ISSN 1473-9348 Volume 2 Issue 6 January/February 2003

ACNR

Advances in Clinical Neuroscience & Rehabilitation

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

Review Articles: Sudden unexpected death in epilepsy; Gluten sensitivity: time to move from gut to brain

Management Topic: Congenital myopathies and muscular dystrophies

Rehabilitation Article: Obstructive sleep apnoea and stroke

www.acnr.co.uk

COPAXONE AUTOJECT2 AVAILABLE

For further information, contact Teva Pharmaceuticals Ltd Tel: 01296 719768 email: info@tevapharma.co.uk

COPAXONE® (glatiramer acetate) PRESCRIBING INFORMATION

Presentation

Glatiramer acetate 20mg powder for solution with water for injection.

Indication

Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients who have had at least two relapses in the preceding two years before initiation of therapy.

Dosage and administration

20mg of glatiramer acetate in 1 ml water for injection, administered subcutaneously once daily. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after.

Children

Not recommended under 18 years of age.

Elderly

No specific data.

Impaired renal function

No specific studies. Monitor renal function during treatment. Consider possibility of deposition of immune complexes.

Contra-indications

Known allergy to glatiramer acetate or mannitol (excipient). Pregnancy.

Special warnings and precautions

Sub-cutaneous use only. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders. Review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone.

Interactions

No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored.

Pregnancy and lactation

Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk.

Undesirable effects

Injection-site reactions (particularly erythema, hypersensitivity, pain, mass, pruritus, inflammation, oedema) are common and usually mild. An immediate post-injection reaction (one or more of vasodilatation, chest pain, dyspnoea, palpitation, tachycardia) was reported at least once in controlled trials by 41% on Copaxone and 20% on placebo. Other reactions reported from clinical trials with a frequency greater than 1 in 10 include flu-like syndrome, asthenia, back pain, headache, constipation, diarrhoea, nausea, arthralgia, anxiety, depression, dizziness, hypertonia, rash and sweating. Rarely, anaphylactoid or allergic reactions and convulsions. Rarely shifts in white blood cell counts and elevated levels of liver enzymes, no evidence of clinical significance.

Overdose

Monitor, treat symptomatically.

Pharmaceutical Precautions

Store Copaxone in refrigerator (2°C to 8°C). May store in refrigerator after reconstitution for up to eight hours.

Legal Category: POM

Package Quantity and Basic NHS Cost

28 vials of Copaxone plus 28 ampoules of water for injection: £510.14. Copaxone administration package, including syringes and needles supplied free of charge.

Product Licence Number

10921/0019

Further Information

Further medical information available on request from Aventis Pharma Limited, 50 Kings Hill Avenue, Kings Hill, West Malling, Kent, ME19 4AH. Other enquiries to: Teva Pharmaceuticals Limited, Barclays House, 1 Gatehouse Way, Aylesbury, Bucks, HP19 8DB.

Date of Review: December 2001.

Date of Preparation: August 2002.

References:

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

Editorial Board and contributors

Roger Barker is co-editor in chief of Advances in Clinical Neuroscience & Rehabilitation (ACNR), and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. He trained in neurology at Cambridge and at the National Hospital in London. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

Alasdair Coles is co-editor of ACNR and contributes our Anatomy Primer. He is a Wellcome Advanced Fellow working on experimental immunological therapies in multiple sclerosis, based at the Dunn School of Pathology in Oxford and Department of Neurology in Cambridge.

Stephen Kirker is the editor of the Rehabilitation section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He graduated from Trinity College, Dublin in 1985 and trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.

David J Burn is the editor of our conference news section and Consultant and Senior Lecturer in Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He qualified from Oxford University and Newcastle upon Tyne Medical School in 1985. His MD was in the functional imaging of parkinsonism. He runs Movement Disorders clinics in Newcastle upon Tyne and Sunderland. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

Andrew Larner is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

Wojtek Rakowicz is a Specialist Registrar in Neurology. After training in Norwich and Cambridge he worked in the Neuromuscular Division at Washington University in St Louis. He is currently at the National Hospital for Neurology and Neurosurgery.

Simon Hickman trained at Cambridge University and Addenbrooke's Hospital. He did his general professional training in Nottingham and is now working as a clinical research fellow at the Institute of Neurology in London. His major interest is in optic nerve magnetic resonance imaging.

Star Reviewer 2002

Congratulations to **Mark Manford**, who is our 'Star' journal reviewer for 2002.

In the past Mark has contributed our Epilepsy management topic, and throughout 2002 he has helped to keep our readers updated with a constant stream of reviews from epilepsy journals.

Many thanks for all your hard work from everyone at ACNR!

ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS WITH EPILEPSY

CONFIDENCE. BY KEPPRA.

ADD-ON THERAPY STARTS WITH

Keppra® ▼
levetiracetam

CONNECTING EFFICACY WITH TOLERABILITY IN AN EASY-TO-USE AED[1]

KEPPRA® Prescribing Information:
Please read Summary of Product Characteristics (SPC) before prescribing.
Presentation: Keppra 250, 500 and 1,000 mg film-coated tablets containing 250, 500 and 1,000 mg levetiracetam respectively. **Uses:** Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy. **Dosage and administration:** *Adults and adolescents older than 16 years:* The initial therapeutic dose is 500 mg twice daily which can be started on the first day of treatment. Depending upon clinical response and tolerability can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. *Elderly:* Adjustment of the dose is recommended in patients with compromised renal function. *Children (under 16 years):* Not recommended. *Patients with renal impairment:* Adjust dose according to creatinine clearance as advised in SPC. *Patients with hepatic impairment:* No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended. **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Warnings and special precautions for use:** If discontinuing treatment reduce dose gradually. **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, *e.g.* driving vehicles or operating machinery. **Undesirable effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (>10%): asthenia, somnolence. *Common* (between 1%-10%): GI disturbances, anorexia, accidental injury, headache, dizziness, tremor, ataxia, convulsion, amnesia, emotional lability, hostility, depression, insomnia, nervousness, vertigo, rash, diplopia. For information on post-marketing experience see SPC. **Legal category:** POM. **Marketing authorisation numbers:** 250 mg x 60 tablets: EU/1/00/146/004. 500 mg x 60 tablets: EU/1/00/146/010. 1,000 mg x 60 tablets: EU/1/00/146/024. **NHS price:** 250 mg x 60 tablets: £29.70. 500 mg x 60 tablets: £49.50. 1,000 mg x 60 tablets: £94.50. **Further information is available from:** UCB Pharma Ltd., 3 George Street, Watford, Hertfordshire WD18 0UH. Tel: 01923 211811. medicaluk@ucb-group.com
Date of preparation: August 2002.

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

© 2002 UCB Pharma Ltd.

UCB Pharma

UCB-K-02-29

contents

january/february 2003

Welcome to the first issue of ACNR in 2003 and thank you for all the feedback that you have provided, ensuring that we continue to deliver a clinically and scientifically relevant journal. In this issue we have a new type of article – a response from Marios Hadjivassiliou to the article we published on the neurological complications of coeliac disease by Connie Tengah and Adrian Wills. This exchange of views highlights not only how contentious these topics can be but also shows the relevance and appeal of the journal. So do keep those comments coming in, as they really do make a difference.

In this edition we also have an update on sudden unexpected death in epilepsy (SUDEP), a situation which every neurologist will sadly encounter at some point in their career. Such cases often lead to intense soul-searching to try and identify how it could have been avoided. This article by Langan and Nashef clearly sets out the pathogenic theories and the unpredictable nature of this condition and that close observation is really the only way of reducing its incidence in patients with on-going ictal activity.

We also continue our series on surgery for Movement Disorders with a useful update on the treatment of Parkinson's disease (PD) by Yianni and Aziz. This article not only summarises the history of neurosurgery in PD, but also gives a balanced account of their efficacy and side effects.

We also have a new author of a series of articles on peripheral nerves, Brian McNamara. Brian has recently moved back to Ireland to take up a consultant post in neurophysiology, having survived a neurophysiological and neurological training in Cambridge. Brian takes a straightforward approach to peripheral nerve disorders and begins with the median nerve and carpal tunnel syndrome. These articles set out the course and lesions of peripheral nerves in an easily digestible and memorable fashion, and over the next few issues this will be developed with other nerves.

We continue with the excellent series of articles by Wojtek Rakowicz. This time it is the turn of congenital myopathies and muscular dystrophies to be reviewed, and as with all his articles, it is elegantly written and illustrated and highlights not only their presentation in childhood but in adults as well.

