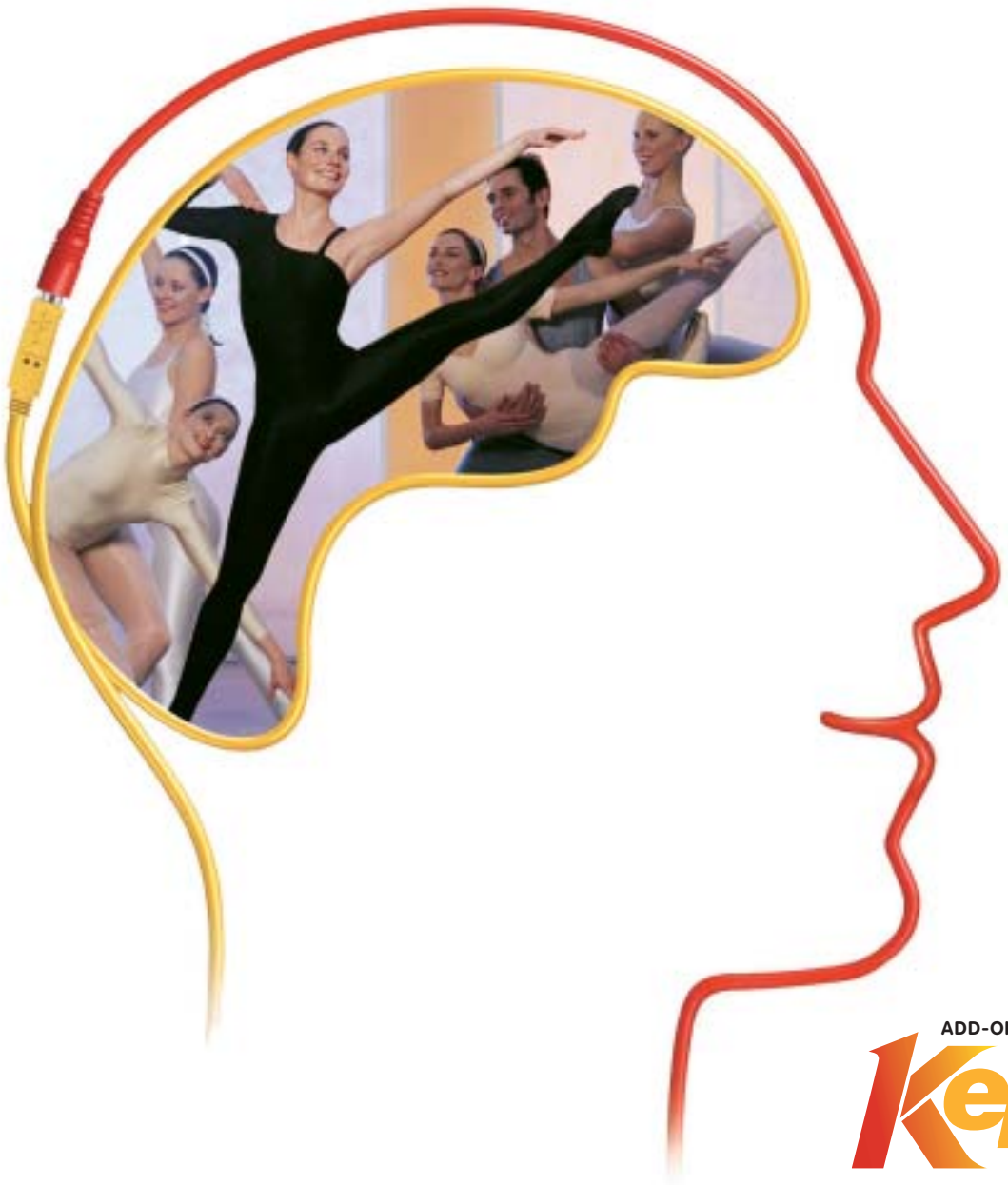
References:
1. Johnson KP *et al. Multiple Sclerosis* 2000; 6: 255-266.
2. Neuhaus O *et al. Neurology* 2001; 56: 702-708.
3. Comi CG *et al. Annals Neurology* 2001; 49(3): 290-297.

ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS WITH EPILEPSY

CONFIDENCE. BY KEPPRA.



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Reference: 1. Cereghino J et al. Neurology 2000;55(2):236-242.

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There are few issues in clinical neurology that create as much controversy as the basis and definition of consciousness and the persistent vegetative state. We are therefore very fortunate to have an authoritative account of this subject from Adam Zeman, a neurologist who has written extensively on this topic. In his article Adam sets out the differences between wakefulness and awareness and suggests that the vegetative state may represent wakefulness without awareness – the patient is clearly awake but there is no evidence of responsiveness to stimuli. Obviously such assessments on patients are fraught with difficulty, including the effects of sedation from drugs and anxieties about the patient being "locked-in", but within the article there is a very helpful Table delineating the cardinal features of these different states of altered consciousness.

The second review article in this issue by Mosimann and Ian McKeith tackles the topic of Lewy bodies and dementia. This is again a contentious issue – namely to what extent is dementia with Lewy bodies (DLB) different from Parkinson's disease with dementia? Indeed those who went to the International Movement Disorder meeting in Florida last November, will remember the debate between Andrew Lees and Charles Duyckaets on this topic (ACNR 2(6): 24). In their article Mosimann and McKeith give a measured account of the subject and whilst they feel more work is needed to resolve the relationship between these 2 disorders, favour the view that they are "different representations of the same neurobiological process".

Yianni and Aziz continue their series on surgery for movement disorders and this time tackle the topic of unusual movement disorders and deep brain stimulation (DBS). This article lists a range of conditions and the anecdotal success that DBS has made in some cases and leaves an impression of what may be possible in the future, rather than what has been proven to work.

Adam Zermansky provides the second in the Management Series on movement disorders, delineating the features of a range of parkinsonian conditions and Doug MacMahon describes his experiences with apomorphine in the more elderly (and more typical) Parkinson's disease patient. In this article he highlights the importance of patient selection – namely those that do best with this therapy tend to be younger with a history of a good L-dopa response.

Tony Redmond's "rehab" article tackles the issue of the assessment of the traumatically injured patient and the need to identify all problems early on, and by so doing ensuring appropriate treatment is started as soon as possible. If this is not done, then catastrophic consequences may result and an argument is made that intensive therapy not only refers to the immediate acute phase of injury but the early stages of rehabilitation.

The usual features are also well represented in this issue. Brian McNamara reveals his approach to the radial nerve and is probably one of the few (if not only) in the neurological fraternity to cite Homer Simpson as a reference source! Again the article is extremely clear, practical and informed and is very helpful to all those encountering this clinical problem. We also have a good selection of meeting reports – some of which can be found only on our website. Each meeting report lists the main points distilled for easy consumption and we have our normal selection of reviewed papers that have recently entered the literature.

Don't forget the website, which contains all issues of the journal, conference reports as well as clinical cases. Finally, keep the feedback coming as it has (and will continue) to shape this unique journal.

Roger Barker, Co-editor

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Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Ropinirole has been associated with somnolence and episodes of sudden sleep onset. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction seen with other Parkinson's disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Adverse reactions** In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo, however, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see 'Precautions' and 'Effects on ability to drive and use machines'). **Effects on ability to drive and use machines** Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Overdosage** No incidences reported. Symptoms of overdose likely to be related to dopaminergic activity.

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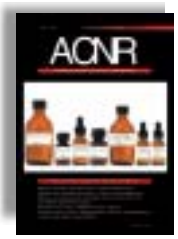
contents

july/august 2003

Cover image courtesy of MindRoom
See The Bigger Picture was a world conference focused on learning difficulties and was aimed at both parents and teachers. It was organised by Mindfield (now called Mindroom) – a charitable organisation set up by a parent who has a child with special needs. More information about this charity can be found on www.mindroom.org.

Seventeen world experts from abroad as well as the UK gave presentations ranging from the main learning difficulties to the implications for teachers when dealing with children with special educational needs. The conference, which attracted over 800 delegates, was unusual in that it looked at the various difficulties from several aspects, such as nutrition, the importance of fatty acids, medication, emotional intelligence, practical solutions and body language as well as current neurological conclusions. For a full report, see pages 40-41.



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Dementia with Lewy bodies and Parkinson's disease dementia - two synucleinopathies

Background

Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are two common syndromes with overlapping clinical symptoms suggesting that they represent different points on a spectrum of Lewy body (LB) disease and that they share similar, underlying neuropathological processes. Parkinson's disease (PD) is associated with a six fold higher risk of developing dementia when compared to healthy elderly controls and longitudinal studies suggest that up to 78% of Parkinson's disease (PD) patients will develop dementia after an average of a decade of motor symptoms[1,2]. Potential predictors for the development of dementia in PD include older age at the onset of motor symptoms, bradykinetic, not tremor dominant parkinsonism, bilateral onset of parkinsonism and declining response to levodopa. Depression, visual hallucinations, executive and visuospatial impairments early in the course of PD are putative risk factors for subsequent cognitive decline[3-6]. Operationalised criteria to define the clinical boundaries between PD and PDD are lacking, although this distinction may have profound clinical implications for prognosis and treatment strategies[7].

Clinical diagnosis

Consensus guidelines for DLB[8,9] suggest that PD patients who develop dementia more than 12 months after the initial motor symptoms should be diagnosed as PDD rather than DLB. The central feature required for a diagnosis of DLB is progressive cognitive decline, severe enough to cause social and occupational functional impairment. Core features are fluctuating cognition, recurrent and persistent visual hallucinations and extrapyramidal motor symptoms (EPS). Guidelines recommend that two of the core clinical features have to be present for a diagnosis of probable and one for a diagnosis of possible DLB[8] (Table 1). Supportive features may increase diagnostic sensitivity. They are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematised delusions and hallucinations in other modalities. Depression and REM sleep behaviour disorder have also been suggested as additions to this list[9]. A history of stroke, focal neurological signs, and the presence of significant comorbid physical illness and brain disorder reduce the certainty with which a diagnosis of DLB can be made.

Studies comparing clinical symptoms of DLB and PDD reveal significant overlap between the two disorders. Fluctuating cognition measured using computerised tests of attentional speed show no differences between DLB and PDD patients[10]. All PDD patients have parkinsonian features and this proportion is less (80-100%) in DLB, but when present, EPS seem to be equally severe. PDD patients develop dementia about 10 years after initial motor features[11] and the arbitrary distinction suggested by the Consensus guidelines possibly reflects diagnostic convenience rather than any significant biological or clinical differences.

Neuropathology

Brainstem and cortical Lewy bodies (LB) are the only features considered essential for a pathologic diagnosis of DLB, although Lewy neurites (LN), concomitant cortical senile plaques, sparse tau-pathology and spongiform changes may also be seen[12,13]. Coincident AD or vascular pathology fulfilling neuropathological diagnosis of AD or vascular dementia also occurs in DLB and PDD and may modify the clinical presentation. Lewy bodies and LN contain alpha-synuclein (Figure 1) and suggest neurobiological links with other synucleinopathies such as multiple system atrophy. In DLB cortical LB density has been associated with cognitive impairment and visual hallucinations[14], but better correlates of symptom formation are with LN, neurone loss, dopaminergic and cholinergic deficits. Alpha-synuclein positive, neuritic degeneration of the striatum has recently been described in DLB and PDD and may explain reduced levodopa responsiveness and neuroleptic sensitivity, in the two syndromes.

Neuropsychology

Prominent executive, attentional and visuospatial dysfunctions, with relatively preserved memory functions are characteristic neuropsychological findings in DLB and PDD. Fluctuation of cognition and attention interfere with cognitive assessments and lead to high variability of cognitive performance[15]. As most PD patients have some executive and visual impairment it is also difficult to set a threshold between PD and PDD.

Neuroimaging

Structural neuroimaging studies find relative preservation of the medial temporal lobes and the hippocampus in DLB compared to AD[16] and functional neuroimaging studies reveal occipital[17] and pronounced nigro-striatal dopaminergic dysfunction in caudate nucleus and putamen[18,19]. In DLB as well as PDD bilateral temporal and parietal perfusion deficits have been reported.

Genetics

Most cases occur sporadically and there are only a few reports of autosomal dominant LB disease families. The Apo-@4 allele is over-represented in DLB as in AD but not in PD without dementia[20]. Most studies find no associations between polymorphism in genes involved in familial AD (e.g. presenilin 1 or 2) or genes involved in familial PD (parkin and alpha-synculein mutations) and DLB or PDD.

Table 1

Consensus guidelines for the clinical diagnosis of probable and possible DLB[8,9]

1. **Central feature**
   - Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function
2. **Core features** (two core features essential for a diagnosis of probable, one for possible DLB)
   - Fluctuation of cognition
   - Recurrent visual hallucinations
   - Spontaneous features of parkinsonism
3. **Supportive features**
   - Repeated falls
   - Syncope
   - Transient loss of consciousness
   - Neuroleptic sensitivity
   - Systematised delusions
   - Hallucinations of other modalities
   - REM sleep behaviour disorder
   - Depression
4. **Features less likely to be present**
   - History of stroke
   - Any other physical illness or brain disorder sufficient enough to interfere with cognitive performance

Dr Urs Peter Mosimann is a clinical research fellow and lecturer in Old Age Psychiatry in the Institute for the Health of the Elderly, Wolfson Research Centre, Newcastle General Hospital. His research focuses on visual perceptive disturbances in degenerative brain disorder such as Dementia with Lewy bodies and Parkinson's disease dementia.

Dr Ian McKeith is a Clinical Professor of Old Age Psychiatry at the Institute for Ageing and Health at the University of Newcastle upon Tyne. His particular interests are in the diagnosis and management of dementia with Lewy bodies. The Newcastle group was instrumental in describing DLB as the second commonest cause of dementia in late life.

Differential diagnosis

Major syndromes to be considered for differential diagnosis are other degenerative brain disorders with EPS, neuropsychiatric syndromes with visual hallucinations, and syndromes with profound fluctuation in cognition. A list of possible differential diagnoses is summarised in Table 2.

Table 2
Differential diagnosis of DLB

1. **Other neuropsychiatric syndromes with extrapyramidal motor symptoms**
   - Parkinson's disease with / without dementia
   - Fronto-temporal dementia with Parkinsonism
   - Multi system atrophy
   - Progressive supranuclear palsy
   - Corticobasal ganglionic degeneration
   - Creutzfeldt-Jacob Disease
2. **Other neuropsychiatric syndromes with visual hallucination**
   - Delirium tremens of different aetiologies
   - Parkinson's disease with / without dementia
   - Psychotic depression
   - Charles-Bonnet-Syndrome
   - Creutzfeldt-Jacob Disease
3. **Other neuropsychiatric syndromes with profound fluctuation**
   - Vascular dementia
   - Delirium tremens

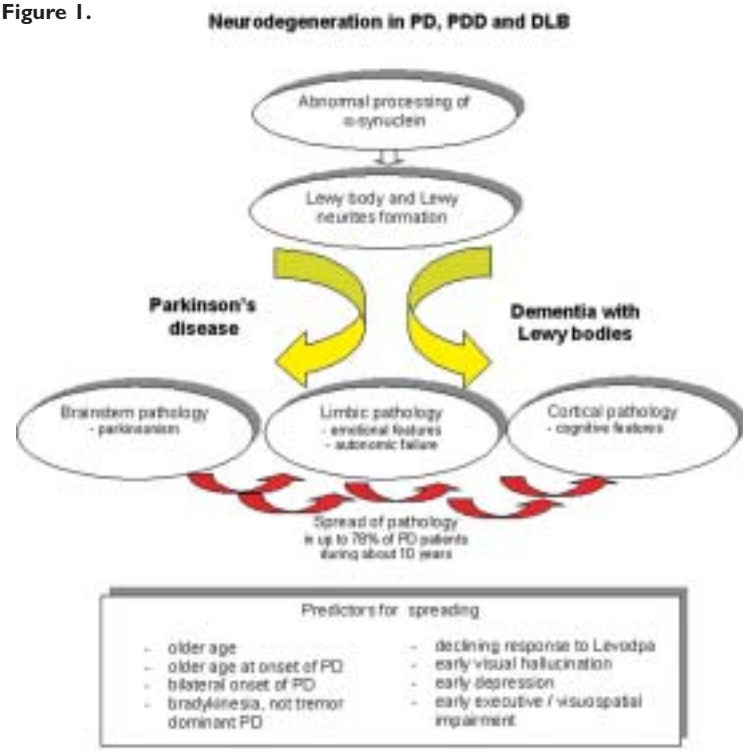
Table 3
Five recommendations for pharmacological treatment of DLB and PDD

1. Identify the key symptom to be treated
2. Avoid drugs with anticholinergic side effects such as: tricyclic antidepressants, low potency neuroleptics, antiparkinsonian anticholinergic drugs, antispasmodics for bladder or gastrointestinal tract
3. Use neuroleptics with caution
4. Prefer L-Dopa monotherapy whenever possible
5. Consider cholinesterase inhibitors for neuropsychiatric and cognitive symptoms

Clinical management

It is the combination of EPS and neuropsychiatric features, which makes pharmacological treatment of DLB and PDD patients very difficult, and often leads to a situation where the improvement of one symptom may only be achieved at the expense of another. The neurochemical dysfunction in DLB and PDD suggest combined cholinergic and dopaminergic deficits implying a need to avoid medications with anticholinergic actions or side effects or dopaminergic antagonism. Tricyclic antidepressants, low potency neuroleptics, antiparkinsonian anticholinergic drugs, antispasmodics for bladder or gastrointestinal tract symptoms should therefore be avoided as they have the potential to impair cognition, exacerbate psychotic symptoms and may be associated with orthostatic hypotension. About 50% of treated patients develop severe side effects when treated with typical or atypical neuroleptics and it is not possible to predict these

Figure 1.



neuroleptic sensitivity reactions in an individual patient before treatment starts. Reported side effects of increased rigidity, immobility, confusion, sedation and postural falls are associated with a 2-3 fold increased mortality risk[21]. Effects and side effects of neuroleptics are poorly investigated in PDD, but caution in their use is urged until more is known. There is converging and consistent evidence that cholinesterase inhibitors (ChE-I) are effective and relatively safe for the treatment of neuropsychiatric and cognitive symptoms in DLB and PDD[22] with major side effects similar to those reported in AD; mainly gastrointestinal symptoms, with nausea, vomiting and diarrhoea. Progression of EPS is uncommon, but hypersalivation, somnolence, orthostatic hypotension and syncope may be more frequent in this population. Whether ChE-I should be the first choice of treatment and which patients are likely to respond remain as open questions.

Conclusion

DLB and PDD share similar clinical and neuropathological features. The aetiology of both disorders and mechanisms triggering the spread of subcortical pathology in PD are unknown. Ongoing and future research has to clarify whether PDD and DLB are different representations of the same neurobiological process, with different initial manifestations or whether they are more independent diseases ending in a similar common pathway. Accumulating evidence favours the former option. Current clinical Consensus guidelines recommend an arbitrary distinction between the two disorders based on the duration of EPS (B1 year) before the manifestation of dementia and even if this does not reflect biological differences it may remain useful in clinical diagnostic practice.

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For a case study on dementia with lewy bodies, see our website www.acnr.co.uk/case%20report.htm

References

1. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P (2003). *Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study.* Arch Neurol;60:387-92.
2. Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P (2001). *Risk of dementia in Parkinson's disease: a community-based, prospective study.* Neurology;56:730-6.
3. Hughes TA, Ross HF, Musa S, Bhattacherjee S, Nathan RN, Mindham RH, Spokes EG (2000). *A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease.* Neurology;54:1596-602.
4. Caparros-Lefebvre D, Pecheux N, Petit V, Duhamel A, Petit H (1999). *Which factors predict cognitive decline in Parkinson's disease?* J Neurol Neurosurg Psychiatry;58:51-5.
5. Stern Y, Marder K, Tang MX, Mayeux R (1993). *Antecedent clinical features associated with dementia in Parkinson's disease.* Neurology;43:1690-2.
6. Woods SP, Troster AI (2003). *Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease.* J Int Neuropsychol Soc;9:17-24.
7. Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E (1999). *Mental symptoms in Parkinson's disease are important contributors to caregiver distress.* Int J Geriatr Psychiatry;14:866-74.
8. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH (1996). *Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop.* Neurology;47:1113-24.
9. McKeith IG, Perry EK, Perry RH (1999). *Report of the second dementia with Lewy body international workshop: diagnosis and treatment. Consortium on Dementia with Lewy Bodies.* Neurology;53:902-5.
10. Ballard CG, Aarsland D, McKeith IG, O'Brien J, Gray A, Cormack F, Burn D, Cassidy T, Starfeldt R, Larsen JP, Brown R, Tovee M (2002). *Fluctuation in attention – PD dementia vs DLB with Parkinsonism.* Neurology;59:1714-20.
11. Aarsland D, Ballard C, McKeith I, Perry RH, Larsen JP (2001). *Comparison of extrapyramidal signs in dementia with Lewy bodies and Parkinson's disease.* J Neuropsychiatry Clin Neurosci;13:374-9.
12. Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW (2002). *Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response.* Arch Neurol;59:102-12.
13. Jellinger KA (2000). *Morphological substrates of mental dysfunction in Lewy body disease. An update.* J Neural Transm Suppl;59:185-211.
14. Harding AJ, Broe GA, Halliday GM (2002). *Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe.* Brain;125:391-403.
15. Lambon Ralph MA, Powell J, Howard D, Whitworth AB, Garrard P, Hodges JR (2001). *Semantic memory is impaired in both dementia with Lewy bodies and dementia of Alzheimer's type: a comparative neuropsychological study and literature review.* J Neurol Neurosurg Psychiatry;70:149-56.
16. Barber R, Ballard C, McKeith IG, Gholkar A, O'Brien JT (2000). *MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia.* Neurology 2000;54:1304-9.
17. Lobotesis K, Fenwick JD, Phipps A, Ryman A, Swann A, Ballard C, McKeith IG, O'Brien JT (2001). *Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD.* Neurology;56:643-9.
18. Hu XS, Okamura N, Arai H, Higuchi M, Matsui T, Tashiro M, Shinkawa M, Itoh M, Ido T, Sasaki H (2000). *18F-fluorodopa PET study of striatal dopamine uptake in the diagnosis of dementia with Lewy bodies.* Neurology;55:1575-7.
19. Walker Z, Costa DC, Walker RW, Shaw K, Gacinovic S, Stevens T, Livingston G, Ince P, McKeith IG, Katona CL (2002). *Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand.* J Neurol Neurosurg Psychiatry;73:134-40.
20. Harrington CR, Louwagie J, Rossau R, Vanmechelen E, Perry RH, Perry EK, Xuereb JH, Roth M, Wischik CM (1994). *Influence of apolipoprotein E genotype on senile dementia of the Alzheimer and Lewy body types. Significance for etiological theories of Alzheimer's disease.* Am J Pathol;145:1472-84.
21. McKeith IG, Fairbairn AF, Perry R, Thompson P, Perry E (1992). *Neuroleptic sensitivity in patients with senile dementia of Lewy body type.* BMJ;305:673-8.
22. McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R (2000). *Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study.* Lancet;356:2031-6.

New Neurosciences forum

The Royal College of Nursing has over 355,000 members and seeks to support member's professional devolvement through education and training programmes at all stages of their careers. In pursuit of this goal over 70 forums exist to bring together a nation-wide network of members with shared interests. A newly formed forum will concentrate on Neurosciences and even before it went live earlier this year it had around 1,400 members.

