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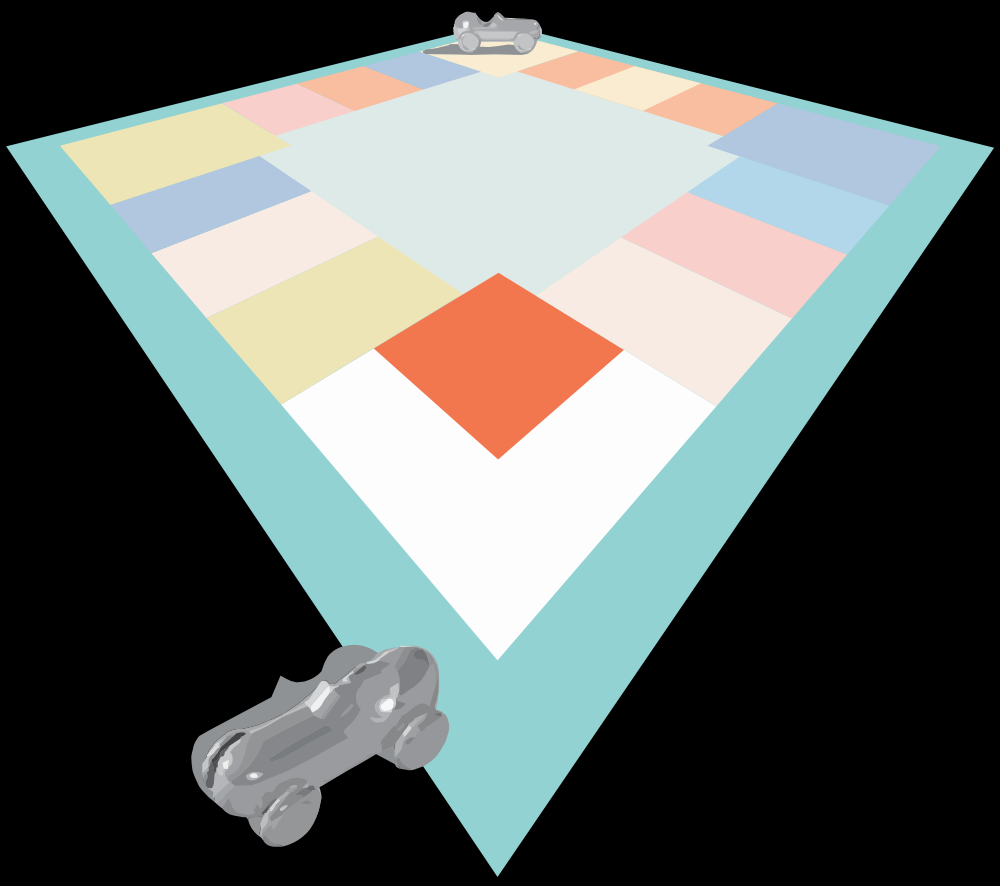

journal reviews • events • management topic • industry news • rehabilitation topic

Review Articles: Spinal and Bulbar Muscular Atrophy - Clinical features and Pathogenesis; Developments in the Treatment of Motor Neurone Disease
Management Topic: Myoclonus
Rehabilitation Article: Upper-limb Exercise in Tetraplegia using Functional Electrical Stimulation

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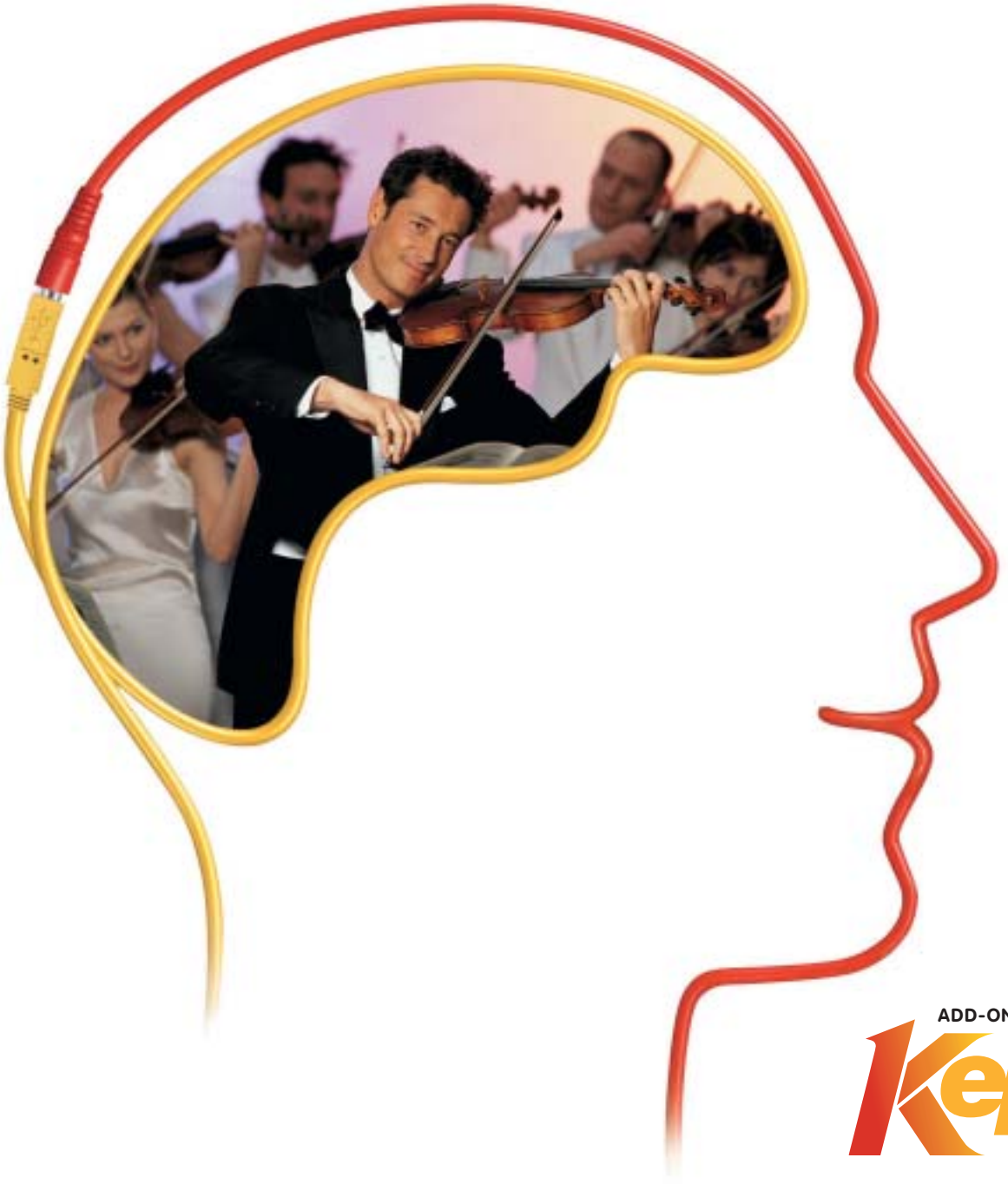

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Date of preparation: March 2003.

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

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This issue of ACNR boasts two magnificent review articles on different types of motorneuron disease. We are delighted that Gen Sobue and colleagues have written a very topical and exciting review on spinal-bulbar muscular atrophy (SBMA) or Kennedy's disease. This disorder is rare but is due to a trinucleotide CAG repeat in the androgen receptor, although the mechanisms that lead to selective cell death as a result of this are unknown. However Sobue and colleagues have recently shown that the translocation of mutant androgen receptors to the nucleus is a critical pathogenic event, and that blocking this process could provide an effective treatment for this disorder. This work which was recently published in Nature Medicine (June 2003; 9:768-773), represents a major step forward in our understanding of this disease, and offers a clear therapeutic target – namely blocking the androgen binding to the receptor in the cytoplasm and by so doing preventing its nuclear translocation. This clearly creates ethical issues in the clinic as it would mean that effective treatment could be used at the cost of infertility. This beautiful account of SBMA is nicely complemented by the article from Pam Shaw and Alice Brockington on new developments in the treatment of other more common forms of motor neurone disease. This review provides a comprehensive account of what is currently known about the pathogenesis of this condition, and how this may lead to new therapies. Thus whilst standard symptomatic and therapeutic agents are discussed, there is also a section on future directions. These two articles therefore provide a comprehensive and up-to-date account on the pathogenesis and therapeutic options for this fatal neurodegenerative condition.

This issue's management topic tackles myoclonus with a case of palatal myoclonus (PLUS video clip) on the web-site. I have tried to take a pragmatic approach to the classification, aetiology and treatment of this movement disorder, which forms the fourth topic in our series on movement disorders.

The rehabilitation article this time presents some fascinating data and possibilities using functional electrical stimulation in cervical cord damage. This account highlights the mechanics of the process and its effect on cardiovascular performance and thus its role in maintaining fitness in patients with limited upper function secondary to cervical cord damage.

This issue also contains the last in our series on peripheral nerves and their neurophysiological investigation by Brian McNamara. This time Brian takes on the brachial plexus, which he describes as "the sceptre that stalks every anatomy student's nightmares". As usual it is packed with common sense and we shall greatly miss his no nonsense approach, which has been a hallmark of his series of wonderful articles.

Our historical account this month is by Andrew Larner, and describes Gilles de la Tourette syndrome in Dr Samuel Johnson, Mr Pancks in Dickens' Little Dorrit and Captain Hardcastle, a schoolmaster to Roald Dahl. As always this account is learned and fascinating, and once more highlights the power of literature to capture neurological conditions.

We also have an interview with the new President of the BNA, Professor Richard Frackowiak. Professor Frackowiak, as many will testify, is a larger than life character who brings great energy and enthusiasm to all that he takes on. He has a formidable track record in research and has very much managed in his work to bridge clinical and basic neuroscience, and is a fine choice for this prestigious post. We wish him all the best, as his appointment reinforces the point that this journal tries to make with each issue - namely that clinical neurology can inform basic neuroscience and vice versa and thus each needs to know what the other is doing.

Finally we have our usual meeting reports and journal review, including a summary of the latest US double blind placebo controlled trial of fetal neural transplantation in Parkinson's Disease. So we hope you enjoy this issue, and do keep the feedback coming so we know what we are missing and can improve upon.

Roger Barker, Co-editor
email.AdvancesinCNR@aol.com

contents

november/december 2003

How a board game is set to help people with Parkinson's

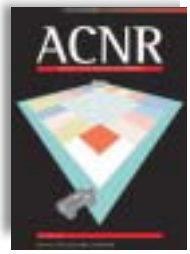
The European Parkinson's Disease Association has just introduced Parkinsonpoly, an interactive patient education resource that uses a board game analogy to engage patient interest, improve understanding and recall. It will help doctors to communicate aspects of Parkinson's disease to their patients.

Parkinsonpoly consists of various patient education tools including a website, a series of patient booklets and other patient material and makes use of visual imagery to help patients recall and absorb information.

People with PD constantly look for information on their disease to know more about how to actively improve their quality of life. But much of the information available on the Internet can be inaccurate, misleading or extreme. People can feel overburdened and confused and those who are not scientifically minded may be switched off by detailed medical information, so that important information on their disease may not always be communicated.

Parkinsonpoly gives people with Parkinson's disease (PD), their families and carers a concise, visual guide to structured information, advice and help.

Parkinsonpoly can be accessed at www.parkinsonpoly.com.



Features

Regulars

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PEACE OF MIND

Spinal and Bulbar Muscular Atrophy - Clinical Features and Pathogenesis

Clinical features

SBMA, or Kennedy's disease, is an inherited lower motor neuron disease characterised by adult-onset muscle atrophy, weakness, contraction, fasciculations, and bulbar involvement[1,2]. The onset of weakness is usually between 30 and 50 years, but often preceded by nonspecific symptoms such as tremor, muscle cramps and fatigue[3,4]. Muscle atrophy and weakness are predominant in the tongue and proximal musculature. Deep tendon reflex is diminished or absent with no pathological reflex. Sensory involvement is largely restricted to vibration sense which is affected distally in the legs[2]. Male patients often demonstrate signs of androgen insensitivity such as gynecomastia, testicular atrophy, impotence and decreased fertility[5,6], some of which are detected before the onset of motor symptoms. Hyperlipidemia, liver dysfunction and glucose intolerance are also seen in some cases[3,7]. SBMA chiefly affects males, whereas females with the mutation are usually asymptomatic even when homozygous[8,9,10]. The prevalence of SBMA has been estimated 1 in 40000 in areas with high ascertainment[11], although a considerable number of patients may have been under diagnosed[12,13].

The disease progresses slowly in general, although repetitive respiratory tract infection often occurs in the advanced stage of the disease, resulting in early death in some patients[4]. No specific treatment for SBMA has been established. Testosterone has been used in some patients, although it has no effects on the progression of SBMA[14,15,16].

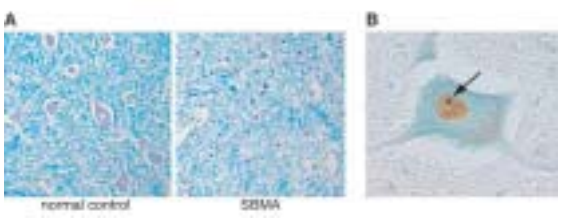
Genetics

The molecular basis of SBMA is the expansion of a trinucleotide CAG repeat, which encodes the polyQ tract, in the first exon of the androgen receptor (AR) gene[17]. The number of CAG repeat within AR is 11 to 35 in normal subjects, but it expands from 40 to 62 in patients[11,17,18]. Expanded polyQ tracts have been found to cause several neurodegenerative diseases including SBMA, Huntington's disease (HD), several forms of spinocerebellar ataxia, and dentatorubral and pallidoluysian atrophy (DRPLA)[19,20,21]. There is an inverse correlation between the CAG repeat size and the age at onset, or the disease severity adjusted for age at examination in SBMA[22,23] as well as other polyQ diseases[19,24]. These observations suggest that common mechanisms underlie the pathogenesis of polyQ diseases, despite the fact that the causative protein for each of the diseases are different except for the existence of polyQ stretch. Although the expansion of polyQ tract in AR disrupts the transcriptional activities of AR[25,26], motor impairment has never been observed in severe testicular feminisation patients lacking AR function[27]. Therefore, as in other polyQ diseases, a toxic gain of mutant AR function has been considered to cause neuromuscular disorder in SBMA.

Pathology

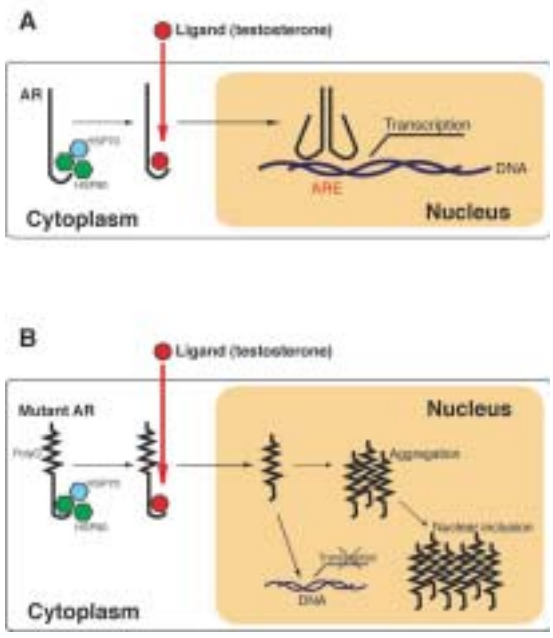
Lower motor neurons are markedly depleted through all spinal segments and in brainstem motor nuclei except for the third, fourth and sixth cranial nerves in autopsy cases of SBMA (Fig. 1A)[2,28]. A striking pathologic hallmark of most polyQ diseases is the presence of nuclear inclusions (NIs), which has been considered relevant to the pathophysiology[19]. In SBMA patients, NIs containing the mutant AR are detected in the residual motor neurons (Fig. 1B)[29] as well as in other visceral organs[30]. Although the exact role of NIs in the pathogenesis is to be elucidated, nuclear accumulation of mutant protein is essential for inducing neuronal cell dysfunction and degeneration in the majority of polyQ diseases[20]. In support of this hypothesis, the dysfunction of nuclear transcriptional regulatory proteins have been considered crucial in polyQ pathogenesis[31,32]. Since ligand facilitates the nuclear translocation of AR, it appears to be logical that SBMA pathogenesis is ligand-dependent (Fig. 2).

Figure 1



Histopathology of SBMA
In Kluver-Barrera's stain of the lumbar anterior horn (A), motor neurons are depleted in SBMA compared with normal control. A residual motor neuron in the lumbar anterior horn shows a nuclear inclusion detected by anti-polyglutamine antibody (B, arrow).

Figure 2



Androgen receptor (AR) dynamics in SBMA
AR is a member of the steroid/thyroid receptor superfamily. In a normal cell (A), AR is confined to a multi-heteromeric inactive complex with heat shock proteins (HSPs) in the cell cytoplasm. Ligand-binding facilitates its dissociation from this complex and translocation into the nucleus. ARs undergo comformational change, form a dimer, bind to androgen response elements (ARE) in the DNA, and function as ligand-dependent transcription factor. In SBMA (B), mutant AR is partially cleaved and translocates into the nucleus in a ligand-dependent manner. In the nucleus, mutant ARs aggregate and form nuclear inclusions as a consequence. This inhibits the function of critical cellular proteins inhibited by soluble and/or aggregated AR, resulting in transcriptional dysregulation. On the other hand, the decreased transactivating function of mutant AR may contribute to the androgen insensitivity and neurodegeneration in SBMA.

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Gen Sobue is Professor of Neurology at Nagoya University Graduate School of Medicine, Nagoya, Japan. He graduated from Nagoya University in 1975, and worked at University of Pennsylvania School of Medicine and Aichi Medical University. He has worked on peripheral neuropathy and neurodegenerative diseases.

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Ligand-dependent pathogenesis

We generated transgenic mice expressing the full-length human AR containing 97 CAGs under the control of a cytomegalovirus enhancer and a chicken ß-actin promoter[33]. The mice (AR-97Q) showed small body size, short life span, progressive muscle atrophy and weakness as well as reduced cage activity, all of which were markedly pronounced and accelerated in the male AR-97Q mice, but were either not observed or far less severe in the female AR-97Q mice. Western blot analysis and immunostaining showed markedly more abundant nuclear accumulation of mutant AR in male mice than in their female counterparts, in agreement with the symptomatic differences with gender. Gender effect on the phenotypes has also been demonstrated in another transgenic mouse model of SBMA[34].

Castrated male AR-97Q mice showed marked improvement of symptoms, histopathologic findings, and nuclear localisation of the mutant AR compared with the sham-operated male AR-97Q mice. In contrast to castration of the male mice, testosterone caused significant aggravation of symptoms, histopathologic features, and nuclear localisation of the mutant AR in the female AR-97Q mice. Since the nuclear translocation of AR is ligand-dependent, testosterone appears to show toxic effects in the female AR-97Q mice by accelerating nuclear translocation of the mutant AR. By contrast, castration prevented the nuclear localisation of the mutant AR by reducing the testosterone level. In support of this hypothesis, the ligand-dependent neurodegeneration has also been revealed in a Drosophila model of SBMA[35]. Alternatively, castration may enhance the protective effects of heat shock proteins, which exert beneficial effects in cell and mouse models of SBMA[36,37].

Based on successful treatment of AR-97Q mice with castration, we investigated the effects of testosterone blockade therapies, using the LHRH analogue and AR antagonist, in the transgenic mice[38]. Leuprorelin and LHRH analogue reduces testosterone release from the testis and showed marked amelioration of symptoms, histopathologic findings, and nuclear localisation of the transgene protein compared with the vehicle-treated AR-97Q mice. Leuprorelin initially increased the serum testosterone level by agonising the LHRH receptor, but subsequently reduced it to undetectable levels. Leuprorelin-treated AR-97Q mice showed transient deterioration of motor function due to this initial increase in testosterone level. This symptomatic and pathologic aggravation was followed by sustained amelioration along with consequent suppression of testosterone production. Our results indicate that leuprorelin is a promising therapeutic strategy of SBMA, and that polyQ pathogenesis is reversible at least in its dysfunctional stage.