Finally the rehabilitation article tackles obstructive sleep apnoea and stroke, and we are very privileged to have Professor Neil Douglas write this article for us. Obstructive sleep apnoea is an increasingly recognised condition, which can present to any number of specialities but especially neurologists. Thus recognising and treating this condition is critical, especially given the consequences of failing to do so. Professor Douglas deals with all aspects of this but concentrates on its relationship to hypertension and stroke.

In addition we have our usual series of articles including conference news which covers the recent ABN and the International movement disorder meeting in Florida in November. At this latter meeting, which attracts huge numbers of specialists from around the world, a new gene for PD was announced (DJ-1) as well as the results from the recent big US neural transplant trial in PD.

Finally I would like to give advance warning that ACNR is a journal of the times and will have its own web-site where you can read all the issues published over the last 2 years…so for those who struggle with the concept of paper you can now go back to your computer.

Roger Barker,
co-editor

Features

6 *Review Article*
Sudden death in epilepsy
Lina Nashef and Yvonne Langan

9 *Review Article*
Gluten sensitivity: time to move from gut to brain
Marios Hadjivassiliou

11 *Management Topic*
Congenital myopathies and muscular dystrophies
Wojtek Rakowicz

14 *Rehabilitation Article*
Obstructive sleep apnoea and stroke
Neil Douglas

19 *Anatomy Primer*
Clinical anatomy of the median nerve
Brian McNamara

21 *Special Feature*
Surgical treatment of Parkinson's disease
Tipu Aziz and John Yianni

23 *Conference News*
ABN/BNPA meeting
International congress of PD and movement disorders

Regulars

web browser 18 events 26 book reviews 28 journal reviews 29 news review 34

ACNR is published by Whitehouse Publishing,
7 Alderbank Terrace, Edinburgh EH11 1SX.
Tel. 0131 477 2335/07989 470278, **Fax.** 0131 313 1110
E-Mail. AdvancesinCNR@aol.com
Publisher: Rachael Hansford
Design & Production: Barbara Newton
Printed by: Stephens & George Magazines, Tel. 01685 388888.

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

Sudden unexpected death in epilepsy (SUDEP)

Authors

Yvonne Langan is a Specialist Registrar in Clinical Neurophysiology in Newcastle. Having graduated from Trinity College Dublin 1991, she was Registrar in Neurology in Dublin from 1994-1996. Dr Langan was Research Fellow at the Epilepsy Research Group, Institute of Neurology, Queen Square from 1996 to 1999, after which she was Neurology SpR in Newcastle upon Tyne.

Lina Nashef is a Consultant Neurologist at Kent & Canterbury and King's College Hospital, and Honorary Senior Lecturer at GKT School of Medicine. She has conducted research in SUDEP and is involved in a genetic association study of idiopathic generalised epilepsy.

Introduction

Individuals with epilepsy have a mortality rate 2-3 times that of the general population.[1-3] This increased mortality is attributable to both the underlying disease and epilepsy itself. The commonest seizure related death is sudden unexpected death (SUDEP), an event which recently has aroused great interest.

Definition

An agreed definition of SUDEP and classification of epilepsy related deaths has not been achieved. We propose the following definition: ".....sudden unexpected, nontraumatic and nondrowning death in an individual with epilepsy with or without evidence for a seizure and excluding documented status epilepticus where postmortem examination does not reveal a cause for death".[4]

In recent years in the UK an estimated 90% of sudden deaths have been referred to the coroner and proceed to postmortem examination but where this is not done, it is necessary to formulate, for the purposes of epidemiological studies, a definition which encompasses possible, probable and definite cases of SUDEP. An approach that has been adopted by various studies.[5-7]

Incidence studies

The incidence of SUDEP has been estimated by a number of investigators who have undertaken both population based and cohort studies and the results of these studies are summarised in tables 1 and 2.

Post-mortem findings

Whilst the definition of SUDEP includes the proviso that no anatomical or toxicological cause of death is found at post-mortem, there are nevertheless certain features which are commonly found at autopsy. This includes pulmonary oedema (deemed insufficient in itself to cause death) increased lung, liver and cardiac weights.[8-10] In addition neuropathological findings have reported decreased brain weights[8] and cerebral oedema[8,11] with structural brain lesions being present in 27- 70% of cases.[8,10-12]

Possible mechanisms

A variety of mechanisms have been proposed for sudden death in epilepsy including disturbances of respiration and cardiac conduction. Apnoea was a frequent finding in a study of ictal cardiorespiratory parameters at the telemetry unit of the National Hospital for Neurology and Neurosurgery.[13] and this hypoventilation, which was primarily central in nature, occurred in the context of both generalised and partial seizures. Obstructive apnoea occurred less commonly in this study but it is likely that in the controlled environment of the telemetry unit, where nursing intervention is likely to minimise airway compromise, the contribution of intrinsic or extrinsic obstructive apnoea to SUDEP may be underestimated.

An important role for hypoventilation is also supported by an animal model in which chemically induced seizures in sheep can cause death in association with a precipitous drop in the partial pressure of oxygen which occurs along with a concomitant rise in pulmonary artery and left atrial pressures resulting in pulmonary oedema - a frequent finding and almost a pathologic hallmark for sudden death in epilepsy (see above[15]). In this animal model care was taken to ensure that airway patency was maintained.[14]

Of further interest with respect to the role of apnoea in SUDEP are the findings of a study in a residential school for children with epilepsy and learning difficulties. The children were closely supervised by experienced staff while at school, including at night. No cases of SUDEP were witnessed during the period of the study suggesting that attention to the recovery of the individual following a seizure, and positioning or stimulating if necessary, may have a role in its prevention.[16]

The development of apnoea during a seizure does not exclude a role for cardiac arrhythmia in SUDEP. Clinical observations of seizures associated with severe cardiac arrhythmias have been reported, mainly involving sinus arrest and bradycardia with the majority of these cases having an epileptic focus located in the temporal lobes.[17-20]

Bradyarrhythmias, often transient have also been noted to occur in the presence of apnoea[13] and proposed mechanisms for this transient bradycardia include a direct effect of the seizure discharge or a response to apnoea mediated by the cardio–respiratory reflex.[21] Sinus tachycardia is a common accompaniment to seizures[22] but although malignant tacharrhythmias also occur the evidence suggests that this is an infrequent occurrence.[23] Experimentally Mameli and colleagues[24] found that various arrhythmias occurred during the paroxysmal discharge when hypothalamic partial epilepsy was induced in hemispherectomised rats, futhermore severe arrhythmias also occurred where there was a mesencephalic or rhombencephalic focus.[25,26]

Prolongation of the QT interval has been postulated to occur in sudden death cases with some investigators finding some evidence of ictal prolongation of the QT and QTc intervals although not beyond the normal ranges.[27] It has already been noted that cases of prolonged QT syndrome may be misdiagnosed as epilepsy[28] and it remains to be seen whether the same genetic predisposition may cause long QT syndrome and epilepsy in a subgroup of patients with idiopathic epilepsy and SUDEP. Autonomic dysfunction leading to an imbalance in cardiac autonomic control may also play a role in SUDEP[29] as investigators have shown reduced heart rate variability in those with epilepsy which may be related to the epilepsy itself, medication and medication withdrawal.[30-32]

A recent study which examined cardiac pathology in SUDEP cases found evidence of perivascular and interstitial fibrosis along with reversible myocyte vacuolisation. The control group, in whom such abnormalities were not detected, did not include individuals with epilepsy dying of other causes and thus the significance of these findings is unclear.[33] Opeskin and colleagues[34] performed detailed cardiac examination on ten SUDEP victims and ten controls, where there was no history of epilepsy and death was due to a non cardiac cause. They found no increase in morphological cardiac conduction system abnormalities in the SUDEP group and neither was there any difference in the level of coronary artery stenoses between the two groups. They qualify their findings by stating that subtle abnormalities of the conduction system were identified in some of the epilepsy related deaths which could have contributed to death by causing cardiac arrhythmia.

Case – control studies to date

Descriptive studies of SUDEP cohorts have reported potential risk factors which include youth, male sex, remote symptomatic

epilepsy, structural findings on neuropathology, severe epilepsy, alcohol abuse, abnormal EEG's with epileptiform changes and greater variations, mental handicap, psychotropic medication, African Americans, lack of compliance with treatment, abrupt medication changes, low antiepileptic drug levels and unwitnessed nocturnal seizures.[35] Case control studies are the way forward in further clarifying risk factors for SUDEP.

Nilsson and colleagues[36] have undertaken the first sizeable case control study. Fifty seven cases were identified of whom 91% had undergone PM examination and a number of conclusions can be drawn: The relative risk of SUDEP increased with increasing number of seizures/year. The estimated RR was 10.16(2.94-35.18) in those with more than 50 seizures/year compared with those who had two seizures/year and RR was 23.2(3.16-170.28) when those having any seizure were compared with those who were seizure free.