Specifically the Neuroscience Forum aims to

- Develop a base of expertise responding to current topical debates within neurosciences
- Promote the art and science of nursing in neurosciences and promote the development of specialist and consultant nurses
- Establish good liaisons with other organisations
- Promote awareness of the specific legal framework of care
- Share good practice in the spirit of mutual support

Background

There has been significant work undertaken by the RCN with the Department of Health on the risk sharing programme for disease modifying therapies for multiple sclerosis. At the forefront of this scheme are MS nurse specialists one of whom is on the new forum executive. The RCN is a registered stakeholder for the NICE guideline development on MS. NICE are also developing guidelines for the administration of the newer epilepsy therapies and the RCN, jointly with the Epilepsy Specialist Nurse Association, was offered two stakeholder places for development of the guidelines.

Other special interest groups including Parkinson's Disease Nurse specialists, Dystonia Nurse specialists, Motor Neurone Disease Nurses and advisers and those with an interest in disability issues have been working closely with the RCN.

Specialist Nurses

Within nursing using the title 'specialist' is contestable, however England's Chief Nursing Officer Sarah Mullally said "They are providing high quality care and information, and patients appreciate that" (Parish 2003). While specialist nurses are playing an increasing role in prescribing and medication management, many patients have limited access to specialist services and are sometimes misunderstood and poorly managed.

People with neurological impairments may well experience stigma and be judged wrongly, even by health professionals. Yet people living with chronic neurological conditions are often very knowledgeable about themselves and as such are beginning to be acknowledged as 'expert'. It is important that we form alliances both across health care disciplines, between generic and specialist services and, of increasing importance, with patients and their representative groups (Scullion 2002).

In 2001 Alan Milburn, the then Health Secretary, announced that there would be a National Service Framework for people with long term neurological conditions. The RCN neurosciences forum has a keen interest in this and plans to hold a national event in 2004 to examine its implications. This NSF was welcomed by the Neurological Alliance who called for improved access to services for patients and more neurologists and other specialists including nurses.

With around 350,000 people requiring help with most of their daily activities and over one million people disabled by their neurological condition (Neurological Alliance 2003), the Neurosciences forum looks set to have a busy first term.

References

Neurological Alliance (2003) *Neuro numbers.* London, Neurological Alliance.

Parish C (2003) Special Delivery. Nursing Standard. 18, 17 pp12-13.

Scullion P (2002) *Neurological patients: the need for alliances.* British Journal of Therapy and Rehabilitation. 9,8, 293.

Philip Scullion is Senior Lecturer in Nursing at the School of health and Social Sciences, Coventry University. He has been in education since 1985 in various roles. Most recently seconded to the Royal College of Nursing as Disability Education Adviser with a broad remit including working with specialist nurses in the field of Dystonia, Epilepsy and MS and getting Disability Discrimination legislation onto the nursing agenda.

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UK Date of text revision: April 2003. APIVER100403.

References: 1. Privitera MD *et al.* Acta Neurol Scand 2003; 107: 165-175.
2. Wheless J, Wang S *et al.* Epilepsia 2001; 42(Suppl 7): (Abstract1.179).

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What is consciousness and what does it mean for the persistent vegetative state?

Adam Zeman is a consultant neurologist in the Department of Clinical Neurosciences, Western General Hospital, Edinburgh. His research interests lie in the neurology of cognition and consciousness. His work is currently supported by a PPP Foundation mid-career award.

Consciousness: wakefulness or awareness?

Consciousness is an ambiguous term. Two senses are of particular relevance to clinical neurology[1,2]:

(i) Wakefulness, alertness: when someone asks whether a patient in the A + E Department is conscious, the question generally refers to the patient's *conscious state*. Is the patient 'conscious' – that is to say awake or alert - as opposed to comatose, anasthetised, drunk or just fast asleep? Three principle states of consciousness are recognised in health - wakefulness, slow wave sleep (SWS) and rapid eye movement (REM or dreaming) sleep - alongside a miscellany of states of pathologically altered consciousness, from coma to brain death (Table 1). Consciousness in this first sense can vary in degree as well as in kind: we can be drowsy, half-asleep or wide awake. Objective criteria, like those of the Glasgow Coma Scale (Table 2), are usually a reliable guide to a patient's conscious state, enabling us to 'operationalise' our clinical assessment. This approach fails, once in a while, when paralysis blocks the usual manifestations of consciousness, for example when wakefulness recovers during anaesthesia with paralysing agents.

(ii) Awareness: while we are wakeful or dreaming, we are always conscious *of* something. The contents of consciousness can be drawn from any part of our psychological armoury: we can be conscious of sensations, perceptions, thoughts, memories, emotions, desires or intentions. This second, more 'inward', sense of consciousness is sometimes picked out by the word 'awareness'. While this term tends to be used to underline the subjective dimension of human experience, we can only ever infer awareness in others on the basis of objective evidence (which of course includes others' reports of their experience). The nature of consciousness in this second sense is a philosophical battlefield. There is a strong philosophical temptation to simplify our world picture by analysing the contents of experience in terms of the behaviour they give rise to, the functions they enable or the neural states which they express. Several philosophers have taken this approach enthusiastically[3], but others can still see no way around the postulate of a 'Cartesian', subjective, mental realm[4].

One pathology of consciousness, the vegetative state (VS)[5,6,7] has been described aptly as a state of 'wakefulness without awareness': this puzzling condition can occur because the brain systems which underlie wakefulness are substantially distinct from those which mediate awareness.

The biology of consciousness

(i) Wakefulness: the cycling of wakefulness, SWS and REM is controlled by a network of structures in the pons, midbrain, thalamus, hypothalamus and basal forebrain which regulate the activation of more rostral parts of the cerebral hemipsheres[8,9]. This arousal network incorporates nuclei transmitting noradrenaline (locus coeruleus), serotonin (dorsal raphe nuclei), histamine (hypothalamus), acetylcholine (nuclei at pons/midbrain junction and in basal forebrain) and hypocretin (hypothalamus). Neurons throughout this network become quiescent in SWS; REM is characterised by selective reactivation of the cholinergic subsystem (Figure 1); REM episodes are terminated by increasing noradrenergic and serotonergic tone. The timing of sleep is normally influenced both by circadian (the light-dark cycle) and homeostatic (fatigue related) factors.

(ii) Awareness: although there is continuing debate about the neural mechanisms of awareness, there is a broad consensus on the following (rather unsurprising) points: the contents of consciousness depend upon shifting coalitions of cortical neurons ('networks' or 'assemblies'), which are often interlinked via the thalamus, are usually distributed around the brain, and incorporate regions concerned with attention and action as well as with perceptual processing[1,2,10,11]. Importantly, cortical activity does not always give rise to awareness[1,2,10,11]. The idea that neurons subserving current awareness may be bound by rapid synchronised oscillations in the gamma frequency range is topical[12].

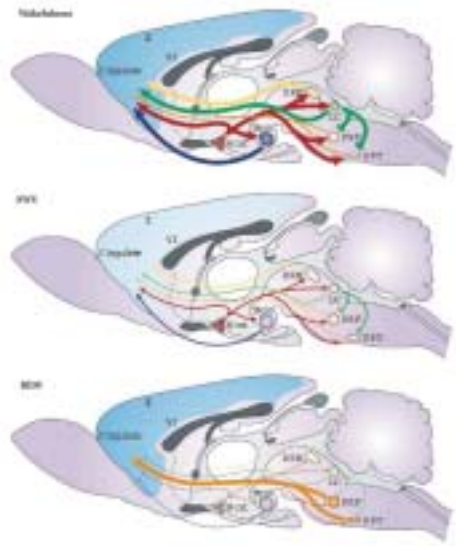
The vegetative state: wakefulness without awareness

The VS, first described in 1972 in the Lancet by Jennett and Plum[5] is an occasional outcome of severe brain injuries, usually traumatic or hypoxic-ischaemic. The clinical picture is somewhat eery. A patient in the VS appears to be awake: his eyes are open, he breathes spontaneously, he may turn fleetingly towards a prominent stimulus, or move spontaneously – grind his teeth, turn his head from side to side, grunt or moan. Yet despite this repertoire of behaviours, there is no evidence of 'a functioning mind': no evidence of discrimination between events or of purposeful behaviour, no sign of understanding or any attempt to communicate.

There is no doubt that such a condition occurs, but it has given rise to confusion. This has had two main sources: terminological and diagnostic. The terminology is explained in Table 3. The condition has sometimes been misdiagnosed for reasons including uncertainty about the nature of the syndrome, inadequate observation, failure to consult those who see most of the patient and the inherent difficulty of detecting signs of awareness in patients with major perceptual and motor impairments.

Studies of the pathophysiology of the VS indicate that it does indeed result from severe damage to the stuctures subserving awareness with relative preservation of the brain stem mechanisms of wakefulness. Autopsies reveal damage to the cortical mantle, cerebral white matter, thalamus or

Figure 1

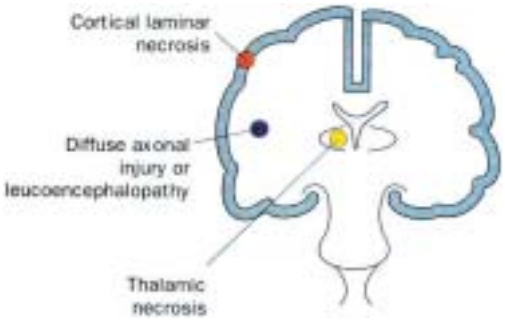


The figure indicates the levels of activity in the brain stem neurotransmitter systems which regulate sleep and waking in the rat (SWS = slow wave sleep, REM = rapid eye movement sleep) Hypocretin is shown in red, noradrenaline in green, acetylcholine in dark brown, serotonin in light brown and histamine in blue. *Reprinted by permission from Nature Reviews Neuroscience (*Vol 3: Congenital myasthenic syndrome (CMS) mutations in the acetylcholine receptor binding site*) copyright (2002) Macmillan Magazines Ltd.*

any combination of these (Figure 2). Functional imaging demonstrates reduction of global cerebral metabolic rates by 40-60%, down to or below the levels occurring during anaesthesia[13]. The metabolism of the upper brain stem is relatively spared. Where evoked cortical activity can be detected, it is fragmentary, with failure to recruit the distributed networks on which awareness is thought to depend. If the VS remits, as awareness recovers so too do previously silent long-range cortical connections[13].

Although the VS always indicates a severe brain injury, recovery can occur[7]. After one month in the VS following a traumatic insult there is a slightly better than even chance of recovering awareness: the chances are considerably less good in non-traumatic cases. But once one year has passed in the VS after trauma, or six months in non-traumatic cases, awareness is very unlikely indeed to recover, and in these exceptional cases, recovery is to a state of extremely severe disability. In these circumstances British courts tend to look favourably on applications for permission to withdraw treatment, reflecting the fundamental importance of awareness to the value we place upon our lives.

Figure 2



This figure indicates the three principal pathologies which give rise to the vegetative state.

Table 1: Some states of impaired consciousness

Condition	Vegetative state	Minimally conscious state	Locked-in syndrome	Coma	Death confirmed by brain stem tests
Awareness	Absent	Present	Present	Absent	Absent
Sleep-wake cycle	Present	Present	Present	Absent	Absent
Response to noxious stimuli	+/-	Present	Present (in eyes only)	+/-	Absent
Glasgow Coma score	E4, M1-4,V1-2	E4, M1-5,V1-4	E4, M1,V1	E1,M1-4,V1-2	E1, M1-3,V1
Motor function	No purposeful movement	Some consistent or inconsistent verbal or purposeful motor behaviour	Volitional vertical eye movements or eyeblink preserved	No purposeful movement	None or only reflex spinal movement
Respiratory function	Typically Preserved	Typically Preserved	Typically Preserved	Variable	Absent
EEG activity	Typically slow wave activity	Insufficient data	Typically normal	Typically slow wave activity	Typically absent
Cerebral metabolism (positron emission tomography)	Severely reduced	Insufficient data	Mildly reduced	Moderately-severely reduced	Severely reduced or absent
Prognosis	Variable: if permanent, continued vegetative state or death	Variable	Depends on cause but full recovery unlikely	Recovery, vegetative state or death within weeks	Already dead

Table adapted from: Royal College of Physicians. The vegetative state: guidance on diagnosis and management. Clin Med 2003: 3(3); 249-254.

Table 2: Glasgow Coma Scale (GCS):

E	Eye Opening	M	Motor function	V	Verbal
1	None	1	None	1	None
2	To pain	2	Extends to pain	2	Grunts
3	To sound	3	Abn flexion to pain	3	Inapprop. words
4	Spontaneously	4	Normal flex to pain	4	Confused
		5	Localises pain	5	Oriented
		6	Normal		

Table 3: Terminology of the vegetative state

Vegetative state (VS):	A state of intermittent wakefulness without awareness, as described in the text.
Persistent VS:	Any VS which has persisted for more than 1 month (arbitrarily).
Permanent VS:	A VS which has persisted for over 1 year following trauma, or for over 6 months following a non-traumatic cause, and which is therefore highly likely to be permanent.

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References

1. Zeman A. *Consciousness.* Brain 2001;124:1263-89
2. Zeman A. *Consciousness: a user's guide.* London: Yale University Press, 2002.
3. Dennett DC. *Consciousness explained.* Boston (MA): Little, Brown; 1991
4. Chalmers DJ. *The conscious mind.* Oxford; Oxford University Press; 1996
5. Jennett B, Plum F. *Persistent vegetative state after brain damage.* Lancet, 1972: I: 734-7
6. Jennett B. *The Vegetative State.* Cambridge: Cambridge University Press, 2002.
7. Multi-society Task Force on PVS (1994) *Medical Aspects of the persistent vegetative state (in two parts).* N Engl J Med 330:1499-1508, 1572-1579.
8. Pace-Schott EF, Hobson JA. *The neurobiology of sleep: genetics, cellular physiology and subcortical networks.* Nature Reviews Neuroscience 2002;3:591-605.
9. Hobson JA, Pace-Schott EF. *The cognitive neuroscience of sleep: neuronal systems, consciousness and learning.* Nature Reviews Neuroscience 2002;3:679-693.
10. Baars BJ. *The consciousness access hypothesis: origins and recent evidence.* TRENDS in Cognitive Sciences Vol 6 No 1 January 2002
11. Rees G, Kreiman G and Koch C. *Neural correlates of consciousness in humans.* Neuroscience Vol 3 261-270, April 2002
12. Engel AK, Fries P, Roelfsema PR, Konig P, Singer W. *Temporal binding, binocular rivalry and consciousness.* 2000. www.phil.vt.edu/ASSC/engel.html
13. Laureys S, Berre J, Goldman S. *Cerebral function in coma, vegetative state, minimally conscious state, locked-in syndrome, and brain death.* Yearbook of Intensive Care and Emergency Medicine 2001:386-396.

Dr. Alois Alzheimer

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A577-ARI236-12-02

Catastrophic injuries - Towards early intervention and rehabilitation

Professor Anthony Damien Redmond is Emeritus Professor of Emergency Medicine, Keele University, Consultant in Trauma/Emergency Medicine and Consultant Advisor in Trauma Rehabilitation.

Professor Redmond has held research posts in the University of Manchester, Medical College of Virginia USA and MRC Trauma Unit and having trained in Accident and Emergency Medicine developed a special interest in the management of Major Trauma. He was formerly Consultant Trauma Team Leader at the North Staffordshire Trauma Centre and subsequently Medical Director of the University Clinical Centre Kosovo. For the last 15 years he has developed and run a number of overseas aid programmes, focused particularly on the care and rehabilitation of the severely injured.

Introduction

A code of best practice on rehabilitation has been drawn up between the Insurance Industry and Personal Injury Lawyers and recommends an appropriate independent expert complete an early assessment of the patient, outwith the medicolegal process, and on behalf of "both sides" to identify any immediate interventions or rehabilitation needs[1]. It has been against this background that I have reviewed a number of "catastrophically" injured patients. (In the medicolegal context a catastrophic injury is in general one where the ultimate financial settlement is likely to be in excess of £1million).

The Patients

I have reviewed 69 patients up to the time of writing - mostly under the code of practice. The majority (61%) had suffered Traumatic Brain Injury following an injury to the head. 25% had Spinal Cord Injury and in all but one this was associated with spinal fracture. The remaining patients had other skeletal injuries. Of course a number of patients had more than one site injured but the principal and most significant injury in terms of disability is detailed in table 1. Not all were life threatening and the catastrophe in some cases was the inability of an unqualified young man to find work following almost complete amputation of their hands.

Head injuries	42 (61%)
Spinal cord injuries	17 (25%)
• Cervical #	4 (6%)
• Thoracic #	12(17%)
• Ischaemic	1 (1%)
Multiple injuries	5 (7%)
Hand injuries	2 (3%)
No injury	2 (3%)
Brachial Plexus Injury	1 (1%)

Table 1: Predominant site of injury

In 14% of cases, review of medical records revealed significant delays in the diagnosis of their principal injury and in a few cases non life threatening but significant injuries in terms of their contribution to overall disability had been overlooked completely. In some cases, had the injury been identified and treated earlier, the "catastrophic" nature of their injury might have been avoided altogether.

In two further cases, the catastrophic injury was at least in part iatrogenic.

Cervical spine fracture	1
Thoracic spine fracture	3
Wrist fracture	1
Brachial plexus injury	1
Hip fracture	1
Subdural Haematoma	1
Internal Derangement of the knee	2

Table 2: Missed Injuries

A potential difficulty when assessing children with head injury and subsequent behavioral problems was the contribution of pre accident morbidity. Two children had significant behavioural problems before the accident, which may in fact have been a significant contributory factor to the accident itself. In another child, a relatively minor road traffic accident may have coincided with the manifestation of autism.

This latter case is part of another potential difficulty for the assessor. When reviewing a case the mechanism of injury may appear to be incompatible with the injury claimed to be its consequence. In two other cases, interview and review of the records revealed at the very least significant exaggeration and possibly fraud. There is a potential dilemma here for the clinician, not anticipated in the original report. The code of best practice directs the independent assessor not to deal with diagnostic criteria or causation; but recommendations for rehabilitation must surely be placed in the overall clinical context. I believe this aspect needs to be revisited.

The Process

Initially I was seeing patients several months and sometimes years after the accident. However over these last eighteen months the interval between accident and review has shortened considerably and now I review most cases while they are still in hospital after the index accident.

Liaison with hospital staff and other treating staff is essential. They must be fully aware of the role of the assessor. The patient's solicitors usually request that arrangements be made through the patients themselves or their relatives. It is essential to make contact with ward staff early on so they can check everything with the patient and that an appointment is made that is convenient all round. Prior contact with the supervising consultant is clearly essential and if medical notes are to be reviewed, the treating clinician is specifically consulted in this regard before the visit takes place. I have found all medical and nursing staff to be extremely helpful and cooperative. I have also learned though to check for myself arrangements made with the hospital by others to ensure proper consultation has taken place.

Understandably there remains suspicion about the process in the minds of some. This is changing and hopefully as a result of the potentially beneficial impact of this approach. I have found even the most initially hesitant of solicitors have warmed to the benefits of an independent medical opinion, particularly when advice is given regularly, promptly and paid for by the insurance company! Cases are ideally seen on a joint basis but when instructed solely by the insurance company the report is provided in the spirit of the code of best practice and made available to both sides.

Early assessment of the patient's injuries, review of their progress and an indication of likely prognosis has been generally well received by all concerned. The prognosis is given and accepted as a guide. Definitive prognosis will await later and separate medicolegal reports. The greatest potential benefit is the identification of early interventions. The need for this additional input is usually related to limited NHS resources. The commonest recommendation has been for assessment/treatment by a Clinical Neuropsychologist (39% of cases). While these have usually been head injured patients, five had no head injury and in two additional cases a recommendation was made that their close relative/carer be included. 21% of head injured patients were referred on to Neurorehabilitation programmes, funded by the relevant insurance company. Further Speech and Language

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GAB577/Mar 03

References
1. Uthman BM, *et al. Arch Neurol* 1998: **55**: 56-62. 2. Suzdak PD and Jansen JA. *Epilepsia* 1995; **36**(6): 612-626. 3. So EL, *et al. Epilepsy Res* 1995; **22**: 221-226. 4. Gustavson LE, *et al. Epilepsia* 1995; **36**: 605-611. 5. Gustavson LE, *et al. Am J Therap* 1998; **5**: 5-16. 6. Gustavson LE, *et al. Am J Therap* 1998; **5**: 73-79. 7. Mengal H, *et al. Epilepsia* 1995; **36**: S160. 8. Mengal HB, *et al. J Pharm Med* 1994; **4**: 141-150. 9. Gabitril SmPC. 10. Leppik IE. *Epilepsia* 1995; **36**(Suppl 6): S10-S13. 11. Leppik IE, *et al. Epilepsy Research* 1999; **33**: 235-246. 12. Krauss GL, *et al. J Neurol Neurosurg Psychiatry* 2003; **74**: 339-343. 13. Sackellares JC, *et al. Epilepsia* 2002; **43**(4): 394-398.

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Therapy was sometimes required. Given the limited physiotherapy resources, particularly in the community, it was perhaps surprising that only 10% required additional therapy.

I remain available to patients and their advisors after my initial assessment and this aspect of the work has grown as the caseload has grown. It is the element probably most appreciated by the patients and their families. Facilitating referral to other specialists and/or arranging scans and x-rays has become an important component of the work. Providing a medical liaison and at times advocacy for the patient can help and if in tandem with the treating clinicians can sometimes reinforce treatment goals. In a small number of cases other previously unrecognised injuries have been identified and addressed. In others it has been possible to circumvent NHS waiting times by arranging further surgery on a private basis.

Although clearly within the remit of others, issues such as accommodation, transport and care assistance could be reinforced to help secure their early implementation. It is clear there is a need for carers and "buddies" that is difficult to meet. One can and often does make such recommendations but identifying suitable candidates is another matter.

One simple immediate improvement to the lives of the injured has been to facilitate the immediate purchase of a laptop computer. This has provided Internet access to relieve isolation and in one case enabled the patient to carry on their professional training at home and in others to begin the process of retraining.

Table 3. Examples where ATLS protocols were not applied

Case 1
A motorcyclist was admitted to hospital with a number of serious injuries. Having been thrown from his motorbike at speed, the mechanism of injury (as emphasised by ATLS) strongly suggested a very high risk of injury to the spine. However in spite of complaining of numbness in the legs each time he was sat up, his spinal fracture was not diagnosed until 3 days later when sitting him up caused paralysis of the lower limbs. Fortunately substantial neurological recovery was secured.

Case 2
A motorcyclist was thrown from his motorbike at speed and admitted to hospital with limb fractures. He did not complain of neck pain but ATLS protocols would demand the mechanism of injury required him to have a neck X ray before discharge. He was not x-rayed. His GP subsequently diagnosed an unstable neck fracture 5 weeks later. He has had neurosurgery with fortunately a good although not complete recovery.

Case 3
A man was ejected from a vehicle on a motorway. This is taught by ATLS as carrying a very high risk of severe injury particularly spinal injury. Nevertheless, in spite of complaining of back pain he was discharged home after a few hours and his multiple spinal fractures ultimately diagnosed by his GP.

Case 4
A man was ejected from a vehicle at speed and incurred a fracture to his forearm. Again the mechanism of injury suggested a very high risk of severe injury. However he was not examined in sufficient detail and his brachial plexus injury missed completely. By the time it was diagnosed at another hospital it was too late to improve the outcome.