By contrast, flutamide AR antagonist, did not ameliorate symptoms, pathologic features, or nuclear localisation of the mutant AR in the male AR-97Q mice, although there was no significant difference in the androgen blockade effects between flutamide and leuprorelin. Although flutamide suppresses the androgen-dependent transactivation, it does not inhibit, but may even facilitate, the nuclear translocation of AR[39,40]. Flutamide also promotes nuclear translocation of mutant AR containing expanded polyQ in a cell and Drosophila model of SBMA[35,41]. This may be the reason why flutamide demonstrated no therapeutic effect in our transgenic mouse model of SBMA.

Therapeutic perspective

As mentioned above, our recent study indicated that leuprorelin exerts therapeutic effects in the SBMA transgenic mouse model. LHRH analogue can easily be applied to human SBMA therapy, because this drug has extensively been used as medical castration in the therapy of prostate cancer[42]. However, any clinical trial using this approach is difficult as the patient's desire for fertility should be taken into account, and the appropriate clinical dose should be carefully determined.

Acknowledgements

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Presentation: Gabitril 5 mg, Gabitril 10 mg, Gabitril 15 mg; film-coated tablets containing 5 mg, 10 mg and 15 mg tiagabine anhydrous (as hydrochloride monohydrate) respectively. Indications: Add-on therapy for partial seizures with or without secondary generalisation where control is not achieved by optimal doses of at least one other antiepileptic drug. **Dosage and Administration:** Adults and Children over 12 years taking enzyme-inducing antiepileptic drugs: 5 mg twice daily for one week, followed by weekly increments of 5-10 mg/day. The usual maintenance dose is 30-45 mg/day. Doses above 30 mg should be given in three divided doses. Gabitril should be taken with meals. In patients not receiving enzyme-inducing drugs: the maintenance dose should initially be 15-30 mg/day. In mild to moderate hepatic disease: the maintenance dose should initially be 5-10 mg given once or twice daily. Children under 12 years: not recommended. **Contra-indications:** Hypersensitivity to tiagabine or excipients. **Warnings and Precautions:** Gabitril should not be used in severe hepatic disease. On withdrawing, taper off treatment over a period of 2-3 weeks. **Drug Interactions:** Antiepileptics that induce hepatic enzymes enhance the metabolism of tiagabine (plasma concentrations of tiagabine may be reduced by a factor of 1.5-3). **Pregnancy and Lactation:** Not recommended. **Side Effects:** dizziness, tiredness, nervousness, tremor, diarrhoea, concentration difficulties, depressed mood, emotional lability, slowness in speech. Recurrence of behavioural problems. Rare cases of non-convulsive status epilepticus, hallucination, delusion, bruising and visual field defects. **Legal category:** POM. **Marketing Authorisation Numbers:** Gabitril 5 mg: PL 16260/0009, Gabitril 10 mg: PL 16260/0010, Gabitril 15 mg: PL 16260/0011. **Basic NHS Price:** Gabitril 5 mg, 100 tablets, £45.37. Gabitril 10 mg, 100 tablets, £90.74. Gabitril 15 mg, 100 tablets, £136.11. **Marketing Authorisation Holder:** Cephalon UK Limited. **Date of preparation:** October 2002. Gabitril and Cephalon are registered trademarks. Full prescribing information, including SmPC, is available from Cephalon UK Limited, 11/13 Frederick Sanger Road, Surrey Research Park, Guildford, Surrey UK GU2 7YD, Medical Information Freefone 0800 783 4869 (ukmedinfo@cephalon.com).

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Developments in the treatment of Motor Neurone Disease

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Introduction

Motor neurone disease (MND) is a progressive neurodegenerative disorder affecting primarily lower motor neurones of the brainstem and spinal cord and upper motor neurones of the cerebral cortex. It is the third most common adult-onset neurodegenerative disease, with an incidence of 1-2 per 100,000. Approximately 5 to 10% of cases are familial. Affected individuals typically develop progressive muscle weakness and wasting that eventually involves both limb and bulbar muscles, combined with upper motor neurone signs such as brisk reflexes and a positive Babinski sign. The disease has a mean age of onset of 55 years. Death usually results from respiratory failure due to weakness of the respiratory muscles, an average of 3 years after onset of symptoms.

There are two aims in the treatment of motor neurone disease. The first, as this is an invariably fatal disorder, is the alleviation of symptoms to maintain quality of life. The second is to slow the progression of neuronal degeneration and ultimately to prevent further loss of motor neurones as early as possible in the course of the disease, before patients have developed significant disability. This article will describe the current symptomatic and disease modifying therapies available in MND, and discuss future directions.

NEUROPROTECTION

Pathogenesis of Motor Neurone Degeneration

An understanding of the molecular pathways that lead to motor neurone death is needed in order to target therapeutic strategies. Considerable advances have been made in the past few years through the development of cellular and animal models of motor neurone injury.

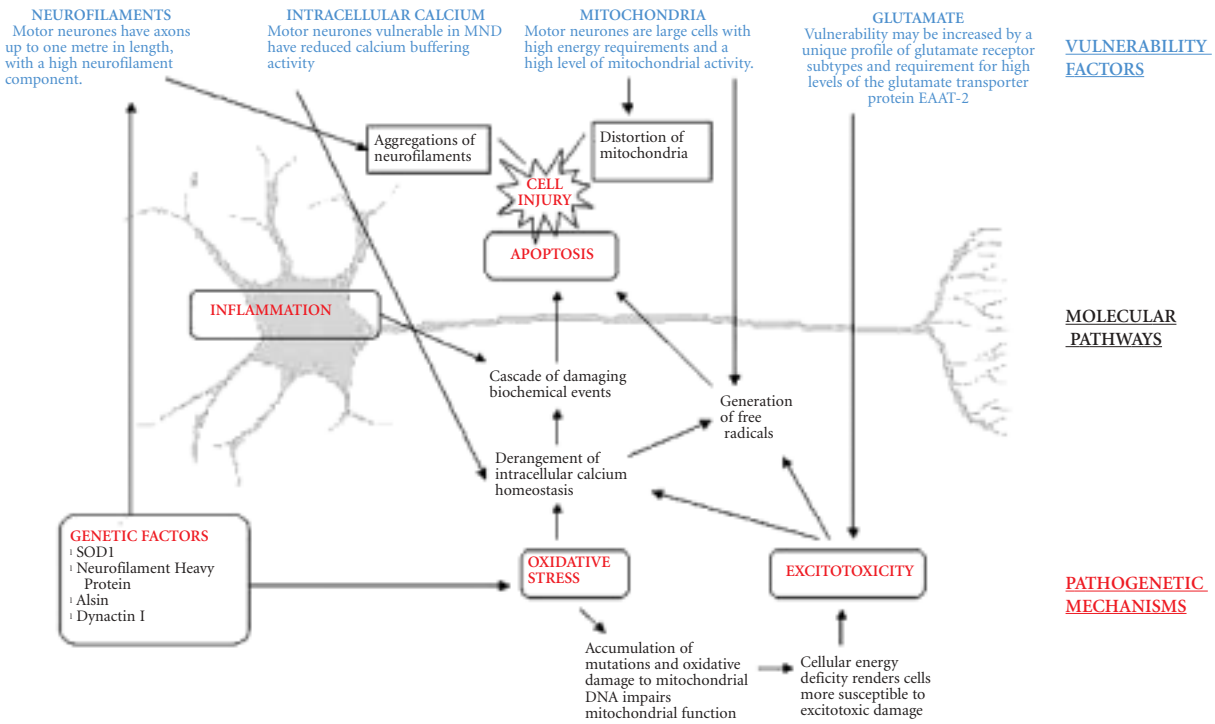
It is thought that multiple pathogenetic processes contribute to neuronal injury, to which motor neurones are selectively vulnerable. There is clinical and pathological evidence of the involvement of neurones outside the motor system, however, and MND is now thought of as a multi-system degenerative disorder in which motor neurones are affected earliest and most severely[1]. Features of motor neurones that underlie their vulnerability, and proposed mechanisms of injury are summarised in Figure 1.

A major advance in understanding motor neurone degeneration was the discovery in 1993 that one-fifth of familial cases are caused by mutations in superoxide dismutase 1 (SOD1), an antioxidant defence protein[2]. Other genetic defects have been identified including genes coding for neurofilament proteins in some apparently sporadic cases of MND; a gene termed *alsin*, encoding a putative GTPase regulator in a rare juvenile form of MND[3, 4], and in one family in *dynactin I* which codes for a protein important in retrograde axonal transport.[5] Other genetic loci linked to familial MND are being investigated in the hunt for disease causing mutations.

These findings may also shed light on the mechanisms of neuronal damage in sporadic MND, in which as yet unidentified genetic susceptibility and environmental factors are likely to interact to trigger the degenerative process via a number of pathogenic mechanisms: [1, 6-8]

- **Oxidative Stress:** An area of particular interest since the discovery of SOD1 mutations in familial MND, oxidative stress leads to accumulation of calcium and free radicals that trigger a cascade of damaging biochemical reactions.
- **Excitotoxicity:** Overstimulation of glutamate receptors causes excessive calcium influx and free radical production.
- **Neurofilament dysfunction:** Abnormal accumulation of neurofilaments, a characteristic feature of the pathology of MND, may be a primary process causing disruption in axonal structure and transport: motor neurone pathology is seen in transgenic mice that express abnormal neurofilament proteins. Alternatively neurofilaments may be prone to oxida-

Figure 1: Vulnerability factors and mechanisms of injury in MND[1, 7]



tive damage, as is seen in mice expressing mutant SOD1 protein.

- **Protein aggregation:** As in other neurodegenerative diseases, misfolding of proteins with the formation of intracellular aggregates is a feature of the pathology of MND, and is seen in the SOD1 transgenic mouse model due to misfolding of mutant SOD1. It is not known whether such aggregated proteins play a role in pathogenesis, or are harmless bystanders.
- **Mitochondrial dysfunction:** Mitochondria show early disruption in mouse models of MND, and are particularly susceptible to oxidative and free radical damage.
- **Inflammation:** Reactive microglia and astrocytes are abundant in pathologically affected areas in human MND. These may release pro-inflammatory molecules that propagate the neurodegenerative process.
- **Apoptosis:** There is evidence that the final common pathway of these processes is activation of the apoptotic cell death pathway which leads to death of motor neurones.

Neuroprotective Therapies

These insights into the mechanisms of neuronal degeneration have led to the development of a number of compounds which protect neurones in cell culture and in animal models of MND. Over 50 potential neuroprotective agents have been tested in clinical trials which have been extensively reviewed elsewhere.[9,10] The larger trials, and their theoretical and experimental basis are summarised in Table 1.

Riluzole

One of these, riluzole (Rilutek) has been shown to slow significantly disease progression in humans. It is the only neuroprotective agent licensed for use in MND. It is a sodium channel blocker whose primary mechanism of action is to reduce excitotoxicity through inhibition of glutamate release although it has been shown to have several other potentially neuroprotective effects.[10]

Two double-blind placebo-controlled trials of riluzole have been carried out in more than 1100 patients.[11-13] A Cochrane review of riluzole therapy in MND[14] concluded that there is a statistically significant, although modest, effect in prolonging survival by approximately 2-3 months. A modest improvement in limb and bulbar function was seen, but no clear effect on muscle strength was demonstrated, and neither trial evaluated quality of life.

In view of the high cost to benefit ratio, there has been controversy about the use of riluzole worldwide. In the UK, its use is recommended by the National Institute for Clinical Excellence (NICE) which estimated the cost of therapy to be £34000 to £43500 per quality-adjusted life year (QALY)[15]. The NICE guidelines and other characteristics of riluzole are summarised in Table 2.

Other Neuroprotective Agents

As shown in Table 1, several compounds that appeared to protect neurones from degeneration in cell culture and animal models have had disappointing results in clinical trials. There are two possible explanations for this. Firstly, the models used may not accurately reproduce human disease. Secondly problems with the design and methodology of clinical trials in the past (Information Box, page 18) could mask a modest clinical benefit.

To improve the design and implementation of clinical trials in MND, the World Federation of Neurology published consensus guidelines in 1998.[16] These recommended the use of El Escorial/Airlie diagnostic criteria[17], defined common inclusion and exclusion criteria and endpoints, including quality of life, and advised on techniques for measuring disease progression.

Future Directions

1. **Novel Disease Modifying Therapies:** Several potential neuroprotective compounds are currently undergoing clinical trials (see Table 3, page 17).
2. **Drug Cocktails:** By analogy with other previously incurable diseases, such as the haematological malignancies and HIV/AIDS, it is likely that neuroprotective therapies developed in the future will be combined with riluzole in a drug 'cocktail' to affect the pathway of neuronal degeneration at multiple levels.
3. **High throughput drug development:** Automated laboratory assays of neurodegeneration can rapidly screen thousands of chemicals to identify lead compounds for drug development. The traditional reluctance of pharmaceutical companies to invest heavily in rarer diseases such as MND has recently been addressed by the emergence of non-profit-making biotech companies using high-throughput drug screening to identify compounds of interest.[18]
4. **Stem Cell Research:** The ultimate goal of MND research is not only to halt neuronal degeneration, but then to restore the original structure and function of the motor nervous system. Pluripotent stem cells, capable of differentiating into different cell types are

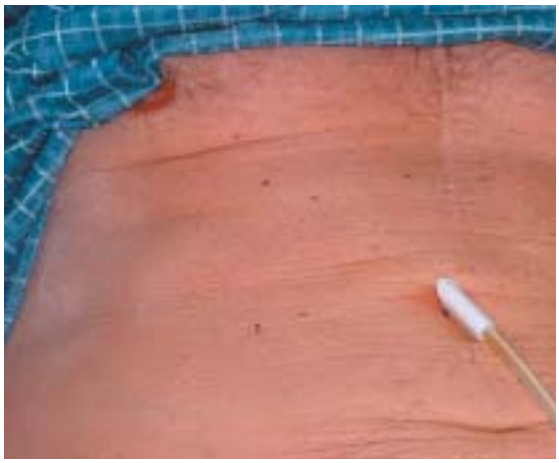


Figure 2: A PEG Tube (24 hours post insertion) in a patient with MND

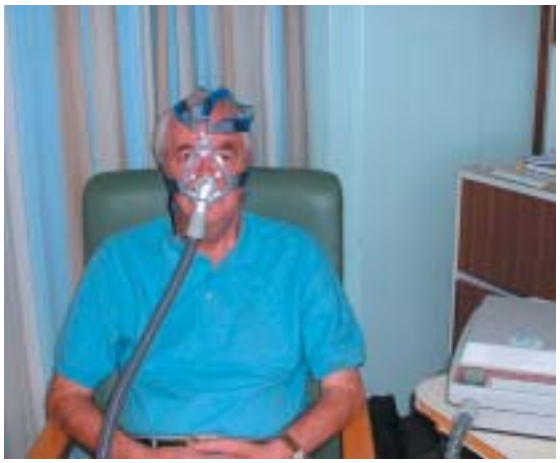


Figure 3: The use of NIPPV in a patient with MND

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Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** ***Pregnancy.*** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. ***Lactation:*** Excretion into breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine -type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £68.32. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £95.76. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** January 2002.

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the obvious candidate for this function. However stem cell technology is at an early stage and large scale clinical trials are likely to be a long way off.[19]

SYMPTOMATIC TREATMENTS

Although neuroprotective therapy in MND is still very limited, symptomatic treatment can substantially alleviate distress and improve quality of life.

There is a growing tendency in the UK for patients with MND to be managed in specialist clinics. This allows for the coordination of a multi-disciplinary team with experience of MND, which includes nursing staff with specialist training, physiotherapist, occupational therapist, speech therapist, dietician, social worker and orthotist. Considerable support is also provided by patient associations such as the MND association (www.alsmndalliance.org)

The management of common symptoms in MND is summarised in Table 4. Respiratory symptoms, nutritional support and terminal care are discussed in more detail:

Respiratory Symptoms

Respiratory muscle weakness develops insidiously during the course of ALS, causing dyspnoea, orthopnoea and symptoms of carbon dioxide retention, which include daytime somnolence, morning headaches and lack of restorative sleep with frequent waking.

The management of respiratory complications includes early recognition and treatment of aspiration pneumonia with antibiotics; chest physiotherapy and postural drainage to clear secretions; sleeping in an upright position to allow patients to breathe more easily at night; sublingual lorazepam for severe anxiety and dyspnoea and small doses of opiates to ease breathlessness in terminal stages.[6]

Non-invasive positive pressure ventilation (NIV) used overnight has been shown to alleviate symptoms of chronic hypoventilation, to improve significantly several measures of quality of life[20], and in two small studies also prolonged survival[21,22] (Figure 2). In the UK few patients are treated with NIV (2.6-3.5% of all MND patients), and there is marked variation in clinical practice.[23] This may partly be due to regional variation in the availability of NIV. The early signs and symptoms of hypoventilation are also subtle and easily overlooked, and there is no clear consensus on the optimal criteria for initation of NIV, or the best method of assessment to detect impending respiratory failure.[24] The results of a

Table 1: RECENT CLINICAL TRIALS IN MND

Pathogenetic Mechanism	Therapeutic Candidate	Rationale	Result of Clinical Trial in MND Patients
Excitotoxicity	Riluzole	Anti-convulsant that blocks presynaptic glutamate release. Slowed disease progression in SOD1 mouse model of MND[29]	**Modest significant survival benefit**[11, 12, 13]
	Branched Chain Amino Acids	Activate glutamate dehydrogenase to reduce glutamate levels	Recent Cochrane review concluded no significant benefit.[30]
	Gabapentin	Reduces glutamate activity. Slowed disease progression in SOD1 mutant mouse models of MND. [29]	Trend towards slowing of disease progression in pilot trial[31] not duplicated in further trial.[32]
	Topiramate	Reduces glutamate activity. Protects against motor neurone degeneration *in vitro*.[33]	No significant benefit.[34]
Oxidative Stress	Vitamin E (⁄ -tocopherol)	Supplementation of the diet of SOD1 transgenic mice with vitamin E delayed onset of symptoms and slowed disease progression. [29]	No survival benefit. Significantly more patients remained in a milder disease state after 12 months treatment.[35]
	N-acetylcysteine	N-acetylcysteine is a precursor of the antioxidant glutathione	No significant difference in survival or disease progression in an under-powered trial.[36]
Neurotrophic Effects	CNTF (subcutaneous)	These neurotrophic factors promote survival of motor neurones *in vitro* and arrest disease progression in the *wobbler* mouse model of MND[37]	No benefit shown, detrimental effect at higher doses.[38, 39]
	BDNF (subcutaneous and intrathecal)		No significant benefit[40] Intrathecal trial terminated early due to increased incidence of adverse events in the treated group (unpublished)
	IGF-1 (subcutaneous)	Promotes motor neurone survival in several models of neuronal injury[41, 42]	Significant slowing of disease progression in US trial not duplicated in a European study. Cochrane review concluded IGF-1 use could not be recommended.[43]
Mitochondrial Dysfunction	Creatine	Phosphocreatine allows the rephosphorylation of ADP to ATP. Oral creatine supplementation may improve cellular energy deficits[44], and prolongs survival in SOD1 transgenic mice.	No significant benefit[45]

Abbreviations: CNTF ciliary neurotrophic factor, BDNF brain derived neurotrophic factor, 1GF-1 Insulin like growth factor - 1

controlled trial of NIV versus supportive care being undertaken in the UK are currently awaited.

Mechanical ventilation via tracheostomy can theoretically extend a patient's life indefinitely but poses considerable ethical dilemmas, and is rarely practiced in the UK, or requested by fully informed patients.

Nutritional Support

Weight loss is universal in MND patients, due to dysphagia and loss of muscle mass. Weight loss, malnutrition and dehydration can aggravate muscle weakness and shorten lifespan, whilst frequent choking spells can make mealtimes intolerable. In early dysphagia, nutrition may be maintained by nutritional supplements, or by altering food consistency. Recipe books are available from the MNDA to help with this.