The risk of SUDEP increased with increasing number of concomitant AEDs 9.89 for three compared with monotherapy. This was a risk factor independent of seizure control as judged by seizure frequency. Seizure severity was not investigated. Other major risk factors were frequent changes of AED dosage compared with unchanged dosage 6.08(1.99-18.56). There was an 18 fold increase in RR associated with epilepsy in childhood compared with onset >45 years of age. The association between SUDEP risk and early onset of epilepsy and SUDEP risk and seizure frequency was weaker for women than men whereas the association between dosage change and increased risk was stronger in female patients. Male patients with localisation related epilepsy had a lower risk when compared to those with idiopathic epilepsy.

Walczak *et al*[37] identified ten probable and ten definite SUDEP cases with the risk of SUDEP being increased by tonic clonic seizures [OR 7(2-24)], number of AEDs [OR 3.8(1.3-11)] when adjusted for the number of all seizures and mental retardation OR4.6(1.2-18).

Preliminary results have also been reported from a large case-control UK study of 154 SUDEP cases, of whom 21 were witnessed.[38] This is the largest case control study to date and all cases underwent post-mortem examination. Risk of SUDEP was greater if a generalised tonic clonic seizure occurred in the last 3 months (OR 10.3(5.6-19.2)) and with increasing number of antiepileptic drugs ever taken (OR4.3(2.1-8.90 for 4 AEDs when compared with 1-2). Those who had never had drug therapy were also at increased risk when compared with those who had taken 1-2 drugs (OR 11.6(4.3-39.4). Recent AED withdrawal i.e. in the last 3 months also increased the risk of SUDEP (OR 2.7(1.1-6.5). Taking carbamazepine appeared to be associated with an increased risk of SUDEP with the OR just achieving significance OR 2(1.1-3.6). The clinical significance of this observation, suggested previously[39,40], is not yet clear and causation should not be assumed as there are many possible interpretations. This study also investigated supervision. There was a decreased risk of SUDEP if the bedroom was shared with someone capable of giving assistance (OR 0.38 (0.2-0.8) and if special precautions such as the use of listening devices were taken (OR 0.3 (0.1-0.86)).

Table 1. Population based studies of SUDEP Incidence

Authors	Incidence rate	Study method
Terrence *et al* 1975	1:1100	Coroner
Leestma *et al* 1984	1:525-1:2000	Coroner
Leestma *et al* 1989	1:370-1:1100	Coroner
Langan *et al* 1996	1:680	Coroner
Ficker *et al* 1998	1:2850	Coroner
Jick *et al* 1992	1:770	>/= 1 AED implies epilepsy
Tennis *et al* 1995	1:1850	
	(definite & probable cases)	>/= 1 AED implies epilepsy
Derby *et al* 1996	1:680	
	(definite & probable cases)	>/= 2 AEDs implies intractable epilepsy

Table 2. Cohort studies of SUDEP Incidence

Authors	Incidence rate	Study method
Lip & Brodie	1:200	Epilepsy clinic
Klenerman *et al* 1993	1:260	Epilepsy institution
Timmings *et al* 1993	1:500	Epilepsy clinic
Nashef *et al* 1995	1:200	Epilepsy clinic
Nashef *et al* 1995	1:300	Residential school
Dasheiff 1991	1:100	Epilepsy
surgery programme		
Sperling 1996	1:150	Epilepsy
surgery programme		
Hennessy *et al* 1999	1:450	Epilepsy
Surgery programme		
Annegers *et al* 1998	1:220	Vagal nerve stimulation
Annegers *et al* 2000	1:588	Vagal nerve stimulation

Clinical implications

This possibility of sudden death should be considered whenever patient management strategies are considered. SUDEP is largely a seizure related phenomenon and the optimisation of seizure control is highly important in its prevention. Effective AED therapy is therefore of paramount importance in the prevention of these tragic deaths. The risk of SUDEP needs to be considered whenever decisions are made about changes, particularly withdrawal of AED therapy as this may increase the risk as a consequence of altered seizure control or severity as a result of changes in reflex function.

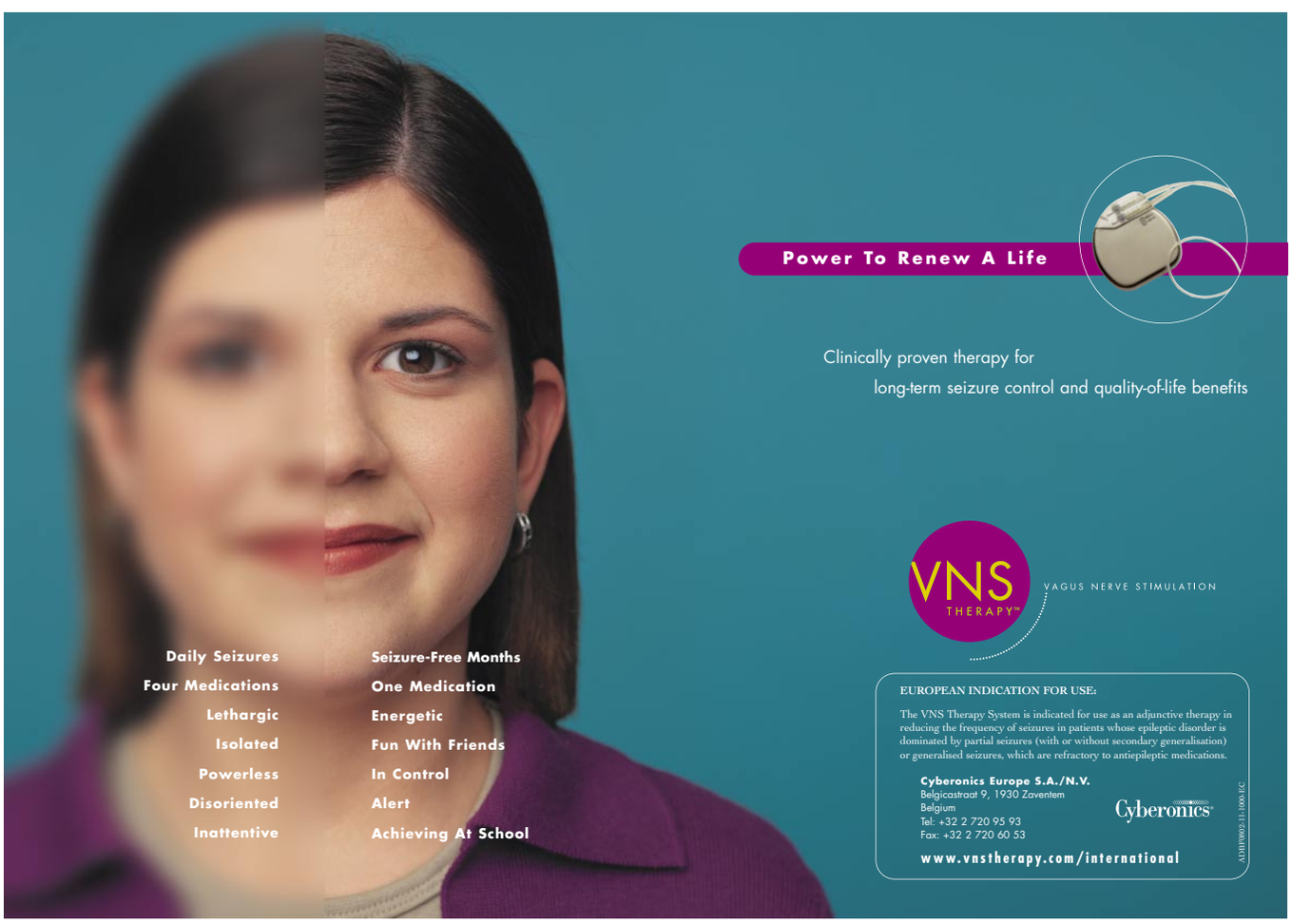
Supervision at night appears to protect against SUDEP. Indeed as the majority of these deaths are unwitnessed, attention to recovery following a seizure and positioning or stimulation as necessary may be important in SUDEP prevention. Every effort should be made to reduce avoidable seizures such as those related to specific trigger factors or to poor compliance with medication. It is thus important that patients be aware of the risks of their condition in order to make balanced decisions about treatment and lifestyle. Such discussion may be difficult and its nature and timing will vary from patient to patient dependent on assessment of individual risk. The issue of supervision at night may be particularly difficult to address, especially in the young adult.

Finally correct certification of epilepsy deaths is vital both for accurate data on SUDEP and other epilepsy related deaths and to allow for the monitoring of trends in mortality and the effectiveness of potential preventive measures discussed here.