Case 5
A young woman was found at the foot of a flight of stairs. She was not moved by bystanders. It is claimed that although now conscious the paramedic sat her up without first checking her neurological status or asking her if she had pain or tenderness in her spine. When upright she complained of severe pain in her back and that she could now not feel or move her legs. She remains permanently paralysed below the waist. Witnesses suggest she was moving her legs prior to being sat up by the paramedic.

Discussion

Having migrated gradually from the resuscitation of the severely injured at the roadside, through their treatment in A&E and now to their discharge into the community, I understand better the gulf perceived by victims and their relatives between the initial acute high-tech curative approach delivered in hospital and their long term care received in the community. Those in the acute sector must manage their expectations better to help bridge this gap. While much of this is a matter of perception there can be a significant hiatus between discharge from acute care to the establishment of a focused rehabilitation programme. The additional funding that insurance companies can bring to certain cases can be used to fill this gap; meeting an individual need and reinforcing the need for more public resources in this area.

While cancer and heart disease are the biggest killers in the western world, these are largely diseases of the middle-aged and elderly. Trauma however is largely a disease of the young[2]. If we look at years of productive life lost rather than crude mortality, trauma dwarfs all other diseases in its impact on society.

This effect is also seen in developing countries where rapid urbanisation is adding a similar burden of injury to an already heavy load of disease. Yet facilities for its mitigation seem woefully poor. By improving the initial care of injured patients we have decreased mortality and reduced morbidity. But head injury is the major component of severe injury in the UK and while more people now survive more severe injuries to the head, inevitably more people will survive with disability. As many of these are victims of accidents, greater cooperation between the NHS and the Insurance industry can lead to benefits all round.

To the outside observer there is an obvious diversity between the duration and content of rehabilitation programmes, including to some extent Neurorehabilitation programmes, offered in the private sector. This can only engender caution about their benefit. When a long expensive programme fails to deliver measurable benefit and this failure then used to justify another, concern is only increased. From my current perspective there appears to be a need for agreed standards and a national framework, which if already established, needs much greater visibility.

There is a particular need for more and shorter early intensive rehabilitation programmes for trauma victims available across the UK. The Insurance Industry and the NHS should find this an area of mutual interest and benefit.

The problems in initial diagnosis I have identified seem to represent similar concerns raised in 1988 when the Royal College of Surgeons published the results of a study into 1000 trauma deaths[3]. The inexperience of the doctors who first saw the patient led to the severity of their injuries being initially underestimated in a significant number of cases. To raise standards the Advanced Trauma Life Support (ATLS) teaching programme was imported from the USA and became a requirement for all those working in A&E.

The purpose of my work has not been to study the standard of initial care of the severely injured and my findings must be viewed with caution. However, the nature of the failure in each case was related to inexperience, and covered within the ATLS programme. Over time it seems the spotlight on trauma has moved away and onto other areas in the NHS. It may be time it was moved back.

References

1. Code of best practice on rehabilitation, Early Intervention and Medical Treatment in Personal Injury Claims, IUA/ABI 1999, revised 2002
   Available from the Association of Personal Injury Lawyers website www.apil.com and the Association of British Insurers (ABI) www.abi.org.uk
2. Stone DH, Jarvis S. *The continuing global challenge of injury.* BMJ 2001;322:1557-1558
3. Anderson ID, Woodford M, deDombal T, Irving M *Retrospective study of 1000 deaths from injury in England and Wales.* BMJ 1988; 296: 1305-1308

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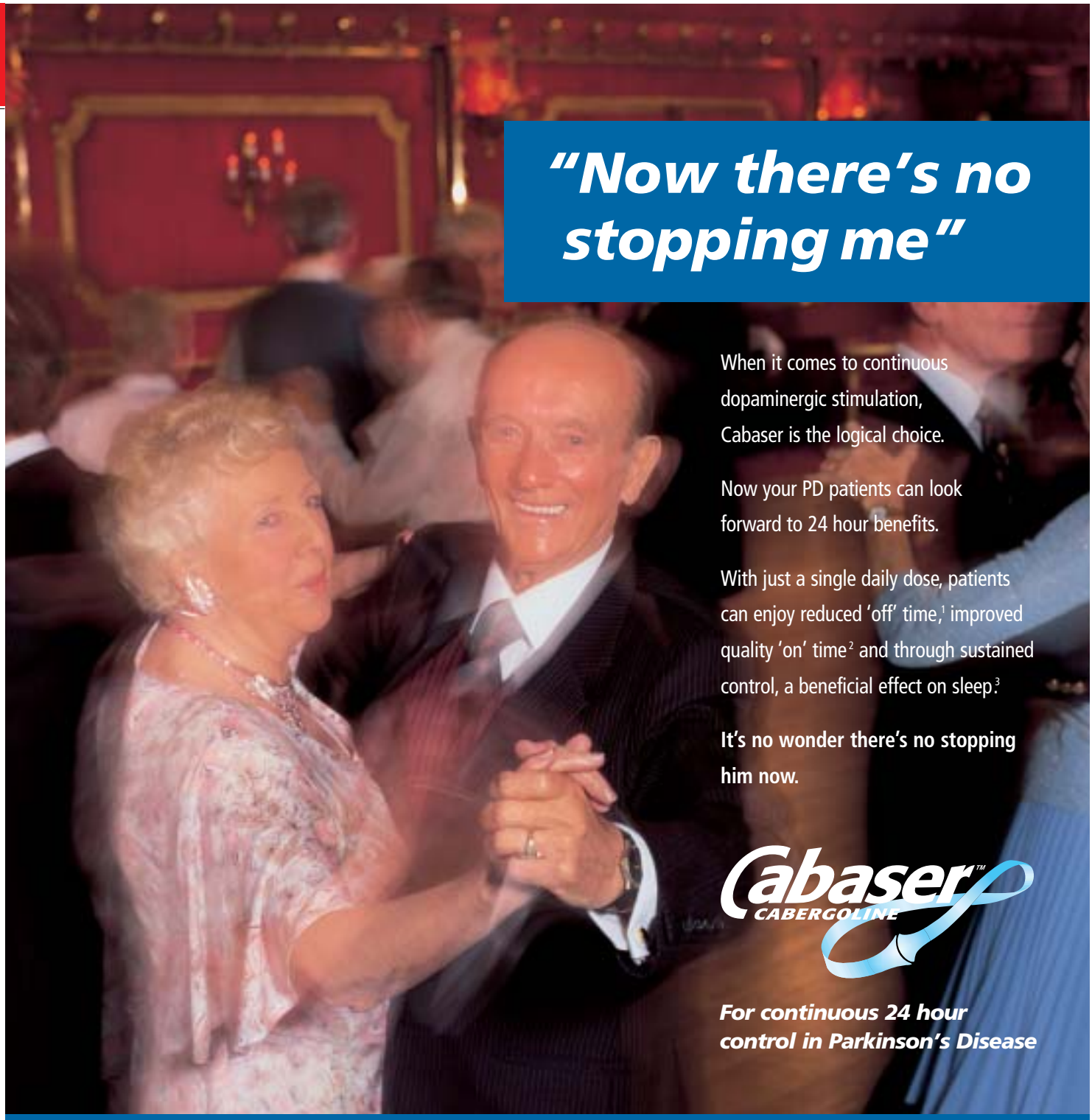

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References: 1. Steiger M J et al. J Neurology 1996; 243: 68-72. 2. Lera G et al Neurology 1993; 43 (Suppl 12):2587-90. 3. Chaudhuri K R et al. Eur J Neurol 1999; 6(Suppl 5): S11-S15.

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Parkinsonism at a Glance

Usually, it is easy to label a patient as Parkinsonian on observing them walk into the consulting room. The early symptoms of impaired dexterity and micrographia, rest tremor, difficulty with repetitive alternating movements such as beating eggs, cleaning teeth and wiping feet on the doormat, difficulty turning in bed, aches associated with muscular rigidity and dystonia, and a general history of slowing down are early pointers. Problems arise, however, when tremor is the only symptom or in classifying the syndrome in its early stages. Sometimes, one may have to wait until later in the disease course when symptoms and signs crystallise into a recognisable pattern. Although this waiting game may not alter ones initial pharmacotherapeutic management, early and accurate diagnosis is not just an academic exercise; the prognosis and problems arising in the different akinetic-rigid syndromes vary significantly and knowing what one is dealing with may aid:

1) Clinical management e.g. the identification of disease-specific complications at an earlier stage
2) Carer understanding and recognition of new problems (e.g. frontal behaviour)
3) Patient and carers to access specific support groups and possible additional services
4) Patients to plan their lives better
5) The planning of service provision (early referral to multi-disciplinary team members, social services, physical aids)
6) Participation in research at an earlier (and possibly more useful) stage in the disease (e.g. potential neuroprotective agents would need to be commenced as early as possible in the disease course).

Diagnosing the akinetic-rigid syndromes

If one was to generate an algorithm to illustrate the thought processes involved in the diagnosis of akinetic rigid (AR) syndromes, after the exclusion of secondary causes of Parkinsonism, i.e. those with an identifiable aetiology (see table 1 for overview and figure), idiopathic Parkinson's disease (IPD) would be the 'default' diagnosis. This makes sense because, although the other akinetic-rigid syndromes can present in exactly the same way, IPD is the most common and thus most likely diagnosis. One would then search for additional, 'atypical', features, which could change this default diagnosis to one of the other neurodegenerative akinetic-arigid syndromes. These atypical features are highlighted in figures 2-5 (MSA, PSP, CBD and DLB). All of these have a worse prognosis than IPD, tending to progress more rapidly. Life expectancy with MSA and PSP averages at around 6-7 years[1, 2] from symptom onset, although can be as little as 2 years.

Although 23% of IPD patients may never develop a tremor[3], it is often the presenting complaint. The tremor-dominant form (TD) tends to have a better prognosis than the postural instability with dysfunctional gait (PIDG) form (more bradykinetic and rigid). Sometimes, in the perceived absence of bradykinesia and rigidity, it may be difficult to differentiate between an early presentation of IPD from other forms of tremor. In IPD, a resting tremor, which can be suppressed volitionally and is less prominent in posture and action, is typical. This, however, is not always the case. If treatment was indicated, one could prescribe a therapeutic trial of a dopaminergic agent. Unfortunately, parkinsonian tremor is much less responsive to treatment than bradykinesia and rigidity, so a negative result would not exclude the diagnosis. To assist the diagnosis, one could arrange a 123I-FP-CIT SPECT scan (DaTscan™). This radioisotope-labelled ligand binds to the dopamine re-uptake transporter protein in the dopaminergic pre-synaptic terminals. So, a reduction in the binding may indicate loss of nigro-striatal neurones. In the case of an obviously abnormal result, with significant reduction in striatal binding, the diagnosis would be clear. The one study examining this found its sensitivity for Parkinsonism being between 95-97% and specificity for essential tremor being between 93-100%[4]. However, this study used clinically obvious cases with no pathological confirmation. Whether one can extrapolate to clinically uncertain cases remains to be seen. Also, it is currently a rather expensive test to use routinely. Longitudinal studies are currently in progress.

Dopa responsiveness

The current pharmacotherapeutic strategy of delaying the introduction of L-Dopa means that dopa-responsivity plays a lesser role in early diagnosis. The response to other treatments, such as dopamine agonists is helpful, although these are less effective at treating the motor symptoms than L-Dopa.

Dopa responsiveness is usually a reassuring sign, as one would expect this to occur in IPD. However, approximately 6% of IPD cases may show very little response[3]. Furthermore, patients with PSP or MSA may also respond to L-dopa[1, 5, 6], such that they may be misdiagnosed as IPD in the early stages, when atypical features are subtle or absent. In these cases, the response may be short lived, prompting a diagnostic review.

Diagnostic Criteria

The diagnosis of AR syndromes remains a clinical one, since there are no investigations that are sensitive and specific enough to differentiate between them. In order to consolidate the diagnosis one could employ the numerous research-based clinical diagnostic criteria. Notwithstanding their unwieldiness and debatable validity (they are based upon retrospective case-note reviews and post-mortem), a recent study confirmed that they did not improve upon the sensitivity and specificity of neurologists' own diagnostic acumen[7].

In practice, one of the main difficulties arises in deciding upon the significance of possible atypical features. For example does a 68-year-old parkinsonian gentleman's urinary and erectile dysfunction mean he has MSA, or are they related to his prostatism and depression? What about his asymptomatic orthostatic hypotension - can it be related to the L-Dopa he is taking? And is the limitation of upgaze in an elderly lady with falls and Parkinsonism significant enough for a diagnosis of PSP? This is where criteria fall down, since they rely on subjective interpretations of objective features. This is where some of the more subtle features, not included in the diagnostic criteria may help with the diagnosis. For example dusky blue hands, nocturnal stridor, sighing, low amplitude myoclonic jerks (sometimes just affecting outstretched fingers when flicked by the examiner, termed polyminimyoclonus) or significantly reduced blink rate. However, this does not negate the usefulness of criteria; the key features contained within them are important to know[8-11] (included in figures) and it is the continuing refinement of such criteria through recognition of practical clinical difficulties that have helped to improve diagnostic accuracy.

Adam Zermansky is a clinical research fellow in Neurology in Newcastle, funded by the PSP Association, U.K. He has previously worked in Birmingham, London, and Manchester. His current research interests are PSP and Indeterminate Parkinsonism (epidemiology, natural history, MR spectroscopy and Electrooculography).

References

1. Wenning GK, Ben-Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. *Clinicopathological study of 35 cases of multiple system atrophy.* J Neurol Neurosurg Psychiatry 1995;58(2):160-166.
2. Litvan I, Mangone CA, McKee A, Verny M, Parsa A, Jellinger K, *et al. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study.* J Neurol Neurosurg Psychiatry 1996;60(6):615-620.
3. Hughes AJ, Daniel SE, Blankson S, Lees AJ. *A clinicopathologic study of 100 cases of Parkinson's disease.* Arch Neurol 1993;50(2):140-148.
4. Benamer TS, Patterson J, Grosset DG, Booij J, de Bruin K, van Royen E, *et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group.* Mov Disord 2000;15(3):503-510.
5. Nath U, Ben-Shlomo Y, Thomson RG, Lees AJ, Burn DJ. *Clinical features and natural history of progressive supranuclear palsy: A clinical cohort study.* Neurology 2003;60(6):910-916.
6. Hughes AJ, Colosimo C, Kleedorfer B, Daniel SE, Lees AJ. *The dopaminergic response in multiple system atrophy.* J Neurol Neurosurg Psychiatry 1992;55(11):1009-1013.
7. Hughes AJ, Daniel SE, Lees AJ. *Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease.* Neurology 2001;57(8):1497-1499.
8. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, *et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop.* Neurology 1996;47(1):1-9.
9. Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, *et al. Consensus statement on the diagnosis of multiple system atrophy.* J Neurol Sci 1999;163(1):94-98.
10. Litvan I. PSP and Corticobasal Degeneration. *In: Quinn NP, editor.* Parkinsonism. London: Balliere; 1997. p. 179.
11. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, *et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop.* Neurology 1996;47(5):1113-1124.
12. Lucking CB, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, *et al. Association between early-onset Parkinson's disease and mutations in the parkin gene. French Parkinson's Disease Genetics Study Group.* N Engl J Med 2000;342(21):1560-1567.
13. Reuter I, Hu MT, Andrews TC, Brooks DJ, Clough C, Chaudhuri KR. *Late onset levodopa responsive Huntington's disease with minimal chorea masquerading as Parkinson plus syndrome.* J Neurol Neurosurg Psychiatry 2000;68(2):238-241.
14. Vingerhoets FJ, Hegyi I, Aguzzi A, Myers P, Pizzolato G, Landis T. *An unusual case of Creutzfeldt-Jakob disease.* Neurology 1998;51(2):617-619.

Figure 2: Progressive Supranuclear Palsy (PSP)

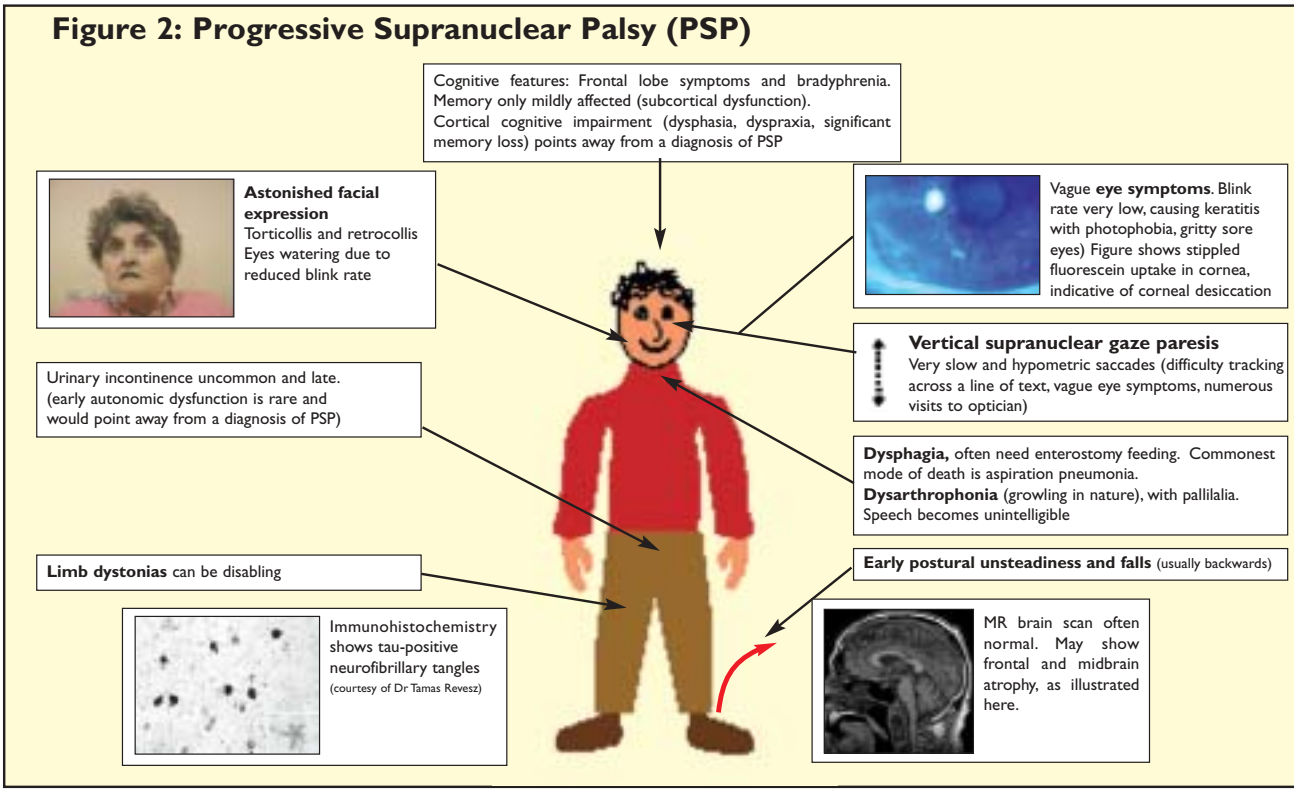


Figure 3: Cortico Basal Degeneration (CBD)

Very asymmetric A-R syndrome with:

- Alien Limb ("my arm has a mind of it's own") : arm elevates, hand grabs things and may interfere with activities of other hand
- Limb dystonia
- Myoclonus
- Dyspraxia
- Cortical Sensory loss

Occasionally, there may be features of PSP.

Both conditions share a similar pathology with tau deposition (4-repeat tau) and may be different ends of the spectrum of one disease process

Table 1: Differential Diagnosis of Parkinsonism According to Identifiable Causes

Disease	Pathophysiology	Characteristic Clinical Features	Diagnosis
Brain Insult: Vascular Parkinsonism	Infarcts in the nigro-striatal pathways	Acute onset, stepwise progression Vascular risk factors Lower body Parkinsonism Low incidence of tremor Poor L-Dopa response Can mimic any A-R syndrome	Brain imaging (**see fig 1**) (Can be difficult though as there is a high incidence of vascular disease in patients with IPD)
Cerebral Tumour	Basal ganglia, midbrain infiltration/compression	Can mimic any A-R syndrome	Brain imaging
Hydrocephalus	unknown	Gait dyspraxia, dementia, urinary incontinence	Brain imaging
Pugilistic Parkinsonism	Repeated head trauma, possibly causing midbrain contusions/haemorrhage	Like IPD	Brain imaging shows evidence of previous midbrain haemorrhage.
Genetic Causes Wilson's disease	Hepatic copper transport protein deficiency; inability to excrete copper in bile, leading to copper deposition in basal ganglia.	Young onset Kaiser-Fleisher rings Psychiatric features Tongue tremor	δ Serum copper $\delta 24^0$ urine copper excretion αSerum Caeruloplasmin Liver biopsy
Parkin	Parkin mutation Autosomal recessive	Young onset Parkinson's disease (44% of <30 yr olds(12))	Genetic testing
Synuclein	/ – synuclein mutation Autosomal dominant	Very rare	Genetic testing
Westphal variant of Huntington's disease. Rarely: late onset	CAG repeat expansion in Huntingtin gene (function unknown) Autosomal Dominant	Young onset, Family History Late onset: may have myoclonus, dystonia, autonomic dysfunction[13]	Genetic testing
Spinocerebellar ataxias, type 2, 3 and 6	SCA gene mutations	Parkinsonism and Cerebellar ataxia (may look like MSA-C) Family History	Genetic Testing
Infectious Whipples disease	The bacterium *Tropheryma whippleii*	Can present like PSP Other neurological features: neuropathy, myopathy, Orofacial myorhythmia Gastrointestinal disturbance	PAS +ve macrophages on duodenal biopsy PCR ofCSF
Post encephalitic	Unknown virus	Previous history of encephalitis Other movement disorders	Essentially clinical
CJD[14]	Prion disease	Psychiatric features, myoclonus, supranuclear gaze paresis	Pulvinar high signal on MR scan with nvCJD 14-3-3 protein in CSF
Toxin Neuroleptics and other drugs	Dopamine receptor blockade	Like IPD	Withdraw drug if possible May take up to 15 months for Parkinsonism to resolve DaTscan to differentiate from IPD
Manganese Carbon Disulphide	Direct neurotoxic effects	Headaches, psychiatric disorders CS_2: also neuropathy	History of exposure
Carbon Monoxide	Ischaemic damage to basal ganglia	Like IPD, very severe, symmetrical	From clinical history ?gas fire at home. Imaging shows basal ganglia infarcts.

Figure 4: Multiple System Atrophy

MSA may take one of 2 forms, with increasing feature overlap as the disease progresses
MSA-C = Cerebellar Predominant
MSA-P = Parkinsonism Predominant

Cognitive symptoms are minimal. May become emotionally labile. Significant impairment should make one think of an alternative diagnosis

Axial rigidity.
If neck dystonia occurs, it usually is in the form of antecollis. Sometimes very painful in a 'coat hanger' distribution.

Oro-facial dyskinesia and dystonias may be secondary to L-Dopa. Dystonic posture shown (arrow)

Oculomotor
May develop hypometric saccadic eye movements, but no gaze paresis.
MSA – C: nystagmus, but not necessarily.

Bulbar Dysfunction

Dysphagia may occur.

Dysarthrophonia (extrapyramidal)
Cerebellar dysarthria in MSA – C

Laryngeal Stridor: Uncommon, but potentially life threatening. Any snoring, nocturnal hypoventilation? May need tracheostomy.