However, if these measures do not prevent continuing weight loss or dehydration, or if mealtimes are ended prematurely due to choking or dysphagia, enteral feeding should be considered. Percutaneous endoscopic gastrostomy (PEG) feeding in MND has been the subject of a recent Cochrane review[25], and represents one of the major advances in symptomatic care for patients, leading to weight stabilisation and adequate nutritional and fluid intake, although a survival benefit has not been convincingly shown. The need for PEG feeding should be anticipated as the risks of the procedure are higher once a patient's FVC falls below 50%.[24]

In some patients, technical difficulties may be experienced in the insertion of a PEG tube. In this situation, a radiologically guided method may be used[26]. In patients with a low vital capacity, the use of NIV during PEG inserion has been shown to improve tolerance and safety of the procedure. [27, 28]

Terminal Care

If MND patients are not ventilated, they will almost always die in their sleep from hypercapnic coma. In the terminal phases of illness the aim of treatment is to ensure that the patient is comfortable, and opiate and anxiolytic medication should be used as required to alleviate discomfort or distress.

Table 2: RILUZOLE THERAPY IN MND

NICE Guidelines	• Riluzole is recommended for the ALS form of MND • Therapy should be initiated by a neurologist, with routine supervision through locally agreed shared care protocols.
Dosage	50mg twice daily
Side Effects	Nausea and vomiting Asthenia, somnolence Headache, dizziness, vertigo
Serious Adverse Effects	• Elevation in liver transaminases Regular monitoring of liver function is advised (every month for 3 months, every 3 months for a further nine months then annually thereafter) • Rare cases of neutropaenia have been reported White cell count must be checked in the case of febrile illness
Contraindications	Renal and hepatic impairment Pregnancy and breast-feeding

Table 3: NEW POTENTIAL NEUROPROTECTIVE AGENTS BEING EVALUATED IN MND[10]

Compound	Mechanism	Evidence
Xaliproden	Oral neurotrophic agent	Neurotrophic effects in animal models of neurodegeneration
Minocycline	Inhibits activation of caspases in the apoptosis cascade and microglial activation.	Prolonged survival in SOD1 transgenic mouse model of MND
Celecoxib	A free radical scavenger and inhibitor of cyclooxygenase (COX). Marked increases in COX-2 have been found in MND spinal cord	
Co-enzyme Q10	A cofactor in the mitochondrial respiratory chain and endogenous anti-oxidant[48]	
Ono-2506	An astrocyte modulator	Neuroprotective effects in cell culture and animal models of neuronal injury.
Pentoxifylline	A phosphodiesterase inhibitor already used in the treatment of peripheral vascular disease	Identified as a potential therapeutic target for ALS through screening in transgenic mice
Novartis TCH346	Anti-apoptotic agent currently undergoing clinical trial in MND.	

Information Box: DIFFICULTIES IN MND CLINICAL TRIAL DESIGN

1. Many trials are underpowered to detect a modest clinical benefit. Approximately half the trials carried out since 1990 have involved 18 patients or less for a mean duration of 24 weeks.[9]
2. MND is a heterogeneous disorder, with features that cause inherent difficulties in trial design:[10]

- **Endpoints difficult to define:** Survival can be extended by respiratory support and PEG feeding.
- **Disease progression hard to measure reliably:** Certain parameters such as muscle strength and bulbar function are difficult to measure reliably. Use of various measures of disease progression has made comparison of past trials difficult.
- **Diagnostic variability:** Diagnosis is clinical and can be difficult. It is made at an ill-defined point in the course of the disease when an estimated 80% of motor neurones have already been lost[46], and it is not possible to detect a pre-clinical phase. Trials cover only a small proportion of the disease course, reducing chances of detecting any neuroprotective effect.

3. Difficulty in translating the effects of drugs beneficial in mouse models, such as mutant SOD1 transgenic mice into effective human neuroprotective therapies: Several drugs effective in SOD1 transgenic mice have not been shown to be beneficial in human trials, for example gabapentin[31,32] creatine[45] and vitamin E[35]. Several reasons have been put forward for this, including starting therapy presymptomatically in mice, and deficiencies in the design of mouse trials including failure to take into account gender and litter effects.[47]

Table 4: SYMPTOMATIC THERAPY IN MND [24, 49]

SYMPTOM	TREATMENT
Muscle weakness and Fatigue	• Physiotherapy to prevent muscle contractures and joint stiffness • Devices to maintain mobility and independence such as ankle-foot orthoses, head supports, mobile arm supports, bathroom aids etc • Acetylcholinesterase inhibitors (pyridostigmine) can cause a short term improvement in fatigue in some patients
Fasciculations Painful **muscle cramps** are common **Spasticity** causes pain and decreased mobility	• Anti-spasticity agents (Baclofen, Tizanidine): Dose must be carefully titrated as loss of tone can worsen mobility • Quinine sulphate for cramps • Low-dose diazepam for cramps or fasciculations
Sialorrhoea (drooling) due to impaired swallowing and facial muscle weakness causes sore lips, dehydration, and embarassment	• Hyoscine transdermal patches, amitriptyline or atropine • Portable suction devices. • Low dose parotid irradiation may be considered if drug treatment is not successful. • B-blockers or carbocysteine reduce viscosity of secretions.
Pseudobulbar Affect : Inappropriate laughter or crying that often accompanies corticobulbar involvement	Responds well to amitriptyline or selective serotonin reuptake inhibitors (SSRIs)
Psychological Problems: **Depression** and **Anxiety**	A grief reaction is a normal response to a devastating diagnosis. Clinical depression is also common and underdiagnosed. It can be treated with tricyclic antidepressants or SSRIs.
Sleep Disorders	Treatment should be directed at the cause of insomnia. Common causes in MND are respiratory insufficiency, anxiety, depression, muscle cramps, and inability to change position. Use of sedatives should be avoided unless other options fail.
Constipation is common secondary to immobility, dehydration and weakness of abdominal muscles	• Review medications (Analgesics and anticholinergics worsen constipation) and ensure adequate fluid intake • Bulk-forming or osmotic laxatives, glycerol suppositories
Musculoskuletal Pain is common due to abnormal stresses on bones and joints	Non-steroidal anti-inflammatories and physiotherapy are most effective
Dysarthria	Simple strategies to improve communication can be taught by a speech therapist. When these become ineffective, a variety of communcation aids are available, such as a light-writer
Dysphagia	See text
Dyspnoea	See text
Terminal care	See text

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Myoclonus

Myoclonus can occur in many different settings and in a range of neurological disorders, as well as being seen physiologically when falling asleep in lectures for example! The essential feature of the condition, which makes it instantly recognisable is the sudden, brief and shock-like nature of the movement (and equates to EMG bursts of activity of about 10-50msec). There are different ways in which it is defined according to: what provokes it; where it is; and what it is associated with neurologically as well as pathophysiologically. As with all movement disorders it can be associated with other involuntary movements.

In this short review I will briefly discuss the different types of myoclonus and their salient features and present a pragmatic approach to the patient with this type of movement disorder.

Clinical evaluation of myoclonus

The initial evaluation is undertaken to decide whether the myoclonus is spontaneous, and this may require a relatively prolonged period of observation. If not present then it is worth trying to provoke it. In the first instance this involves getting the patient to move (such as putting their hands out in front of them) which typically provokes action myoclonus, and in some cases holding the hands out in front causes them to flap (asterixis) which reflects negative myoclonus (which equates to a brief loss of EMG activity). Finally in order to see whether there is any stimulus sensitivity, one should flick the distal finger joints and/or make a sudden loud noise (clap hands) to see if either of these manoeuvres provokes a reflex myoclonus.

This having been achieved the next question is to decide the distribution of the myoclonus and this may provide clues as to aetiology and pathophysiological origin. In particular is the myoclonus confined to one area (i.e. focal such as a jerking limb for example); is it segmental (adjacent body parts- shoulder), multifocal (widely distributed, unpredictable and not synchronised) or generalised (synchronised jerks affecting most of body).

Finally one examines the patient to see whether there are other associated systemic or neurological abnormalities which are associated with the myoclonus.

Defining the pathophysiological basis is not necessary although focal myoclonus is normally of focal origin - so involves the cortex or spinal cord, whilst subcortical sites of origin produce generalised or multifocal myoclonus.

Investigation of myoclonus

History and examination is followed by a series of investigations that may help identify the cause, although the nature of the tests will to some extent be determined by the duration and type of myoclonus and whether it is associated with other neurological or systemic abnormalities.

Full biochemical screen looking for major electrolyte, renal or hepatic abnormalities and consider arterial blood gases.

Autoantibody screen in particular looking for coeliac disease; paraneoplastic syndromes and anti-GAD for jerking stiff man syndrome.

Imaging to exclude cerebrovascular, neoplastic or obvious neurodegenerative condition as well as focal lesion in patients with focal myoclonus, especially in spinal and propriospinal myoclonus.

EEG to see whether there is evidence that myoclonus is part of an epileptic syndrome or whether the patient has epilepsia partialis continua as well as looking for CJD.

SEPs, which are giant in cortical myoclonus, and is therefore most consistently found in the rare group of patients with progressive myoclonic epilepsy

More sophisticated neurophysiology can also be undertaken such as jerk-locked EMG to EEG back averaging, but this is not routinely available in most hospitals.

Other tests to be considered

- Genetic tests – looking for DRPLA and mitochondrial disease
- Skin biopsy – looking for neuronal ceroid lipofuscinosis (NCL).
- Axillary skin biopsy – looking for Lafora body disease and Unverricht-Lundborg disease
- Muscle biopsy – looking for mitochondrial disease as well NCL, Lafora body disease
- Enzyme assays in urine and blood – looking for sialdosis, gangliosidosis and Gaucher's disease
- Systemic investigation looking for a primary malignancy – CT chest/abdomen; whole body PET scan etc
- Brain biopsy – looking for vasculitis and possibly to confirm the nature of a neurodegenerative disorder

Treatment of Myoclonus

In many cases treatment is not necessary, as there is either a clear underlying aetiology that needs rectifying; the myoclonus does not cause any major disabilities; or the myoclonus is in the presence of advanced neurodegenerative disease.

If drug therapy is required the most successful are:

- Clonazepam for all forms of myoclonus
- Sodium valproate for most forms of myoclonus
- Piracetam for post-anoxic myoclonus
- Levetiracetam for post-anoxic myoclonus
- Tetrabenazine is said to be helpful for segmental myoclonus
- Botulinum injections for some forms of focal myoclonus, especially hemifacial spasm
- Other drugs that may have a role include primidone for cortical myoclonus and fluoxetine in postanoxic and action myoclonus.

Some myoclonic syndromes

ESSENTIAL MYOCLONUS/MYOCLONIC DYSTONIA

This is a heterogeneous condition, which consists of widespread myoclonus affecting all four limbs, trunk, neck, and face, occurring at about 10 to 50/min, enhanced by action and sensory stimuli. Onset is usually

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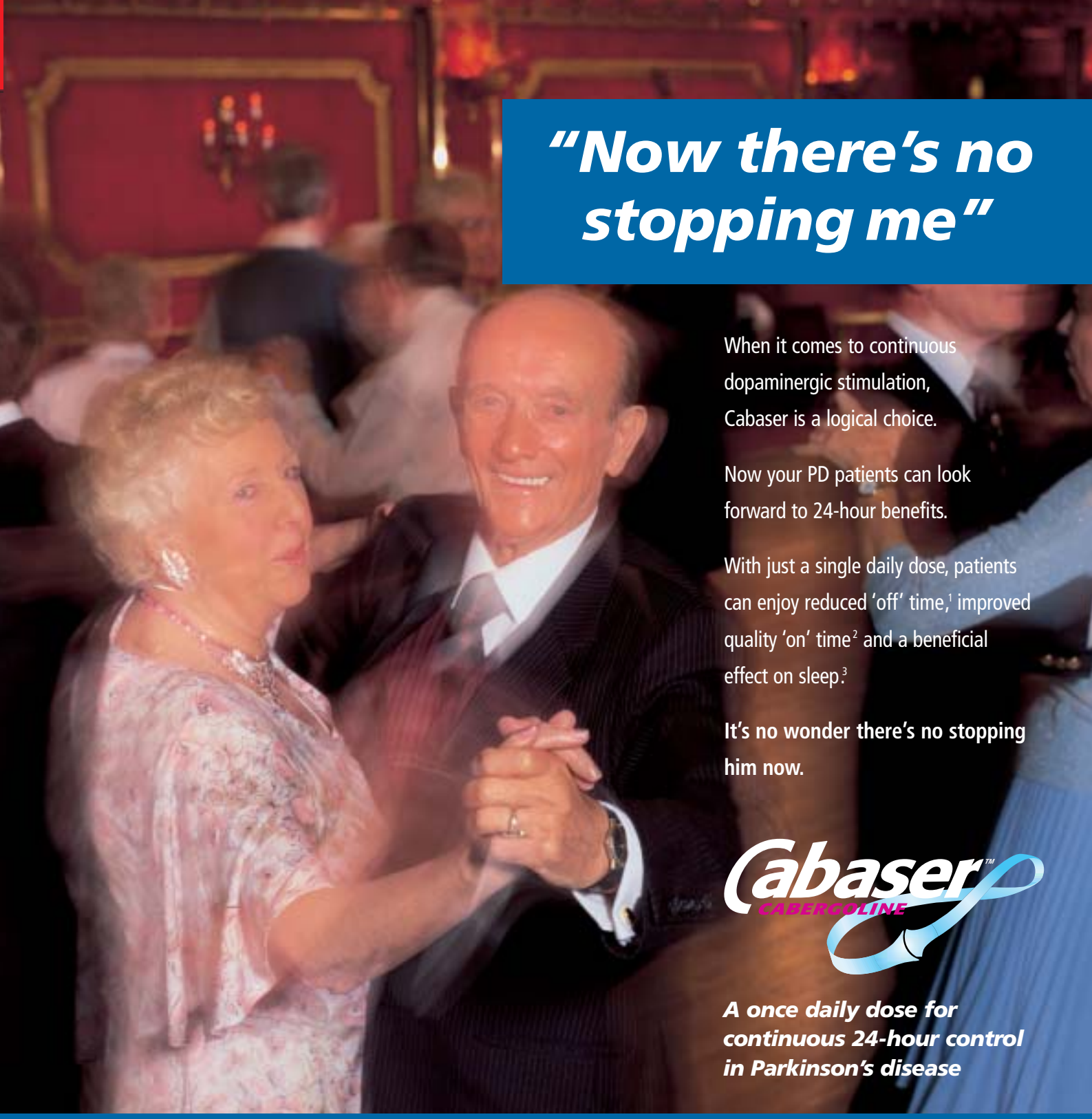
Table 1. The classification of myoclonus

Clinical Presentation	Clinical Distribution	Neurophysiological Origin	Aetiology
• Spontaneous - typically seen normally or in patients with metabolic encephalopathies or CJD • Action - which occurs during active muscular contractions, and is very disabling. • Reflex - which occurs to somesthetic, visual and auditory stimuli.	• Generalised • Multifocal • Segmental • Focal	• Cortical (often associated with giant SEPs) • Subcortical (brainstem and includes hyperekplexia; brainstem reticular myoclonus and palatal myoclonus) • Spinal (typically associated with a focal spinal cord lesion) • Propriospinal	• Physiological • Essential • Symptomatic



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Cabaser should not be used in association with macrolide antibiotics since systemic bioavailability of Cabaser and adverse effects could increase. The effects of alcohol on overall tolerability of Cabaser are currently unknown. **Pregnancy and Lactation:** Based on limited clinical experience, cabergoline does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities. As a precautionary measure, it is recommended that women seeking pregnancy discontinue Cabaser one month before intended conception, in order to prevent possible foetal exposure to the drug. If conception occurs during therapy, treatment is to be discontinued as soon as pregnancy is confirmed. Do not use in nursing mothers as lactation may be inhibited; no information on the excretion of cabergoline in maternal milk in humans is available. **Undesirable Effects:** Events most frequently reported in clinical studies were dyskinesia, hyperkinesia, hallucinations or confusion. Other events include nausea, vomiting, dyspepsia and gastritis, as well as dizziness and hypotension. Symptomatic pleural effusion/fibrosis has been reported with a frequency <2%; in these cases discontinuation of Cabaser is expected to lead to immediate improvement of symptoms. Cabaser has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. In view of Cabaser's pharmacological class, other reported events include angina (reported in 1%), erythromelalgia (0.4%) and peripheral oedema (6%). CNS events are more common in the elderly. **Overdose:** No incidences reported in the proposed indication. 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in childhood or adolescence, but disability is strikingly mild in most cases. There is no progression, intellect is normal, fits do not occur, and no other deficit appears. Some patients report that alcohol helps their jerks.

Whilst many cases are sporadic, in some cases there is a positive family history suggesting an autosomal dominant condition with variable penetrance and expression.

In some case the myoclonus may be associated with dystonia (myoclonic dystonia) – with the latter often being the dominant clinical feature. It often shows a dramatic response to alcohol and is associated in some cases with mutations in the ©sarcoglycan gene, but is genetically heterogenous with associations with the D2 receptor gene (chromosome 11q23) and a Canadian family linked to chromosome 18p11.

PROGRESSIVE MYOCLONIC ENCEPHALOPATHIES (PME)

Most of the diseases causing a progressive myoclonic encephalopathy are rare and a discussion of them lies outside the scope of this short review. Those that cause this:

- with cognitive decline and epilepsy include Lafora body disease; neuronal ceroid lipofuscinosis (in the form of Kuf's disease in adults); MERFF, sialidosis; DRPLA
- with minimal cognitive involvement and epilepsy include Unverricht-Lundborg disease and the progressive myoclonic ataxias (e.g. coeliac disease and some of the SCAs)
- with significant cognitive decline and no epilepsy include the neurodegenerative disorders such as CJD, corticobasal degeneration, Alzheimer's disease and in some advanced cases of HD.

STATIC MYOCLONIC ENCEPHALOPATHIES: POSTANOXIC ACTION MYOCLONUS (LANCE-ADAMS SYNDROME)

This is a distinct entity that may appear after a period of cerebral anoxia, typically respiratory arrests in the context of an acute asthmatic attack. After recovery of consciousness, such patients exhibit muscle jerks affecting face, trunk, and limbs, often provoked by sensory stimuli, and strikingly elicited by willed voluntary action. The condition has been associated with abnormalities of brain 5-HT, as 5-hydroxytryptophan can produce a dramatic response in some patients. However the side-effects of this therapy, in particular the development of the eosinophilia myalgia syndrome (EMS) has meant that other treatments such as clonazepam, piracetam, and more recently levetiracetam are preferred.

MYOCLONIC EPILEPSIES

In the myoclonic epilepsies, epileptic seizures are the obvious and dominant feature of the illness. There is some confusion in separating the many conditions that may cause this syndrome, which occurs particularly in children. A convenient, if arbitrary, distinction is based on the age of onset and is discussed in ACNR (Mark Manfords series on Epilepsy. See www.acnr.co.uk volumen I archive).

FOCAL MYOCLONUS

Spinal myoclonus

Repetitive, often rhythmical, myoclonic jerking restricted to a limb, or even to a few muscles of an arm or leg, may occur with a focal myelitis, spinal cord tumour or angioma, or after spinal cord trauma. The rhythmic muscle jerking occurs spontaneously, at 20 to 180 per minute, is not affected by peripheral stimuli, often persists in sleep, and is not associated with any change in the EEG. Anticonvulsants and tetrabenazine may help, but it is often very difficult to control.

Table 2 Causes of myoclonus

Generalised myoclonus

Essential myoclonus

Non-progressive condition in which myoclonus is only or most important neurological symptom and sign.

Progressive myoclonic encephalopathies (PME)

Conditions in which there is obvious myoclonus (with or without seizures) as part of a progressive encephalopathy.

- With demonstrable metabolic cause (e.g. Lafora body disease, mitochondrial encephalomyopathy (esp.MERFF); Sialidosis; Neuronal ceroid lipofuscinosis)
- Hereditary myoclonus with no known metabolic cause (e.g. Familial myoclonic epilepsy (Unverricht–Lundborg disease); rarely seen in HD and DRPLA)
- Other sporadic diseases (e.g. Subacute sclerosing panencephalitis (SSPE), Creutzfeldt–Jacob disease, Alzheimer's disease, Parkinsonian plus conditions- especially corticobasal degeneration; paraneoplastic; vasculitis; coeliac disease)
- Metabolic myoclonus (e.g. uraemia, hepatic failure, CO2 narcosis)

Static myoclonic encephalopathies

Condition in which there is obvious myoclonus after some acute and now static cerebral insult. E.g. Postanoxic action myoclonus (Lance–Adams syndrome).