References

1. Zielinski JJ. *Epilepsy and mortality rate and cause of death*. Epilepsia 1974; 15: 191-201.
2. Cockerell OC, Johnson AL, Sander JW, Hart YM, Goodridge DM, Shorvon SD. *Mortality from epilepsy: results from a prospective population-based study*. Lancet 1994; 344: 918-921.
3. Nilsson L, Tomson T, Farahmand BY, Diwan V, Persson PG. *Cause-specific mortality in epilepsy: A cohort study of more than 9,000 patients once hospitalized for epilepsy*. Epilepsia 1997; 38: 1062-1068.
4. Nashef L. *Sudden Unexpected Death in Epilepsy: Terminology and Definitions*. Epilepsia 1997; 38: S6-S8.
5. Leestma JE, Annegers JF, Brodie MJ, *et al. Sudden unexplained death in epilepsy: observations from a large clinical development program*. Epilepsia 1997; 38: 47-55.
6. Tennis P, Cole TB, Annegers JF, Leestma JE, McNutt M, Rajput A. *Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada*. Epilepsia 1995; 36: 29-36.
7. Jick SS, Cole TB, Mesher MD, Tennis P, Jick H. *Sudden Unexplained Death in Young Persons with Primary Epilepsy*. Pharmacoepidemiology and Drug safety 1992; 1: 59-64.
8. Leestma JE, Walczak T, Hughes JR, Kalelkar MB, Teas SS. *A prospective study on sudden unexpected death in epilepsy*. Ann Neurol 1989; 26: 195-203.

9. Earnest MP, Thomas GE, Eden RA, Hossack KF. *The sudden unexplained death syndrome in epilepsy: demographic, clinical, and postmortem features*. Epilepsia 1992; 33: 310-316.
10. Hirsch CS, Martin DL. *Unexpected death in young epileptics*. Neurology 1971; 21: 682-690.
11. Vickery BG. *Mortality in a Consecutive Cohort of 248 Adolescents who underwent diagnostic evaluation for Epilepsy Surgery*. Epilepsia 1997; 38: S67-S69.
12. Thom M. *Neuropathologic Findings in Postmortem Studies if Sudden Death in Epilepsy*. Epilepsia 1997; 38: S32-S34.
13. Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. *Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy*. J Neurol Neurosurg Psychiatry 1996; 60: 297-300.
14. Johnston SC, Horn JK, Valente J, Simon RP. *The role of hypoventilation in a sheep model of epileptic sudden death*. Ann Neurol 1995; 37: 531-537.
15. Johnston SC, Darragh TM, Simon RP. *Postictal pulmonary edema requires pulmonary vascular pressure increases*. Epilepsia 1996; 428-432.
16. Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. *Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty*. Epilepsia 1995; 36: 1187-1194.
17. Howell SJ, Blumhardt LD. *Cardiac asystole associated with epileptic seizures: a case report with simultaneous EEG and ECG*. J Neurol Neurosurg Psychiatry 1989; 52: 795-798.
18. Fincham RW, Shivapour ET, Leis AA, Martins JB. *Ictal bradycardia with syncope: A case report*. Neurology 1992; 42: 2222-2223.
19. Dasheiff RM, Dickinson LJ. *Sudden unexpected death of epileptic patient due to cardiac arrhythmia after seizure*. Arch Neurol 1986; 43: 194-196.
20. Jallon P. *Epilepsie et coeur*. Rev Neurol 1997; 153: 173-184.
21. Spyer KM. *Central nervous control of the cardiovascular system*. In: Bannister R, Mathias CJ, eds. Autonomic Failure, 3rd ed. 1998: 55-77.
22. Blumhardt LD, Smith PEM, Owen L. *Electrocardiographic accompaniments of temporal lobe epileptic seizures*. Lancet 1986; 1: 1051-1056.
23. Keilson MJ, Hauser A, Magrill JP, Goldman M. *ECG abnormalities in patients with epilepsy*. Neurology 1987; 1624-1626.
24. Mameli P, Mameli O, Tolu E, *et al. Neurogenic myocardial arrhythmias in experimental focal epilepsy*. Epilepsia 1988;29: 74-82.
25. Mameli O, Mameli P, Tolu E, *et al. Analysis of central cardioarrhythmogenic triggers in experimental epilepsy*. Epilepsy Res 1990; 7:210-218.
26. Mameli O, Melis F, Giraudi D, *et al. The brainstem cardioarrhythmogenic triggers and their possible role in sudden epileptic death*. Epilepsy Res 1993; 15: 171-178.
27. Tavernor SJ, Brown SW, Tavernor RME, Gifford C. *Electrocardiograph QT lengthening associated with epileptiform EEG discharges - A role in sudden unexplained death in epilepsy?* Seizure 1996; 1: 79-83.
28. Ballardie FW, Murphy RP, Davis J. *Epilepsy: a presentation of the Romano Ward syndrome*. British Medical Journal 1983; 24: 896-897.
29. Schraeder PL, Lathers CM. *Paroxysmal autonomic dysfunction, epileptogenic activity and sudden death*. Epilepsy Res 1989; 3: 55-62.
30. Hennessy MJ, Tighe M, Polkey CD, Nashef L. *Sudden withdrawal of carbamazepine increases cardiac sympathetic activity in sleep*. Neurology 2001; 57: 1650-1654.
31. Massetani R, Strata G, Galli R, *et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability*. Epilepsia 1997; 38: 363-369.
32. Tomson T, Kenneback G. *Arrhythmia, Heart Rate Variability and Antiepileptic drugs*. Epilepsia 1997; 38: S48-S51.
33. Natelson BH, Suarez RV, Terrence CF, Turizo R. *Patients with epilepsy who die suddenly have cardiac disease*. Arch Neurol 1998; 55: 857-860.
34. Opeskin K, Thomas A, Berkovic S.F. *Does cardiac conduction pathology contribute to sudden unexpected death in epilepsy*. Epilepsy Res 2000; 40: 17-24.
35. Shorvon S. *Risk factors for sudden unexpected death in epilepsy*. Epilepsia 1997; 38(Suppl 11): S20-S22.
36. Nilsson L, Farahmand BY, Persson P, Thiblin I, Tomson T. *Risk factors for sudden unexpected death in epilepsy: a case control study*. Lancet 1999; 353: 888-893.
37. Walczak T, Leppik IE, D'Amelio M, *et al. Incidence and risk factors in sudden unexpected death in epilepsy*. Neurology 2001; 56: 519-525.(Abstract)
38. Langan Y. *Prevention of sudden unexpected death in epilepsy*. Thesis 2002.
39. Timmings PL. *Sudden unexpected death in epilepsy: Is carbamazepine implicated?* Seizure 1998; 7: 289-291.
40. Nilsson L, Bergman U, Diwan W, Farahmand BY, Persson PG, Tomson T. *Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case control study*. Epilepsia 2001; 667-673.



Gluten sensitivity: time to move from gut to brain

In response to a recent article in the July/August ACNR by Tengah and Wills, Marios Hadjivassiliou has written this article. The issue of neurological complications in coeliac disease is a contentious one and these two articles take rather different approaches on the subject, illustrating the difficulty in proving causality in medicine rather than simply describing associations or epiphenomena. Nevertheless the neurological complications of coeliac disease remains a topic of great interest and I hope that these two articles will spur more clinicians and scientists to re-evaluate this area in terms of incidence, pathogenesis and therapy. -RB

Scepticism in the face of new ideas has long prevailed in the medical profession, and is usually healthy. Dissemination of medical advances and research now occurs rapidly and the pace of change of clinical practice has consequently increased. There is a general expectation of quicker assimilation of sound scientific observations and with it increasing demands placed on individuals to assess the scientific value and rigor of published material. The authors of review articles are in a particular position of responsibility to produce dispassionate and informed material, and reluctance to accept scientific evidence just because it does not conform to traditional thinking or because of personal bias may ultimately deprive patients of potential treatment.

An example of such reluctance is the notion that gluten sensitivity is solely a disease of the bowel. The evidence that gluten sensitivity can primarily affect other organs, with sparing of the bowel, is not new. In 1966 Marks and her colleagues demonstrated an enteropathy in 9 of 12 patients with Dermatitis Herpetiformis (DH)[1]. It was later shown that the enteropathy and the skin rash were gluten dependent but skin involvement could occur without evidence of gut involvement. Moreover patients with DH characteristically have few if any gastrointestinal symptoms,in contrast to patients with coeliac disease (CD). Nowadays, dermatologists treating DH are not very interested in the state of their patients' bowel mucosa. Such patients do not routinely have a small bowel biopsy, but are treated immediately with a gluten-free diet.