Pyramidal Dysfunction
If present, usually just brisk reflexes and sometimes extensor plantars

Cerebellar Dysfunction
Predominates in MSA-C (by definition), but can occur later in MSA-P.

Limb dystonias can be disabling

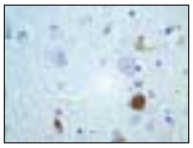
Early postural unsteadiness and falls usually forwards/sideways
(if backwards think ? PSP)
MSA-C: cerebellar ataxia

Autonomic Dysfunction

Orthostatic hypotension is common. Symptoms may be just dizziness on standing, but may lead to increased fall frequency and blackouts.

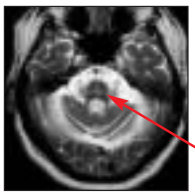
Dusky, cold hands due to autonomic dysfunction.

Urinary incontinence + erectile dysfunction occurs early.



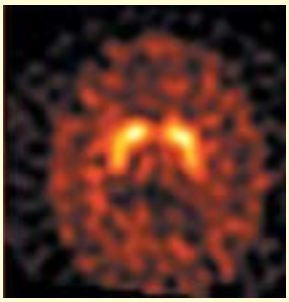
(Courtesy of: Dr Evelyn Jaros, Dept of Cellular Pathology, Newcastle General Hospital, U.K.)

Immunohistolochemistry shows ⁄ - synuclein-positive glial cytoplasmic inclusions.

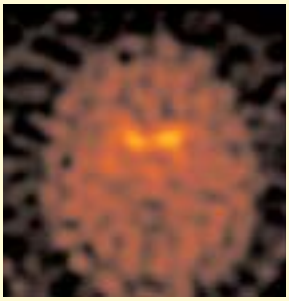


MR brain scan is often normal. May show high signal in the pons (hot cross bun sign - as illustrated). Cerebellar atrophy may be seen in MSA – C.

Figure 6: [I-123]FP-CIT SPECT (DaTSCAN™)



Normal



Parkinson's Disease

Figure 5: Dementia with Lewy Bodies (DLB)

Cognitive dysfunction

Early cortical cognitive dysfunction, especially:
- Executive
- Visuospatial (e.g. clock drawing)
- Memory impairment a later feature

Fluctuating **Confusion** (can vary from lucid to confused over a short time period)

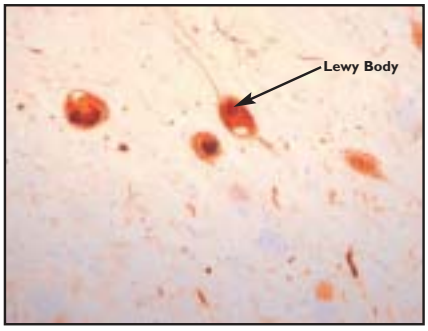
Hallucinations (usually visual, but may be auditory, olfactory)

+

Spontaneous Parkinsonism

Occurs around or after onset of cognitive dysfunction

Other features (occur later in disease course):
- Antecollis
- Myoclonus
- Dysphagia
- Supranuclear Gaze Paresis (often can only differentiate between PSP and DLB at this stage via meticulous history from close carer of early cortical cognitive dysfunction).



Lewy Bodies

Immunohistochemistry shows ⁄ -synuclein-positive intra-neuronal inclusions, **Lewy bodies**, in the substantia nigra and cortex (as in IPD).

Pathologically, the frequency-density of cortical Lewy bodies defines the diagnosis, although degree of dementia does not correlate well with this.

**(Immuno image courtesy of:
Dr Evelyn Jaros, Dept of Cellular Pathology,
Newcastle General Hospital, U.K.)**

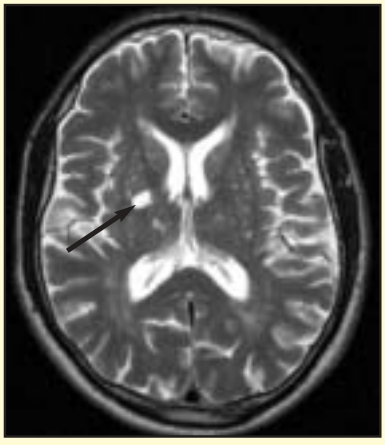


Figure 1: Vascular Parkinsonism

Multiple lacunar infarcts affecting the basal ganglia
(arrow highlights largest one)
Sometimes may be coexistent with other AR syndromes making diagnosis difficult
Typically lower body Parkinsonism predominates with minimal tremor and less dopa responsive than IPD

With thanks to Dr David Burn for his assistance in preparing this Management Topic

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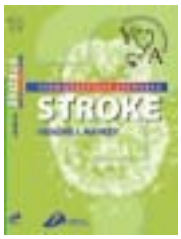
'Your Questions Answered: Stroke'



Author: Graeme J Hankey
Publisher: Churchill Livingstone
ISBN: 0443071462s
Price: £19.99

As a trainee hospital specialist my initial impression was that this book was not for me, but I was wrong. It forms part of the 'Your Questions Answered' series of books from Churchill Livingstone, aimed 'to appeal to GP's, nurses and other health professionals' the back cover informs us. However, the preface explains that although 'written primarily for GP's, it also hopes to address many questions…[from]…general physicians, neurologists in training, medical students, stroke patients, carers of stroke patients and the general public'. And therein lies the rub.

The contents of this book are extremely well suited to hospital doctors of a wide variety, but the style and layout is tailored to try and encompass the very broad readership hoped for. The pedigree of the author is not in doubt, and as might therefore be expected the writing is clear and succinct. Throughout the 359 pages there is a helpful synthesis of evidence and experience to inform discussion about both common and rarer issues, such as whether to close a patent foramen ovale (probably not it seems, p273). There are excellent chapters on risk factors and secondary prevention, and I enjoyed the discussions of diffusion and perfusion weighted MRI, differential diagnosis of amaurosis fugax, the explanation of antiphospholipid syndrome and so on. In other words the content is good and well referenced.

There is an attempt to fish out important facts (presumably for GP's, the main target audience), and to highlight side effects using icons. The 'important facts' were indeed as billed, but the side effects icon served no purpose other than to remind us that drugs and interventions indeed have side effects. This comes to a head on pages 254-255 where eight of the nine questions answered display the eye-catching side effect symbol (the other being labelled an 'important fact')…and all this alarm about aspirin. The contents of these two pages are extremely clear and useful, but not enhanced by icon abuse to a prescribing audience familiar with the concept of side effects. Indeed might so many icons persuade someone less familiar with weighing up risks and benefits (the intended patient readership this time) to avoid aspirin at their peril?

For patients there is an attempt to answer common questions at the end of each chapter, but unfortunately I suspect that even some of these might prove rather difficult to unravel for patients (despite explanation of homonymous hemianopias and suchlike), yet provide little new information for doctors not already covered in the main body of text.

I understand that publishers need to maximise sales, but in this case I worry that the intended breadth of readership might prove an achilles heel, and result in a good book being missed by hospital doctors (who would benefit most from its contents) and not so well received by its main target audience.

A.W.Michell, Cambridge

Single-case and small-*n* experimental designs: a practical guide to randomisation tests

Author: John B. Todman & Pat Dugard
Publisher: Lawrence Erlbaum Associates, Mahweh, New Jersey & London
ISBN: 0-8058-3554-7
Price: £47.95

Classical parametric and non-parametric analyses make assumptions about how experimental data is related to the population from which it is drawn, which are valid for large series but less so in small series. Randomisation (or exact) tests use the real experimental data and make far fewer assumptions about its distribution and are therefore more appropriate in studies with less than 10 in each group, or single cases with less than 50 observations.

This book explains the arguments for and against statistical, as opposed to visual, graphical analysis in single case studies, and in general it should be possible to design a study to allow both. Randomisation tests require a lot of computation, which has only been widely available as personal computers became more powerful. Even now it may take several minutes for each analysis, as opposed to a few seconds with classical parametric tests.

Fortunately a CD containing macros to do the analysis using Excel, SPSS or Minitab is included with this book. Eight different study designs and their analysis are explained, and worksheets are included on the CD in which to enter your experimental data. These range from a single case cross over design, in which the time of change from baseline to intervention is chosen randomly, to a small group repeated measures test. The power of these tests to identify a particular outcome is also described, and references to help design your own specific tests are given.

This clearly written and easily read book is very useful source of information on how to design single case and small case studies with a view to statistical as well as visual analysis. I have found it difficult to find such advice, and the software solution to analyse the results, elsewhere. I think this book would be very useful addition to any department planning single case and small series research, and its modest cost will immediately be offset by the savings from not buying exact tests modules for other statistical software.

Stephen Kirker, Cambridge

Deep brain stimulation for unusual movement disorders

The development of deep brain stimulation in the treatment of Parkinson's disease as an effective and safe therapy has led clinicians to explore the treatment of disorders for which there has been no effective treatment. Such therapy does not require the ablation of tissue and as a result does not preclude future newer treatments should they become available. Furthermore, because such electrodes can be externalised for extended periods the clinician and patient can both assess any benefits that may accrue. Given that no permanent lesions are made it is also possible to implant several electrodes in different target sites to select the best target for long term effects.

We present cases where deep brain stimulation has proven to be effective in some unusual movement disorders.

Camptocormia

A 38 year old gentleman was referred with a 10 year history of severe repetitive spasms of the abdominal muscle such that sitting up or standing were impossible. He had a brief course of anti-psychotics for severe depression several years previously, which may have been relevant to the causation. On the understanding that pallidal stimulation in Parkinson's disease can improve dystonic aspects of the condition, the patient was offered bilateral pallidal deep brain stimulation.

The electrodes were then externalised for a week's observation period. During this period stimulation allowed him to sit unaided and he perceived the benefit to be significant enough to go onto full implantation of the Kinetra pulse generator. Within six months he was able to walk with one stick.

After 18 months his symptoms recurred. It was found that one of the leads had fractured and after surgical re-implantation, his symptoms rapidly improved. This confirmed that the benefits seen were due to deep brain stimulation and not psychological.

Anterocollis

A 79 year old gentleman was referred with severe anterocollis of several years duration. Botulinum injections were not feasible given the muscle groups involved. He developed severe swallowing problems with repeated episodes of aspiration pneumonia requiring several admissions to the local intensive care unit. Spasmodic torticollis we knew responds to bilateral pallidal stimulation and on this basis he consented to surgery. Under general anaesthesia bilateral pallidal electrodes were implanted and externalised. He was then observed over a week and it was noted that his neck posture was improving. He therefore underwent a full implantation of the pulse generator.

Six months after surgery he is now able to eat and drink normally and his neck has assumed an erect posture. Interestingly, EMG studies of his neck muscles before stimulation showed that the sternocleidomastoid muscle on the right was active but the contralateral was not, nor were the trapezius muscles bilaterally. With chronic stimulation normal activity has returned to all muscle groups.

Lesch-Nyhan Syndrome

Although not as obvious as the above two as a movement disorder, Lesch-Nyhan is a genetic condition characterised by crippling self-mutilation associated with dystonia. Taira *et al* have described bilateral pallidal stimulation in a 19 year old man with the intention to alleviate the dystonia. Interestingly, his self-mutilating behaviour also improved.

Senile Chorea

A 67 year old right handed lady developed choreic movements over 6 years affecting the right limbs, trunk, face, tongue and to a lesser extent the left side of her body. Investigations, including MRI and genetic testing, had failed to identify a cause for the symptoms. Activities of daily living were difficult, and she was unable to mobilise outside, due to poor mobility and embarrassment. Left pallidal and Vop thalamic electrodes were implanted in view of the predominantly right-sided symptoms. Pallidal stimulation almost completely abolished the right limb movements, and temporarily improved the orofacial chorea.

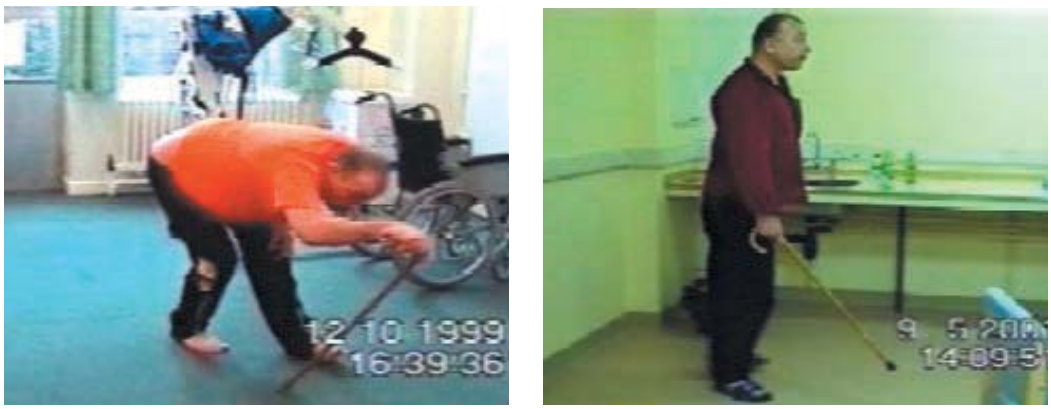
However, although after six months chorea in the right limbs remained suppressed, left-sided movements had become more prominent. This was addressed by initiating thalamic stimulation after turning off the pallidal stimulator. This eliminated almost all choreoform dyskinesia and has continued to do so for two years.

Choreo-acanthosis:

Burbaud *et al* have reported a case of a 43 year old man with choreo-acanthocytosis and severe oro-mandibular and truncal spasms. He was treated with bilateral stimulation of the Vop nucleus of the thalamus with successful alleviation of spasms such that he was able to eat and walk again.

Professor Tipu Z Aziz studied physiology at University College London graduating in 1978. During this time he developed his keen interest in the role of the basal ganglia in movement disorders. He studied medicine at King's College London (1978-1983) and obtained his surgical fellowship in 1987 following which he pursued a career in neurosurgery. He is currently a consultant neurosurgeon at the Radcliffe Infirmary, Oxford and Charing Cross Hospital London. He is an expert in functional neurosurgery and has a special interest in the surgical treatment of movement disorders.

Mr. John Yianni trained at University College London, qualifying in 1996. He completed his basic surgical training in Oxford, obtaining his surgical membership in 1999. Subsequently he joined the Oxford Movement Disorder Group based at The Radcliffe Infirmary Oxford, where he is currently clinical research fellow working towards an MD. His field of interest includes stereotactic functional neurosurgery for movement disorders, in particular dystonia.



Camptocormia. Pre-op (left) - Involuntary truncal flexure making normal gait impossible and causing lumbar pain. Post-op (right) - Able to stand and walk upright for short distances without support.

Senile Chorea. Pre-op (left) - Continuous choreic movements of right arm, face and tongue. Beginning to affect left hand and foot. Post-op (right) - Right limb chorea abolished with temporary improvement in other areas.

> "What is emerging is that quite a few unusual movement disorders may well have dystonia as the underlying aetiology."

Head tremor

Head tremor in isolation has not generally been considered an indication for surgery yet there is a report of two cases of head tremor that have been successfully treated by bilateral thalamic stimulation.

What is emerging is that quite a few unusual movement disorders may well have dystonia as the underlying aetiology. If this is so, bilateral pallidal or thalamic stimulation may well be of benefit. Given the inherent risks of surgery this should be offered only when all medical therapies have been tried to no effect. At the same time it should not be withheld until too late for benefits to accrue i.e. after postural abnormalities have become fixed.

The nature of such cases renders it unrealistic to expect randomised controlled studies of treatment efficacy, hence it is important that carefully studied case reports are published. Nevertheless, with time it is fairly clear that the number of established conditions responsive to deep brain stimulation can only expand.

Future possibilities

Levo-dopa resistant akinetic disorders are conditions for which medical treatment is palliative only. Such conditions as progressive supranuclear palsy and multi-system atrophy in common with Parkinson's disease show degeneration of a brain stem nucleus called the pedunculopontine nucleus (PPN). The PPN receives an inhibitory input from the medial pallidum which is increased in parkinsonian conditions. It has been well recognised that in rodents stimulation both chemically and electrically induces movement. We have studied the effects of stimulating the PPN in the parkinsonian primate model and have shown that microinjections of bicuculline (a GABA antagonist) has a very profound effect on reversing akinesia. Given this, it is likely that deep brain stimulation of this site may be of use in alleviating the "on" medication freezing in late Parkinson's disease and hopefully in L-Dopa resistant parkinsonian disorders.

References:

Berk C, Honey CR. *Bilateral thalamic deep brain stimulation for the treatment of head tremor.* Report of two cases. J Neurosurg. 2002 Mar;96(3):615-8.

Burbaud P, Vital A, Rougier A, Bouillot S, Guehl D, Cuny E, Ferrer X, Lagueny A, Bioulac B. *Minimal tissue damage after stimulation of the motor thalamus in a case of chorea-acanthocytosis.* Neurology. 2002 Dec 24;59(12):1982-4.

Nandi D, Aziz TZ, Giladi N, Winter J, Stein JF. *Reversal of akinesia in experimental parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus.* Brain. 2002 Nov;125(Pt 11):2418-30.

Nandi D, Parkin S, Scott R, Winter JL, Joint C, Gregory R, Stein J, Aziz TZ. *Camptocormia treated with bilateral pallidal stimulation.* Journal of Neurosurgery, Vol.97, 461-466, 2002.

Taira T, Kobayashi T, Hori T. *Disappearance of self-mutilating behavior in a patient with lesch-nyhan syndrome after bilateral chronic stimulation of the globus pallidus internus.* Case Report. J Neurosurg. 2003, Feb, 98(2):414-416.

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We would like to thank Medtronic for their sponsorship of this article.

Clinical anatomy of the radial nerve

In the immortal words of Homer Simpson , one of the great commentators on modern society, "Alcohol is the cause of, and solution to, all of life's problems!". It certainly causes its fair share of disease and injury in the peripheral nervous system and this includes the radial nerve. This nerve is the most frequent target of that peculiar alcohol related neuropathy,"Saturday night palsy". So this issue I thought I might briefly review the clinical anatomy of the radial nerve.

Anatomy

The radial nerve is the main continuation of the posterior chord of the brachial plexus. Consequently it receives branches from each nerve root from C5/T1. After leaving the axilla the nerve gives three sensory branches (Table 1) and innervates the three heads of the triceps muscle and the small anconeus muscle (this latter muscle being used by many Neurophysiologists to assess for a decrement on repetitive stimulation in myasthenia gravis). The nerve then snakes its way down the humerus in the spiral groove, after which it gives muscular branches to brachioradialus, the long end of the extensor carpi radialus and supinator and then bifurcates into a sensory and motor branch. The sensory branch, the superficial radial nerve travels in the forearm over the radial bone and over the extensor tendons to the thumb where it can easily be palpated and supplies most of the dorsal surface of the hand. This superficial location makes the radial nerve a useful marker for assessing sensory axonal loss in polyneuropathy.

At the elbow the motor branch of the radial nerve becomes the posterior interosseous nerve and enters the extensor compartment through the supinator muscle under the arcade of Frohse (Figure 1). There it supplies the remaining extensors of the wrist, thumb and fingers (Table 2).

For the anoraks amongst you the Posterior interosseous nerve does have some sensory branches to the interosseous membrane and articulation between the radius and ulna.

Table 1: Sensory Branches of the Radial Nerve

Arm
Posterior Cutaneous Nerve of the Arm
Lower Lateral Cutaneous Nerve of the Arm
Posterior Cutaneous Nerve of the Forearm
Forearm
Superficial Radial Nerve

Clinical

Radial Neuropathy at the Spiral Groove

By far the most common radial neuropathy is due to external compression or trauma to the radial nerve in the spiral groove. The external compression can occur because of immobilisation of the arm. After intoxication, the classical description is that the patient falls asleep with the arm draped over a chair, "Saturday Night palsy". It is my own experience that when getting history from these patients the story of intoxication is often clear, but patients have difficulty in remembering which chair may have been involved. The close association with the humerus in the spiral groove also renders the radial nerve vulnerable to injury when there is fracture of the shaft of the humerus (figure 2). In some cases this injury is iatrogenic when the orthopedic surgeons repair the humerus with meccano. Clinically these patients present with wrist drop, weakness of finger extension, sensory disturbance and sensory loss in the distribution of the superficial radial nerve. There is some weakness of supination but elbow extension is spared as the branches to the triceps originate before the spiral groove.

Other Radial Neuropathies

The radial nerve may also be vulnerable to external compression from inappropriate use of crutches. In these patients, in addition to wrist drop and weakness of supination there is also weakness of elbow extension and sensory loss in the distribution of the more proximal cutaneous branches. The posterior interosseous branch of the radial nerve may also become entrapped in the supinator muscle under the arcade of Frohse. This is easily distinguished from injury or compression in the spiral groove by the following features:

1. There is no sensory involvement.
2. The sparing of the brachioradialus and the long end of the extensor carpi radialus results in radial deviation when the patient attempts to extend the wrist. Rarely, the superficial radial nerve may become entrapped by tight fitting watches, bands, bracelets, handcuffs. This results in sensory symptoms without wrist drop.

Neurophysiological Evaluation

In patients presenting with uncomplicated "Saturday night palsy" I normally start by doing sensory nerve conduction studies from the symptomatic and the contralateral side. It is important to remember to leave the studies for about two weeks after presentation as initially they are likely to be normal. Although it is possible to perform radial motor conduction studies I find it more convenient to localise radial nerve lesions with needle EMG. In the classical "Saturday Night Palsy" there will be denervation in the distribution of the posterior interosseous nerve (for example Extensor digiti communis) and muscles innervated by the main trunk of the radial nerve

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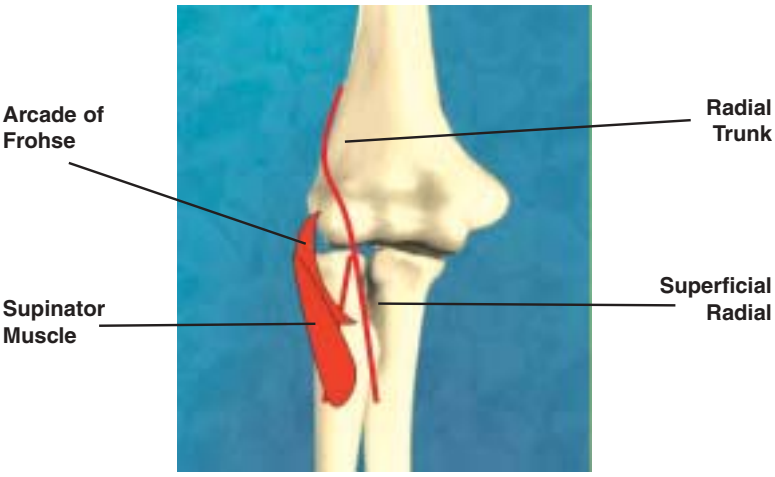


Figure 1: Course of the Radial Nerve at the elbow: after the spiral groove the nerve divides into the posterior interosseus and superficial radial branches, the posterior interosseus passes into the supinator under the fibrous arcade of frohse.

below the spiral groove will also be involved (Brachioradialus for example). However, triceps will be spared. In a Posterior interosseous Nerve Palsy, not surprisingly, the superficial radial nerve response is spared and there is denervation in the distribution of the posterior interosseous nerve only. In traumatic radial nerve injury, there may be additional injury to the Brachial plexus so it is worth examining muscles supplied by the posterior chord but not the radial nerve (the deltoid for instance). It is also worth examining the other main nerves in that limb. It will sometimes be necessary to see patients very early after injury before clear signs of denervation (such as fibrillations) have developed. In those cases the aim is simply to demonstrate whether the nerve sheath is intact or not, and if there are voluntary motor units in muscles supplied below the site of injury then the nerve bundle is at least partially intact. Finally, in those patients presenting with "Saturday Night Palsy" it is worthwhile, if you have time, performing a full neuropathy screen for a sub-clinical alcohol polyneuropathy.