Myoclonic epilepsies

Conditions in which epilepsy is the main problem, but myoclonus is present.

Focal myoclonus

Conditions in which the myoclonus is restricted to one small discrete part of the body

- Spinal myoclonus
- Propriospinal myoclonus
- Palatal myoclonus (see Case on ACNR website, www.acnr.co.uk)
- Hemifacial spasm
- Cortical myoclonus
- Epilepsia partialis continua

Epilepsia partialis continua

Encephalitis, tumour, abscess, infarct, haemorrhage, or trauma to the cerebral cortex may rarely cause repetitive, rhythmic muscle jerking once or twice a second, confined to one collection of muscles, persisting even in sleep for days, weeks, or months. Usually the damage involves not only the cerebral cortex, but also deeper structures including the thalamus. Because of its large cortical representations, the most common site of epilepsia partialis continua is the hand and in all cases the focal source may spread to give secondary generalised seizures. Treatment is with anticonvulsants, but may be difficult.

Hemifacial spasm

Hemifacial spasm occurs at a frequency of about 1; 100,000 people, most commonly affects middle-aged or elderly women, and usually appears without obvious cause. Rarely, it may be symptomatic of obvious facial nerve compression. The condition consists of irregular, but repetitive clonic twitching of the muscles of one side of the face with each spasm closing the eye and drawing up the corner of the mouth. At this stage, a mild facial weakness and contraction becomes evident, but a frank facial palsy never develops. Facial sensation is normal and there are no other physical signs in idiopathic hemifacial spasm.

Treatment with drugs is usually unrewarding. Posterior fossa exploration has been advocated especially if there is evidence of facial nerve compression but injection of botulinum toxin into the facial muscles, repeated every 3 to 4 months, is a simpler and usually effective treatment.

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Upper motor neurone syndrome and spasticity

Edited by: MP Barnes and GR Johnson
Publisher: Cambridge University Press
ISBN: 0-521-79427 7
Price: £34.95

"What – a whole book on spasticity? " my (medical) parents said. Yes, and it is one that achieves a good balance between the technical and the clinical aspects of the syndrome. The book is aimed at health professionals involved in treating adults or children with spasticity, including neurologists and other clinicians, therapists, orthotics experts and engineers. Despite this wide spread, or perhaps because of it, the book does bring out many features of spasticity that each discipline tends individually to forget, and works well in painting an overview with sufficient detail to satisfy aficionados.

The book brings out the many controversies about even the most basic statements and assumptions, including such pitfalls as the inappropriate use of parametric statistics for Ashworth scales. Individual interventions are hard to assess amidst the statistical noise and heterogeneity of problems encountered alongside spasticity.

Introductory chapters cover pathophysiology in enough detail to provide considerable food for thought. The chapter on measurement focuses on impairment and leaves discussion on disability and quality of life rather scattered about the rest of the book. Separate chapters detail the aims, methods and practical details of the available treatments, with appropriate weighting given to physical therapies and preventive measures. Neurologists will find relevant coverage of the "side issues" that we farm out to others and perhaps in consequence find rather opaque, such as seating, positioning and orthoses, as well as the more traditionally "medical" areas such as oral and intrathecal drugs, nerve and motor point blocks, and surgical options. There is a realistic assessment of the value of botulinum toxin. The wide coverage of adult spasticity is distributed between many chapters, with paediatric spasticity more focused and perhaps in consequence it is easier to assimilate and appreciate the options and priorities for children. For instance, the physiotherapy chapter nicely clarifies the options and thought processes of therapists working with children, but says little specifically about adults, leaving the reader to draw this information from the various other chapters.

I would recommend this book to any health professional who deals with patients with spasticity – which includes most neurologists. It is well balanced and readable, and will bring you up to speed in the subject.

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Practical Neurology

Edited by: José Biller
Publisher: Lippincott Williams & Wilkins (2nd edition)
ISBN: 0-7817-3019-8
Price: £53.50

José Biller has some impressive authorial and editorial credits to his name (Localisation in Clinical Neurology, Iatrogenic Neurology) and this book is also, in my view, a winner. Not to be confused with the journal of the same name, nor the book (by the late Professor Bryan Matthews) from which that journal took its name, Practical Neurology is a multi-author text, with all but one of the contributors being American.

Although physically small, the book is large on content, with over 800 pages of densely written text. Chapters in section I, devoted to diagnosis, follow a fairly consistent format, considering sequentially the pathophysiology /aetiology, clinical features, and evaluation of various clinical problems. Section II is devoted to treatment of particular conditions. Algorithms are included where appropriate; few illustrations (black and white) punctuate the text. One sometimes gets a bit boggled by the multiple subdivisions of chapter subheadings, but I suppose these may help the reader who is "dipping in" rather than reading systematically.

There are differences of emphasis in the American, as opposed to European, approach, especially in the treatment section (for example, the use of phenobarbital in epilepsy; no mention of pizotifen for migraine prophylaxis; use of ChEIs viewed as "reasonable" in frontotemporal dementia). One may quibble with some points: LP is listed prior to brain imaging in the evaluation of delirium; there is no mention of SPECT scanning in diagnosis of dementia syndromes; catatonia is labelled a purely psychiatric phenomenon; IgA deficiency is not mentioned as a contraindication to the use of IVIg; angiography is said to confirm the diagnosis of cerebral vasculitis. There are occasional typographical errors, and the index is not all-encompassing. However, this is nit-picking, and the mass of information and its systematic organisation means one has no hesitation in recommending this book. Bryan Matthews's Practical Neurology (3rd edition, 1975) was my favourite neurological text as a medical student; this namesake is a worthy successor. Indeed, I see this as a serious competitor to some of the big texts (Neurology in Clinical Practice, Brain's), and you don't need to undertake a body-building course to be able to carry it around. And it's (much) cheaper!

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Mild Cognitive Impairment: Aging to Alzheimer's Disease

Edited by: Ronald C Petersen
Publisher: Oxford University Press 2003
ISBN: 0-19-512342-5
Pages: p269
Price: £39.50

Mild cognitive impairment (MCI) is a concept that has been introduced to refer to individuals who have subjective memory complaints, normal activities of daily living, and normal general cognitive function but who are memory impaired for their age yet are not demented (i.e. do not fulfil widely accepted diagnostic criteria for dementia syndromes). However the concept is heterogeneous: aficionados delineate amnestic MCI, multiple domain MCI, and single non-memory domain MCI. A subgroup of these patients, most particularly those with amnestic MCI, in fact have incipient or preclinical Alzheimer's disease (pAD), since perhaps 10-15% of MCI patients "convert" to AD each year.

The meaning of MCI varies depending on the diagnostic criteria used: some have equated MCI with specific scores on clinical rating scales (e.g. Clinical Dementia Rating = 0.5; Global Deterioration Scale = 3) but the editor of this volume is at pains to point out that MCI remains a clinical diagnosis which can only be approximated by single rating stages.

Whatever one makes of the concept, there can surely be little doubt that there is a transitional period, perhaps of many years duration, between normality and the clinical declaration of AD (most evident from pathological studies), and that identifying pAD would be highly desirable if a therapy which halts or slows AD progression were known. This multi-author text, featuring many well-known figures in the AD field, reviews evidence for this concept from the perspectives of clinical features, neuropsychiatry, neuropsychology, neuroimaging (structural and functional), neuropathology, and plasma and CSF biomarkers.

Defining norms against which to make comparisons is a frequent theme (especially in the neuropsychology sections), which leaves this reviewer wondering whether the subtle signals of pAD can be reliably distinguished from the noise of so-called normal, healthy, or successful aging.. If so, then presumably the concept of MCI will become redundant?

Despite this reviewer's misgivings about the concept, MCI is certainly an area of significant research interest currently, with many groups undertaking studies. This book gives an accessible and informative overview of current understanding.

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Upper-limb Exercise in Tetraplegia using Functional Electrical Stimulation

Introduction

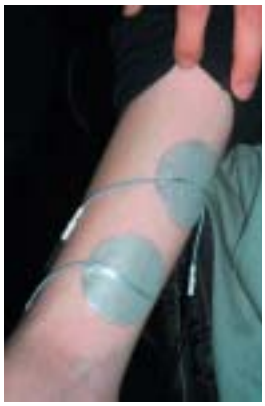
Cervical spinal cord injury can result in dysfunction in both the lower and upper limbs (tetraplegia), and may be accompanied by a range of secondary complications. The degree of upper-limb dysfunction depends upon the level and completeness of the lesion; in this paper we consider tetraplegics with a neurological level in the range C4-C6.

A person with a C5- or C6-level injury will generally retain control of the shoulder and elbow flexor muscles (biceps), but will have no control of the hand, wrist or elbow extensors (triceps). With a complete C4 injury voluntary control of the entire arm is lost. Thus, we propose that functional electrical stimulation (FES) of the biceps and triceps muscles may enhance the efficacy of cyclical upper-limb exercise. Alternatives for partial restoration of function include tendon transfer surgery or mechanical orthoses[1].

Previous FES research for C4-C6 tetraplegics has focused on systems for hand function[2,3] and improved working area (i.e. overhead reach)[4,5,6,7], but the provision of upper-limb exercise modalities using FES assistance has been neglected. This is important because the lack of effective exercise can lead rapidly to severe cardiopulmonary deconditioning in this population.

Methods

With functional electrical stimulation, low levels of pulsed electrical current are applied to motor nerves. If the depolarisation threshold is exceeded, action potentials will be propagated and the associated muscle fibres will contract. Here, we use adhesive electrodes attached to the skin surface in the area of the target muscle (see figure 1).



For FES to function properly, it is necessary that the target muscles retain central innervation. Damage to the cell bodies, nerve roots or peripheral nerves may occur around the site of the spinal trauma, and this can lead to denervation of the associated muscle fibres. Thus, a test of target muscle innervation should be included in the assessment of candidates.

The overall setup is shown in figure 2 and consist of a motor-driven arm-crank ergometer (ACE), a pattern generator and a neuromuscular stimulator[8]. The arm-crank ergometer (TheraVital, Medica Medizintechnik, Germany) has an electric motor which can actively move the cranks if the moment applied by the user is not sufficient to drive the cranks, or it can resist the cranking movement, acting as a load. The levels of active support and resistance can be adjusted. The device provides measurements of the crank angle and of the angular velocity which are used in the pattern generator to decide when each muscle group is to be stimulated. The pattern generator uses the angular velocity to adjust the nominal stimulation pattern (which is based on the measured crank angle) to compensate for the delay between stimulation and muscle contraction. The stimulation intensity is set by a "throttle" which is implemented as a potentiometer. The pattern generator drives the neuromuscular stimulator (Stanmore Stimulator, UK) which delivers electrical pulses to the four stimulation channels: left and right biceps, and left and right triceps. The moment generated at the cranks is measured and, together with the angular velocity, used to calculate the power output.

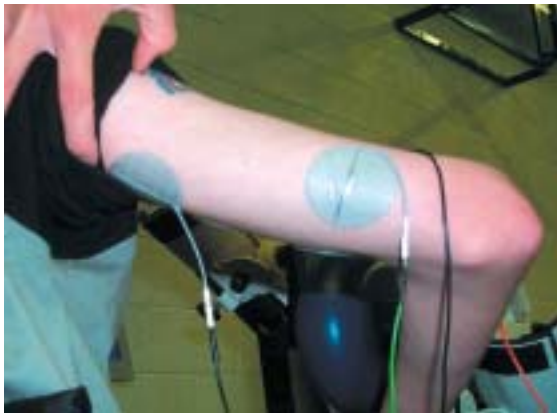


Figure 1: Location of electrode pairs over the biceps (top left) and triceps (above) muscles.

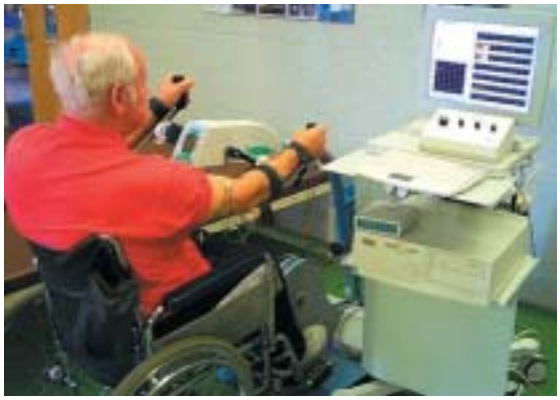


Figure 2: FES-assisted arm cranking ergometer.

Exercise Response Results

Four people with a C4-C6 level SCI are involved in our experimental evaluation of the proposed systems for FES-assisted upper limb exercise[9]. Muscle strength data are recorded throughout each subject's participation. Changes in cardiopulmonary fitness are monitored by measuring oxygen uptake during rigorously-specified exercise tests, which are performed at test points throughout the FES-assisted ACE exercise programme. Spirometry measurements are also made to assess pulmonary function. Together, these measurements allow us to evaluate possible functional and health benefits of this form of exercise in tetraplegia.

As an illustration, data for one subject are presented here. This person is 38 years old, with a C6 (incomplete) SCI. The injury occurred 17 years ago. The FES-ACE training programme consists of a one-month muscle strengthening and familiarisation period, followed by a progressive three-month FES-assisted ACE exercise training programme.

Figure 3 shows the set-up used for exercise testing, using a portable breath-by-breath gas exchange measurement system (MetaMax 3B, Cortex, Germany). A baseline test prior to the start of the FES-ACE training programme revealed that this subject could attain a maximum power output of around 7 W initially. The maximum oxygen uptake recorded in this baseline test was around 0.8 l/min, which is typical for a tetraplegic. The data from tests carried out after just two months of FES-

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ACE exercise are shown in figure 4, when the maximum power output reached was around 30 W and the maximum oxygen uptake was 1.3 l/min. Generally, the greater an individual's maximal oxygen uptake, the greater his (or her) cardiopulmonary fitness. Thus, the steady increase in both maximum oxygen uptake and maximum power output following a progressive FES-assisted arm-cranking exercise regime illustrates its potential benefits to the tetraplegic population.

Figure 3: Incremental exercise test set-up.

Clinical and Therapeutic Implications

Societies with modern health care systems now have a cohort of tetraplegic patients living into their sixties and beyond. These patients are unable to voluntarily recruit enough large muscle groups to maintain cardiovascular fitness and are at high risk of cardiovascular disease. FES-assisted arm cranking devices offer an option for regular exercise, which is otherwise unavailable for people with limited or no upper limb movement. We have shown increases in oxygen uptake and power output following an FES programme and it seems likely that this is a genuine cardiovascular training effect as seen in non-spinal-injured subjects.

We have noted other less obvious but important benefits including improvement in upper arm muscle bulk, which improves self-image. Subjects have also commented on their feelings of exercise fatigue after an FES session. Non-spinal-injured people recognise post-exercise tiredness as a part of everyday life. Tetraplegic subjects may not have experienced "normal" fatigue for many years and the return of this sensation can be rewarding and stimulating. The exercise and movement itself is also rewarding for patients who may have little or no voluntary power below the neck.

We anticipate other medical benefits of FES exercise including maintenance of existing shoulder power and upper limb joint range of movement. These will help daily activities such as transfers, weight shifts, and manual wheelchair propulsion where that is feasible.

Health care commissioners will not fund such treatment unless we can show direct clinical benefits. The improvements in cardiovascular fitness are encouraging and provide a basis for larger trials. The set-up costs are small when compared to overall tetraplegic care costs and we believe there may be a case for long term prescription of FES exercise for tetraplegic people who can commit to the daily regime which is probably necessary to achieve and maintain the improvement in fitness.

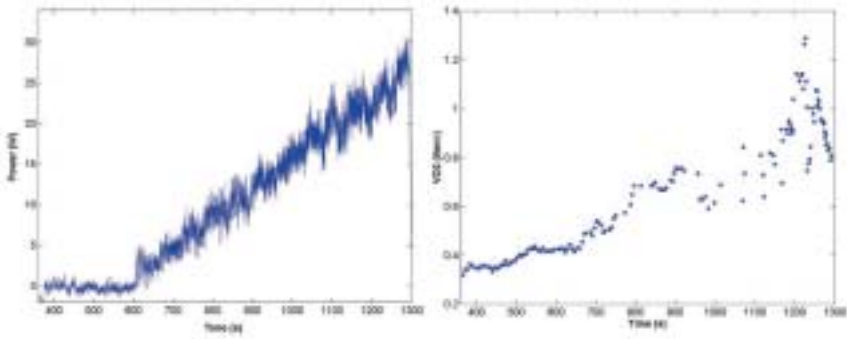

Figure 4: Incremental test data. Increasing power output (left) and oxygen uptake response (right) data for one subject, after two months of exercise intervention, are shown here.

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Three Historical Accounts of Gilles de La Tourette Syndrome

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Surely no neurologist today can be unaware of the diagnosis of Tourette's syndrome or disorder. However, this familiarity was not always so. Although the eponymous description was published in 1885, the first full description is accredited to Itard in 1825, and a possible case dating back to the fifteenth century has been found.[1] Herein, three accounts suggestive of individuals suffering from Tourette's syndrome are presented, dating from the eighteenth, nineteenth, and early twentieth centuries, two predating Tourette's publication. The sources are a biography, a novel, and an autobiography.

Case 1: Dr Samuel Johnson (1709-1784)

The great English writer, critic, lexicographer and moralist was noted by many of his contemporaries to have involuntary movements. For example, in his biography, *Life of Johnson*, published in 1791, James Boswell writes:

> That the most minute singularities which belonged to him, and made very observable parts of his appearance and manner, may not be omitted, it is requisite to mention, that while talking or even musing as he sat in his chair, he commonly held his head to one side towards his right shoulder, and shook it in a tremulous manner, moving his body backwards and forwards, and rubbing his left knee in the same direction, with the palm of his hand. In the intervals of articulating he made various sounds with his mouth, sometimes as if ruminating, or what is called chewing the cud, sometimes giving a half whistle, sometimes making his tongue play backwards from the roof of his mouth, as if clucking like a hen, and sometimes protruding it against his upper gums in front, as if pronouncing quickly under his breath, *too, too, too* … Generally when he had concluded a period, in the course of a dispute, by which time he was a good deal exhausted by violence and vociferation, he used to blow out his breath like a whale.

The illustrator William Hogarth also noted Johnson's movements:

> Mr Hogarth came one day to see Richardson [the author of *Clarissa*] … While he was talking he perceived a person standing at a window in the room, shaking his head, and rolling himself about in a strange ridiculous manner. He concluded that he was an ideot [*sic*], whom his relations had put under the care of Mr Richardson, as a very good man.

The diarist Fanny Burney (later Madame d'Arblay) describes Johnson thus:

> I have so true a veneration for him, that the very sight of him inspires me with delight and reverence, notwithstanding the cruel infirmities to which he is subject; for he has almost perpetual convulsive movements, either of his hands, lips, feet or knees, and sometimes of all together.

All these excerpts suggest the presence of motor and vocal tics. Accounts suggestive of obsessive-compulsive behaviour are also to be found in the biography. For example, Boswell noted:

> He had another particularity, of which none of his friends ever ventured to ask an explanation. It appeared to me some superstitious habit, which he had contracted early, and from which he had never called upon his reason to disentangle him. This was his anxious care to go out or in at a door or passage, by a certain number of steps from a certain point, or at least so as that either his right or his left foot, (I am not certain which,) should constantly make the first actual movement when he came close to the door or passage. Thus I conjecture, for I have, upon innumerable occasions, observed him suddenly stop, and then seem to count his steps with a deep earnestness; and when he had neglected or gone wrong in this sort of magical movement, I have seen him go back again, put himself in a proper posture to begin the ceremony, and, having gone through it, walk briskly on …

Mr S Whyte used his opera glass to observe Johnson approaching along a London street:

> I perceived him at a good distance walking along with a peculiar solemnity of deportment, and an awkward sort of measured step … Upon every post as he passed along, I could observe he deliberately laid his hand; but missing one of them, when he had got at some distance, he seemed suddenly to recollect himself, and immediately returning back, carefully performed the accustomed ceremony, and resumed his former course, not omitting one until he gained the crossing. This … was his constant practice.