In refining the pathological spectrum of the bowel mucosa in the context of gluten sensitivity Mike Marsh performed a series of elegant experiments looking at gluten load and mucosal pathology in patients with gluten sensitivity[2]. He demonstrated that mucosal pathology correlated with gluten load, and defined a spectrum of lesions ranging from the pre-infiltrative (type 0, histologically normal mucosa) to the atrophic hypoplastic (type 4). Thus, he demonstrated that you can have gluten sensitivity but have a normal bowel mucosa. Marsh's observations were considered somewhat eccentric at the time, yet now most scientific papers grade gut pathology using the "Marsh classification".

Authors

Marios Hadjivassiliou is an Honorary Clinical Senior Lecturer at The University of Sheffield and a Consultant Neurologist at Sheffield Teaching Hospitals NHS trust and Chesterfield Royal Hospital. His MD thesis was on the neurological manifestations of gluten sensitivity. His current research interests include the neurological manifestations of systemic diseases with an emphasis on gluten sensitivity as well as the aetiology of "idiopathic" ataxias. He runs a weekly gluten sensitivity/neurology clinic as well as an ataxia clinic.

Richard Grünewald is an Honorary Clinical Senior Lecturer at the University of Sheffield and Consultant Neurologist at Sheffield Teaching Hospitals NHS Trust and Barnsley District General Hospital. His current research interests also include the pathophysiology of dystonia, the role of metabolic abnormalities in Parkinson's disease and memory dysfuntion in epilepsy.

Nine years ago we started working on the concept that gluten sensitivity can be principally a neurological illness. Perhaps the best characterised disorder we have studied is gluten ataxia.[3] It is unscientific to suggest that neurological "associations" of gluten sensitivity such as ataxia are purely coincidental. Pathological studies and published prevalence figures confirm the contrary view. Table one summarises the published studies [4,5,6,7,8,9] concerning the prevalence of gluten sensitivity in patients with ataxia. Although it is true that some studies are of small patient numbers with limited power and lack of adequate control populations, the more carefully executed studies with adequate controls are conclusive: there is a significantly higher prevalence of gluten sensitivity in patients with "idiopathic" sporadic ataxia than those with familial ataxia or control subjects. Variations in the prevalence between studies is likely to reflect differences in the antigliadin assay used (hence the necessity of comparison with control populations) as well as geographical variations.

Several clues to the neuropathological basis of these disorders are emerging. Neuropathological data from patients with gluten ataxia suggest an inflammatory process with T-cell infiltration primarily of the cerebellum and ultimately the loss of Purkinje cells.[3] Patients with gluten ataxia have antibodies against Purkinje cells and anti-gliadin antibodies cross-react with epitopes on Purkinje cells.[10] The CSF in these patients shows oligocolonal bands in more than half and upregulation of the chemokine IP-10, a T cell chemoattractant, when compared to controls.[11] Seventy percent of patients with gluten ataxia have the same HLA genotype[12] as found in patients with coeliac disease. There is an increased incidence of autoimmune diseases amongst patients with gluten ataxia (unpublished observation). Perhaps more compelling evidence still, comes from the results of the effect of gluten free diet in patients with gluten ataxia. Gluten free diet results in improvement of the ataxia in patients within a year of a strict gluten free diet when compared to controls.[13] Yet the prevalence of an enteropathy in patients with gluten ataxia is only about 24%.[12]

Despite this overwhelming evidence of a gluten-driven immune pathogenesis, some continue to propose (without any corroborative scientific data) that "trace element" deficiency due to the enteropathy is a possible explanation. As only a quarter of these patients have an enteropathy, it is difficult to imagine how such a deficiency might arise, let alone what chemical might be deficient.

Whilst CD, DH and gluten ataxia are all manifestations of gluten sensitivity, it is wrong to propose that DH and gluten ataxia should fall under the umbrella of CD, implying that they are all one and

Study details	sporadic ataxias	familial ataxias	normal controls
	antigliadin positive / total number tested **(percentage positive)**		
Hadjivassiliou et al (UK)[4]	59/143 **(41%)**	8/51 **(14%)**	149/1200 **(12%)**
°Pellecchia et al (Italy)[5]	3/24 **(13%)**	0/23 **(0%)**	N/A
Burk et al (Germany)[6]	12/104 **(11.5%)**	N/A	**(5%)**
Bushara et al (USA)[7]	7/26 **(27%)**	9/24 **(37%)**	N/A
Abele et al (Germany)[8]	13/98 **(13%)**	1/15 **(6%)**	**(5%)**
°Luostarinen et al (Finland)[9]	44 **(16.7%)**	N/A	**(2%)**

Table 1: A list of studies looking at the prevalence of antigliadin antibodies in patients with sporadic ataxia and controls. All but one of these studies show a significantly higher prevalence of gluten sensitivity in patients with sporadic ataxia compared to controls. Studies without controls are not included. Studies marked with ° refer to prevalence of coeliac disease. N/A: not available.

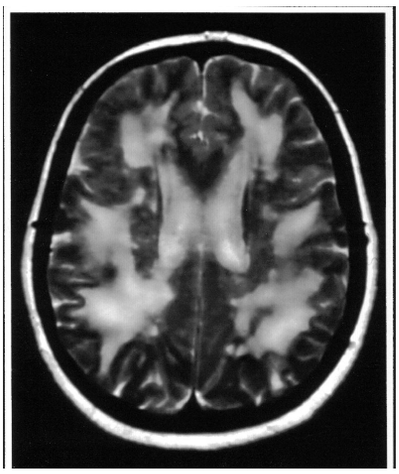


Figure 1. MRI of one of our patients with gluten sensitivity, episodic migraine-like headaches and white matter abnormalities.[17] The patient remains asymptomatic 5 years after the diagnosis of gluten sensitivity and the introduction of gluten free diet. The clinical and radiological characteristics distinguish this entity from MS. The response to diet, lack of family history and absence of progression exclude CADASIL as an alternative diagnosis.

the same disease. It is true that if one looked hard enough in patients with DH one would find some degree of enteropathy in most. It is also true that 8 to 10 percent of patients with CD may develop neurological dysfunction (this figure is likely to be higher if these patients underwent detailed neurological assessment). However, if these diseases are one and the same one would expect the reverse to be true: patients presenting with CD should all have DH and patients presenting with gluten ataxia should all have CD, clearly not the case.

The notion that it is the prolonged exposure to gluten that causes neurological dysfunction in patients with gluten sensitivity (postulated to be the case in patients with DH who may not be as strict with their diet) is unsubstantiated. If the duration of exposure to gluten was pivotal in the development of gluten related diseases, classic CD would not typically present between the age of 6 to 18 months of age. It is likely that the type and prevalence of neurological dysfunction in DH is similar to that found in patients with established CD. A recent study looking at neurological dysfunction in 35 patients with DH did not have the power to determine if the prevalence of neurological dysfunction is different in DH than in CD, but a very large difference was excluded.[14] The majority of people with genetic susceptibility to gluten sensitivity (HLA DQ2) are exposed to gluten for all their lives but do not develop CD, DH or gluten ataxia. The factors responsible for the development of gluten-driven pathology are more complicated than duration of exposure.

It is of considerable interest to question why patients with gluten sensitivity manifest with such diverse organ involvement, albeit with some overlap. Clues to an answer may be found in the role of transglutaminases. Tissue transglutaminase is the antigen recognised by endomysium antibodies, the most sensitive and specific marker of gluten sensitive enteropathy (CD). Apart from crosslinking proteins, tissue transglutaminases (of which there are several types) deamidate glutamine-donor substrates, such as gliadin proteins. It has been postulated that this process may result in the creation of neoepitopes that could play a role in the immune pathogenesis of other diseases.[15] A recent study reported that patients with DH have antibodies with low affinity for tissue transglutaminase but very high affinity for epidermal transglutaminase.[16] This results in an immune response and clinical manifestations in the skin, the main site of epidermal transglutaminase production. An analogous situation may exist in the case of gluten ataxia where an immune response directed towards neural transglutaminases may result in clinical manifestations primarily in the brain or the peripheral nervous system and not the gut. Characterisation of the antigen recognised by Purkinje cell antibodies found in the serum of patients with gluten ataxia may contribute further in resolving the possible pathogenic mechanism.

We must advance such concepts by abandoning historical misconceptions and reviewing current literature in an analytical and disinterested way. It is time to move on from gut to brain.