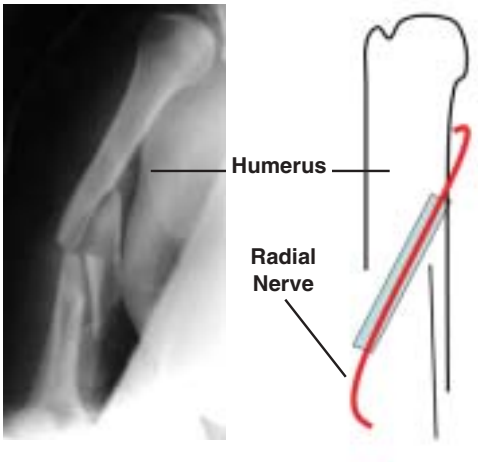


Figure 2: Radiograph from a patient who presented with wrist drop after a fracture of humerus the accompanying schematic shows how the nerve is vulnerable to trauma because of its close relationship to the bone

Table 2: Motor Branches of the Radial Nerve

Arm
Triceps (Three Heads)
Anconeus
Elbow
Brachioradialus
Long head of extensor carpi radialus
Supinator
Posterior Interosseus Nerve
Extensor Carpi Radialus (Short head)
Extensro Digitorum Cmmunis
Abductor Pollicis Longus
Extensor Indicis Proprius
Extensor Pollicis Longus
Extensor Pollicis Brevis

The use of Apomorphine in the older patient

Judging from the media reporting of Michael J Fox and Muhamed Ali, and more recently of Tom Isaacs on his historic walk around the coastline of Britain, one might think that PD mainly affected young males. However, without in any way detracting from the impact upon the lives of these brave young men, the mean age of onset of this disease is typically 60-65 years and problems of motor fluctuations do not commonly start to occur until more than five years have elapsed from diagnosis. Consequently, numerically the majority of complex problems will be found in patients in their seventh or eighth decade. In contrast to the younger patient who is more susceptible to the more dramatic motor fluctuations and dyskinesias, the older patient whilst certainly not immune to their occurrence, is more troubled by psychiatric sequelae, and particularly dementia[1]. What then is the role of apomorphine in this patient group?

Apomorphine (APO-go®) is a dopaminergic agonist with a similar pharmacological profile of action to dopamine, exhibiting both D1 and D2 type effects. It has proven efficacy in the treatment of Parkinson's disease (PD) and is now widely used in the treatment of advanced Parkinson's disease. Previous articles in this ACNR series have demonstrated this and alluded to the theoretical and practical issues that arise. Currently, it has to be given by intermittent subcutaneous injection or by continuous infusion, which limits its use to cases of Parkinson's disease that are refractory to oral medication. Other dosage forms have been studied - and it can be administered by sublingual, intranasal, transdermal and rectal routes, but each has drawbacks, and we have the greatest experience with subcutaneous injection[2,3]. We published a protocol for its use, and have audited the results of its use as a challenge, and in continued therapy[4].

We have had more than a decade of experience with this dopamine agonist, and our experience confirms that apomorphine is a valuable drug. Our experience was similar to previously published series[3,4].

The demographic details of our patients are shown below.

Total tested n (m:f)	60 (39:21)
Mean Age at test (range - years)	67.5 (45-85)
Mean Age at Onset of PD (range - years)	57.8 (25-82)
Duration of PD (range - years)	9.4 (0.5-32)
Hoehn & Yahr (range)	4.2 (3-5)

Our protocol included pre-treatment with oral domperidone 30 mg thrice daily for a minimum of 48 hours, reducing in chronic use as tolerance develops. Most patients were admitted, partly due to logistics in this rural county, but also because we were using this drug in some quite disabled patients who would have found day-case testing difficult. This aspect remains under review.

We saw a relief of individual patient symptoms in between a third and 100%. We saw good responses in immobility and patients with severe "off" period symptoms including pain, painful dystonia, and control of dyskinesia in a number of patients with continued treatment. A beneficial response was most likely in patients with long duration of disease and younger age of onset, having had a good initial response to levodopa and those without cognitive impairment.

The **mean age at test** for the good responders was 65 which although 5 years younger than the non-responders did not achieve statistical significance. The **age at onset** is significantly different; those who responded well developed PD at 53 years whereas the non-responders had an age at onset of 68 years.

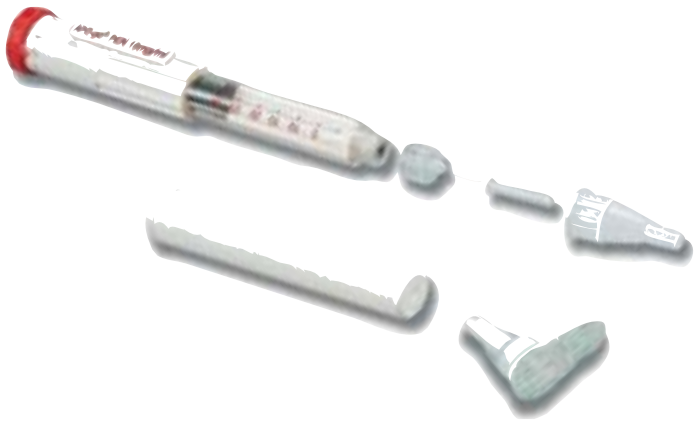
Similarly there was a highly significant difference between those who had had Parkinson's for well over 10 years who had a good response whereas those with a short duration of symptoms (3.2 years mean) had a poor

Dr Doug MacMahon is Consultant Physician with special responsibility for the elderly and Lead Physician, Royal Cornwall Hospital NHS Trust. He has particular interests in Parkinson's disease, community care and rehabilitation. He is past chair of the British Geriatrics Society (BGS) Policy Committee, PDS Nurse steering group, and BGS Parkinson's Section and is a member of several editorial boards. He has written over 70 publications and 19 book chapters and presented at many national and international meetings.

PREDICTORS OF RESPONSE

Parameter Response:	Good	Partial	None	p
n	32	14	10	
Age at test mean (range) years	65.8 (47-74)	66.4 (45-83)	72.9 (47-86)	0.109
Age at onset mean (range) years	53.4 (25-82)	59.1 (36-78)	68.6 (41-83)	0.0075
Gender Male : Female	18 : 14	10 : 4	8 : 2	n.s
Duration of symptoms mean (range) years	12.2 (2-32)	7.4 (0.5-17)	3.2 (0.5-8)	0.0001
Good response to L-dopa	30	10	6	0.013
No response to L-dopa	2	4	4	0.013

The APO-go Pen



response mainly because of inclusion of cases of multi-system atrophy. There is also a strong correlation with the response to levodopa with those patients who had had a good response to also show a good response to apomorphine – and conversely those who had a poor response to levodopa correlated with a poor response to apomorphine. We noted that none of the 5 patients who had cognitive problems or hallucinations responded positively.

Side effects of test doses (n=60) included hypotension (9), dyskinesia (6), drowsiness (4), nausea/faint (2), and confusion (1). Side effects were generally reversible quite rapidly. Patients who had shown a good response to the challenge dose were subsequently offered apomorphine as treatment.

With continued usage and experience the frequency of problematic side effects was reduced. Persisting nausea occasionally occurs despite domperidone. Mild sedation in a few patients and occasional neuro-psychiatric complications have been seen.

These patients had been using apomorphine for an average duration of 4 years (range 1-6yrs). 21 have remained on bolus therapy with a typical average daily dose of about 9 mg (range 2-20 mg.), 8 of them went onto the syringe drivers with a typical daily dosage of 80 mg per day (range 40-120mg.) typically given over 12 hours.

Subsequently, five have died (3 syringe driver patients, 2 bolus apomorphine takers) showing the mortality in this group of patients. Six have discontinued (4 syringe driver patients, 2 bolus apomorphine takers) because of side effects and some of the bolus patients have decided to stop for various reasons. Two have had surgery, one of those has discontinued apomorphine, one continues with bolus doses.

In long term use, skin nodules and bruising are common side effects, the prevalence of which has been reduced by dilution of apomorphine with equal volumes of normal saline. Ultrasound was used to disperse subcutaneous nodules.

One particularly gratifying anecdote is of a widow who was able to stay at home rather than be admitted to a nursing home for about 4 years by use of apomorphine. Local district nurses supported her and although experiencing some visual hallucinations – typically of a black cat coinciding with the onset of relief of her PD symptoms – she welcomed these since her disease was so well relieved by this drug. Ultimately she died from an unrelated cause (a myocardial infarct).

Conclusions

Apomorphine has established its place in the treatment of patients with Parkinson's disease and some patients with parkinsonism as a valuable mode of treatment when patients have become refractory to oral drugs. It is useful in patients in whom there is diagnostic or therapeutic uncertainty, and for those patients who are considered unsuitable for neurosurgery.

Whilst the Parkinson's or movement disease clinic is desirable to support the use of this drug, the availability of a specialist nurse is essential. Older patients may need admission for testing, but provided they have shown a good response to oral levodopa and are not demented, they may benefit equally from this drug as do their younger counterparts, and its use can help even quite elderly patients to maintain their independence.

The APO-go Pump

References

1. Friedman A. *Old-onset Parkinson's disease compared with young-onset disease: clinical differences and similarities.* Acta Neurol Scand 1994 Apr;89(4):258-61
2. JR Playfer. *Drug therapy. Parkinson's Disease in the Older Patient.* Eds JR Playfer, JV Hindle. Arnold, London 2001; pp 298-9 ISBN 0 340 75914 3
3. Manson AJ, Turner K, Lees AJ. *Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: Long-term follow-up study of 64 patients.* Mov Disord 2002 Nov;17(6):1235-41
4. DG MacMahon. *The Use of Apomorphine in Clinical Practice.* Advances in Neurology ed G. Stern 1999;80:529-33

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Events Diary

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by August 6th, 2003. An extended version of this diary is available on our website at www.acnr.co.uk

2003

July

FEBS 2003 meeting on Signal Transduction
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ISAN 2003: Advancing Autonomic Neuroscience after the Genome
4-8 July, 2003; Calgary, Canada
Dr Joseph Davison,
E. jdavison@ucalgary.ca
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Learning Disabilities - Focus on Research
7-8 July, 2003; Tel. Susan Hooper on 0115 924 9924 x 42329, or Janet O'Flynn on 0115 924 9924 x 44085

Techniques & Applications of Molecular Biology
7-10 July, 2003; Coventry, UK
Fax. 02 476 523 701,
E. charlotte.moonan@warwick.ac.uk

8th Meeting of the International Society for the History of Neurosciences
7-10 July, 2003; Windsor, UK
www.ishn.org/call2003.htm

Vocational Rehabilitation in Long Term Conditions
9 July, 2003; Leeds, UK
Tel. 0113 3055086, E.
adele.archer@lcmhst-tr.northy.nhs.uk

CNS 2003: The Annual Computational Neuroscience Meeting
6-10 July, 2003; Alicante, Spain
Chris Ploegaert, E. cp@bbf.uia.ac.be, www.neuroinf.org/CNS/cns2003

BSRM/AFRM Spring Meeting
10-11 July, Cambridge, UK
Tel. 01992 638865, E.
admin@bsrm.co.uk

Exercise, Rehabilitation & Brain Repair
10-11 July, 2003; Cambridge, UK
Tel. 01992 638865, E.
admin@bsrm.co.uk

104th Meeting of the British Neuropathological Society
10-11 July, 2003; Glasgow, UK
http://www.bns.org.uk, E.
secretary@bns.org.uk

6th IBRO World Congress of Neuroscience
10-15 July, 2003; Prague, Czech Republic
Tel. 420 28400 1444, Fax. 420 28400 1448,
E. ibro2003@guarant.cz

4th International Conference on Acoustic Neuroma and other CPA Tumours
13-17 July, 2003; Cambridge, UK
Barbara Ashworth, Tel. 01223 847 464, Fax. 01223 847 465

Multidisciplinary Care in Parkinson's Disease & Parkinsonism from Science to Practice - BGS PD Special Interest Group
15 July, 2003; London, UK
Tel. 020 7561 5400, E.
info@mepltd.co.uk

The Role of EEG in Childhood Epilepsy
17 July, 2003; Lingfield, UK
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338,
E. klaird@ncype.org.uk,
www.ncype.org.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
18 July, 2003; Widnes, UK
Sam Loughran,
Sam_loughran@hotmail.com
Tel. 0151 420 7619

EPTA Summer Scientific Meeting
18 July, 2003; London, UK
E. nigel.hudson@phnt.swest.nhs.uk

17th Mexican Congress on Neurological Surgery
19-25 July, 2003; Monterrey, Mexico
Dagoberto Tamez, Tel. 55 55 430 013, Fax. 55 55 430 013, E.
smcirneu@dsi.com.mx

Oxford Summer School on Connectionist Modelling
20 July-1 August, 2003; Oxford, UK
Tel. 01865b 271 353, E.
susan.king@psy.ox.ac.uk

Neural Networks and Expert Systems in Medicine & Healthcare
21-23 July, 2003; Tel. 0114 225 5338, Fax. 0114 225 5337, E.
conference21@shu.ac.uk

August

Learning Disabilities
7 August, 2003; Gloucester, UK
Epilepsy Action, Tel. 0113 210 8800,
E. rwood@epilepsy.org.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
15 August, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

11th International Congress of the IPA
17-22 August, 2003; Chicago, US
Tel. 001 847 784 1701,
Fax. 001 847 784 1705,
E. chicago2003@ipa-online.org

Pain in Older People
19 August, 2003; Stoke on Trent, UK
Mrs Olwyn Mander,
Tel. 01782 554995, Fax. 01782 747319,
E. mea07@keele.ac.uk

17th World Congress on Psychosomatic Medicine
23-28 August, 2003; Waikoloa, Hawaii
Tel. 001 808 547 4406, Fax. 001 808 585 5040, E. icpm2003@aol.com

12th International Symposium on Intracranial Pressure & Brain Monitoring (ICP2003)
24-28 August, 2003; Hong Kong
Tel. +852 2632 2951, Fax. +852 2647 3074, E. icp2003@cuhk.edu.hk,
www.surgery.cuhk.edu.hk/icp2003

23rd International Summer School of Brain Research
25-29 August, 2003; Amsterdam, The Netherlands
Fax. 31 20 696 1006,
E. o.pach@nih.knaw.nl

1st Congress of the International Society for Vascular Behavioural & Cognitive Disorders
28-31 August, 2003; Goteborg, Sweden
Tel. +46 31 708 60 00,
E. vas-cog2003@gbg.congrex.se
www.congrex.se/vas-cog2003

7th Congress of the European Federation of Neurological Societies
30 August - 3 Sept, 2003; Helsinki, Finland Tel. +43 1 880 00 270, Fax. +43 1 88 92 581, E.
Headoffice@efns.org

September

PD Academy - A Masterclass in the Management of Parkinson's Disease
September 2003; Cornwall, UK
E. events.redpublishing@btopenworld.com

IX International Congress of Inborn Errors of Metabolism
2-6 September, 2003; Brisbane, Australia
Tel. +61 2 9290 3366,
Fax. +61 2 9475 0364

8th European Meeting on Glial Cell Function in Health & Disease
3-6 September, 2003; Berlin, Germany
http://euroglia2003.glia.mdc-berlin.de/

The Paradox of Sleep: An Unfinished Story
3-4 September, 2003; Lyon, France
Dr Peirre-Herve Luppi, Tel. + 33 478 771 003, Fax. +33 478 771 022
E. luppi@sommeil.univ-lyon1.fr

8th Congress of the World Muscle Society
3-6 September, 2003; Szeged, Hungary
www.wms2003.com/info.htm

European Association of Neurosurgical Societies 2003 Congress
7-12 September, Lisbon, Portugal
Fax. 351 218 473 746,
E. stephanie.garfield@virgin.net

British Aphasiology Society 2003
8-10 September, 2003; Newcastle, UK
E. dorothy.bell@ncl.ac.uk

IPCAT 2003; Workshop on Information Processing in Cells & Tissues
8-11 September, 2003; Lausanne, Switzerland
Christof Teuscher, Tel. 0041 21 693 66 30, Fax. 0041 21 693 37 05

4th National Conference on Falls & Postural Stability
9 September, 2003; London, UK
Hampton Medical Conferences, Tel. 020 8977 0011, Fax. 020 8977 0055
E. hmc@hamptonmedical.com

European Regional Meeting of the Cognitive Science Society - EuroCogSci2003
10 September, 2003; Osnabruck, Germany
Tel. +49 541 969 4830, Fax. +49 541 969 6229, E. eurocogsci03@uos.de

MS Trust Study Days
10 September, 2003, Penrith, UK
Tel. Catherine Thornley on 01462 476704.

11th Congress of the International Headache Society
13-16 September, 2003; Rome, Italy
Tel. +31 20 6793218, Fax. +31 20 6758236, E. IHC2003@lgce.nl

British Sleep Society 15th Annual Scientific Meeting
14-16 September, 2003; Cambridge, UK
E. martin.king@papworth.nhs.uk
Fax. 01487 840618

XV International Congress of Neuropathology
14-18 September, 2003; Turin, Italy
Newtours spa, Via San Donato 20, 50127 Florence, Italy.
Tel. 0039 055 33611,
Fax. 0039 055 336 1250,
E. icnp2003@newtours.it

Epilepsy Nurse Association Annual Conference
15-16 September, 2003; London, UK
Christine Morley, Tel. 01482 617635,
E. christine.morley@herch-tr.nhs.uk

Neuro-Behavioural Rehabilitation in Severe Brain Injury: Challenging Behaviour & Complex Neuro-Disability
16 September, 2003; London, UK
Tel. 020 8780 4500 x 5236,
E. conferences@rhn.org.uk

6th Annual Advanced Rehabilitation Course, University of Nottingham
16-19 September, 2003; Nottingham, UK
Tel. 0115 924 9924 x 42378,
E. janet.o'flynn@nottingham.ac.uk

IFCN/AAEM International Congress
16-20 September, 2003; San Francisco, US
E. saadkins@aaem.net

Central Nervous System Infections
17 September, 2003; Liverpool, UK
Emily Thompson, tel. 0151 298 2999,
E. mnt@gnc.u-net.com

1st International Symposium on CNS Germ Cell Tumors
17-19 September, Kyoto, Japan
Fax. 81 49 294 4955, E.
rnishika@saitama-med.ac.jp

British Society of Neurological Surgeons Autumn Scientific Meeting
17-19 September, 2003; Cardiff, Wales
E. admin@sbns.freeserve.co.uk

19th Congress of ECTRIMS
17-20 September, 2003; Milan, Italy
Professor Dr Giancarlo Gomi, Tel. +390 2 2643 2881, Fax. +390 2 2170 2881, www.akm.ch/ectrims2003,
E. info@akm.ch

12th Nordic Meeting on Cerebrovascular Diseases
17-20 September, 2003; Oslo, Norway
Tel. +47 22561930, Fax. +47 22560541,
E. stroke@congrex.no

35th Annual General Meeting of the European Brain & Behaviour Society
17-20 September, 2003; Barcelona, Spain
http://seneca.uab.es/ebbs-2003/

International Association of Biomedical Gerontology Congress
19-23 September, 2003; Cambridge, UK
Aubrey de Grey
E. ag24@gen.cam.ac.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
19 September, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

Signalling Processes & Structures in Nervous System in Health & Disease
19-20 September, 2003; Dresden, Germany
Tel. +49 03916713088,
Fax. +49 03916713097,
E. georg.reiser@
medizin.uni-magdeburg.de

International Syncope Conference
20-22 November, 2003; Newcastle upon Tyne, UK
E. info@syncope-conference.co.uk

16th Congress of the European College of Neuropsychopharmacology
20-23 September, 2003; Prague, Czech Republic
E. secretariat@ecnp.nl

MSIF 2003 International Conference
20-24 September. 2003; Berlin, Germany
E. dmsg@dmsg.de, www.dmsg.de

16th ECNP Congress 2003
20-24 September, 2003; Prague, Czech Republic
E. ecnpreg@congrex.nl

Epilepsy Action Meeting
30 September, Wales, UK
Epilepsy Action, Tel. 0113 210 8800, E. rwood@epilepsy.org.uk

October

ABN Autumn Scientific Meeting
1-3 October, 2003; Glasgow, UK
E. karen.reeves@theabn.org

National Tremor Foundation 2003 Conference
3 October, 2003; Chester, UK
Tel. 01708 386399, Fax. 01708 378032,
E. tremorfoundation@aol.com

XIth World Congress of Psychiatric Genetics
4-8 October, 2003; Quebec, Canada
CHUL Research Centre, RC-9800, 2705 boul Laurier, Sainte-Foy, Quebec, Canada. Fax. 001 418 654 2753,
E. psygen2003@crchul.ulaval.ca,
www.psygen2003.ca

2nd Emirates Neuroscience Conference
4-9 October, 2003; Dubai, UAE
Tel. +971 4 2666416, Fax. +971 4 2666894, E. jiqbal49@emirates.net.ae

Panamerican Congress of Neurology
8-12 October, 2003; Santiago, Chile
Tel. +56 2 232 9347, Fax. +56 2 231 9287, www.soc-npsnc.cl

Management of Childhood Epilepsy
9 October, 2003; Lingfield, UK
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338,
E. klaird@ncype.org.uk,
www.ncype.org.uk

New Directions in Dementia
9 October, 2003; Liverpool, UK
Tel. 01517 269002, Fax. 01517 268228,
E. joanna@evensis.com

25th International Epilepsy Congress
12-16 October, 2003; Lisbon, Portugal
Tel. +353 1 4097796, F. +353 1 455 4648, E. Info@epilepsycongress.org

Commissioning of Services for Complex Neurological Disorders
14 October, 2003; London, UK
Tel. 020 8780 4534,
E. kandrews@rhn.org.uk,
www.rhn.org.uk/institute

MS Trust Study Days
15 October, 2003, Peterborough, UK
Tel. Catherine Thornley on 01462 476704.

Alzheimer's Disease - Dementia Care in an Ageing Society
15-17 October, 2003; Kyoto, Japan
Tel. +81 75 823 6544,
Fax. +81 75 823 6545

18th Congress of SOFMERR
16-18 October, 2003; Lille, France
Tel. 02 51 464848

North West Nurses Epilepsy Forum (Learning Disabilities)
17 October, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

EPTA Autumn Scientific Meeting
17-18 October, 2003; Manchester, UK
E. nigel.hudson@phnt.swest.nhs.uk

ACTRIMS
19 October, 2003; California, USA
Tel. 001 212 476 0465, Fax. 001 212 499 0741, E. actrims@nmss.org

Emotions 2003, The (Non) Expression of Tilburg
19 October, 2003; Netherlands
E. Emotions2003@tilburguniversity.nl

ANA Annual Meeting
19-22 October, 2003; San Francisco, US
Tel. 952 545 6284, Fax. 952 545 6073,
E. lorijanderson@msn.com

Rehabilitation Medicine, Community Services & Assistive Technology
21 October, 2003; London, UK
E. enquiries@empowernet.org

3rd International Course on Carotid Angioplasty and other Cerebrovascular Interventions
23-25 October, 2003; Frankfurt am Main, Germany. Fax. 49 6 106 770 384,
E. nkoebke@convents.biz

10th Annual Meeting of the American Society of Neurorehabilitation
23-26 October, 2003; Tucson, USA
www.asnr.com/meeting/10th.htm

Vascular Dementia
23-26 October, 2003; Prague, Czech Republic
Kenes International, PO Box 50006, Tel Aviv 61500, Israel. Tel. +972 3 5140018/9, Fax. +972 3 5172484

Developing Epilepsy Services
30 October, 2003; Aberdeen, UK
Epilepsy Action, Tel. 0113 210 8800,
E. rwood@epilepsy.org.uk

Weekly CME in London
31 October-7 November, 2003; London, UK
Michael Kessler, Tel. 0800 334 6578, Fax. 404 252 2728,
E. mk@worldwidecme.com

November

MS Trust 7th Annual Conference
2-4 November, 2003; Harrogate, UK
Tel. MS Trust on 01462 476704.