What explanations for these features were contemplated by Johnson's contemporaries?

Boswell stated:

> The infirmity … appeared to me … to be of the convulsive kind, and of the nature of that distemper called St Vitus's dance; and in this opinion I am confirmed by the description which Sydenham gives of that disease. "It manifests itself by halting or unsteadiness of one of the legs which the patient draws after him like an ideot [*sic*]. If the hand of the same side be applied to the breast, or any other part of the body, he cannot keep it a moment in the same posture, but it will be drawn into a different one by a convulsion, notwithstanding all his efforts to the contrary."

It is interesting that Boswell, no medical man, should have been familiar with the works of Thomas Sydenham (1624-1689). As we have seen, Fanny Burney was also of the opinion that the movements were convulsive, as was the writer Alexander Pope:

> [Johnson] has an infirmity of the convulsive kind that attacks him sometimes, so as to make him a sad spectacle.

However, the painter Sir Joshua Reynolds took a different view

> Those motions or tricks of Dr Johnson are improperly called convulsions. He could sit

> motionless, when he was told to do so, as well as any other man; my opinion is that it proceeded from a habit which he had indulged himself in, of accompanying his thoughts with certain untoward actions.

This suggests that the movements were suppressible (perhaps a portrait painter was particularly adept at getting people to sit still). However, Boswell counters by stating:

> I still however think that these gestures were involuntary; for surely had that not been the case, he would have restrained them in the publick [*sic*] streets.

The neurologist Lord Brain was a devoted Johnsonian and wrote about his movements,[2] but ascribed them a psychological origin. His failure to mention Tourette's syndrome may perhaps reflect general neurological unawareness of the condition at the time of writing. It was left to later authors to suggest that Johnson in fact had this disorder.[3,4]

Case 2: "Mr Pancks"

The novelist Charles Dickens (1812-1870) was an author of fecund imagination but also with an acute eye for human oddity or idiosyncrasy. Many subsequent readers have thought they could detect particular neurological conditions in his characters.[5] One such is Mr Pancks, from the 1857 novel *Little Dorrit:*

> he … snorted and sniffed and puffed and blew, like a little labouring steam-engine.
> Mr Pancks here made a singular and startling noise, produced by a strong blowing effort in the region of the nose, unattended by any result but that acoustic one.
> … Mr Pancks, snorting and blowing in a more and more portentous manner as he became more interested, listened with great attention …

Clear as these decriptions of vocal tics are, there are fewer suggestions of motor tics, although Pancks is described as "darting about in eccentric directions" and of stirring up his hair. Obsessive-compulsive behaviour is suggested by his keeping a notebook in "dictionary order" and by descriptions of his tendency to nail-biting:

> … snorted Pancks, taking one of his dirty hands … to bite his nails, if he could find any …
> …with the fingers of his right hand in his mouth that he might bite the nails …

Furthermore, another behavioural feature may fall within the spectrum of obsessive-compulsive behaviour: trichotillomania:

> Mr Pancks took hold of himself by the hair of his head, and tore it in desperation … All the time, [he] was tearing at his tough hair in a most pitiless and cruel manner. [He] took hold of his hair again, and gave it such a wrench that he pulled out several prongs of it.

The suggestion that this all reflected a diagnosis of Tourette's syndrome was first made by Cosnett.[6]

Case 3: "Captain Hardcastle"

The popular children's author Roald Dahl (1916-1990) recalled a schoolmaster, a veteran of the first World War, encountered when he was 9 years old (1925-6), as recounted in his autobiographical work *Boy: Tales of childhood* (1984):

> We called them masters in those days, not teachers, and … the one I feared most of all … was Captain Hardcastle.
> Captain Hardcastle was never still. His orange head twitched and jerked perpetually from side to side in the most alarming fashion, and each twitch was accompanied by a little grunt that came out of the nostrils.
> Prep was in progress. Captain Hardcastle was … twitching his head and grunting through his nose. … The only noises to be heard were Captain Hardcastle's little snorting grunts …

What explanation did the boys have for this?

> Rumour had it that the constant twitching and jerking and snorting was caused by something called shell-shock, but we were not quite sure what that was. We took it to mean that an explosive object had gone off very close to him with such an enormous bang that it had made him jump high in the air and he hadn't stopped jumping since.

Conclusion

Considering the striking clinical features of Tourette's syndrome, it is perhaps not surprising that the condition should have attracted the attention of creative writers, as well as neurologists. Acute observers of nature, including writers and painters may, without the benefit of specific medical training, record medical conditions, sometimes prior to their description by members of the medical professions.

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The Brachial Plexus

I have always been a great believer in not doing today what can be safely put away until tomorrow. Hence I seem to have spent every Sunday night during my teenage years rushing to finish Friday's homework. Each issue before writing these primers I would say to myself, "I really must tackle the brachial plexus, as a working knowledge of it is essential for anyone engaged in peripheral neurophysiology". Of course I would take one look at the brachial plexus in the anatomy textbooks and rapidly chicken out. However, as this is the last of this little series there is no hiding place, so here it is, the sceptre that stalks every anatomy student's nightmares, the brachial plexus.

The brachial plexus lies between the neck and the axilla with the distal portion lying behind the clavicle and the pectoral muscles. It is formed from the C5, C6, C7, C8 and T1 nerve roots and is best understood by dividing it into three parts; trunks, divisions and cords. The upper trunk is formed from the C5 and C6 roots, the C7 root becomes the middle trunk and the lower trunk is formed by the C8 and T1 roots. Each trunk then divides into an anterior and a posterior division giving six divisions that unite to form cords at the level of the clavicle. The three posterior divisions unite to form the posterior cord, the anterior divisions of the upper and middle trunks form the lateral cord while the anterior division of the lower trunk carries on to form the medial cord. The major peripheral nerves of the upper limb are formed from the cords in the following way:

- the posterior cord gives rise to the radial and axillary nerves;
- the lateral cord gives rise to the musculocutaneus nerve; and
- the medial cord forms the ulnar nerve.

The median nerve is formed from branches of the medial and lateral cord. The other branches of the cords are shown in table 1 and figure 1. There are three branches that arise proximal to the cords and these are the dorsal scapular, the suprascapular and the long thoracic nerve (figure 1).

The causes of brachial plexopathy are outlined in table 2. The top three causes in my experience are trauma, neuralgic amyotrophy and radiation plexopathy, and typically the brachial plexus is diffusely affected in these conditions so it is unusual to come across a pure middle trunk plexopathy for instance. Furthermore evaluation of a traumatic plexopathy is often complicated by nerve trauma elsewhere in the upper limb, for example axillary or radial nerves as a result of a fractured humerus.

Neuralgic amyotrophy has had more names than the artist formerly known as "Prince", being variously known as brachial plexitis, brachial amyotrophy and Parson-Turner syndrome. It often presents like a mononeuropathy, so it is not uncommon for the patient to develop a syndrome indistinguishable from either an anterior interosseus or long thoracic nerve palsy.

Post radiation induced brachial plexopathy often presents years after the initial treatment, typically after radiotherapy for breast, lung and neck cancers. It needs to be distinguished from a recurrence of the primary malignancy, and in this respect it is worth looking for myokimia on EMG as this is a common finding in radiation plexopathies.

The best known localised lesion of the brachial plexus are lower trunk plexopthies, as these arise as a result of local infiltration by tumours or as a result of a fibrous band that runs from a rudimentary tirst rib to the first thoracic rib.

The neurophysiological assessment of brachial plexus lesions is like a good book - it cannot be rushed. It is worth giving them two slots on an EMG list. Plexopathies can be distinguished from root lesions using sensory nerve conduction studies as in a pure radiculopathy there

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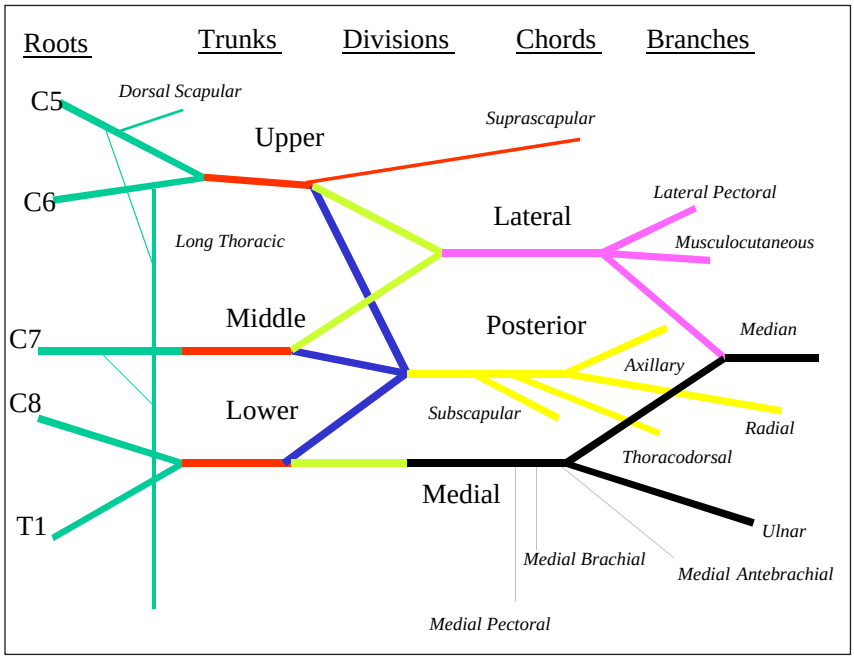
Table 1: Branches of the brachial plexus

Roots	Branches
C5	Dorsal scapular nerve
C5, C6, C7	Long Thoracic Nerve
Trunks	
Upper	Suprascapular nerve
Divisions	
Cords	
Lateral	Lateral Pectoral
	Musculotaneous
	Median
Medial	Median
	Ulnar
Posterior	Subscapular
	Thoracodorsal
	Axillary
	Radial

Figure 1: Schematic Diagram of the Brachial plexus. Roots are shown in green, the anterior divisions in green and the posterior divisions in blue. Branches are labelled in italics.



will be denervation on EMG but sparing of the sensory nerve action potentials. Sensory assessment should aim to cover all three trunks (table 3), it is particularly important to perform sensory nerve conduction studies on the medial lateral cutaneous nerves of the forearm as these nerves are not prone to entrapment neuropathies which can confound the study of median and ulnar nerves in older patients. Motor nerve conduction studies across the brachial plexus are possible but not particularly useful in this instance. F wave studies can be helpful as they give some idea of proximal motor conduction, the principal limitation of routine motor nerve conduction studies is that they only cover one trunk of the brachial plexus (lower trunk). With needle EMG, the aim is to study muscles from each trunk and each cord. If a muscle is denervated then the finding can be confirmed by studying a muscle supplied from the same part of the brachial plexus but by a different peripheral nerve. For example if triceps is denervated then you should study the deltoid, if the deltoid is dennervated then the lesion involves the posterior cord.

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Table 2: Some of the causes of Brachial Plexopathy.

Trauma
Birth Trauma (Klumpe's Palsy and Erb's Palsy)
Traction Injury
Penetrating Injuries
Neoplasm
Apical Lung Tumours
Compression by Axillary lymph nodes (Metastatic Tumours, Lymphomas)
Direct Infiltration
Inflammatory Causes
Neuralgic Amyotrophy
Radiation Plexopathy

Table 3: Sensory nerve action potentials that should be measured in assessment of brachial plexus lesions.

SNAP	Cord	Trunk
Lateral Cutaneous Nerve of the forearm	Lateral	Upper
Radial to thumb	Posterior	Upper
Median to thumb	Lateral	Upper
Median to middle finger	Lateral	Middle
Ulnar to little finger	Medial	Lower
Medial Cutaneous Nerve of the forearm	Medial	Lower

Corrective Statement regarding advertisement for Provigil®

At the MHRA's request, Cephalon would like to issue the following statement regarding our recent advertising campaign for Provigil (modafinil), which features images of driving.

Cephalon would like to point out that, while Provigil reduces excessive daytime sleepiness (EDS) in patients with narcolepsy and obstructive sleep apnoea/hypopnoea syndrome, this does not mean that such patients can assume that they will never doze off while driving and should seek advice from their healthcare professional. A reassessment of the patient's tendency to EDS after a trial of the product is required before any advice can be given as to whether or not a sufficient level of wakefulness has been resumed for the patient to be safe to drive. This process of assessment may also include the Driving and Vehicle Licensing Authority (DVLA).

Section 4.7 of the SPC draws attention to possible undesirable effects of Provigil that are relevant to driving "There is no information available concerning the effects of Provigil on vehicle driving and/or the ability to operate machinery. Undesirable effects such as blurred vision or dizziness might affect ability to drive (see 4.8 Undesirable Effects)".

Cephalon have now ceased using this campaign. We regret that our message was not perceived as intended and apologise for any confusion that may have been caused by this advertisement. Further information regarding the use of Provigil may be obtained from the Medical Information Department, Cephalon UK Limited, 20 Alan Turing Road, Surrey Research Park, Guildford, Surrey, GU2 7EH, or by calling Freefone 0800 783 4869.

National Stroke Nursing Forum

Nurses and other health and social care professionals with an interest in stroke nursing can now join the newly launched National Stroke Nursing Forum to access a central point of information and support, and network with others.

The Forum, developed by stroke nurses to meet the needs of those involved in stroke nursing, was launched at the third National Stroke Nurses Conference in Birmingham.

NSNF Chair, Tim Ayers, Consultant Nurse in Stroke (Exeter, East and Mid Devon Primary Care Trusts) said the organisation's main objectives are to provide a forum for discussion between all health professionals with an interest in stroke nursing and enable sharing of best practice. He said the forum would also provide nurses with a collective voice to influence policy development; and facilitate the development of a career pathway for nurses in the field of stroke.

The main feature of the Forum, which has been supported by an educational grant from Boehringer Ingelheim Ltd, will be an interactive website that can be accessed by members. As well as providing latest information and news, the website will allow networking with colleagues across the UK via a chat room and contact service. A regular newsletter is also under development.

Specific steering groups will focus on networking/communication; research development and education; and policy and service development.

Margaret Goose, Chief Executive of The Stroke Association welcomed the initiative adding, "We congratulate the stroke nurses who have developed the Forum for taking this lead, which will help drive forward the changes necessary to improve stroke care for patients and carers."

Mary Hopper, Team Leader, NSF for Older People, Department of Health said that the Forum would facilitate communication between all those involved in stroke nursing. She added, "The Forum will be an invaluable information resource for me to effectively consult with the whole of the UK. This is a unique initiative and I applaud the professionalism, energy and dedication of all those involved in it."

For more information about the Forum and/or to register, log on to www.nationalstrokenursingforum.com. Annual membership costs £10.

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 December 6th, 2003. An extended version of this diary is available on our website at www.acnr.co.uk

2003

November

British Neuropsychological Society Autumn Meeting
5-6 November, 2003; London, UK
E. georgina.jackson@nottingham.ac.uk

Persistent Vegetative State
6 November, 2003; London, UK
Tel. 020 7290 2984, E. cns@rsm.ac.uk

Brain Injury: The Rehabilitative & Neuropsychiatric Interface
6-7 November, 2003; Florida, US
Tel. 001 813 903 4844,
Fax. 001 813 978 5852,
E. frank.valva@med.va.gov

Dystonia in 2003
8 November, 2003
E. clive.woodard@medtronic.com

Annual Meeting of the Society for Neuroscience
8-13 November, 2003; New Orleans, US
Tel. Jamie Swank, 001 202 462 6688,
E. info@sfn.org

Creating Symbolised Resources
11 November, 2003; Lingfield, UK
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338,
E. klaird@ncype.org.uk,
www.ncype.org.uk

11th Annual Meeting, International Alliance of ALS/MND Associations
13-19 November, 2003; Milan, Italy
Fax. 01604 638 289,
E. alliance@alsmndalliance.org

European Society of Gene Therapy
14-17 November, 2003; Edinburgh, UK
Congrex Sweden AB
Tel. +46 8 459 66 00,
Fax. +46 8 661 91 25,
E. esgt@congrex.se

Advanced Course in the Treatment of Parkinson's Disease & Extrapyramidal Disorders
18 November, 2003; Pescara, Italy
Tel. +39 064 455 618,
Fax. +39 064 455 618,
E. limpe@interfree.it

Parkinson Parkinsonism Dementia: Work in Progress
19-21 November, 2003; Pescara, Italy
Fax. 39 064 455 618,
E. limpe@interfree.it

Good Practice in Epilepsy
20 November, 2003 Birmingham, UK
Epilepsy Action, Tel. 0113 210 8800,
E. rwood@epilepsy.org.uk

Living with Thalidomide
20 November, 2003; Leeds, UK
Tel. Linda at the Thalidomide Trust, 01480 474074

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

3rd King's Neuromuscular Disease Symposium
21 November, 2003; London, UK
Tel. 020 7848 6122,
E. lynette.clover-simpson@kcl.ac.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
21 November, 2003; Widnes, UK
Sam_loughran@hotmail.com,
Tel. 0151 420 7619

The Management of the Advanced Parkinson's Disease Patient
21 November, 2003
E. clive.woodard@medtronic.com

11th Asian-Australasian Congress of Neurology
22-26 November, 2003; Singapore
Dr Balaji Sadasivan,
Tel. 657 381 871,
Fax. 657 387 691,
E. enquiries@aasns.com

Good Practice - Diagnosis and Epilepsy
27 November, 2003; Bristol, UK
Epilepsy Action,
Tel. 0113 210 8800,
E. rwood@epilepsy.org.uk

2nd All-Wales Stroke Conference
28 November, 2003; Cwmbran, Gwent
Dr E A Freeman, St Woolos Hospital, Stow Hill, Newport, South Wales NP20 4SZ

Challenges & Opportunities in Providing Sexual Health Services for People with Learning Disabilities
28 November, 2003, UK
Tel. 020 7290 3934,
E. learning-disability@rsm.ac.uk

December

Neurological Rehabilitation
4 December, 2003; London, UK
Tel. 020 7290 2984, E. cns@rsm.ac.uk

Epilepsy Specialist Nurses Association South East Locality
4 December, 2003; Chalfont St Peter, UK
Tel. 01494 601 300 x 2159,
E. marchmail@ukgateway.net

BSRM Winter Meeting & AGM
8 December, 2003; London, UK
Tel. 020 7935 1174 x 300/436/252, or
E. conferences@rcplondon.ac.uk

An Introduction to Microarray Technology & Its Applications
8-9 December, 2003; Warwick, UK
Dr Steve Hicks,
Tel. 024 76 523540,
Fax. 024 76 523701,
E. s.j.hicks@warwick.ac.uk

Work & The Musculoskeletal Conditions - BSRM/BSR/RCP Meeting
9 December, 2003; London, UK
Tel. 020 7935 1174 x 300/436/252, or
E. conferences@rcplondon.ac.uk

The Cambridge Dementia Course 2
10-12 December, 2003; Cambridge, UK
E. penny.pearl@addenbrookes.nhs.uk

International EEG Course
10-11 December, 2003; Chandigarh, India
Tel. 91 172 2744568,
Fax. 91 172 2744401,
E. sudesh@prabhakars.com

The Brain and the Psyche: A meeting of Minds
17 December, 2003; London, UK
E. events@bna.org.uk,
Tel. 0151 794 5449/4943

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

2004

January

15th International Congress on Parkinson's Disease
12-16 January, 2004; Beijing, China
Tel. +86 10 65249989 x 2456,
Fax. +86 10 65123754,
E. xvicpd@chinamed.com.cn

Update on Neuro MR Techniques
13 January, 2004; London, UK
BIR Scientific Meetings, Tel. 0870 873 0334, E. tamara.anderson@bir.org.uk

Austrian Stroke Meeting
16-17 January, 2004; Austria
E. klaus.berek@bkh-kufstein.at

British Paediatric Neurology Association 2004
23-25 January, 2004; Sheffield, UK
E. info@bpna.org.uk

Workshop on Botulinum Toxins in Neurological Practice
30 January, 2004; London, UK
E. khenley@movementdisorders.org

February

Annual Meeting of the International Neuropsychological Society
4-7 February, 2004; Baltimore, US
Tel. 001 614 263 4200,
Fax. 001 614 263 4366, E. ins@osu.edu