References

1. Marks J, Shuster S, Watson AJ. *Small bowel changes in dermatitis herpetiformis.* The Lancet 1966; ii: 1280-1282.
2. Marsh M. *Gluten, Major Histocompatibility Complex and the small intestine.* Gastroenterology 1992; 102:330-354.
3 Hadjivassiliou M, Grünewald RA, Chattopadhyay AK, Davies-Jones GAB, Gibson A, Jarratt JA *et al. Clinical, radiological, neurophysiological and neuropathological characteristics of gluten ataxia.* The Lancet 1998;352:1582-85.
4. Hadjivassiliou M, Grünewald RA, Davies-Jones GAB. *Gluten sensitivity as a neurological illness.* J Neurol Neurosurg Psychiatry 2002;72:560-563
5. Pellecchia MT, Scala R, Filla A, De Michele G, Ciacci C, Barone P. *Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features.* J Neurol Neurosurg Psychiatry 1999;66:32-5.
6. Bürk K, Bösch S, Müller CA, Melms A, Zühlke C, Stern M *et al. Sporadic cerebellar ataxia associated with gluten sensitivity.* Brain 2001;124:1013-19.
7. Bushara KO, Goebel SU, Shill H, Godfarb LG, Hallett M. *Gluten sensitivity in sporadic and hereditary cerebellar ataxia.* Ann Neurol 2001;49:540-3.
8. Abele M, Bürk K, Schöls L, Schwartz S, Besenthal I, Dichgans J *et al. The aetiology of sporadic adult-onset ataxia.* Brain 2002;125:961-968.
9. Luostarinen LK, Collin PO, Paraaho MJ, Maki MJ, Pirttila TA. *Coeliac disease in patients with cerebellar ataxia of unknown origin.* Ann Med 2001;33(6):445-9.
10. Hadjivassiliou M, Boscolo S, Davies-Jones GAB, Grünewald RA, Not T, Sanders D, Simpson JE, Tongiorgi E, Williamson CA, Woodroofe NM. *The humoral response in the pathogenesis of gluten ataxia.* Neurology 2002; 58: 1221-1226.
11. Mahad D, Oates K, Williams C, Grünewald RA, Howell SJL, Woodroofe MN, Hadjivassiliou M. *Gluten ataxia is immune mediated.* J Neurol Neurosurg Psychiatry 2002;72:140.
12. Hadjivassiliou M, Grünewald RA, Sharrack B, Sanders D, Lobo A, Wood N, Williamson C, Woodroofe N, Davies-Jones GAB. *Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics.* Brain (in press).
13. Hadjivassiliou M, Grünewald RA, Davies-Jones GAB. *Gluten ataxia: The effect of gluten fee diet.* Ann Neurol 2002;52: S63.
14. Wills AJ, Turner B, Lock RJ, Johnston SL, Unsworth DJ, Fry L. *Dermatitis Herpetiformis and neurological dysfunction.* J Neurol Neurosurg Psychiatry. 2002;72:259-61
15. Schuppan D, Esslinger B, Trapp D, Dieterich W. *Tissue transglutaminase as coeliac disease autoantigen.* In *Proceedings of the workshop on transglutaminases, protein cross-linking and coeliac disease.* September 2001 Tampere, Finland.
16. Sardy M, Karpati S, Merkl B, Paulsson M, Smyth N. *Epidermal transglutaminase (Tgase 3) is the autoantigen of dermatitis herpetiformis.* J Exp Med 2002;195:747-57.
17. Hadjivassiliou M, Grünewald RAG, Lawden M, Davies-Jones GAB, Powell T, Smith CML. *Headache and CNS white matter abnormalities associated with gluten sensitivity.* Neurology 2001;56:385-388.

Correspondence to:

Dr M Hadjivassiliou, Dept of Neurology, The Royal Hallamshire Hospital, Sheffield S10 2JF
E.mail: m.hadjivassiliou@Sheffield.ac.uk

Congenital myopathies and muscular dystrophies

Author

Dr Wojtek Rakowicz is a Specialist Registrar in Neurology. After training in Norwich and Cambridge he worked in the Neuromuscular Division at Washington University in St Louis. He is currently at the National Hospital for Neurology and Neurosurgery.

Congenital myopathies are a distinct group of inherited disorders of skeletal muscle which (1) present predominantly in the perinatal period; (2) are non-progressive or only very slowly progressive; (3) share some clinical features and (4) have characteristic structural abnormalities on muscle immunohistochemistry. 'Congenital' myopathies can present later in childhood and these children may have a milder course. Occasionally, adults presenting with limb-girdle weakness or exercise intolerance have the same histological findings. Multiple gene defects can give rise to similar clinical and ultrastructural phenotypes so the congenital myopathies remain defined by muscle immunohistochemistry.

Congenital muscular dystrophies (CMDs) are distinguished by the immunohistochemical finding of prominent 'dystrophic' changes: muscle fibre necrosis and regeneration, increased endomysial connective tissue, and replacement of muscle with fat tissue. Classical CMDs are clinically confined to the musculoskeletal system but other CMDs are characterised by significant cerebral neuronal migration defects and eye abnormalities. Classical CMDs are further subdivided according to the presence or absence of merosin (laminin-2).

Presentations and management

Congenital myopathies are most commonly evident at birth with infants exhibiting a loss of axial and appendicular tone ('**floppy infant**'), decreased spontaneous movement and, later, delayed acquisition of motor milestones. However, congenital muscle disease has to be distinguished from more common causes of the same presentation, especially systemic disease or global developmental delay (Table 1).

In utero weakness from any cause can result in **skeletal deformities** and **contractures**. Recognised skeletal deformities include congenital dislocation of the hips, kyphoscoliosis and pes cavus. Contractures are particularly common in, but not specific to, CMDs. **Arthrogryposis** is the term used to describe multiple severe bony deformities and contractures in the newborn.

Facial weakness and **respiratory insufficiency** are more common in congenital myopathies (Table 2) but no single clinical finding is diagnostic. These features may also be present in congenital myasthenia or congenital myasthenic syndrome.

Table 1. Causes of hypotonia in infants

anatomical localisation	pathological processes
central nervous system	*deep tendon reflexes typically preserved*
brain/systemic disease	hypoxic-ischaemic encephalopathy sepsis congestive cardiac failure
brainstem	Down's syndrome Prader-Willi syndrome
craniocervical junction	congenital malformations perinatal cord injury
motor unit	
anterior horn cell	spinal muscular atrophy
peripheral nerve	hereditary motor-sensory neuropathy
neuromuscular junction	myasthenia myasthenic syndromes
muscle	congenital myopathies metabolic myopathies muscular dystrophies

Laboratory investigations can be non-specific (mildly raised serum creatine kinase) or difficult to interpret (EMG in a neonate). In the absence of a family history, muscle biopsy is necessary for diagnosis.

Supportive medical intervention is limited to monitoring respiratory function, cardiac function (core pulmonale) and spinal scoliosis. In addition, individuals with central core disease have to be screened for susceptibility to malignant hyperthermia and warned of the risks of anaesthetic agents.

Congenital myopathies

CENTRAL CORE DISEASE

Central core disease was the first congenital myopathy to be described and many of its clinical features are characteristic of this group of disorders. Infants present at or shortly after birth with hypotonia, areflexia, delayed motor milestones, proximal limb weakness and often mild facial weakness. Accompanying skeletal abnormalities include short stature, kyphoscoliosis, pes cavus and congenital dislocation of the hips. The condition is usually non-progressive with affected children remaining ambulatory into adult life. Central core disease can present in adulthood with muscle cramps or limb-girdle weakness but may also be asymptomatic. An important additional part of the phenotype, specific to central core disease, is the co-existence of susceptibility to anaesthesia-related malignant hyperthermia in one third of patients. Individuals within the same family may exhibit one or both phenotypes. At-risk individuals can be screened with an *in vitro* contracture test performed on a fresh muscle sample.

Central core disease is inherited in an autosomal dominant fashion with mutations in the ryanodine receptor gene (*RYR1*) accounting for up to 50% of cases. The gene encodes a sarcoplasmic reticulum calcium channel that releases intracellular calcium as a step in excitation-contraction coupling. The characteristic immunohistochemical finding is the presence of densely packed disorganised myofibrils ('cores') in the centre of the majority of type 1 muscle fibres. These cores extend along the length of the fibres, excluding mitochondria and many muscle enzymes (cytochrome oxidase, NADH), giving rise to a characteristic central pallor (Fig. 1a.).

NEMALINE MYOPATHY

Typical **nemaline myopathy** presents sporadically at birth with severe floppiness and weakness. Feeding difficulties are common and respiratory muscle involvement can be a cause of early death but improvement and weaning are usually achieved. Childhood presentations, characterised by weakness and delayed motor milestones, are relatively benign and individuals usually remain ambulant. Affected children typically have an elongated, weak face, tent-shaped mouth due to facial weakness, a high-arched palate and a nasal voice. Limb weakness is diffuse and initially greater in proximal muscles but distal weakness is also a feature of some of the nemaline myopathy syndromes.