New Neurosurgery for Children
5 November, 2003; London, UK
Tel. Melanie Armitage, RSM on 020 7290 3934, Fax. 020 7290 298.

ISPRM Satellite Symposium – Botulinum Toxin Type A : Sustaining improvements and delaying surgery in spasticity

May 2003, Prague

This satellite symposium extended to nearly most of the afternoon because of significant interest and interactive discussions. As the audience entered the large arena they were provided with an interactive hand-held remote control system to partake in the interactive symposium. It certainly had overtones of the popular television series 'Who Wants to be a Millionaire?'

The symposium was ably chaired by Dr Anthony Ward who started the proceedings with an introductory talk on Botulinum Toxin Type A.

The interactive audience participation gave a clear feedback from the projected bar charts on the screen, that the majority of the audience were clinicians involved in rehabilitation medicine; which was not surprising as this was the World Congress in Physical and Rehabilitation Medicine.

The first presentation was a double act of Dr. Guy Molenaers from Leuven in Belgium along with his senior physiotherapist Kaat Desloovere, on the applications of Botulinum toxin Type A in children with cerebral palsy and its potential to delay and prevent surgery. This was certainly a slick presentation which used a combination of dual projections, video clips, interactive discussions, and an element of information overload of gait analysis data in these children. In cerebral palsy the problems were primary because of problems related to the neuronal lesion affecting tone, balance, selectivity and strength. This then leads on to secondary problems of contractures and bony deformities and later on to tertiary problems of coping responses and obvious gait abnormalities.

> "The expert speakers and the audience feedback confirmed that Botulinum Toxin Type A did lead to sustained improvements and did delay surgery in spasticity"

The clear message was of an integrated inter-disciplinary multi-level approach, with management and disease spectrum to be considered in continuum. Of note, higher dosages of toxin of 25 units/Kg were used in these children of age range from 2–10 years of age, procedure under general anaesthesia, after a detailed assessment involving gait analysis and EMG studies. Post injections they used daytime leaf spring orthoses, followed by nighttime resting orthoses with additional intensive physiotherapy at an optimal input of 3 sessions per day. It was evident that there was potential to delay and prevent surgery in relevant cases with a decrease in associated hospital costs, decreased risks and improved integration of these children in society. The parting message of the presentation was that more important than price is the value of appropriate intervention and management.

The next presentation was by Dr Franco Molteni from Italy, on the use of BOTOX in adult spasticity of the lower limbs. Quoting several published studies, Dr Molteni then went on to to present a variety of video case studies which demonstrated that 10 metres walk and calculation of walking speed along with video clips of the patients' gait were notable outcome measures of the patient management.

Professor Petr Kanovsky's presentation on BOTOX in adult spasticity involving upper limbs was the next presentation. Being from the home team, it was a succinct presentation which provided a reminder of the multicentre, double-blind study published in the NEJM last year, but more importantly updated delegates on the results of the open label study which proves the benefits of BOTOX are sustained for a long period of time. These results are due to be published this year.

The next presentation was of video case studies with interactive discussion by Dr Guy Molenaers and his team, in which they addressed dose selection and targeting muscles for Botulinum Toxin Type A injections in cerebral palsy management. It was reassuring to note that 70% of the audience agreed with, what was the actual treatment modality in these cases much to Dr Molenaers' obvious relief.

The meeting did overrun by about 25 minutes, but it was time spent in a worthwhile manner. It was evident that established experts agreed with the management strategies and the not-so-expert group were able to pick up most important pointers to assist in their management protocols.

In conclusion, the expert speakers and the audience feedback confirmed that Botulinum Toxin Type A did lead to sustained improvements and did delay surgery in spasticity.

Dr Jai Kulkarni,
Manchester Royal Infirmary

Anthony Ward: Chair of the ISPRM satellite symposium

Guy Molenaers and his team presented video case studies with an interactive discussion

Petr Kanovsky discussed BOTOX use in upper limb spasticity

Franco Molteni: discussed the use of BOTOX in adult spasticity of the lower limbs

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Consortium of Multiple Sclerosis Centres

May, 2003; San Diego, USA

Neurologists interested in multiple sclerosis should take notice of the Consortium of Multiple Sclerosis Centres. It was set up in 1986 by a panel of neurologists who felt that the National Multiple Sclerosis Society of the US was too focused on aetiology and cure, neglecting care, in the widest sense, of people with multiple sclerosis. To begin with their work was perhaps more fluffy than most neurologists would be comfortable with. But they have recently widened their scope to evangelise good neurological practice. For instance, at this meeting they held informative sessions on standards in CSF analysis and MRI techniques. A month ago, they held a meeting on the significance of neutralising antibodies in interferon therapy, which was considered too highly charged to be held in the US and so took place in London. Here are my highlights:

Find out more about the CMSC at www.mscare.org

- One of the sexy topics of multiple sclerosis research at present is cortical pathology. It seems we had forgotten that the grey matter contains myelinated fibres. Unpublished data from Bo and colleagues in Norway was presented to show that up to 24% of frontal cortex (10% of parietal cortex) may be demyelinated in multiple sclerosis patients.
- As usual, there was much talk at this conference about the need for early treatment of multiple sclerosis. Yet, interestingly, I was unable to find a single US neurologist who had adopted the new "McDonald criteria" for diagnosis of MS in their practice. This allows for the diagnosis of definite multiple sclerosis after one clinical event, if a scan three months later shows an active lesion.
- Epidemiological studies, the rockbed of multiple sclerosis research, are becoming more and more widespread. For instance, the first such studies in Latin American countries reported a prevalence of 1-5 / 100,000, which does not make a lot of sense when disease incidence was also recorded at 1 / 100,000. Typically, when prevalence is measured again, it goes up; witness the 2002 prevalence of 49 / 100,000 in Novosibirsk, a city in Asian Russia, compared to 29 / 100,000 in 1986. This probably reflects increased diagnostic accuracy.
- One of the curiosities of multiple sclerosis research has been that bladder symptoms seem to respond to any treatment, however wacky, such as hyperbaric oxygen. So it was no surprise, but nonetheless interesting, to read that a study of 41 patients treated with either standard medical care, acupuncture or combinations of the both all improved post micturition bladder volume and general measure of well-being (the SF-36). Great medicine, that placebo.
- With great fanfare, the "final results" of The EVIDENCE trial were reported. If ever there was a case of flogging the horse that had already bolted, this was it. The juice from the EVIDENCE data has already been squeezed out and we were offered the pith on a silver platter. EVIDENCE was always designed more to help lawyers than clinicians. To recap, Betaseron® was the first interferon onto the US patch. Avonex® appeared next and soon dominated the market, even acquiring hallowed "orphan drug" status with the FDA. This meant that Rebif®, which contains the same active ingredient as Avonex, was not allowed across the Atlantic from Europe, where it was doing very well. So Serono, who make Rebif, quite reasonably set up a trial (EVIDENCE) to mount a legal challenge on Avonex's orphan drug status on the grounds of efficacy. They showed that Rebif was more effective that Avonex at reducing relapses and MRI lesion formation over a 48-week period. This is not terribly surprising, as Rebif is over four times the dose of Avonex (44mcg of IFN-€1a, given subcutaneously three times weekly, versus 30mcg given IM once weekly). Clearly an effect over 48 weeks is neither here nor there to someone in their twenties faced with multiple sclerosis. But the paper was published, the FDA was impressed and the gates for Serono to enter the US multiple sclerosis treasure trove were opened. Fair enough. But Serono maintained blinding in the trial until the last patient had completed 48 weeks treatment, which means that the average time on the trial was 64 weeks. And so they want to tell us the final "final results"….

Alasdair Coles, ACNR Co-editor,
Addenbrooke's Hospital

The 2nd World Congress of the International Society of Physical and Rehabilitation Medicine

18-22 May, 2003; Prague, Czech Republic

Transcranial magnetic stimulation in rehabilitation medicine

Transcranial Magnetic Stimulation (TMS) is beginning to be used for therapeutic purposes in rehabilitation, as well as for assessment.

S. Wolf *et al* (USA) and M. Lissens (Belgium) reviewed the latest developments regarding the clinical applications of TMS. S Wolf *et al* presented TMS applications relevant to stroke rehabilitation. The emergence of TMS for mapping cortical motor areas and Motor Evoked Potentials has made it possible to identify marked plasticity in the motor cortex and to evaluate the extent of motor recovery in stroke patients after rehabilitation. Using this technique, the group reported the effect of intense physical therapy and Constraint Induced therapy on cortical plasticity. Furthermore, TMS is useful in predicting the prognosis of neurologic recovery and thus helping in patient selection for therapy to improve outcome with stroke rehabilitation.

The Belgium group presented an application of TMS, not only in motor recovery and prediction of prognosis, but also in predicting the presence of reflex sympathetic dystrophy and measuring significant defect in central conduction for neurogenic respiratory failure.

A group from Japan presented a case study of 47 year old man with chronic right hemiplegia following left putaminal haemorrhage. He had an improvement in hand function after therapy with TMS.

Neuropathic pain

Dr A A Fisher *et al* from the USA presented an improved technique for the treatment of neuropathic pain. They suggested paraspinal block (PSB) as a specific therapeutic modality in treating patients with neuropathic pain who failed to respond to other conventional therapies. Spinal segmental sensitisation (SSS) is a consistent phenomenon present in patients with neuropathic pain. SSS was diagnosed by the presence of dermatomal, myotomal hyperalgesia and sympathetic abnormalities. They proposed that PSB alleviated pain by reversing SSS to normal sensitivity.

Their prospective study comprised 36 patients with chronic neuropathic pain but with different underlying causes. Half had CRPS and the rest suffered one of the diagnoses of phantom and stump pain, spinal cord injury pain, traumatic brain injury, post herpetic neuralgia or incision neuroma. Patients received weekly intervals of PSB with 1% Lidocaine aiming into the posterior primary ramus at the level of SSS. The mean number of PSB needed was 2.5+/-1.6 and dermatomal and myotomal hypersensitivities were markedly reduced. The authors concluded that pain reduction was still significant 5.9 months follow-up after the treatment and allowed patients to increase participation in rehabilitation programmes.

Psychopharmacology in the treatment of agitation after acquired brain injury

Controlling psychomotor agitation can be extremely difficult in patients with brain injury, either at the acute or chronic phase. Trying to balance between using sedative medication and their negative effects on cognition is a challenge in this patient group. A group from Italy presented the use of olanzapine in agitated behaviour after traumatic brain injury. Due to its widespread receptor blocking mechanism on dopamine, serotonin, muscarinic, alpha adrenergic receptors, and its atypical neuroleptic action with less extrapyramidal side-effects, olanzapine was chosen to control post traumatic (brain injury) psychomotor agitation.

Six young male patients (mean age 35 +/- 15 yrs) with GCS <7 had variable dose of olanzapine (range between 2.5 – 12.5 mg/day) at least for six months. Among them, five patients had post traumatic brain injury and the one subarachnoid haemorrhage. All needed olanzapine once they regained consciousness due to an immediate presentation of psychomotor agitation. The extent of agitation was assessed by ABS (Agitated Behaviour Scale).

The authors concluded that despite the need of further higher evidence based research like RCT, olanzapine proved to be effective and tolerable in severe brain injury of both traumatic and non-traumatic origin. Olanzapine did not cause a marked sedation, although it was started at a low dose of 2.5 mg/day and increased slowly later on. It also restored a better sleep/wake pattern to the patients during early PTA (Post Traumatic Amnesia).

Scientific basis for spasticity outcome measures

Mr Johnson from the UK presented a paper aimed at increasing reliability and validity in measuring spasticity. The author combined clinical Modified Ashworth Scale (MAS) and biomechanical techniques. It was pointed out how difficult it is to measure pure reflex component of spasticity without passive soft tissue visco-elasticity properties which might be involved in the development of contractures clinically. MAS is not completely reliable and valid due to inconsistencies in the hierarchy of its points, and it cannot solely measure reflex component of spasticity. The author's biomechanical principle was based on reflex excitability and measuring reflex amplitude, latency and duration. It was tested in 14 stroke patients and 17 normal subjects. The reduced latency indicated an increased motor neurone excitability but the amplitude reduction was an unexpected result. The author concluded by pointing out the lack of clinical scales and benefit of adding biomechanical techniques in measuring "true" spasticity.

The 2nd World Congress of the ISPRM presented a variety of topics in rehabilitation medicine. Innovative diversities, outcome measures and specific interventions were presented in branches of rehabilitation medicine such as brain and spinal cord injuries, stroke rehabilitation, orthopaedic and musculoskeletal disorders as well as special groups such as geriatric and paediatric populations. I look forward to the next congress of the ISPRM in Brazil in 2005.

Dr Naing, SpR in Rehabilitation Medicine,
St Mary's Hospital, Portsmouth

5th World Congress on Brain Injury

23-26 May, 2003; Stockholm, Sweden

The Fifth World Congress on Brain Injury consisted of plenary, parallel, workshops and poster presentations. The congress abstracts were published in the May issue of Brain Injury, now the official journal for the International Brain Injury Association, who held the congress in association with Kong Li Carolinska Medico Chirurgiska Institute.

Dr J D Macklis questioned the reasons behind the absence of neurogenesis in the post-natal cortex and whether this is due to limits of endogenous precursors potential or lack of signal for neuronal differentiation. Through the manipulation of transplanted or endogenous precursor cells (stem cells), it is possible to achieve cellular reconstruction and cellular repair of complex neocortical circuitry. He confirmed that it is possible for immature neurons to integrate in the adult cortex and join complex circuitry and questioned if it is possible to generate new neurons from precursor cells within the adult brain? And whether such neurons can become functional and contribute to complex behaviour?

Dr O Lindvall from Sweden presented the results from 350 Parkinson's disease patients who have undergone neural transplantation with primary dopaminergic neurons transplanted in the striatum. He provided evidence that the grafted dopaminergic neurons can survive, form connections, re-innervate the striatum and survive for ten years and are able to become integrated functionally in the human brain. Issues relating to availability of foetal stem cells, functional outcome, standardisation and troublesome dyskinesia were raised.

Dr J Frisen outlined the source for stem cell treatment as being embryonic stem cells, neuronal stem cells from embryonic tissue, stem cells from other tissues and finally neuronal precursor cells from the adult brain.

Dr J Weiseberg shifted the emphasis in his paper to assistive technology concentrating on controlling mechanical devices by central brain – machine interface based on peripheral signals collected through surface and needle EMG from multiple muscles and the application of such recordings to the artificial hand project at Lund University.

His paper concluded that it is possible to achieve control of a robot in real time through the reconstruction of movement using brain activity. Current research is concentrating therefore on providing feedback, closed loop control (visual, tactile and direct) cortical feedback, functional control of a device. Improved adaptive algorithms, implantation chips for signal recording and chronic cortical recordings in humans.

Papers in the afternoon started with an epidemiological study from J Bazarian on lateral automobile impacts and the risk of traumatic brain injury. He stressed the fact that the relative number of deaths and the severity of traumatic brain injury (TBI) from such impacts is increasing. H S Goldsmith presented a paper on the potential benefits of omentum transportation in traumatic brain injury. Dr Karen concluded that the autonomic nervous system is dysfunctional during the early stages post injury and therefore heart rate variability following TBD is not a useful predictor of functional outcome.

In a keynote presentation, Mike Hallett introduced the general principles of plasticity in brain injury as the capability of the brain to undergo change and of the continuous competition between body parts for representation in the central nervous system. The use of a body part enhances representation and disuse leads to loss of representation.

Animal experimental studies on the effects of enriched environment on recovery following brain injury were presented by B Johanson. The studies demonstrated increased sprouting and increase cell proliferation in the hippocampus even when the hippocampus was not involved in the primary lesion.

The clinical relevance or recent evidence demonstrating that functional alterations in motor cortex organisation are accompanied by changes in dendritic and synaptic structure, as well as the regulation of cortical neurotransmitter systems, was a paper presented by R Nudo.

E D Beiger's paper on functional imaging following acquired brain injury overviewed all the latest techniques. He emphasised that it is important that such imaging modalities are integrated when assessing acquired brain injury.

A paper on fatigue and attention following TBI concluded that TBI participants in the study with higher fatigue levels as assessed by Visual Analogue Scale for Fatigue (VAS-F) and Fatigue Severity Scale (FSS) exhibited significantly slower and more variable reaction time.

The relationship between persistent post concussional syndrome and the impairment of occulomotor and visuomotor function can provide sensitive markers of cerebral function following closed head injury and could supplement assessments identifying potential post concussive syndrome patients.

Computer assisted problem solving training was a pilot study from Hong Kong.

Further MRI evidence of brain spasticity and neuronal synchronisation during movement preparation after TBI were two interesting papers presented that afternoon.

Quality management; 6,800 TBI patients from injury to re-entry in the community demonstrated the German perspective, was an epidemiological study spanning two years and compared two regions in Germany.

Ylvisaker described a project started in 1995 of community support for adolescents and young adults with cognitive and behavioural disabilities after brain injury. It emphasised the importance of staff training, the apprenticeship of people with brain injury and the cascade of training, the Malec and Mayo Clinic out-patient programme in brain injury rehabilitation, its inclusion criteria, goals, staffing and group treatments.

Leon-Carrion emphasised the need for a combined pharmacological and neuropsychological approach in rehabilitation of people with emotional disorders following brain injury.

B A Wilson presented evidence for successful treatment of every day memory problems using neuropager. The message in this paper was that rehabilitation makes economic and clinical sense and that it is possible to combine theory, scientific methodology and clinical relevance within a rehabilitation programme.

Zafonte discussed advances in the role of dopaminergic agents in brain injury, their mechanisms.

The congress ended with a key note presentation from Zasler on pharmacology therapy in rehabilitation and TBI. This was a detailed review of the up to date pharmacological treatment, its applications, its rules, side effects and the variety of agents available.

Mr Derar Badwan
Consultant in Rehabilitation Medicine,
The Royal Leamington Spa Rehabilitation Hospital

12th European Stroke Conference

May, 2003; Valencia, Spain

This meeting, probably attended by a couple of thousand delegates took place from 21st to 24th May in Spain's third largest city. A significant cohort of vascular neurologists and stroke physicians/care of the elderly physicians from the UK attended, but I think it reasonable to say that particularly amongst the former group there was some disappointment at the content of the meeting. This largely reflects an absence of important clinical trials that have come to fruition recently (with one notable exception – the Asymptomatic Carotid Surgery Trial – although sadly preliminary results of this study were not presented at the ESC).

Clopidogrel continues to be aggressively marketed and a multitude of further trials are planned to follow on from MATCH (clopidogrel plus aspirin versus clopidogrel alone to prevent recurrent (cerebro)vascular events)and there is promise for ximelagatran (a direct thrombin inhibitor) for the prevention of stroke and embolism in patients with AF.

Cerebral microbleeds are increasingly found on haemosiderin sensitive gradient echo MR sequences, many presenting as minor non-disabling stroke or "TIA" which may historically have been thought to be due to small ischaemic stroke. Not just in the elderly (probably reflecting cerebral amyloid angiopathy) but also in the younger patient are such changes being found.

What to do with the PFO in cryptogenic stroke remains a vexing question for the neurovascular clinician. An afternoon session attempted to provide some insight, but it probably gave greater insight into dogmatic practice in some centres than into understanding uncertainty. It became readily apparent that PFOs are being detected in many young patients seeing physicians with nonspecific symptoms such as dizziness and closure is being offered in the belief that the PFO is to blame. We heard from a German centre that has admirable experience in endovascular closure of PFOs in almost 1200 patients although there seems to be a 3% risk of developing AF thereafter (despite or because of closure?). The same unit suggested, after analysing data from 597 patients that the annual cerebral ischaemia recurrence rate after the index event and before the closure was 24% and that this fell to 2% after closure.

This annual recurrence rate is quite at odds with the single prospective study of PFO and/or ASA in cryptogenic stroke (appreciating the former series almost certainly included some patients with definite paradoxical embolism who are likely to be at higher risk) and the casual observer could easily be misled to the belief that any PFO found in any patient with a stroke should be closed. Of course what we need are appropriately designed randomised trials and fortunately these are commencing.

During the final session, recent trial data was presented, the most clinically interesting being findings from the Stroke Prevention by Oral Thrombin Inhibitors in Atrial Fibrillation (SPORTIF III) study and the Women's Health Initiative (WHI).

SPORTIF III looked at the novel oral direct thrombin inhibitor Ximelgatran, which is a fixed BD dosing oral anticoagulant, which achieves therapeutic efficacy on day 1 and requires no blood coagulation monitoring, which is obviously a highly attractive feature. Ximelgatran was compared with dose-adjusted warfarin, with a target INR of 2-3. SPORTIF III was a randomised open-label trial, with blinded end-point assessment involving 3,407 patients at 259 sites in 23 countries across Europe, Asia and Australia. Recruited patients had non-valvular AF plus at least one other risk factor for stroke. 1.6 % of patients per year on ximelgatran had strokes compared to 2.3% on warfarin in the intention to treat analysis. There was a relative risk reduction in stroke of 41% (p=0.018) in the on treatment analysis of Ximelgatran patients vs. warfarin treated. There was no significant difference in the rates of haemorrhagic stroke or fatal bleeding between treatments. The main problem identified with this new drug however, was a greater than 3 times the upper limit of normal elevation of transaminases in 6.5% of patients. This was not associated with any symptoms and reduced after drug cessation.

The WHI study is the first randomised placebo controlled trial of combined estrogen plus progestin in the primary prevention of cardiovascular disease, in healthy post menopausal women. The study included 8,102 women, aged 50-79, in 40 clinical centres across the USA. An excess risk of stroke was found in all age groups, independent of vascular risk factors, including hypertension, diabetes, smoking and hypertension. There were 133 strokes in the HRT treatment group and 93 in the placebo group. For all stroke the intention-to-treat hazard ratio (HR) was 1.33 (95% CI: 1.02, 1.73) This excess risk was apparent in all age groups.

Peter Martin, Consultant Neurologist,
Kirsty Harkness, SpR Neurology,
Addenbrooke's Hospital, Cambridge

'See The Bigger Picture'

2-3 April, 2003; Edinburgh, UK

This conference took place in Edinburgh in April, 2003. It focused on learning difficulties and was aimed at both parents and teachers. It was organised by Mindfield (now called Mindroom) – a charitable organisation set up by a parent who has a child with learning difficulties. More information about this charity can be found at its website: www.mindroom.org. This website is currently being developed and it will (when fully developed) contain information on the different learning disabilities as well as information about its other activities for anyone who is interested.