Presidents Prize & Hughlings Jackson Lecture
5 February, 2004; London, UK
Tel. 020 7290 2984, E. cns@rsm.ac.uk

The Global College of Neuroprotection & Neuroregeneration Annual Conference
8-10 February, 2004; Zermatt, Switzerland
Tel. 01159 692 016, Fax. 01159 692 017,
E. info@gcnpnr.org

4th International Symposium on Coma & Death
24-27 February, 2004; Havana, Cuba
Tel. +537 22 8382/21-9496, E. migdalia@palco.cu

Edinburgh Clinical Trials Management Course 2004
25-27 February, 2004; Edinburgh, UK
E. ectmc@skull.dcn.ed.ac.uk,
Tel. 0131 537 2913

British Neuropsychiatry Association Annual Meeting
26-27 February, 2004; London, UK
Gwen Cutmore, Tel/Fax: 01621 843334,
E. gwen.cutmore@lineone.net

March

Endocrinology for Non-endocrinologists & Neuroly for Non-neurologists
2 March, 2003; Glasgow, UK
Tel. 0141 221 6072, Fax. 0141 221 1804,
E. mgt.cooper@rcpsglasg.ac.uk

2nd Intraoperative Imaging in Neurosurgery Meeting
3-11 March, 2004; Zurich, Switzerland
Fax. 41 13 849 330,
E. iiin@congressorg.ch

2nd Asia Pacific Congress on Distraction Osteogenesis
5 -10 March, 2003; Male, Maldives
E. dr_lakshmi1980@yahoo.com,
contact@distraction2004.com

3rd International Syncope Symposium
5 March, 2003; Stratford-upon-Avon, UK
E. trudie@stars.org.uk

Life Sustaining Treatments & Vegetative State: Scientific Advances & Ethical Dilemmas
17-20 March, 2004; Rome, Italy
E. gigli.gianluigi@aoud.sanita.fvg.it,
Fax. 0039 0 432 552 719

Austrian Society of Neurology Meeting
18-20 March, 2003; Austria
E. klaus.berek@bkh-kufstein.at

2nd Cambridge Workshop on Universal Access and Assistive Technology
22-24 March, 2-4; Cambridge, UK
E. Aejaz.Zahid@bdgh-tr.trent.nhs.uk

36th International Diagnostic Course: diseases of the Brain, Heart & Neck
27 March - 2 April, 2004; Davos, Switzerland
Fax. 00-41 13 849 339,
E. idkd@congressorg.ch

April

2nd Meditteranean Congress of Neurology
2-4 April, 2004, Nicosia, Cyprus
Fax. 35 - 725 721 644,
congress@congresswise.com

Spring Meeting of The British Neuropsychology Assocation
18-20 April, 2004; Modena, Italy
E. georgina.jackson@nottingham.ac.uk

American Academy of Neurology 56th Annual Meeting
24 April-1 May, 2004; San Francisco, US
Tel. 1 651 695 1940,
Fax. 1 651 695 2791

May

14th European Congress of Physical & Rehabilitation Medicine
12-15 May, 2004; Vienna, Austria
Tel. +43 1 405 13 83 22,
E. ecprm2004@medacad.org,
www.ecprm2004.org

13th European Stroke Conference
12-15 May, 2004; Mannheim, Germany
E. hennerici@eurostroke.org

June

11th Asian & Oceanian Congress of Neurology
3-6 June, 2004; Singapore
E. claire_lee@ttsh.cm.sg

3rd Brain Stem Society Meeting
11-12 June, 2004; 2004
Fax. 39-0 55 570 227,
E. m.daliana@oic.it

The Movement Disorder Society's 8th International Congress of Parkinson's Disease & Movement Disorders
13-17 June, 2004; Rome
Fax. 414 276 3349,
E. congress@movementdisorders.org

8th European Congress of Research in Rehabilitation
13-17 June, 2004; Ljubljana, Slovenia
Tel. ++386 1 437 66 00,
E. crt.marincek@mail.ir-rs.si

12th World Congress of the International Association for the Scientific Study of Intellectual Disabilities
14-19 June, 2004; Montpellier, France
Fax. 020 610 812,
E. felce@cardiff.ac.uk

5th World Stroke Congress
23-26 June, 2004
Tel. 00972 3 5140000,
E. stroke2004@kenes.com

14th Meeting of the European Neurological Society
26-30 June, 2004; Barcelona, Spain
E. gerard.said@bct.ap-hop-paris.fr

July

9th International Conference on Alzheimer's Disease & Related Disorders
17-22 July, 2004; Philadelphia, US
Tel. 001 312 335 5813,
Fax 001 866 699 1235,
E.internationalconference@alz.org

August

1st International ICSC Symposium on Cognitive Neuro Science
29 August-1September, 2004; Stirling, UK
www.icsc-naiso.org,
E. i.aleksander@ic.ac.uk

September

8th Congress of the European Federation of Neurological Societies
4-9 September, 2004; Paris, France
Tel. 0043 1 880 00 270,
Fax. 0043 1 88 92 581,
E. Headoffice@efns.org

7th International Neurotrauma Symposium
12-16 September, 2004; Adelaide, Australia
Tel. +61 8 8379 8222,
Fax. +61 8 8379 8177,
E. events@plevin.com.au
www.plevin.com.au/ints2004

32nd Annual Scientific Meeting of the British Psychophysiology Society
13-15 September, 2004; Manchester, UK
E. Dr D Bentley,
deborah.bentley@man.ac.uk

12th World Congress of Psychophysiology - The Olympics of the Brain
18-23 September, 2004; Thessaloniki, Greece
Fax. 3-0-2 103 301 844,
E. olympia@travelplan.gr

2005

June

16th International Congress on Parkinson's Disease & Allied Disorders
5 June, 2005; Berlin, Germany
Tel. 0049 30 300 6690,
Fax. 0049 30 305 7391,
E. Berlin@cpo-hanser.de,
www.cpo-hanser.de

11th International Congress of the IPA
(International Psychogeriatric Association)

17-22 August, 2003; Chicago, Illinois, USA

The leading theme of this congress was 'Enhancing human connection in the age of new technologies: implications and opportunities'. About 1550 participants from more than 62 countries were faced with the challenge of choosing from a cornucopia of 6 plenary sessions, 116 symposia and 294 posters.

In his outstanding public lecture 'Rinsing the challenge of Age' T Kirkwood, UK addressed different fundamental questions of longevity. Longevity is a reality and we live on average twice as long as we did two hundred years ago; 85% of babies born today will reach the age of 65 years. Human beings are programmed to survive and there are no genes which drive ageing, because ageing is caused by the accumulation of damage in cells - e.g. due to impaired DNA copying or repair. Genes determine about 25% of longevity while the rest is governed by environment, nutrition, lifestyle and exercise. The latter variables are potential targets for preventive strategies.

Life-span risk factors for the development of dementia need more consideration in relation to prevention (I Skoog, Sweden). Vascular cognitive impairment (VCI) might be prevented by modifying atherogenic risk factors - and dietary factors such as vitamin E, monosaturated fats and fish consumption (P Gorelick, USA). Of all these risk factors, hypertension in midlife seems to be particularly important for preventive strategies. K Rockwood, Canada presented a three year longitudinal follow-up study of non-cognitive vascular impairment and showed that most common behavioural symptoms are decreased initiative (61%) followed by decreased mood (33%). J O'Brien, UK showed how impairments in processing speed and executive function were associated with severity of white matter hyperintensities and cortical grey matter loss in non-demented stroke survivors. Depression with first onset in old age has been associated with vascular changes seen on neuroimaging (D Steffens, USA) and neuropathological changes, which are different from those found in younger adults (A Thomas, UK). Cerebral vascular factors may associate with a poor outcome (D Ames, Australia) and cognitive impairment related to depression may persist even after recovery of depression and be related to structural brain changes.

The internet is a source for isolated patients with mobility restriction, and increasing numbers of people search the internet for health information, although selection and validation of information remains difficult as there are more than 70,000 health related websites. (S Czaja, USA). Telemedicine is another valuable method which could improve communication among health professionals and reach patients in traditionally underserved institutions such as nursing home residents and patients in rural communities (B Jones, USA and L Van Bussel, Canada). Simulated video presence of a loved family member can improve depression and agitation in nursing home residents (A Hamer, Netherlands) and multi-media profiling including video-interviews can assist carers to access patient information quickly and easily (C Allen, UK).

The potential of new technologies to improve safety in transportation seems enormous. D O'Neill, Ireland addressed driving abilities in elderly, mentally ill patients, who are at risk for driving impairment either due to their illness or their medical treatment. As driving is an overlearned skill, preventive strategies focusing on behavioural and functional impairment might be more effective to detect drivers at risk. The efficacy of preventive screening methods to improve safety has still to be established. Self-regulation of driving in elderly seems to be effective; people aged over 65 have the lowest crash-risk per head, although more fatalities result from each crash. The latter might be due to the fact that car safety equipment, such as airbags, is not yet designed for elderly frail people. The symposium Lewy body disease and dementia (J. O'Brien, UK), addressed clinical boundaries of Dementia with Lewy bodies in comparison to AD and Parkinson's disease dementia (PDD). Compared to AD, DLB is characterised on neuroimaging by greater parieto-occipital hypoperfusion, greater reduction in dopaminergic uptake of caudate and a relative preservation of the temporal lobe and hippocampus. DLB and PDD are differentiated by the sequence of symptom appearance. PDD and DLB share many pathological, neurochemical and clinical features (D Aarsland, Norway) and both are often associated with REM sleep behaviour disorder (B Boeve, USA). R Hamilton, showed how ApoE4 allele is related to widespread LB formation in AD subjects.

J Cohen-Mansfield, USA gave an impressive overview of how non-pharmacological strategies can improve functional status of daily living and behavioural and psychological symptoms in dementia (BPSD). Such interventions include the cognitive, behavioural and social interventions to empower patients. A Parpura-Gill, USA illustrated how bathing, a relevant activity which can increase agitation and be traumatic for patients and caregiver, can be transformed into an engaging therapeutic intervention. D Ripich, USA then illustrated how the FOCUSED communication training program can improve communication skills. Treatment effects of bright light therapy were addressed in another session, where J Byrne, UK presented the findings of a randomised controlled trial, and showed beneficial effects on sleep disorder in dementia.

Pharmacological treatment strategies addressed newer indications of cholinesterase inhibitors (ChE-I) in vascular dementia (S Gauthier, Canada), Dementia with Lewy bodies (K Edwards, USA) and Parkinson's disease dementia (D Aarsland, Norway). Long term treatment (i.e. 24 month) of vascular or mixed vascular dementia with Galantamine in an open label extension study seems safe and effective and treatment effects of donepezil in vascular dementia seems to be comparable to AD (A Burns, UK). ChE-I have also significant efficacy in the treatment of BPSD (e.g. C Holmes, UK; A Monsch, Switzerland). Memantine protected neurons from glutamate neurotoxicity in mice (W Danysz, Germany) and decreased amyloid-€levels in neural cell lines (D Lahiri, USA). The clinical implication of these findings needs to be investigated.

In the final plenary session (G Cohen, USA) discussed the important phenomenon that children have a positive view of elderly relatives, but a biased negative view towards ageing in general. Such a global view may be influenced by the often negative description of elderly in fairytales. Be aware of ageism - improvement of public education may help to bridge between young and old.

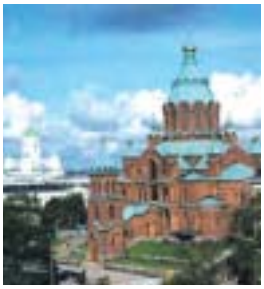
The interested reader may find all abstracts of this conference published in: International Psychogeriatrics 2003; 15 (suppl 2): 1- 385.

UP Mosimann and S Pakrasi,
Newcastle upon Tyne

Venue: Chicago, Illinois

European Federation of Neurological Societies

30 August - 2 September, 2003; Helsinki, Finland



Venue: Helsinki, Finland

The 7th Congress of the EFNS was held at the Helsinki Fair Centre in Helsinki, Finland and large numbers of participants came from all over Europe, as well as Australia and the US.

It is always difficult to comment on the overall impact of the meeting in terms of new discoveries and changes in neurological practice given the large number of presentations and parallel sessions that are run. The various items that caught our particular eyes were:

- The work of Ken Smith (London) demonstrating cogently that axonal loss in multiple sclerosis may result from abnormalities in sodium loading which in turn leads to changes in intracellular calcium as a result of a reverse of a sodium calcium exchange pump. Blocking this influx of sodium may, therefore, have an impact upon axonal integrity and Ken Smith presented interesting experimental work not only in vitro but in the EAE model. This is leading to the possibility of a drug trial in MS looking at flecainide and its effect on axonal loss.
- Field of movement disorders. There was a very lucid account by Cristina Sampaio (Lisbon) on the evidence for the use of various drug therapies in Parkinson's disease. This was a sobering experience as it is quite clear that many of the drug therapies have no actual basis in terms of proper controlled trials. However, it emerged from this work that the efficacy of deep brain stimulation is probably very similar to that of apomorphine infusions and thus abandoning pharmacological therapies in favour of deep brain stimulation in advanced PD patients might not necessarily be always the right decision.
- Wolfgang Oertel (Marburg) gave a very comprehensive account of the incidence of sleep disorders including restless leg syndrome and its association with Parkinson's disease both pathologically and physiologically. The basic message from this talk was that these conditions are very common and that there is probably a degree of overlap between REM sleep disorder, Parkinson's disease and restless leg syndrome in terms of pathophysiological behaviour given their sensitivity to dopaminergic agents.
- There was also a fascinating satellite meeting, which looked at the evidence of neuroprotection with dopamine agonists in early Parkinson's disease. This explored not only possible in vitro mechanisms for this (stabilisation of mitochondrial membrane potential) but the recent clinical evidence that this can be seen in patients. This latter area relies heavily on functional imaging, and many intriguing questions were raised including whether levodopa interferes with dopamine uptake and by so doing influencing the scan result. If true, then the neuroprotection of dopamine agonists may turn out to be an artefact created by an apparent worsening in signal by L-dopa.
- At the Basal Ganglia Club meeting there was a superbly comprehensive and authoritative account on the aetiology and management of dystonia by Jo Jankovic. The major messages from his talk were: any child with cerebral palsy should be given a trial of levodopa (which many now adopt in their standard clinical practice already); polypharmacy for dystonia is often necessary and that surgical interventions are emerging as a very useful therapy in people with severe generalised dystonias especially if they carry the DYT1 gene.
- There was also a fascinating account by Mark Edwards (London) demonstrating that DYT1 gene carriers have abnormal neurophysiology within the cortex similar to that seen in the manifest patient. This suggests that people with the DYT1 gene have abnormalities of cortical excitability but that some other trigger is necessary for this to become expressed clinically - possibly trauma. In this respect there was a most entertaining and illuminating lecture on the focal dystonia of Robert Schumann which also involved the playing of some of his pieces of music. This presentation by Eckart Altenmüller(Bern), also included a brief discussion on the thwarted solo career of Scriabin who appeared to have developed a myofascial syndrome of his right arm which prevented him from playing the piano and led to him increasingly composing pieces of music, for the left hand. This led on to discussions about the origin of such task specific dystonias, the consensus being that there are disturbances in sensory motor coupling within the somatosensory motor cortices and that the blurring of cortical representations of adjacent body causes the dystonia. This has led to the advent of constraint therapy as a way of trying to re-organise sensory information and mapping and by so doing should help treat some forms of dystonia. Some clearly believe this is useful (e.g. Priori - Milan), whilst others do not (Jankovic - USA).
- Martin Farlow (Indianapolis) presented the results of a placebo-controlled trial of the NMDA receptor antagonist memantine (Ebixa) in over 400 patients with moderate to severe Alzheimer's disease (AD; MMSE 5-14) already receiving stable doses of the cholinesterase inhibitor donepezil. The combination was well tolerated (better than placebo) and by 24 weeks there was significant improvement in cognition and less decline in function. Memantine/donepezil combination therapy may therefore be an option for AD in the future.
- Triau (Leuven) discussed some results from the AWARE ("Aricept washout and rechallenge") study in which patients with AD who seemed not to respond to 24 weeks of donepezil (single-blind treatment) were randomised to either withdrawal or continuation of therapy (double-blind). Cognitive, functional and behavioural benefit was found in 75% of those continuing as compared to the withdrawals. A small proportion of patients on continuing therapy did show further cognitive decline but had functional and behavioural improvement. Hence, patients showing an initial decline on donepezil treatment may still derive benefit from continued therapy.
- James Callaway (San Diego) discussed the past, present and future of vaccination therapy for AD, or, as the company (Wyeth-Elan) prefers to call it, immunotherapy. Immunological and neuropathological study of the cases of meningoencephalitis which brought the phase II trial of AN1792 to a premature close suggests that an aberrant T-cell response to amyloid beta-peptide was the cause of the side effects. Reduction in cortical amyloid plaques was seen in one patient who died after experiencing side effects from immunotherapy. Clinical trials using immunoconjugates or modified peptides which eliminate the T-cell response to amyloid beta-peptide are planned for the near future.

In addition to the intellectual fare, the congress also offered cultural stimulation. A judicious choice of sessions provided music by Schubert (arr. Liszt), in addition to Schumann and Scriabin ("Music and Neurology") as mentioned above, and by Prokofiev, as well as an historical review of Finnish contributions to neuroscience ("History of Neurology").

Roger Barker , Cambridge Centre for Brain Repair
Andrew Larner, Walton Centre for Neurology & Neurosurgery

Interview with Professor Richard Frackowiack, BNA President

Professor Richard Frackowiak has recently been appointed to the presidency of the BNA. He is a rare breed, in that he is well respected both by clinical neurologists and neuroscientists. His research over the years has been impressive to say the least, with huge numbers of high impact papers highlighting the power of functional imaging in normal and disease states. He has been pioneering in the use of such scanning in delineating how the human brain actually functions normally and what can go wrong in disease. He has enormous energy and enthusiasm and has been inspirational to many trainee neurologists wishing to pursue careers in neurological science. He is an ideal person to take on this prestigious post, given his work which has straddled both basic neuroscience and neurological disease, and certainly my times as his registrar at Queen Square were memorable - RAB

How would you describe the role of the BNA?
To create a friendly environment within which young neuroscientists can exchange information, create networks that will be useful in their careers, expose themselves to their peers in an atmosphere that is rigorous but less intimidating than at major international meetings and to have a fun time with people who have similar interests but different experiences of neuroscience.

How do you see neuroscience informing clinical neurology and vice versa?
Science generates pathogenic ideas that clinical neurology needs to translate into diagnostic tests. It identifies therapeutic targets and treatments that clinical neurology must assess and evaluate. Clinical neurology poses relevant problems and provides material for investigation. The methods of rigorous science in controlled systems and observational science in humans must be appreciated by both constituencies so that relevant questions are asked and answered.

Is there an increasing need for neurologists and neuroscientists to work together, given the drive towards making all research clinically relevant?
Blue skies research is very important but so is problem solving. Our paymasters demand relevance and so, as a scientific constituency that deals with human ailments like dementia, stroke, neurodegeneration and developmental disorders – all of which are increasing with an enlarging and ageing population – we are in the spotlight and must deliver. The rapid translation from basic science to treatment is vital, especially in times of crisis (eg AIDS).

In other areas such as rehabilitation from brain injury the opportunities for progress are so new that clinicians and scientists must work together to understand what each is attempting to achieve. In general I believe that in modern science co-operation is better than bitter rivalry, or worse still any desire to maintain disciplinary purity.

How can we involve more clinical members in the work of the BNA?
By advertising, by encouragement, by indicating how much clinicians have to gain from exposing their work in a wider scientific forum and vice versa. By providing an intellectual as opposed to a professional home.

Do you think there is a problem in the UK that neurologists in training are being dissuaded from undertaking neuroscientific research?
There are problems arising from the rigid control of training numbers in neurological medicine. It is important that bright research hungry young clinicians do not become disenchanted because they see academic careers as disadvantageous in achieving professional status. Clinical scientific role models are important. The excitement of good science is more important still, as is the support of an intellectually challenging peer group.