The inheritance of nemaline myopathy is most commonly autosomal recessive but can be autosomal dominant. The disease has been linked to mutations in three very different genes (encoding α-actin, tropomyosin-3 and nebulin) but it is unclear how these bring about a common phenotype. Careful examination of the parents, possibly combined with muscle biopsy, is needed to confirm the mode of inheritance. The name of nemaline myopathy is derived from the histological hallmark of granules or rods of filamentous material (*nema* = thread in Greek) which tend to aggregate under the sarcolemma (Fig.1b). Nemaline rods are accumulations of disorganised Z-disk mater-

Table 2. The major clinical features of the congenital myopathies and congenital muscular dystrophies

Main Clinical Features	hypotonia	limb weakness	facial weakness	respiratory insufficiency	clinical CNS involvement	eye involvement	additional features
Congenital Myopathies							
Central Core Disease	•	•	(•)				± malignant hyperthermia
Nemaline Myopathy	•	•	•	•			
Centronuclear Myopathy	•	•	•	•		ptosis	severe course (usu.); ophthalmoplegia
Congenital muscular dystrophies							
Merosin-positive CMD	•	•		(•)			
Merosin-deficient CMD	•	•		•			white matter changes on MRI
Fukuyama CMD	•	•	•	•	•		severe course; seen in Japan
Muscle-Eye-Brain Disease	•	•		•	•	•	
Walker-Warburg Syndrome	•	(•)		•	•	•	severe course; blind at birth

ial, best seen in sections stained with the modified Gomori trichrome technique. Rods can also be seen in denervated muscle and in HIV myopathy.

CENTRONUCLEAR (MYOTUBULAR) MYOPATHY

Centronuclear myopathy most commonly presents in boys (*X*-linked) at birth with severe hypotonia and weakness. Ventilatory insufficiency and feeding difficulties may lead to death over days to weeks though longer survival occurs in a subset of infants. Evidence for the condition starting in utero comes from a maternal history of polyhydramnios or of miscarriages/perinatal death of male infants. As with nemaline myopathy, affected infants have an elongated, expressionless face, tent-shaped mouth and a high-arched palate. Kyphoscoliosis and pes cavus may be present. Autosomal recessive and dominant forms that are more mild have onsets later in childhood or early adulthood. Facial weakness remains a prominent feature, usually accompanied by ophthalmoplegia and ptosis and proximal muscle weakness.

The histological characteristic of centronuclear myopathy is the presence of small muscle fibres that, in addition to the normal peripherally located nuclei, contain rows of centrally placed internal nuclei (Fig.1c). The histological similarity of the appearance to fetal myotubes gave rise to the name myotubular myopathy but fibre architecture and protein expression are in an adult pattern. Centronuclear myopathy has been linked to mutations in the *MTM1* gene that encodes myotubularin, a ubiquitous non-receptor protein tyrosine phosphatase which might be involved in signal transduction during late myogenesis. Multiple internal nuclei are also seen in myotonic dystrophy which should be excluded by genetic testing.

OTHER CONGENITAL MYOPATHIES

Numerous histological abnormalities have been described in infants with congenital myopathies but these are either infrequent or not fully established nosological entities. **Congenital fibre-type disproportion,** characterised by an increased number of small type 1 fibres, constitutes a heterogeneous group of disorders with a relatively nonprogressive course. The mechanism of weakness in these individuals remains a puzzle. Small type 1 fibres are also seen in other congenital myopathies such as nemaline and centronuclear myopathies. **Multicore (minicore) disease** is a mild non-progressive disorder in which muscle fibres contain multiple cores that share many of the features of those seen in central core disease but are smaller in size (minicores) and not confined to the centre of the fibre. Facial weakness, ptosis and ophthalmoplegia are also commonly seen. Multicore disease can be caused by mutations in *RYR1*, the gene responsible for central core disease.

Congenital muscular dystrophies (CMDs)

CLASSICAL CMDs

Merosin-deficient CMD accounts for around a half of classical CMD and has a consistently severe phenotype with multiple contractures and joint deformities (arthrogryposis) at birth. Infants can succumb to respiratory failure and death but, if adequately supported, they can often be weaned off ventilatory support. A proportion will achieve independent sitting but independent standing or walking is almost never achieved. Mental development is usually normal although minor learning disabilities and seizures do occur. It is therefore somewhat paradoxical that brain MRI consistently demonstrates diffuse white matter signal changes. Nerve conduction velocities are frequently slowed reflecting the ubiquitous expression of merosin in basement membranes.

Merosin (laminin-2) is a member of the laminin family of trimeric ($\alpha\beta\gamma$) extracellular matrix glycoproteins that interact with cells through surface receptors (integrins and α-dystroglycan). Mutations in the laminin α2 chain result in a deficiency of merosin ($\alpha2\beta1\gamma1$). The diagnosis of merosin-deficient CMD is dependent on demonstrating absent merosin staining on muscle immunohistochemistry (cf. Fig.1d).

The clinical phenotype of **merosin-positive CMDs** is more heterogeneous than merosin-deficient CMD but it is generally a milder disorder and the brain MRI is normal. Most of these children achieve the ability to stand and walk independently by age four. The condition is similar to congenital myopathies with little or no progression though contractures may develop late.

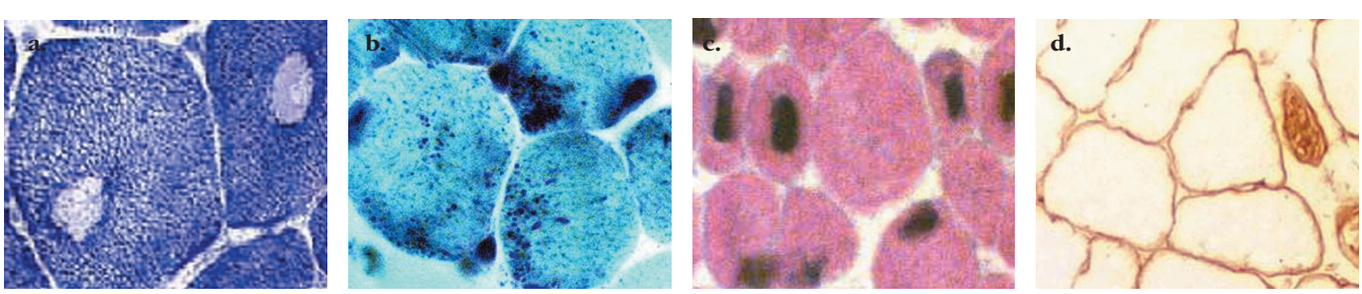


Figure 1: Characteristic immunohistochemical appearance of (a) central core disease (NADH); (b) nemaline myopathy (modified Gomori trichrome); (c) centronuclear myopathy (H&E); (d) normal merosin staining of basal lamina in muscle and nerve.

OTHER CMDs

Fukuyama CMD is characterised by motor problems similar to classical CMD but with evidence of additional facial weakness and CNS disease with severe mental retardation and convulsions. Brain malformations, including polymicrogyria, pachygyria and agyria may be seen on MRI imaging. Brain CT scans are also characteristically abnormal with frontally predominant white matter lucencies. The disease is slowly progressive: affected children rarely walk and most die by 10 years of age but some individuals survive into early adulthood. Fukuyama CMD is mainly seen in Japan with an estimated incidence approximately half that of Duchenne's muscular dystrophy.

Muscle-Eye-Brain (MEB) disease and **Walker-Warburg Syndrome** (WWS) are characterised by eye abnormalities in addition to neuronal migration defects. Children with MEB are usually able to stand and to walk but have marked mental retardation, severe myopia, retinal dysplasia, cataracts and optic atrophy. Death is usually in the first or second decade but some individuals survive well into adulthood. Babies with WWS are blind at birth and have severe eye, facial and limb abnormalities. The disease follows a progressive course leading to death within months. Muscle involvement is less prominent in WWS than in the other CMDs.

Congenital presentations of muscular dystrophies

Congenital presentations of myotonic dystrophy (DM1), facioscapulohumeral dystrophy and Duchenne's muscular dystrophy are well recognised. Congenital **myotonic dystrophy** is associated with massive expansions (>1000) of the triplet repeat region in the *MPK* gene and is usually maternally-inherited. Affected parents are often asymptomatic and need to be examined closely. Congenital PROMM (DM2) has not yet been observed. Congenital **facioscapulohumeral dystrophy** is often a sporadic disorder due to new mutations. An extremely elevated serum creatine kinase at birth is suggestive of a **dystrophinopathy** and should be followed with a search for reduced or absent dystrophin staining on muscle immunohistochemistry. Definitive genetic testing is available for all three diseases but will be normal in a third of boys with Duchenne's muscular dystrophy as many point mutations cannot be routinely screened in such a large gene.