This was the first conference to be run by the charity, and this attracted an impressive number of experts from abroad and the UK. The presentations covered the main learning difficulties and also the implications for teachers when dealing with children with learning difficulties.

Christopher Gillberg from Göteborg in Sweden started the conference with an interesting overview of research into ADD and ADHD and the change (mainly within Scandinavia) to the use of the term DAMP (which stands for Deficits in Attention, Motor skills and Perception). He explored the distinction between attention deficits (which do not necessarily lead to hyperactivity) and attention deficits linked to hyperactivity. The way diagnosis was carried out was explained and the role of medication (traditionally Ritalin) was considered. In addition, there was emphasis on the need for other types of intervention before medication is used.

The second presentation by the same speaker focused on autism and autistic spectrum disorders, stating that at least four variants have been identified. Again research findings were presented and the origins of autistic spectrum disorders were considered. The evidence suggests a clear genetic link in severe cases; however, brain lesions were also identified as a possible cause. The fact that autistic spectrum disorders often occur with a range of other difficulties was explained. It was suggested that dysfunction in at least four different areas of the brain are associated with autism and that neural dysfunction linked either to genetic factors or brain damage (lesions) was responsible. Autism is not associated with social class or social deprivation (except possibly in severe cases). It was stressed that it was important to treat those with autistic spectrum disorder as people first – and not as 'autistics'. It was also clear that the environment has to adjust to take into account the needs of those with autistic spectrum disorders and that there are interventions that enable those with autistic spectrum disorders to integrate into society more successfully.

This presentation was followed by one by Svenny Kopp (also from Sweden). She concentrated on exploring the incidence of ADHD in girls. The main message from this presentation, which was based on a longitudinal study of girls, was that there is likely to be underdiagnosis of ADHD in girls. Girls are more likely to be diagnosed as having 'learning difficulties' than ADHD even when they present similarly to boys who are diagnosed as ADHD. However, the ratio between boys and girls in terms of diagnosis has changed from 6-9 boys to 1 girl in 1987, to 2.3 boys to 1 girl in 1999.

Another presentation on ADHD – this time in relation to executive function in the brain followed on. It was presented by Thomas Brown from Yale University. It outlined a particular model of ADHD and emphasised (as had the others) that the behaviours exhibited by a child with ADHD were outwith the control of the child. The child with ADHD can display a great deal of concentration when engaged in an activity that motivates him/her; however, this kind of attention is not sustainable when motivation is lacking … and the child is not able to control this. This particular presentation focused strongly on the role of medication for ADHD and stated that no other alternatives had been demonstrated to be of benefit. (more of this later ...)

Finally on the Wednesday there was a presentation from a different perspective. This presentation came from Loretta Giorcelli from Sydney, Australia. Her focus was on how to deal with children with learning difficulties in the classroom. Her approach emphasised the need to work with teachers and support them in developing ways of dealing with the particular difficulties that children with learning difficulties present.

The Thursday sessions started with a presentation by Sam Goldstein from University of Utah (Neurology, Learning and Behaviour Centre). It had an intriguing title – which set the scene for the talk – 'Good days are when bad things don't happen'. This was a quote from a child with ADHD that Sam Goldstein had worked with in his clinic. The message about the causes of learning difficulties were similar to the previous presentations – but this presentation included examples of children that Sam Goldstein had worked with. One particularly interesting example was an adult (diagnosed with ADHD) who had dropped out of school and starting working in a labouring job. However, he gradually realised that he wanted to better himself ... and he finally was admitted to Harvard!

The following session seriously questioned the emphasis placed on Ritalin in treating children with ADHD. One of the earlier speakers had argued that this was the only way to deal with ADHD. Alex Richardson (Senior Research Fellow at Oxford) presented an alternative. Her work has focused on the role of nutrition in developmental disorders and in particular on the role of fatty acids. There is now clear experimental evidence that for some children a change in diet can have a considerable effect on their behaviour and their performance. She quoted an interesting study with a different population – a study carried out in a prison. The difference in behaviour (and reoffending) was striking for a number of participants. There were significant differences between the experimental group who were given a specific diet which included ensuring sufficient fatty acids and those in the control group. Similar studies have been carried out on children with dyslexia – and for some of these children the use of a fatty acid supplement has led to better performance. So there was a clear message – diet can make a difference!

The final main session was presented by Samy Molcho from Vienna. His focus was on the need to interpret non-verbal language of children with learning difficulties. Samy Molcho is one of the most famous mime artists of the 20th century so this was a presentation with a difference! He illustrated his points through his performance (and at times stunned the audience as he appeared in amongst them). However, the message was clear – non-verbal communication is important and an understanding of both our non-verbal messages to others and those from others can greatly enhance our communication. This is especially so when dealing with children who may have difficulties with language.

Finally, one of the parallel sessions explained the issues surrounding investigating children with learning difficulties. This talk came from David Fitzpatrick from the Western General Hospital in Edinburgh. His talk focused on those with severe and global learning difficulties. The main emphasis was on the major diagnostic tools – when and how these should be used. It also considered the impact on a family when a child is diagnosed with GLD (global learning difficulties).

This was a fascinating conference which provided insights into research in this area and also the issues around diagnosis and treatment. There is a CD Rom with transcripts from the conference available from Mindroom. Well worth its £5. For more information please contact: Mindroom on 0131 653 6235 or E.Mail: moreinfo@mindroom.org The new and state of the art website will be launched complete with information, links and professional board at the end of September.

Dr. Elisabet Weedon,
Perth College and UHI Millenium Institute.

Learning Disabilities Conference – Gloucester – 7 August 2003

Areas

Counties – West Midlands, Avon, Dorset, Hampshire, Herefordshire, Worcestershire, Wiltshire, Devon, Cornwall, Somerset, West Berkshire, Gloucestershire, Monmouthshire, & South Wales

Towns – Birmingham, Bristol, Worcester, Droitwich, Gloucester, Hereford, Southampton, Kidderminster, Bath, Weston-Super-Mare, Reading, Slough, Windsor, Exeter, Plymouth, Torquay, Poole, Cheltenham, Tewkesbury, Malvern

Facts and Figures

Venue:	Ramada Hotel & Resort, Matson Lane, Robinswood Hill, Gloucester, GL4 6EA
Date:	Thursday 7 August 2003 (9.30am – 4.30pm)
Booking Info:	0113 210 8778
Target Attendees:	Consultants, Junior Medical Staff, Midwives, GP's, Health Visitors, Specialist Nurses, A&E Staff, Social Workers, Counsellors, Learning Disability Teams, all those with an interest in Teaching
Speakers:	Professor Stephen Brown, Dr Mark Scheepers (Learning Disabilities Consultant), Mary Evans (Community Nurse), Nicola Waycott (Epilepsy Specialist Nurse), Dr Katarzyna Sieradzan (Consultant Neurologist), Mr Kevin Kelly (Epilepsy Specialist Nurse)
Topics:	Clinic & Patient Management, Pharmacology, SIGN Guidelines, National Sentinel Audit & Action Plan, Women's Issues, The Role of the Community Learning Disability Nurse, Children's Learning Disabilities and Surgery, Learning Disability Service v Neurological Service, Epidemiology, Rescue Medication, Risk Assessment, Differential Diagnosis

Local Contacts

Lucy Rollinson, Monica Cooper, Ruth Wood, Judy Stutchberry @ Epilepsy Action, and/or any of the speakers.
E-mail: l.rollinson@epilepsy.org.uk or r.wood@epilepsy.org.uk
Website: www.epilepsy.org.uk

EA shares their knowledge and vision for epilepsy through their conferences, allowing you to get a head start in NHS Planned initiatives & current developments. You are the decision makers whom we intend to collaborate with to improve care and challenge initiatives. Our aim is to raise the awareness of current issues concerning learning disabilities and epilepsy.

Other Conferences

Area	Date	Topic
Kent	19 September 2003	Good Practice
North Wales	30 September 2003	To be arranged
Aberdeen	30 October 2003	Developing Epilepsy Services
Birmingham	20 November 2003	Good Practice
Bristol	27 November 2003	Diagnosis & Epilepsy

epilepsy action

The power of belief; Psychosocial impact on illness, disability and medicine

12 May, 2003; National Museum of Wales, Cardiff, UK

I attended this conference in the hope of acquiring some new perspectives on those patients with significant disability in whom - from a neurological perspective - we are unable to find a cause. These patient's problems may not be susceptible to the reductionist and formulaic approach by which we arrive at a pathological diagnosis and I felt the need to acquire some new behavioural software to help me deal with these patients. This conference, including the banter over coffee, provided this.

All of the talks contained insights and useful frameworks of thinking which can be applied directly to patients with neurological diseases. By emphasising the perspective of the patient and the views they hold, the relevance and appropriateness of the medical model was put into its proper context. As a non-psychologist the following summary will inevitably be open to criticism, but in it I will try and convey some of what was said.

Professor Robert Horne (Brighton) talked about patient's beliefs about their medication and the impact this has on compliance and outcome; both are related to the perceived need for the medication and concerns regarding the side effects. The problem may be more common in chronic conditions, such as hypertension and diabetes, and may become increasingly relevant to neurology as more treatments are introduced which do not alleviate symptoms eg Riluzole.

Professor Irving Kirsch (University of Connecticut) lectured on 'Placebo: The Role of Expectancies in the Generation and Alleviation of Illness'. The opposite of a placebo effect is a nocebo effect and examples of both were described. Placebos are the most studied medication and the effect varies as a function of the colour, the current dose, mode of administration and the brand name of the supposed medication. Placebo effects can also be additive. The importance of paying attention to expectancy – that of the patient and doctor - was emphasised and this is obviously an important component of any form of treatment. Although tongue in cheek, a strong case was put for being able to prescribe placebo tablets for a variety of conditions!

Professor Peter Salmon (University of Liverpool) talked about patient's beliefs regarding their medically unexplained symptoms and the implications for diagnosis and treatment. The paradox of a doctor making a diagnosis of medically unexplained symptoms but yet providing traditional symptomatic interventions was highlighted. Whilst some sympathy was expressed for the general practitioner struggling with a huge differential diagnosis, the conclusion seemed to be that greater engagement and better explanation from doctors is the only alternative and symptomatic interventions are inappropriate. This is a considerable challenge for general practitioners and the needs of this group of patients may be better addressed by other professionals.

A presentation on beliefs about mental disorders and their treatment from Professor Anthony Jorm (Australian National University) introduced the concept of mental health literacy, a term used to describe the knowledge amongst the general public of mental disorders. Apparently members of the public are poor at recognising specific disorders or different types of psychological distress. Their views differ from mental health experts in beliefs about the causes and treatments of mental disorders. Stigmatising attitudes are widespread and hinder recognition and the seeking of appropriate help. These factors have limited the development of family and community support for people with mental disorders. The use of handbooks and websites to educate the general public was described with the emphasis being on those who have not presented themselves to health care professionals.

After lunch Professor Derick Wade (University of Oxford) gave a lecture entitled 'Enablement: Remarketing Socio-medical Expectations in Rehabilitation'. The World Health Organisation classification of illness (pathology, impairment, activities and participation) was discussed and the central role of appropriate goal setting described. The importance of seeing the patient as someone who should be setting their own goals in conjunction with health care professionals was emphasised; arresting comparisons were made with the consultant appraisal process! Enablement is the new alternative word to rehabilitation and I think it is going to take off.

The presentations before and after our afternoon coffee focused on back pain, obstacles to recovery and how education of the public can make a difference to the attitudes of doctors and the patients.

Professor Kim Burton (Huddersfield) emphasised the importance of psychosocial factors in maintaining persisting symptoms and disability and how these can be identified. The role of inappropriate or erroneous beliefs held by patient and practitioner are important obstacles to recovery. An impressive public policy initiative in Australia was described by Professor Rachel Buchbinder (Monach University); this appears to have led to an impressive reduction in the number of claims for low back problems. Interestingly it appears that TV commercials helped the medical practitioners as much as the patients. Unfortunately the impact of prime time TV commercials appears to wane after 2-3 years. This may turn out to be an appropriate way to manage a number of other chronic conditions, funds permitting.

The lecture entitled 'Clinician Bias in Diagnosis and Treatment' by Dr Duncan Double (University of East Anglia) described over diagnosis and over treatment, the relationship of this bias to the positivist orientation of medical practice and the way that this leads to a focus on progress related to bodily mechanisms as seen in 3 areas. 1) A diagnostic bias against the personalist perspective of emotion and mental disorders. 2) Doctors over-estimation of patient's expectations for, and of, treatment. 3) A lack of adequate awareness of psychological aspects of suggestion in the doctor/patient relationship including the placebo and nocebo effects of medication.

The final presentation was the perfect Sunday supplement type end to the conference. The concept of subjective validation was explained using clairvoyance and people who claim extra-sensory perceptual powers as an example. I will never be able to look at my own work in the same light again!

Overall the day was about the way in which patients look to health professionals to help them understand their story better, the factors influencing the way they tell their story, and how health professionals interpret it. It was generic stuff, a huge part of the day to day practice of all healthcare professionals whether they deal with backs, bones, brains or bile ducts. The beliefs held by people, with or without an identifiable 'medical' problem, appear to be the most important determinant of whether they thrive, or fail to thrive. Thought provoking stuff!

Tom Hughes, Consultant Neurologist, University Hospital of Wales & Rookwood Hospital, Cardiff

National Museum of Wales

This meeting was jointly organised by Professor Peter W Halligan, Professor of Neuropsychology, Cardiff University and Professor Mansel Aylward CB, Chief Medical Adviser, Department for Work and Pensions.

EDITOR'S CHOICE

COGNITION: BDNF polymorphisms and their significance - from molecule to man and back

Brain-derived neurotrophic factor (BDNF) is a well-characterised neurotrophic factor that has been shown previously to modulate hippocampal plasticity and function. In this paper Danny Weinberger and colleagues have explored what effects the BDNF val66met polymorphism has on its secretion and function in cultured cells and in human subjects using an array of different investigative tools. This approach is of the utmost importance as it suggests that common polymorphisms in genes with a CNS function may be important in cognitive performance and the clinical expression of CNS disorders.

In this study they demonstrated that:

- Cell cultures manipulated to express either the val-BDNF or met-BDNF polymorphisms were investigated. Val-BDNF localises to dendrites and the cell body, whilst met-BDNF is localised solely to the cell body. Furthermore these two forms of BDNF had different subcellular localisations, with val-BDNF being associated with vesicles unlike met-BDNF. Finally activity-induced release of met-BDNF was much less than that seen with val-BDNF.
- In a study on 600 different human subjects the BDNF genotype predicted performance on verbal episodic memory tasks: met/met homozygotes did worse than either val/val homozygotes or met/val heterozygotes.
- There were different hippocampal fMRI activation patterns in two of these genotypes on the N-back working memory task (val/val versus met/val). The val/met subjects showed an abnormal bilateral hippocampal activation compared to baseline, whilst val/val subjects showed hippocampal deactivation patterns.
- Heterozygotes had lower N-acetyl-aspartate measures on MRS than val/val homozygotes, suggesting a specific reduction in hippocampal neuronal integrity/synaptic activity.

This impressive study therefore suggests that different polymorphisms in the BDNF gene subtly alter the distribution of its product within the cell and so change activity dependent secretion. This in turn affects synaptic function and cognitive performance!

The extent to which this applies to other common genetic polymorphisms in neurotrophic factors and/or neurotransmitters is not known. However studies such as this show the power of linking clinical performance to cell culture systems, and by so doing raises many questions on the origins of disease heterogeneity. *-RAB*

The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function.

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger SR.
CELL
2003: 112: 257-269.

EPILEPSY: and alcohol dependence ?

You might argue that I am stepping outside my remit of talking about epilepsy this month but this paper has gladdened my heart in an area where to date, therapeutic nihilism has been the rule. Alcohol is the commonest cause of seizures in young adults in many societies and when I am faced with a patient with alcohol-related seizures I vacillate between telling the patient to come back when they have stopped drinking and feeling sorry for them and giving treatment even though it is of no proven benefit. Among the existing drugs, do you give one that is metabolised in the liver and whose levels may fluctuate wildly, one that may precipitate hepatic encephalopathy or one that is renally excreted? Here is a possible way forward.

The rationale for the paper is that alcohol cravings are thought to be mediated by dopaminergic projections from the tegmentum to the nucleus accumbens and cortex. Alcohol reduces GABA receptor activity in the tegmentum and may enhance this dopaminergic activity. Chronic alcoholics may have increased glutamate activity. Topiramate seems to enhance $GABA^A$ activity via a non-benzodiazepine site and reduce dopamine activity so block the effects of alcoholism.

In this double-blind study 150 drinkers were randomly allocated to topiramate or placebo and followed up for 12 weeks. Topiramate was titrated to 300mg over 8 weeks. The patients were given "brief behavioural compliance-enhancement treatment" by a nurse to ensure they took the drugs. I am not quite sure what this means but it sounds either scary or exciting, depending on your inclinations.

The measures used were self-reporting of the number of drinks per day, the number of drinks per drinking day, the number of abstinent days, the number of heavy drinking days, gamma GT, self-reported craving, drinking obsessions and a measure called automaticity of drinking. Dropouts were high (a statistical not a psychosocial observation). Twenty-seven left the placebo and 20 the treatment arm, mostly because they were lost to follow-up or just chose to leave the study. Adverse events were few. All the measures improved in the placebo arm. Just making drinkers aware of what they are doing and engaging them in research, taking an interest perhaps, helps in the short term. The topiramate group was dramatically better on all the measures, for example 45% abstinent days versus 15%, probability of heavy drinking 35% versus 75% for placebo by the end of the study. This is only a short term study but it is not often that one sees such clear-cut results and the graphs of placebo and topiramate diverge impressively to the end of the study. Of course the idea that 300mg of topiramate is ever blind to the consumer is a little naive but I do not think this negates the results of a potentially important study.
It so happens this study exactly coincides with topiramate receiving its monotherapy licence in the UK - any Janssen-Cilag reps reading this review can contact me for the number of an account in an obscure Swiss bank. *-MM*

Oral topiramate for the treatment of alcohol dependence: a randomised controlled trial.

Johnson BA, Ait-Daoud N, Bowden CL, DiClimente CC, Roache JD, Lawson K, Javors MA and Ma JZ.
LANCET
2003;361:1677-85

★★★ RECOMMENDED

EPILEPSY: sex and electricity

In a lean month, after my scan of the journals for other articles of interest to review, I settled on an old standard; you can't go wrong with sex. In this study, 130 males aged 8-18 (mean 14 years) were recruited. Roughly half had focal and half generalised epilepsy. They had been taking antiepileptic drugs for 1 to 5 years, although the authors are a little vague on this. There were 63 age-matched controls, many relatives of the patients. A full range of measurements were made including height, weight, penile length (don't ask) and testicular dimensions and volume. Individuals were staged from P1-P5 according to how advanced they were in puberty. Laboratory measures included testosterone, oestradiol, LH and FSH. The only differences between patients and controls was at age 16. A variety of measures were less advanced and the most striking result was that only around half of patients were in stages 4 and 5 of puberty compared to all the controls. Total testosterone levels were higher at all ages in patients but free testosterone levels were lower. This is probably due to enzyme-inducing anti-epileptic drugs which induce sex hormone binding globulin. The ratio of free testosterone to oestradiol was lower in patients at all ages. LH and FSH levels tended to be higher and the authors suggest this may be due to impaired Leydig cell function. If these findings are replicated, then hormonal development will be on the prescribing agenda in males with epilepsy as well as for females. *-MM*

Physical and Hormonal Profile of Male Sexual Development in Epilepsy.
El-Khayat HA, Shatla HM, Ali GKH, Abdulgani MO, Tomoum HY, Attya HA,
EPILEPSIA
2003;44:447-52

PARKINSON'S DISEASE: what causes L-dopa induced dyskinesias?

The regular reader of this journal will know that this is a question that is regularly visited. However the significance of this subject to the management of PD is of course huge, because if we understood this complication of therapy better, then we MIGHT be able to prevent dyskinesias or treat them more effectively once they are a problem. A recent paper in Nature Neuroscience by Picconi *et al* provides a new piece in the jigsaw by suggesting that synaptic changes in the corticostriatal projection may be critical in the development of L-dopa induced dyskinesias.

In this experiment the investigators used a standard rat model of Parkinson's disease (PD), namely the unilateral 6-OHDA medial forebrain bundle lesion, and then gave the rats chronic, low therapeutic doses of L-dopa. This leads to the development of abnormal involuntary movements in about 50% of animals over a 21-day period, which thus gave them their two experimental groups.

These two groups were then further investigated to find out what was different between them. Firstly there were no differences in the extent of dopaminergic denervation between the 2 groups, both behaviourally and biochemically. However there were differences when the striata of these animals were subject to more extensive neurophysiological testing. Using a slice preparation it was shown that in both groups of animals, L-dopa restored striatal LTP in the 6-OHDA lesioned rat, but that the reversal of this process using low frequency stimulation (so-called depotentiation) was abnormal in the dyskinetic versus non-dyskinetic animals. This failure to adequately induce a depotentiation response appeared to be related to D1 receptor signalling and the generation of high levels of phosphorylated DARPP-32, which in turn caused a reduction in protein phosphatase 1 activity. In other words the genesis of dyskinesias related to abnormal post-synaptic phosphorylation and a loss of bi-directional plasticity. This in turn may lead to the pathological storage of abnormal motor information, which could be important in the expression of dyskinesias and would suggest that D2 receptor agonists may be a good way of preventing dyskinesias.

This is a thought provoking and interesting study, but the obvious question that arises is why do only some animals develop this problem? This is not resolved in this paper, but at least this study highlights the subtle changes that may be important in the genesis of these disabling symptoms in advancing PD, and these could be exploited therapeutically. *-RAB*

Loss of bi-directional striatal plasticity in L-dopa induced dyskinesia.
Picconi B, Centonze D, Hakansson K, Bernardi G, Greengard P, Fisone G, Cenci MA, Calabresi P.
NATURE NEUROSCIENCE
2003; 6: 501-506.

MALARIA: speech and language sequelae of severe malaria in Kenyan children

Investigations of acquired speech and language disorders in children are still relatively rare in comparison to studies of adults. While the language effects of focal trauma and diseases endemic to the UK have been studied to some degree, the effects of tropical diseases are almost unreported. According to the authors of this study, most survivors of severe falciparum malaria are reported to make a full neurological recovery.

The study reports speech and language outcomes of 25 Kenyan children admitted to hospital with severe falciparum malaria and 27 who had not been exposed to the disease. None of the children with malaria had been exposed to drugs associated with CNS disturbance. A comprehensive battery of assessments was adapted to be culturally appropriate and administered at least 2 years after onset of the disease (around age 6 – 7). Exposed children were found to have lower scores on each assessment, significant differences in performance being found on tests of comprehension, syntax, content words and function words. No differences were found between children who had suffered cerebral and non-cerebral malaria. Speech was generally not affected.

The authors acknowledge that some of the results may have been affected by the adaptation of the test materials, the conclusions reinforce the notion that diagnoses of complete neurological recovery should be treated with caution in groups that have not been comprehensively studied. *-RBody*

Carter, J.A., Murira, G.M., Ross, A.J., Mung'ala-Odera, V. and Newton, C.R.J.C.
BRAIN INJURY,
3002; 17:3, 217-224.