What are your aspirations for British Neuroscience, and the BNA in particular over the next ten years?
British Neuroscience was the tops in the 50s and 60s. Funding for young neuroscientists is relatively good, there is no reason why we should not become tops again. The size of the UK is a problem, especially in comparison with our main competitor, the all-dominant USA. The solution in my eyes lies in Europe. There are so many intelligent, bright, numerate and ambitious neuroscientists on our continent, so many good laboratories to go to, to learn from. There are so many sources of funding to move and taste the different expertise and cultures in Europe that it should not be beyond us to look outwards, to escape from national parochialism and to embrace a European view of excellence in our field.

For those contemplating following in your footsteps can you estimate how much of your time is going to be spent on society business? Will you have to give up any of your clinical work?
Time will tell!

Richard Frackowiak MA, MD, DSc, FRCP, FMedSci, Dr (hon causa,Liege) is Vice-Provost (Special Projects) of University College London. He moved to the post from the Deanship of the Institute of Neurology, Queen Square which he held for 4 years. He is a Professor of Neurology and a Wellcome Trust Principal Clinical Research Fellow. He previously chaired the Wellcome Department of Imaging Neuroscience and its Functional Imaging Laboratory where he retains a research activity, holds a programme grant and remains a Principal Investigator. His scientific interest is in structural and functional brain mapping in health and disease. He obtained his research degree at the MRC Cyclotron Unit. He has won the IPSEN and Wilhelm Feldberg prizes. His scientific output includes over 300 peer reviewed papers and the books "Human Brain Function" and "Brain Mapping: The Disorders" published by Academic Press. He is 2nd in the list of authors of high impact neuroscience papers published in the decade 1989-1998 and is the 4th most highly cited British biomedical scientist in the decade 1990-1999.

EDITOR'S CHOICE

Camel antibodies prevent amyloidosis

Amyloidogenesis, the aberrant assembly of a protein or protein fragment into fibrils with subsequent plaque deposits, is a common pathogenic mechanism underlying many neurological diseases, including Alzheimer's Disease and prion diseases. This study involves the well-characterised human lysozyme protein. This protein may be amyloidogenic in its mutant form, and different point mutations in its gene causes non-neuropathic systemic amyloidosis. The authors investigate inhibition of amyloid fibril formation of a specific mutant lysozyme protein (D67H). They describe the novel use of antibodies derived from camelids (dromedarys). Camels uniquely produce functional antibodies devoid of light chains and are thus composed of heavy chains only making them more stable and soluble. They derived a camelid antibody fragment raised against the wild-type lysozyme protein and used this to inhibit in vitro mutant protein amyloid formation and aggregation.

An array of elegant biophysical data is presented to demonstrate that specific antibody binding to the mutant lysozyme prevents its aggregation in vitro by significantly reducing the mutant protein's ability to form a partially unfolded species; an event which is thought to be key in initiating aggregation and subsequent fibril formation. Interestingly, the antibody epitope does not include the site of mutation or any significant portion of the structure destabilised by the mutation. Thus, it is proposed that the stabilisation of the mutant lysozyme by the antibody interaction is a result of transmitted conformational changes, akin to the action of allosteric effectors at the active site of an enzyme. These long-range conformational changes are reported to restore global structural co-operativity to that of the wild-type protein.

This paper is interesting in terms of therapeutics because it demonstrates that preventing the formation of an aggregation-prone species by an antibody is a valid strategy for the treatment of the large family of amyloidogenic diseases. Moreover, it highlights that the antibody interaction need not impede the normal function of the protein as it may occur away from sites essential for functioning. The use of camelid antibodies in human therapeutics is novel; once humanised, they make attractive candidates for immunotherapies because of their small size, solubility, and simple but stable structure. *– LMS, SJT*

A camelid antibody fragment inhibits the formation of amyloid fibrils by human lysozyme.

Dumoulin M, Last AM, Desmyter A, Decanniere K, Canet D, Larsson G, Spencer A, Archer DB, Sasse J, Muyldermans S, Wyns L, Redfield C, Matagne A, Robinson CV, Dobson CM
NATURE
2003: 424: 6950: 783-788

NEUROIMMUNOLOGY

★★★ RECOMMENDED

Cannabis may prevent nerve death

The political arguments for the legalisation of cannabinoids have included its potential therapeutic effects, fuelled amongst other things by the David Baker's Nature paper three years ago demonstrating their anti-spasticity effect in animals. The MRC UK trial of the effects of cannabinoids on spasticity in multiple sclerosis has come to an end. No doubt its results, when announced, will cause much medical and political wrangling.

Now, David Baker's group have added further fuel to the fire with an elegant demonstration that cannabinoids may prevent neuronal death in acute inflammation. He induced his established model of chronic relapsing EAE in normal mice and those knocked out for the cannabinoid receptor gene CB1. Each had a similar clinical course of acute EAE but afterwards the CB1 knock-outs were much more disabled and had lost more spinal cord axons. The only caveat to the interpretation that cannabinoids mediate neuroprotection is that the CB1 knock-outs had reduced axonal density prior to EAE suggesting a developmental failure. So CB1 agonists were given to acute EAE and acute experimental allergic uveitis in doses that had no immunosuppressive effect; there was no change in the inflammatory infiltrate but axonal/photoreceptor damage was reduced. The mechanism? Well, calcium fluxes induced by NMDA agonists were more prolonged in CB1 knock-outs and kainic acid induced seizures and death at much lower doses in these animals.

Taken together, these observations suggest that cannabinoids may reduce the excitotoxic effects of acute inflammation on axons. If translated to multiple sclerosis, this would mean that cannabinoids would not alter relapse frequency but would reduce the disability acquired as a result of each relapse. If cannabinoids are approved as a treatment of spasticity, there will be ample opportunity to test this hypothesis. *-AJC*

Cannabinoids inhibit neurodegeneration in models of multiple sclerosis.
Pryce G, Ahmed Z, Hankey DJ, Jackson SJ, Croxford JL, Pocock JM, Ledent C, Petzold A, Thompson AJ, Giovannoni G, Cuzner ML, Baker D.
BRAIN.
2003;126: 2191-202.

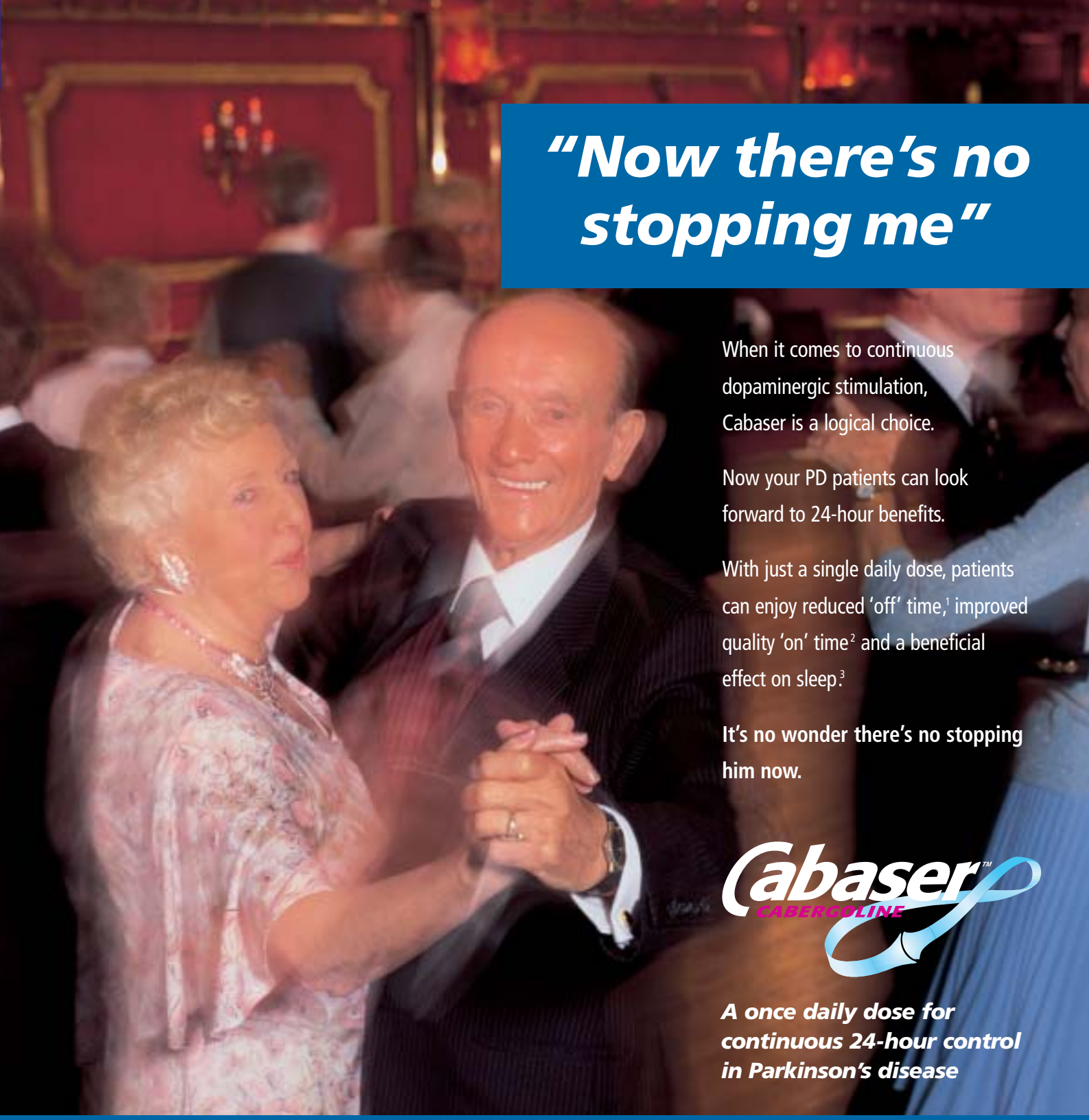
Rehabilitation of acute relapses of multiple sclerosis.

There is an ever increasing body of evidence supporting the benefit of rehabilitation in treating patients with Multiple Sclerosis(MS)- see Nov/Dec 02 issue of ACNR for a comprehensive review. However despite the common clinical pattern of relapse in MS few studies have looked specifically at the role of rehabilitation in managing relapses (indeed many have excluded them). This study looked at whether there is benefit of adjunctive multi-disciplinary team MDT rehabilitation (as opposed to "standard care" therapy) along with the standard 3 day treatment of intravenous Methylprednisolone (IVMP) for relapse in MS.

After randomisation the intervention group received a planned MDT assessment and then treatment depending on goals set during assessment. The primary outcome measures used were the Amended Motor Club Assessment (AMCA), which measures motor impairment, and Guy's Neurological Disability Scale (GNDS). Secondary ones used were the Barthel Index (BI), Human Activity Profile (HAP), and the SF-36. All were carried out on admission, and at one and three months later. A total of 40 patients completed the study, 20 in each arm.

There was no baseline difference between groups in patient characteristics or primary measures. At three months there was both a statistical and clinically significant change from baseline in the AMCA, GNDS, BI and HAP scores of the intervention arm. The SF-36 did not reach statistical significance in the intervention arm. The intervention group also received significantly more therapy (though this wasn't standardised) which was statistically correlated with the improved outcome measures. This group were also more frequently referred on for whatever available outpatient therapy so it is not possible to ascertain whether the community or hospital setting accounted for the benefits noted. Therapists included MS nurse specialists, physio-, occupational & speech and language therapists as well as orthotists. Rehabilitation physicians were not included as part of the MDT but thankfully there is other evidence in the literature to support their role in benefiting patients with MS. *-JM*

A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment.
J Craig, CA Young, M Ennis, G Baker, M Boggild
JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY.
2003;74: 1225-1230.



"Now there's no stopping me"

When it comes to continuous dopaminergic stimulation, Cabaser is a logical choice.

Now your PD patients can look forward to 24-hour benefits.

With just a single daily dose, patients can enjoy reduced 'off' time,[1] improved quality 'on' time[2] and a beneficial effect on sleep.[3]

It's no wonder there's no stopping him now.

Cabaser™
CABERGOLINE

A once daily dose for continuous 24-hour control in Parkinson's disease

CABASER® (CABERGOLINE). Abbreviated Prescribing Information. Before prescribing see Summary of Product Characteristics. **Presentation:** Cabaser tablets: Containing 1, 2 or 4 mg cabergoline. **Uses:** The treatment of symptoms of Parkinson's disease, as adjuvant therapy to levodopa plus dopa-decarboxylase inhibitor, in patients affected by 'on-off' mobility problems with daily fluctuations in motor performance. Improvement of motor deficit has been demonstrated while permitting a substantial decrease in L-dopa dose. **Dosage and Administration:** Adults and elderly patients: The recommended therapeutic dosage is 2-6 mg/day as adjuvant therapy to levodopa, given as a single daily oral dose. Dose should be titrated slowly against efficacy and tolerability. A starting dose of 1 mg daily is recommended; the dosage of concurrent levodopa may be gradually decreased, while the dose of Cabaser is increased. In view of the long half-life of the compound, the dose may be increased in gradual weekly or bi-weekly intervals by increments of 0.5-1.0 mg, up to optimal doses. Use in Children: not recommended. **Contra-indications:** Hypersensitivity to any ergot alkaloid. **Warnings:** In patients with severe hepatic insufficiency the dose should be reduced accordingly. Cabaser is an ergot derivative. Fibrotic reactions have occurred after prolonged usage of ergot derivatives. Patients with a history of such disorders should not be treated with Cabaser. Renal insufficiency has not been shown to modify Cabaser kinetics. Caution is advised in patients suffering from severe cardiovascular disease, Raynaud's syndrome, peptic ulcer, gastrointestinal bleeding or a history of major psychotic illness. In cases of unexplained high ESR, or emergence of respiratory symptoms, a chest X-ray is recommended to exclude pleural effusion/fibrosis. Symptomatic hypotension can occur following administration of Cabaser: particular attention should be paid when administering Cabaser concomitantly with other drugs known to lower blood pressure. Cabaser has been associated with somnolence and, uncommonly, sudden sleep onset. Patients who have experienced somnolence and/or an episode of sudden onset of sleep must refrain from driving or operating machines, until such recurrent episodes and somnolence have resolved. Furthermore a reduction of dosage or termination of therapy may be considered. **Drug Interactions:** No pharmacokinetic interaction with levodopa or selegiline has been observed in clinical studies in Parkinsonian patients. Concomitant use of other ergot alkaloids with Cabaser is not recommended. Cabaser should not be administered concurrently with drugs which have dopamine antagonist activity since these might reduce Cabaser's efficacy. Cabaser should not be used in association with macrolide antibiotics since systemic bioavailability of Cabaser and adverse effects could increase. The effects of alcohol on overall tolerability of Cabaser are currently unknown. **Pregnancy and Lactation:** Based on limited clinical experience, cabergoline does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities. As a precautionary measure, it is recommended that women seeking pregnancy discontinue Cabaser one month before intended conception, in order to prevent possible foetal exposure to the drug. If conception occurs during therapy, treatment is to be discontinued as soon as pregnancy is confirmed. Do not use in nursing mothers as lactation may be inhibited; no information on the excretion of cabergoline in maternal milk in humans is available. **Undesirable Effects:** Events most frequently reported in clinical studies were dyskinesia, hyperkinesia, hallucinations or confusion. Other events include nausea, vomiting, dyspepsia and gastritis, as well as dizziness and hypotension. Symptomatic pleural effusion/fibrosis has been reported with a frequency <2%; in these cases discontinuation of Cabaser is expected to lead to immediate improvement of symptoms. Cabaser has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. In view of Cabaser's pharmacological class, other reported events include angina (reported in 1%), erythromelalgia (0.4%) and peripheral oedema (6%). CNS events are more common in the elderly. **Overdose:** No incidences reported in the proposed indication. Symptoms of overdose are likely to be related to dopaminergic activity. **Legal Category:** POM. **Basic NHS Cost:** 20x1mg £75.45; 20x2mg £75.45; 16x4mg £75.84 all bottles. **Product Licence Numbers:** CABASER 1mg: PL0022/0169, CABASER 2mg PL0022/0170, CABASER 4mg: PL0022/0171. **Product Licence Holder:** Pharmacia Laboratories Limited, Davy Avenue, Milton Keynes, MK5 8PH, United Kingdom. **Date of Preparation:** January 2003. **References:** 1. Steiger MJ, El-Debas T, Anderson T *et al*. J Neurology 1996; 243: 68-72. 2. Lera G, Vaamonde J, Rodriguez M *et al*. Neurology 1993; 43 (Suppl 12): 2587-90. 3. Högl B, Rothdach A, Wetter TC *et al*. Neuropsychopharmacology July 16th 2003; Advanced online publication: 1-5, www.nature.com/npp/journal/v20p/ncurrent/

Pfizer

PARKINSON'S DISEASE

★★★ RECOMMENDED

A double-blind study, trial of bilateral fetal nigral transplantation in Parkinson's disease

This much awaited study, mentioned previously in ACNR when it was presented at the International Movement Disorder meeting last year in Miami, has now eventually been published in the Annals of Neurology. It involves the transplantation of 34 patients with advanced Parkinson's disease. The study was a prospective double-blind placebo controlled trial in which patients were randomised either to no transplant, transplant with small amounts of foetal tissue, namely one foetus per side or a four-donor per side group. Whilst there was clear PET study evidence of increased dopaminergic signal in the grafted donor transplant group this did not correlate with clinical improvement. The primary end point of the study did not improve and worryingly significant numbers of the patients developed dyskinesias that persisted after overnight withdrawal of dopaminergic medication (56%).

The study has clearly been well developed and was originally devised to address the question of the optimum amount of donor tissue that is required for optimal therapy. It is clear that whilst four-donor per side patients have done better than the one donor the overall analysis of the three groups shows no significant effect on the primary end point. However, post mortem studies clearly show that there are more dopaminergic cells surviving in the four-donor group compared to the one donor group, which fits in with the PET study. Furthermore, whilst there has been no overall benefit if one subdivides the patients into those with relatively mild disease with a UPDRS score of less than 49 there is clearly a significant benefit compared to those with more advanced disease.

The take home message for me in this study is that whilst transplantation has produced a negative outcome in this study if one actually addresses issues of patient selection one can clearly see that there are a group of patients who would benefit from the procedure. These tend to be those PD patients who have less severe disease and, therefore, probably have a lower risk of developing dyskinesias post transplantation. However in the current climate it would seem that this study coming on the back of the PD transplant study of Freed *et al* in 2001, will lead rightly to a period of re-evaluation before any further similar trials can be considered *-RAB*

A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease.

Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, Shannon KM, Nauert GM, Perl DP, Godbold J, Freeman TB.

ANNALS OF NEUROLOGY

2003;54(3):403-14

Transfer of the von Hippel-Lindau gene to neuronal progenitor cells in treatment for Parkinson's disease

One of the major problems in the use of neural stem cells for treating Parkinson's disease is their reluctance to turn into dopaminergic neurons. There have been a number of studies which have tried to rectify this, including using hypoxic culture conditions and erythropoietin. Yamada *et al* have taken a slightly different approach, capitalising on the von Hippel-Lindau gene which is known to be intimately involved with oxygen sensing (see ACNR 3.2). The authors take rat embryonic neural precursor cells and transduce them with von Hippel-Lindau gene and show that this greatly increases the neuronal and especially the dopaminergic yield from these cells. This is not only shown in vitro but in the standard 6 hydroxydopamine lesion model of Parkinson's disease. This effect of the VHL gene is enhanced by GDNF.

This study is important because it shows that it may be possible to increase dopaminergic yield and thus develop a cell therapy which can be used in Parkinson's disease clinically. However the study does have a few caveats - for example, the neural precursor cells are never passaged and therefore it is debatable the extent to which they are truly stem cells. Furthermore the net effect of the transplants is to produce large numbers of dopaminergic cells which have a modest effect on drug induced rotation and this coupled to the histology makes one wonder the extent to which these are fully functional nigral dopaminergic neurons.

Overall though this study offers encouragement to those who feel that stem cells therapies may be of value although clearly based on the above transplant study further work needs to be done in deciding which patients if any should receive such dopaminergic rich transplants *-RAB*

Transfer of the von Hippel-Lindau gene to neuronal progenitor cells in treatment for Parkinson's disease.

Yamada H, Dezawa M, Shimazu S, Baba M, Sawada H, Kuroiwa Y, Yamamoto I, Kanno H.

ANNALS OF NEUROLOGY

2003 Sep;54(3):352-9.

PRION DISEASE

★★★ RECOMMENDED

Variant Creutzfeldt Jakob Disease is transmitted to the central nervous system via the sympathetic ganglia of the gut

Variant Creutzfeldt Jakob Disease (vCJD) is thought to be caused by dietary exposure to the bovine spongiform encephalopathy (BSE) agent and there is now good experimental evidence form strain-typing studies that BSE and vCJD are linked to the same prion strain. However the oral route of human contamination and the pathways that lead to neuroinvasion are not known. Experiments in mouse scrapie models have demonstrated that cells from the lymphoreticular system are involved in the peripheral replication of prions, and that the sympathetic nervous system supports propagation from the gut lymphoid tissue to the central nervous system (CNS). This study demonstrates that a similar process occurs in man. They demonstrate, using immunohistochemical techniques, the accumulation of the abnormal disease-associated isoform, PrPSc, in the neurons of sympathetic ganglia of three vCJD patients. These observations provide strong evidence to implicate the gut-associated sympathetic ganglia in the transmission of infectious prions to the CNS after oral exposure. If this is also the case for food animals infected with prion disease then removal of infected sympathetic nervous system tissues from contaminated carcasses in abattoirs should be addressed. In addition these findings also strengthen the case for peripheral prophylactic treatment of prion diseases prior to the stage where neuroinvasion has occurred. *- LMS, SJT*

The sympathetic nervous system is involved in variant Creutzfeldt-Jakob Disease

Haik S, Faucheux BA, Sazdovitch V, Privat N, Kemeny JL, Perret-Liaudet A, Hauw JJ

NATURE MEDICINE

2003: 9: 9: 1121-1123

ALZHEIMER'S DISEASE

Dopamine D2 receptors and cognitive decline in Alzheimer's disease

Alzheimer's disease leads to impaired acetylcholinergic systems and these are often cited as one of the causes of cognitive decline, particularly relating to learning and memory. Certain drugs already target these systems. However, patients' brains post mortem also show decreased D2 receptors in both the hippocampus and amygdala compared to control brains. Here it is argued that D2 receptor availability is reduced in temporal regions in early Alzheimer's disease in vivo and that this is associated with patients' dysfunctional memory.

Post mortem studies have shown that D3 receptors are largely absent from extrastriatal temporal regions investigated here so although [11C]FLB-457 has high affinity for both D3 and D2 receptors, binding of the novel antagonist was taken to represent binding to D2 receptors specifically. Patients were given neuropsychological tests. It is not stated whether controls were. Fourteen patients in early stages of AD, and 11 age and sex matched controls underwent PET (Positron Emission Tomography). Medication history was known. Structural MRI brain scans used to map PET data showed cortical and hippocampal atrophy in AD patients compared to controls. PET results showed that D2 receptor binding potential in the right hippocampus was significantly positively associated with verbal memory performance on two tests and it was deduced that atrophy of the hippocampus was not the sole explanation. As the authors suggest, investigating dopaminergic systems alone and in conjunction with acetylcholinergic approaches could offer new opportunities for drug development. *-LAJ*

Hippocampal dopamine D2 receptors correlate with memory functions in Alzheimer's disease.

Kemppainen N, Laine M, Laakso M P, Kaasinen V, Någren K, Vahlberg T, Kurki T and Rinne J O.

EUROPEAN JOURNAL OF NEUROSCIENCE

2003: 18: 149-154.

Talking to relatives with Alzheimer's disease

Many areas of speech and language therapy in neurological conditions have seen a shift in emphasis over the last few years to include training of carers in the management of communication disorders. This is based on the simple recognition that it takes (at least) two to tango, or in this case to communicate. As the authors of this study point out, people with Alzheimer's disease (AD) are often unable to modify their own communicative behaviour. While clinicians may offer intuitively appealing strategies, as yet these lack empirical support.

This study involved 'wireless audio-recorded interactions' between 18 people with AD and their carers during the course of everyday activities around the home. Carers' reports of the strategies they use were compared with their actual occurrence in interaction and then analysed in relation to the success or otherwise of conversations.

The results highlighted several strategies that carers reported using frequently but which occurred only rarely and others that they appeared to be unaware they were using. The least successful strategy was slowing the rate of speech, which was significantly associated with subsequent communication breakdowns. Using relatively simple grammatical constructions was much more successful, though it is somewhat more difficult to teach.

The recognition that carers' interactive style can serve to make communication either better or worse in AD has important implications when clinicians are prioritising their input. Identification of successful and unsuccessful strategies can only serve to make that process more effective. ***-RB***

Effectiveness of communication strategies used by caregivers of persons with Alzheimer's disease during activities of daily living.
Small, J.A., Gutman, G., Makela, S. and Hillhouse, B.
JOURNAL OF SPEECH, LANGUAGE, AND HEARING RESEARCH
2003; 46:2, 353-367.

★★★ RECOMMENDED

Do antimuscarinic agents increase Alzheimer-type pathology?

To explore the hypothesis that muscarinic receptor antagonism might promote Alzheimer-type pathology (since cholinergic therapy seems to have beneficial effects in AD, promoting non-pathogenic APP metabolism), brains of non-demented Parkinson's disease (PD) patients were examined for plaques and neurofibrillary tangles (NFT) and the findings correlated with use of antimuscarinic drugs. These were prescribed for movement or bladder control (benztropine, orphenadrine, trihexyphenidyl; oxybutinin) or for depression (tricyclic antidepressants [TCAD]: amitriptyline, imipramine).

Cortical plaque density was significantly higher in those receiving chronic (> 2 years) muscarinic receptor antagonist treatment compared to the untreated and those receiving short-term (< 2 years) treatment. Although rarely observed, NFT were twice as common in the long-term as compared to short-term and untreated groups. No significant intergroup differences were found with TCAD use although there was a trend to increased pathology in chronic users. However, this may be an incidental finding since depression may be a risk factor for developing dementia in PD.

The data are consistent with the possibility that prolonged anti-muscarinic drug use may accelerate beta-amyloidosis and plaque formation. This may have implications for therapeutic use of anticholinergs as "tremorlytic" agents in PD. ***-AJL***

Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs.
Perry EK, Kilford L, Lees AJ, Burn DJ, Perry RH.
ANNALS OF NEUROLOGY
2003;54(2):235-238

COGNITION

Language function in corticobasal degeneration

Although originally described as a movement disorder (asymmetric parkinsonism, apraxia), it has been increasingly recognised that corticobasal degeneration (CBD) is also characterised by cognitive impairments, amongst which language dysfunction may be prominent, although no systematic studies have been reported.

In this study from Cambridge, ten patients with clinically diagnosed CBD (one confirmed pathologically) were assessed with various neuropsychological tests to probe language function. Although 8 of the 10 patients had no clinically apparent aphasia, testing showed phonologic and oral spelling impairments to be prevalent, as evidenced on tests of nonword reading, phoneme blending and phoneme segmentation. Semantic memory, word-picture matching, and naming were normal or only mildly impaired. Tests tapping visuospatial, constructional and frontal functions did show impairments, as previously defined in CBD.

The authors of this study suggest that the language dysfunction observed in CBD forms a continuum overlapping with cases of progressive nonfluent aphasia.

However, as with all studies involving clinically ascertained cases of CBD, there is a "but": CBD phenocopies are well described, with pathological substrates including Alzheimer's disease, Pick's disease, progressive supranuclear palsy, non-specific histology, and even Creutzfeldt-Jakob disease. It would seem that clinical phenotype reflects the neuroanatomical distribution of pathological change, rather than the precise histological nature of that change. Hence it is doubtful whether careful language testing would prove helpful in the premortem diagnosis of CBD. ***-AJL***

Language function and dysfunction in corticobasal degeneration.
Graham NL, Bak T, Patterson K, Hodges JR.
NEUROLOGY
2003;61:493-499.

The neuroanatomy of visual neglect

The neuroanatomical substrates of visual neglect have been debated. A role for the posterior parietal lobe has long been assumed, but recently a counter claim has been made suggesting damage to the superior temporal gyrus is crucial. Masud Husain and his colleagues have looked at this issue by studying a group (n = 35) of unselected right cerebral hemisphere stroke patients with and without neglect, and mapping their lesions with high resolution MRI protocols (i.e. these were not scans done for clinical purposes). Neglect was ascertained by abnormal performance on shape cancellation tasks, line bisection tasks, or both, corroborated by evidence from everyday behaviour.

In patients with middle cerebral artery territory infarcts (n = 24; 14 with neglect, 10 without) the critical area was defined as the angular gyrus on the lateral surface of the inferior parietal lobe. Superior temporal gyrus was involved in some but not all of these patients. In patients with posterior cerebral artery territory infarcts (n = 11; 5 with neglect, 6 without) the critical area was defined as the parahippocampal gyrus in the medial temporal lobe. These areas have known neurobiological connections. Inferior frontal areas, implicated in some cases of neglect, were neither necessary nor sufficient to cause neglect in this series of patients.

Although lesion volume might be a confounding factor, nonetheless this study suggests that lesions of the angular gyrus and parahippocampal gyrus are critical to the development of visual neglect. ***-AJL***

The anatomy of visual neglect.
Mort DJ, Malhotra P, Mannan SK, Rorden C, Pambakian A, Kennard C, Husain M.
BRAIN 2003;126(9):1986-1997

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, 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 Alsaadi *et al* in California reminds us to cautiously interpret 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

The anti-epileptic properties of nail varnish remover

Smell is of course the most potent stimulus to memory and this article about the anti-epileptic properties of acetone brought back vivid memories of my mother's nail varnish remover. I can hear all the male readers' Oedipal sighs of recognition.

The ketogenic diet has been used for refractory epilepsy for many years, especially in children. Its anti-epileptic properties are indisputable but the mechanism is unknown. This study was triggered by the observation that acetone levels are substantially elevated by the ketogenic diet. Dose-response tests were carried out in four rat models of epilepsy; maximal electroshock which models tonic seizures; subcutaneous PTZ test, a model of absence seizures; amygdala kindled seizures and a further model of atypical absences of Lennox Gastaut syndrome. Animals were then injected intraperitoneally with four different doses of acetone. In all four models acetone had a significant effect on seizures with a clear dose-response curve, and a potency similar to valproic acid, affording nearly 100% protection at the higher doses used. Cerebrospinal fluid acetone concentration paralleled the doses used.

This study provides evidence that acetone concentrations may be important in the anti-epileptic effect of the ketogenic diet. Patients should however be advised against illicit forays into their mother's make-up cabinets. *-MRAM*

Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet.
Likhodi, SS, Serbanescu I, Cortez MA, Murphy P, Snead OC III, Burnham WM.
ANNALS OF NEUROLOGY
2003;54:219-26.

Autosomal dominant nocturnal frontal lobe epilepsy

ADNFLE is due to mutations of the nicotinic acetyl choline receptor and most sufferers respond well to carbamazepine. Leniger *et al* describe a new mutation with variable penetrance and a clear response to carbamazepine, shared by most patients with this condition. They expressed the ACh receptor in Zenopus oocytes and studied it electrophysiological characteristics. The mutant receptors showed no difference in the time-course of the current evoked by ACh but a marked increase in sensitivity to ACh. Suppression of ACh-evoked currents by carbamazepine was much greater in the mutant receptor preparation than in controls. This has been observed previously for other mutations and has been postulated to be an effect of the mutations on the sodium ion pore, affecting the binding properties of carbamazepine.

Varadkar *et al* describe 3 patients in one family whose ADNFLE was not responsive to a wide variety of anti-epileptic drugs, but eventually came under control with acetazolamide. When I worked with the group publishing this letter, we admitted a patient from abroad with nocturnal frontal lobe epilepsy characterised by curious attacks with singing at the onset. He is the only patient I have ever known to be controlled with acetazolamide monotherapy. ADNFLE had not been described at that stage but this article convinces me he suffered with the same condition. More important than the nostalgic meanderings of a time-expired reviewer is how this might relate to the mechanism of the mutation. Clearly something different is happening as these patients do not respond to carbamazepine. Perhaps this mutation inhibits carbamazepine binding but acetazolamide may indirectly affect sodium fluxes by its action on hydrogen ions. Its effect on ion channel disorders is well known. I await more frogs' eggs with interest. This is only the second form of rational prescribing in epilepsy that I know of. The other is ethosuximide for absence epilepsy, acting on T-type calcium channels in the thalamus, implicated in this condition. Both are of course genetic epilepsies, and are likely to have a purer mechanism than acquired epilepsy but they offer the hope that a magic bullet can be found for at least some of the epilepsies. *-MRAM*

A new Chrna4 mutation with low2 penetrance in nocturnal frontal lobe epilepsy.
Leniger T, Kananura, C, Hufnagel A, Bertrand S, Bertrand D, Steinlein O.
EPILEPSIA
20003;44:981-5.

Acetazolamide and autosomal dominant nocturnal frontal lobe epilepsy.
Varadkar S, Duncan JS, Cross JH.
EPILEPSIA
2003;44:986-987.

REHABILITATION

★★★ RECOMMENDED

Virtual sandwich making

Many patients recovering from head injury need to relearn kitchen skills. This can take a long time and teaching and supervising patient's practice in simple kitchen tasks is very labour intensive. Given the limited occupational therapy time available one way to provide more practice is to use a simulator. These days 3-D interactive images are used to train astronauts and surgeons to perform tricky procedures. Why not use them in rehabilitation of head injured subjects? Virtual reality kitchen environments offer the potential to allow patients to practice in the absence of a therapist and can provide information about performance to both the patient and therapist.

A group in the USA have developed software to create a virtual kitchen environment that can be used to make a virtual sandwich and prepare soup from a virtual can. The simulated environment was tested on 54 consecutive subjects with head injury and performance of virtual soup and sandwich preparation was compared with actual soup and sandwich making. Performance of both was assessed by scoring the time and errors observed in completing the task. In addition to the validity of the virtual meal preparation, the reliability of performance was assessed.

The virtual reality scores were found to be reproducible and consistent on repeat testing and the virtual kitchen task was found to be valid. When the groups' virtual reality performance was compared with actual kitchen performance a moderate and statistically significant correlation (r=0.63) was found. In actual fact the patients' virtual performance scored higher than actual performance. The authors put forward a number of possible explanations for this: immersion in virtual reality could increase subject's attention; there could be more distractions in a real kitchen. It's also possible that most of the subjects being young were better at interacting with computer graphics than performing real kitchen tasks. There are a myriad of complex sensorimotor interactions involved in preparing a simple sandwich in a real kitchen with real food and kitchen tools and equipment. However despite the limitations in reality of the virtual reality kitchen the study showed it to be a promising tool for those who need practice in remembering the steps need to complete a simple kitchen task. There is at least one other advantage; virtual washing up is probably quicker than real.*-AJT*

A virtual reality environment for evaluation of a daily living skill in brain injury rehabilitation.
Zhang L, Abreu BC, Seale GS, Masel B, Christiansen CH, Ottenbacher KJ.
ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION
2003: 84: 1118-1124

Another cause of train delays

The new DG2A train/delay generator is a compact, battery powered trigger source which can be used for producing repetitive stimulation or for studies of Effective Refractory Period (ERP) through the production of a delayed second pulse.

Various modes allow output pulses to be produced singularly, continuously or in a burst. In each mode (except free run), outputs can be initiated by a front panel button, a trigger/gating pulse or a suitable foot switch.

The unit has control of train duration, pulse repetition rate within that train and latency of the delayed pulse. It has two BNC outputs, one producing a pulse to trigger other equipment and the other producing either a delayed version of the same or by toggle switch selection, pairs of delayed and non-delayed. The DG2A is an ideal trigger source for Digitimer's DS2A and DS3 Isolated Stimulators.

For more information contact Digitimer Ltd, Tel: 01707 328347, Fax: 01707 373153, E-Mail: sales@digitimer.com

VT-Eye confocal microscopy system

VisiTech International has just released the VT-Eye, a new confocal microscopy system capable of imaging even the briefest physiological events. The VT-Eye uses novel solid-state technology to acquire up to 400 confocal images per second, making it the ideal system for temporal and spatial resolution of cellular events.

The VT-Eye is available as a modular or turnkey system and offers a range of lasers, rapid focusing and wavelength selection devices to enable ultra-fast, multi-spectral confocal imaging in three dimensions and over time. It is configurable with up to four high sensitivity detectors for fluorescent, reflected and transmitted light confocal microscopy. The VT-Eye is compatible with research grade microscopes, enabling easy upgrade from wide-field to confocal microscopy. The system is driven by a flexible, comprehensive software package capable of fully supporting multi-dimensional experiments.

The VT-Eye complements VisiTech International's existing range of dynamic live cell imaging systems.

For further information contact Visitech on Tel: 0191 5166 255.

Atypical antipsychotic for first episodes of schizophrenia

A new atypical antipsychotic with a unique pharmacological profile could become the "treatment of choice" for first episodes of schizophrenia, according to a leading psychiatrist.

Speaking at the 16th European College of Neuropsychopharmacology (ECNP) in Prague recently, Dr Sophia Frangou, senior lecturer in psychiatry at London's Institute of Psychiatry, suggested that aripiprazole should be an ideal treatment for schizophrenia. She made her comments following presentation of an in vitro study showing that aripiprazole behaved as a partial agonist at cloned D2L receptors. Dr Frangou said, "This study is encouraging because it shows aripiprazole behaves consistently both in vitro and in clinical practice. A partial agonist should be an ideal treatment, especially for first episodes."

Results presented at last year's ECNP meeting showed that when 311 stable schizophrenia patients were switched from olanzapine, risperidone or haloperidol to aripiprazole, symptoms improved and extrapyramidal symptoms, prolactin levels and weight gain were reduced. Patients switched from olanzapine to aripiprazole showed a statistically significant weight loss of 2.0kg ($p<0.001$) and a significant reduction in prolactin levels of 5.8g/ML.

Aripiprazole, co-marketed by Bristol Myers-Squibb and Otsuka Pharmaceuticals, is due to be launched in the UK next year.

For more information contact Rhonda Siddall, E-Mail: RhondaSiddall@aol.com

Crowd gets jumping in New York

Thanks to Siemens Medical Solutions sponsorship, UK band, 'You Jump First', recently played to an audience of 1,500 at the Organisation for Human Brain Mapping (OHBM) conference, New York. They used the opportunity to raise funds for The Children's Cancer Charity at Barts Hospital, London. Siemens sponsored t-shirts sold at the gig to raise money.

The band members are more than just musicians. Front man Dr Adrian Owen is a Medical Research Council (MRC) Senior Scientist at the Cognition and Brain Sciences Unit (CBU) in Cambridge and Assistant Director for Activation Studies, Wolfson Brain Imaging Centre, University of Cambridge. Dr Tina Gutbrod, the other vocalist is also a Developmental Psychologist at University of Hertfordshire. Dr Anja Dove the violinist is doing a Post-doctoral fellowship in neuroimaging at MRC CBU. Dr Fran Ebling, Guitarist is a Reader in Neuroendocrinology, University of Nottingham Medical School. Dr Mark Patterson, the bassist is currently one of the Editors of Public Library of Science and was formerly the Editor, Nature Reviews Genetics. Dr Philipp Gutbrod the Drummer is the sole non-scientist of the group, he is an Art Historian in Berlin, Germany. Jessica Grahn Cellist is a Phd Student in Brain Imaging, MRC CBU.

Siemens' sponsorship gave the band a chance to combine their two passions, as they were able to attend the conference as well as playing in front of the crowd. "The conference was excellent. The largest gathering of brain imagers in the world which gets better and better every year. The combination of methods and basic neuroscience is unbeatable and, of course, everyone is there." Adrian said.

For further information contact Siemens, Tel: 01344 396156.

The Medelec® Synergy range of EMG/EP/IOM Instruments

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For further information contact Linda Shaw at Oxford Instruments Medical UK on 01483 748415 or Email sales.medical@oxinst.co.uk

Imagine if you were in a queue.
And you suddenly couldn't move.
And, instead of help you
got abuse.

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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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