HEAD INJURY: a trial of sit to stand practice in head injury patients

Evidence for the effectiveness of physical therapy for improving motor function in brain damaged patients is limited. There is a steady trickle of trials showing that task specific practice is effective but one problem for both researchers and therapists is deciding how much improvement is clinically significant. Commonly used motor assessments are designed to pick up change in patients with a wide range of ability. They use ordinal or category scales to score performance of a variety of tasks, so in setting their objectives the research team decide they want to see a change in total score of a number of points. However, since change scores are not derived from interval data it is difficult to see how the results of the trial will relate to patients' function in clinical practice. In a trial of intensive task specific practice with head injury patients researchers have resolved this problem by concentrating on one task – sit to stand and measuring outcome with the number of times the sit to stand task was accomplished in 3 minutes.

24 brain injured patients in a rehabilitation unit were recruited to the trial. All were able to get to standing with minimal (standby) help. Many could sit to stand at least 3 times in 10 seconds at the start of the trial. All the patients received their usual inpatient therapy programme. Those randomly allocated to the experimental group received in addition 4 weeks of repetitive training of sit to stand which followed a graded programme and a step up exercise. The step up exercise was given to increase lower limb strength and coordination. The aim was to complete 100 sit to stand repetitions and 60

step-ups a day five days a week. As well as the number of sit to stands the patients' oxygen consumption during the 3 minute test was also measured before and after the 4 weeks of training.

On average the experimental group patients completed 87 repetitions of sit to stand and 42 step-ups a day. They all improved the number of sit to stands they could complete; increases ranged from 7 to 70 (mean improvement of 62%), but remained slower than normal. The control group increases were less; range 1 to 38 and two of the control patients recorded fewer stands on post test than on the pretest (mean improvement of 18%). The between group results are statistically significant but more importantly it is easy for both patients and therapists to see the clinical value of the intensive practice. *-AJT*

A randomised controlled trial of the effects of intensive sit-to-stand training after recent traumatic brain injury on sit to stand performance.

Canning CG, Shepherd RB, Carr JH, Alison JA.
CLINICAL REHABILITATION
2003: 17: 355-362

WAR NEUROSURGERY: In tempora belli……Vietnam remembered

Patrick Kelly is known primarily for his outstanding contribution in the field of stereotactic resection of cerebral tumours. In this fascinating record of his personal experiences in a naval hospital he describes in vivid detail the physical and emotional consequences of his surgical tour of duty in the Vietnam war. This article, initially presented as the Richard C Schneider Lecture at the American Association of Neurological Surgeons Annual Meeting in Chicago, April 2002, takes the reader on a harrowing journey. The background to the conflict is detailed, as is its aftermath, including alarming figures relating to divorce rates and post traumatic stress disorder amongst veterans. The rapid evacuation of casualties from the heat of battle to base hospitals allowed very prompt resuscitation and surgical treatment; description of the organisation of key elements in this process is accompanied by individual examples of tragedy, human frailty, bravery and success. Differences between management of American soldiers and the local Vietnamese – due to the ultimate lack of rehabilitation resources for the latter – are highlighted. The overall survival rates of over 90% at base hospitals, despite the severity of the injuries treated, is a testament not only to the skills of the medical personnel but also to the courage of the helicopter crews. Despite moral outrage at the stupidity of the conflict Dr Kelly found purpose in the tasks to which he was assigned. Just occasionally an article is worthy of reading by practitioners across the entire extent of medical disciplines. This extraordinary account, beautifully written and well illustrated, is a prime example. *– RR*

Vietnam, 1968-1969: A place and a year like no other.
Kelly P J.
NEUROSURGERY
2003: 52: 927-943

★★★ RECOMMENDED

MOTOR NEURONE DISEASE: creatine trial proves negative

Creatine has been shown to increase muscle strength in healthy individuals and is commonly used as a dietary supplement by athletes. It has a role in mitochondrial ATP production and has been used as an "ergogenic aid" in mitochondrial myopathies and other neuromuscular disorders. Since mitochondrial dysfunction may contribute to the anterior horn cell loss in motor neurone disease (MND), and creatine has been shown to extend survival time in transgenic mice with mutations of the superoxide dismutase (SOD) gene, there were high hopes for the clinical efficacy of creatine in MND.

In this Dutch study, 175 MND patients entered a randomised, double-blind, placebo-controlled trial and were followed for 16 months. Creatine monohydrate was given in the active arm at 5 mg bd, ten times the normal daily dietary intake. Primary end-points were event free survival (death, tracheostomy, persistent assisted ventilation) and there were various secondary end-points based on functional measures. Using a sequential trial design, it was possible to stop the trial early when the null hypothesis of indifference was accepted. Creatine had no beneficial effects on survival or disease progression, as assessed by rate of deterioration of arm muscle strength or vital capacity.

This disappointing result seems definitive. Confounding, for example placebo patients taking creatine, which is easily available in health food shops, was excluded by urine testing, which also confirmed excellent compliance in the treated patients. The statistical methods used may, I feel sure, be open to argument. However, of perhaps more relevance pragmatically, it is possible that the treatment came too late in the natural history of the disease, on average 500 days after symptom onset, and may explain the discrepancy with the results in SOD1 mice, treated 40 days before symptom onset.

Prescription of creatine in MND would therefore seem to offer only false hope to patients. The authors advocate efforts to find alternative treatments for MND.*-AJL*

A randomised sequential trial of creatine in amyotrophic lateral sclerosis.
Groeneveld GJ, Veldink JH, van der Tweel I *et al.*
ANNALS OF NEUROLOGY
2003;53(4):437-445

EPILEPSY: when to scan and how to interpret the result

A couple of recent articles in the JNNP have served to remind us of the purpose and potential pitfalls of scanning patients with seizures. In the first of these, Dr Wieshmann from the Walton Centre, Liverpool, retrospectively reviewed 495 scan results available from 919 outpatients seen in general neurology or specialist epilepsy clinics. The type of scan performed depended on the clinical presentation and suspected diagnosis, but overall was roughly equally divided between CT, MRI with 5mm slice width and MRI with 1.5mm slices. The results showed that about 18% of those with single seizures had a scan abnormality, and none of the patients with idiopathic generalised epilepsy (IGE) or non-epileptic attacks showed any abnormality (results roughly comparable to previous studies). Interestingly, about 40% of patients with IGE were none the less scanned, and potential reasons for this are discussed. The key learning point, however, was that even in this centre about 30% of patients with localisation-related epilepsy were not scanned. This is contrary to accepted guidelines, and important since in those that were scanned more than half the results were abnormal.

The second article by Dr Alsaadi *et al* in California reminds us to interpret cautiously abnormal scans. They provide follow-up data on outcome after temporal lobe surgery on 15 patients with large non-neoplastic extra-temporal lesions on their scans. In only nine cases was hippocampal atrophy present. The surgery was performed on the basis of seizure semiology and EEG investigation both suggesting a temporal focus. All 6 of the patients with a large extra-temporal lesion but no hippocampal atrophy present on the MRI were improved by temporal surgery (without lesionectomy), four becoming completely seizure free. Overall nine of the 15 patients became seizure free, the other 6 gaining at least significant improvement. They remind us not to rush to conclusions on the basis of scan results, but to concentrate on the clinical assessment and other investigations since the abnormality seen on the scan may not be the seizure focus. These patients seem to do well without lesionectomy but with temporal surgery alone if this is felt to be the focus. *- AWM*

Clinical application of neuroimaging in epilepsy.
Wieshmann UC.
JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2003; 74; 466-470

Potentially misleading extratemporal lobe lesions in patients with temporal lobe epilepsy.
Alsaadi TM, Bateman LM, Laxer KD, Barbaro NM, Austin EJ, Garcia PA.
JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2003; 74 566-569

★★★ RECOMMENDED

MULTIPLE SCLEROSIS: the story of a dog, a dodgy virus and D-110

What goes around, comes around. In the 1970s, Cook and Dowling noted that three sisters, who lived together, all developed multiple sclerosis after their dog had an encephalopathy. They then showed an apparently significant association of pet ownership with multiple sclerosis in New York and hence suggested that the canine distemper virus might be responsible for multiple sclerosis.

This story has come to the fore with a twist, through the work of Hans Lassmann in Vienna, who is one of the leading multiple sclerosis neuropathologists. His team systematically screened 101 post mortem multiple sclerosis brains for the presence of different viral antigens, including using ten different (?!?) antibodies against various components of the canine distemper virus. (This huge effort perhaps explains why there are 14 authors!). One of these antibodies, D-110, selectively bound to oligodendrocytes within "type III" plaques. This is one of four different types of multiple sclerosis lesion, described by Lassmann. It appears to be a primary oligodendropathy, with myelin dystrophy in the absence of inflammation. The similarity in appearance to the effect of ischaemia on white matter is further emphasised by the fact that D-110 immunoreactivity is also seen in acute ischaemic lesions. The other antibodies against the canine distemper virus, and a targeted PCR study, showed no evidence of the virus itself- so D-110 was picking out something quite different.

They next turned to live patients with multiple sclerosis. They could not find the D-110 antigen in the patients' sera, but they did in the CSF of 24% of patients with relapsing-remitting multiple sclerosis which was significantly higher than controls. It would be wonderful if these patients were those with the "type III" of multiple sclerosis pathology. This correlation could only be studied in 4 patients with combined CSF and brain biopsy samples: the only one to have pathological Type III lesions was also the only one to have an elevated CSF D-110. Debates about the pathological heterogeneity of multiple sclerosis have been academic until now, as it has been impossible to distinguish the types by any clinical or laboratory marker. But maybe Lassmann, led down an unpromising alley by spinster spinsters and their sick dog, has stumbled upon one. - ***AJC***

A new paraclinical CSF marker for hypoxia-like tissue damage in multiple sclerosis lesions.

Lassmann H, Reindl M, Rauschka H, Berger J, Aboul-Enein, Berger T, Zurbriggen A, Lutterotti A, Bruck W, Weber J, Ullrich R, Schmidbauer M, Jellinger K, Vandevelde M.
BRAIN
2003: 126: 1347-57

★★★ RECOMMENDED

COGNITION: where two can be better than one- scanning a visuo motor context

Experimental situations have shown that reaction times to presented stimuli tend to be faster when more than one copy of the stimulus is presented at the same time. This finding is known as the "redundant target effect". The current authors favour an explanation where faster reaction times arise because the two stimuli somehow produce greater activation (Miller 1982, 86). Recently, investigators have assumed that this abstract "coactivation" model is reflected neurally. These researchers aimed to show where neural summation occurred, e.g. at a perceptual stage, a cognitive/ decision level or at a later motor locus.

Six right-handed volunteers were scanned using eFMRI (event related functional magnetic resonance imaging) while performing a task responding to left, right and redundant flashes of light. Redundant flashes were counterbalanced for left, right and bi-lateral presentation. Subjects' reaction times showed successfully that the redundant target effect could be replicated in the scanner. Changes in the BOLD (blood oxygen level dependent) effect during eFMRI were sought (an indirect measure of neural activation). The study hypothesised that brain regions having greatest coactivation would show greater BOLD responding during redundant trials when two copies of the stimuli were presented. Bilateral premotor regions were implicated here leading the authors to suggest that the functional basis of the redundant target effect is premotor and "at late stages of motor preparation".

High spatial resolution eFMRI supplements quality temporal information from EEG, and can be used to derive information concerning possible functional loci of established behavioural effects. Perhaps rehabilitation settings could apply redundant targets to help patients respond earlier to multiple copies of visual memory aids. ***-LAJ***

Interhemispheric visuo-motor integration in humans: the effect of redundant targets.

Iacoboni M and Zaidel E.
EUROPEAN JOURNAL OF NEUROSCIENCE
2003: 17: 1981-1986

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S. Karger AG - Medical and Scientific Publishers,Allschwilerstrasse 10, CH - 4009 Basel, SWITZERLAND.
Tel. 0041 61 306 11 11, Fax. 0041 61 306 12 34, E-Mail. t.nold@karger.ch www.karger.com

Cerebral Cortex
Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP. Tel. 01865 267154, Fax. 01865 267985.

Clinical Rehabilitation, Multiple Sclerosis
Arnold, 338 Euston Road, London NW1 3BH. Tel. 020 7873 6339, Fax. 020 7873 6325,
E-Mail.arnoldjournals@hodder.co.uk,www.arnoldpublishers.com/journals

Current Opinion in Neurology
Lippincott Williams & Wilkins, 241 Borough High Street, London, SE1 1GB. Tel 0207 940 7564, Fax 0207 940 7530
Email. rmclachl@lww.co.uk, www.Lww.co.uk

Epilepsia
Blackwell Publishing, Commerce Place, 350 Main Street, Malden, MA 02148-5018, USA. Tel. 888 661 5800, Fax. 781 388 8270,
www.blackwellscience.com/epi

Neuroscan Compumedics launches new products

Neuroscan, a leading manufacturer of neurophysiological research equipment, has announced the launch of Synamps®, Stim® and Scan 4.3.

When Synamps was released in 1992, it was hailed as the most powerful amplifier in the world - more than 1300 Synamps now serve researchers around the globe. Neuroscan have now launched the Synamps® amplifier, which is said to raise the research standard for electrophysiological amplifiers once again. It would be impossible to list here all the new and advanced specifcations of Synamps® (USB 2.0 interface, 24 bit DataStream, etc.). Please visit www.advancedmedicalequipment.com for more information and a complete list.

Stim® is now completely Windows XP compatible and, unlike other similar products, timing is perfectly synchronized (yes, in a Windows environment!) to the recording system. There is a free upgrade to all users of Scan version 4.0 or higher - upgrade details are on the website.

Advanced Medical Equipment, sole distributor for Neuroscan in the UK and Ireland, would be happy to provide more information or demonstrate any of these new products.
E-Mail. info@advancedmedicalequipment.com for more information.

advanced MEDICAL equipment ltd

NB. Following the success of Scan School over the past 2 years, Advanced Medical Equipment are pleased to announce Scan School will be taking place 17-21 November 2003. Full details on the website.

Neuroscan

New Möller-Wedel Hi-R 20-1000 neurosurgical microscope with senso-servo technology

Haag-Streit UK have introduced the new Moeller-Wedel Hi-R 20-1000 neurosurgical microscope. Named for its high-resolution apochromatic optics, high-reaction senso-servo drive and it high-range working distance, the Hi-R 20-1000 is said to offer surgeons true colour, increased depth of field and smooth precise one-hand control. Fine XY corrections can be made via joy pad on the fourteen-function handle.

Newly calculated apochromatic optics and residual aberration correction enhance colour fidelity, provide strong contrast and maximum resolution. The 25mm stereo base combined with the integrated switchable diaphragm ensures maximum depth of field. The Hi-R 20-1000 also features a 6 times zoom facility and a variable objective for working distances from 224 510mm. The Light Router LR1000 replaces the former double eyepiece head and beam splitter and comes equipped with an eyepiece head which is inclinable by + / - 100 degrees. The light path can be switched between an observer microscope and facing eyepiece.

The senso-servo drive technology allows smooth and precise motion for aiming and rapid repositioning in critical situations. The senso-servo drive has been optimised for precise one-hand control. The FS4-20 floorstand that accompanies the Hi-R 20-1000 retains its equilibrium when the accessories remain on the microscope or are stored in the overhead compartment.

For further information please contact customer services on 01279 414969.

Epilepsy – what women should know

Epilepsy is the most common neurological problem in pregnancy and epilepsy affects about 0.5% (1 in 200) of the population.

There are about 75,000 women of childbearing age with epilepsy in the UK and about 2,000 pregnancies a year in women with epilepsy.

Issues regarding pregnancy and contraception should be considered in any women of childbearing age with epilepsy and treatment is likely to be necessary for a minimum of 2 years and maybe for many years.

The possibility of pregnancy at some stage in the future should therefore be considered in the management of any pre-menopausal female with epilepsy, unless the type of epilepsy is one that she is likely to grow out of, such as childhood absence attacks.

In essence, all women with epilepsy who are contemplating pregnancy should have their diagnosis reviewed and the need for treatment and choice of medication considered.

A comprehensive patient leaflet covering this subject has been written by Dr M D O'Brian, Guys Hospital with the endorsement of the National Society for Epilepsy and sponsored by UCB Pharma.

If you would like to obtain copies, please contact UCB Pharma on Tel. 01923 211811, or use the reader enquiry which is enclosed with this magazine.

Mobile phone solutions for the disabled

SRS Technology and Motorola have announced a collaboration to develop mobile telephone solutions for the disabled. The first product, the SRS mobile phone kit was released at the end of April.

The SRS mobile phone kit now makes it possible for a disabled person to operate a mobile phone using the SRS 100 environmental control system. The SRS mobile telephone can be operated from a joystick, a single button switch or the keys of the SRS 100.

The kits allows the user to make and receive phone calls and even play games on the phone.

Jurek Sikorski, Chief Executive of SRS Technology said "We are delighted to be working with motorola on the development of mobile phone solutions. Our customers have been asking for an interface for mobile phones for some time – it is probably the most frequently requested new product we are asked to develop".

For further information contact SRS Technology on Tel. 01922 456882.

'BioSomnia' - a new concept in sleep monitoring

A single channel portable sleep monitor: BioSomnia is a lightweight, battery powered portable monitor processing a single channel of EEG overnight. BioSomnia is easy to use, with electrode montages below the hairline to simplify patient hook up.

BioSomnia analyses the EEG signal in real time and easy to use software displays information on sleep latency, duration, fragmentation and Microarousals.

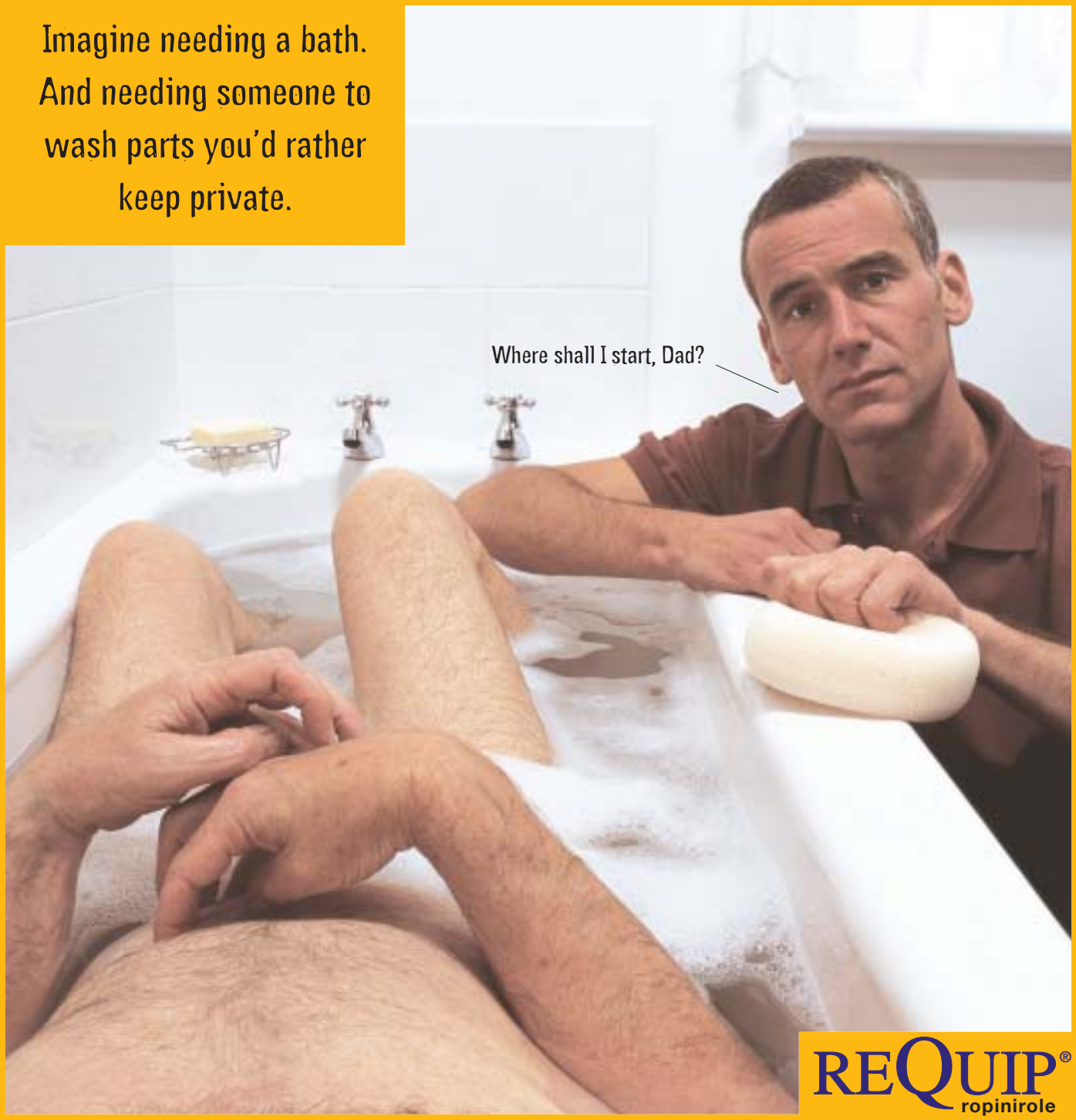
A full interactive hypnogram is also available.

Effective treatment of sleep disorders requires good diagnosis, yet doctors lack the means to measure sleep easily and objectively in the patient's home.

BioSomnia meets this need and offers a cost effective sleep analysis tool for laboratory or home studies.

For further information contact Oxford BioSignals Ltd,
Tel. 01865 336170, Fax. 01865 335180, www.Oxford-BioSignals.com

Imagine needing a bath. And needing someone to wash parts you'd rather keep private.



REQUIP® ropinirole

FIGHTS PARKINSON'S. DEFENDS DIGNITY.

REQUIP (ropinirole) Prescribing Information
Presentation 'Requip' Tablets, PL 10592/0085-0089, each containing ropinirole hydrochloride equivalent to either 0.25, 0.5, 1, 2 or 5 mg ropinirole. Starter Pack (105 tablets), £43.12. Follow On Pack (147 tablets), £80.00; 1 mg tablets – 84 tablets, £46.20; 2 mg tablets – 84 tablets, £92.40; 5 mg tablets – 84 tablets, £184.80. **Indications** Treatment of idiopathic Parkinson's disease. May be used alone (without L-dopa) or in addition to L-dopa to control "on-off" fluctuations and permit a reduction in the L-dopa dose. **Dosage** Adults: Three times a day, with meals. Titrate dose against efficacy and tolerability. Initial dose for 1st week should be 0.25 mg t.i.d., 2nd week 0.5 mg t.i.d., 3rd week 0.75 mg t.i.d., 4th week 1 mg t.i.d. After initial titration, dose may be increased in weekly increments of up to 3mg/day until acceptable therapeutic response established. If using Follow On Pack, the dose for 5th week is 1.5mg t.i.d., 6th week 2.0mg t.i.d., 7th week 2.5mg t.i.d., 8th week 3.0mg t.i.d. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually by around 20%. When switching from another dopamine agonist follow manufacturer's guidance on discontinuation. Discontinue ropinirole by reducing doses over one week. Renal or hepatic impairment: No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. Elderly: Titrate dose in normal manner. Children: Parkinson's disease does not occur in children – do not give to children. **Contra-indications** Hypersensitivity to ropinirole, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Ropinirole has been associated with somnolence and episodes of sudden sleep onset. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction seen with other Parkinson's disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Adverse reactions** In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo, however, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see 'Precautions' and 'Effects on ability to drive and use machines'). **Effects on ability to drive and use machines** Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Overdosage** No incidences reported. Symptoms of overdose likely to be related to dopaminergic activity.

POM

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