Acknowledgements

The author would like to acknowledge Anne Connolly for helpful comments about an earlier version of this manuscript; and Alan Pestronk for permission to reproduce photographs from http://www.neuro.wustl.edu/neuromuscular/.

Further reading

Dubovitz V (2000) *Congenital muscular dystrophy: an expanding clinical syndrome.* Ann Neurol 47: 143-144

Taratuto AL (2002) *Congenital myopathies and related disorders.* Curr Opin Neurol 15(5):553-61

Tome FMS, Guicheney P and Fardeau M (1998) *Congenital muscular dystrophies.* In: Neuromuscular Disorders: clinical and molecular genetics. Emery AEH (ed.) John Wiley & Sons Ltd., London

Correspondence Address

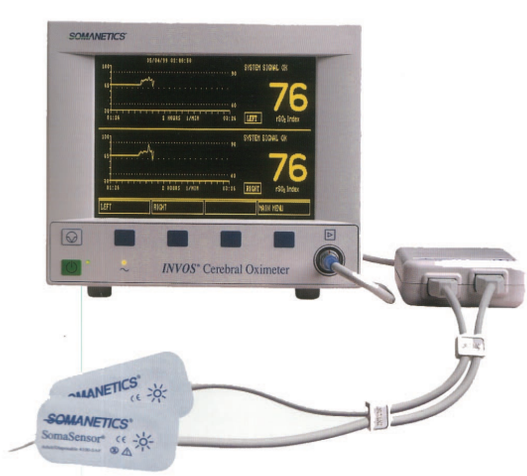
Dr Wojtek Rakowicz, Dept. of Neurology,
National Hospital for Neurology and Neurosurgery,
Queen Square,
London WC1N 3BG.
E.Mail. adalbert@doctors.org.uk

INVOS Cerebral Oximeters

State-of-the-Art Neuro Protection

The INVOS Cerebral Oximeter is the first patient monitoring system to noninvasively and continuously monitor changes in the regional oxygen saturation of the blood in the cerebral cortex of the brain.

Use of the system allows medical professionals to monitor changes in cerebral oxygen saturation and take corrective action. Research indicates that this can prevent or reduce neurological injuries associated with surgery and other critical care situations and, therefore, reduce the cost of care.

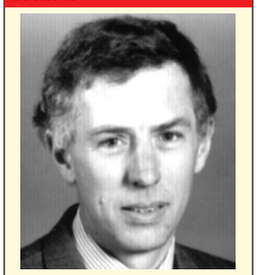


tyco Healthcare

Tyco Healthcare (UK) Ltd
Medical Division, 154 Fareham Road, Gosport, Hampshire PO13 0AS
Tel. 01329 224226, Fax. 01329 224083, E-Mail. marketing@tycohealth.com

Obstructive sleep apnoea and stroke

Author



Neil J Douglas is Professor of Respiratorory & Sleep Medicine at the University of Edinburgh, Director of the Scottish National Sleep Centre and Vice-President of the Royal College of Physicians of Edinburgh. His research interests focus on the causation, consequences and treatment of Sleep Apnoea. He is a member of the Editorial Boards of the American Journal of Respiratory and Critical Care Medicine, Sleep, Sleep Medicine and Sleep Medicine Reviews.

Introduction

The obstructive sleep apnoea/hypopnoea syndrome is one of the most common and important medical conditions to be identified in the last 50 years. Around 2% of middle-age men and 1% of middle-age women[1] have a combination of increased irregular breathing at night with daytime sleepiness, this combination being the hallmark of the obstructive sleep apnoea/hypopnoea syndrome (OSAHS; Table 1). There is now irrefutable evidence from placebo controlled randomised treatment trials that OSAHS results in not only daytime sleepiness but also impaired cognition, mood, quality of life, and driving performance and raised blood pressure[2]. This article will focus on the inter-relationships between sleep apnoea and stroke, examining the evidence that each may cause the other.

OSAHS as a cause of hypertension

Early epidemiological investigation showed an increase in hypertension amongst snorers[3;4] but confounding factors such as obesity, age, gender and alcohol makes interpretation of these observations difficult. The same was true of studies suggesting the association between OSAHS and hypertension[5]. Dog model studies have shown that recurrent apnoeas can produce both night time and sustained daytime hypertension[6]. Studies in rats indicate that intermittent nocturnal hypoxaemia can produce daytime hypertension, even in the absence of upper airway obstruction[7].

More recent epidemiological studies in which strenuous attempts have been made to exclude confounders strongly suggest an association between sleep apnoea and daytime hypertension. Convincing evidence comes from the Wisconsin cohort study in which 1060 members of the working population had their breathing studied during sleep and were then followed-up. At the initial study, those found to have more than 25 apnoeas+hypopnoeas/hr of sleep had a 5 fold risk of being hypertensive[8]. The increase in risk of hypertension was greater in thinner patients who had abnormal breathing during sleep. At follow-up 4 years later, those with more than 15 apnoeas had a 2.9 fold increased chance of developing new hypertension[9] independent of confounders. Other cross sectional studies in normal populations[10;11] or OSAHS patients[12] have also indicated a 1.4-7 fold increased risk of hypertension, once allowance has been made for other risk factors.

A careful case control study found that patients with OSAHS had a significantly higher blood pressure than matched control subjects, but that these increases were only significant during the sleeping period and in the afternoon[13] (see Fig. 1).

More direct evidence that OSAHS causes hypertension comes from two studies showing that CPAP therapy reduces 24 hr blood pressure[14;15]. The decreases are greatest in those with significant nocturnal hypoxaemia, those with more than twenty 4% oxygen desaturations/hr of sleep having drops in mean 24 hr systolic and diastolic blood pressure of 5mmHg[14]. Taken together, these studies convincingly indicate that OSAHS causes elevation of systemic blood pressure, which is most marked during the hours of sleep. Averaged over a 24 hr day, this increase may be relatively small but a 5mm fall in 24 hr diastolic pressure decreases stroke risk by around 40%[16].

Table 1. Clinical features of OSAHS

- Daytime sleepiness
- Impaired concentration
- Unrefreshing nocturnal sleep
- Nocturnal choking
- Nocturia
- Loud snoring

OSAHS as a cause of stroke

As yet, there is no direct evidence of increased stroke rate in patients previously found to have OSAHS, although this has been suggested from uncontrolled studies. Several studies suggest that snoring is associated with an increased risk of stroke[17;18] but these are complicated by potential confounders. Although some of these studies have relied on patients recall of snoring, and thus they may be criticised for possible ascertainment bias, longitudinal studies of population whose snoring history was recorded at baseline have also shown an increased frequency of stroke in snorers[19]. A case control study has shown no increased frequency of irregular breathing during sleep in TIA patients compared to carefully matched controls, but this study could have been under powered[20]. It is thus impossible at present to conclude that upper airway narrowing during sleep is a significant cause of stroke, but the proven association between OSAHS and hypertension makes this highly likely.

"Several studies suggest that snoring is associated with an increased risk of stroke"

Stroke as a cause of sleep apnoea

Numerous recent studies have shown that irregular breathing during sleep is very common after strokes[21-25] (Table 2). This abnormality is commonest in the first few weeks with over half of all patients having increased apnoeas and hypopnoeas during sleep in the first few days after stroke. There is spontaneous resolution of the irregular breathing during sleep over the first 3 months in around 50% of these patients[21;24].

These respiratory events comprise a combination of obstructive apnoeas and hypopnoeas along with central apnoeas and hypopnoeas, some of the latter in the form of Cheyne-Stokes respiration.

These data pose several unresolved questions. Firstly, does the increased irregular breathing after stroke contribute to inattention and sleepiness, which might impair the rehabilitation of the patient? There are several ongoing studies which have attempted to treat stroke victims who have increased irregular breathing with continuous positive airway pressure (CPAP) and examined outcomes thereafter. There is consensus that this is a very difficult group of patients to treat with CPAP but some groups feel that CPAP results in benefit[26] while others found no major benefits[25]. There are several ongoing studies further examining this question and their results should be awaited before all patients with stroke are screened for OSAHS and

Table 2. Relationship of stroke and OSAHS

1. OSAHS causes hypertension and thus probably stroke
2. Stroke causes apnoeas and hypopnoeas
3. Unknown whether treatment of apnoeas and hypopnoeas after stoke helps outcome

Profile
human systems

Profile's extensive range of CPAP devices for the treatment of OSA.

By combining the best sleep technology, humidification and state-of-the-art data collection, the REMstar® family has evolved to make life easier for both the patients and sleep specialists.

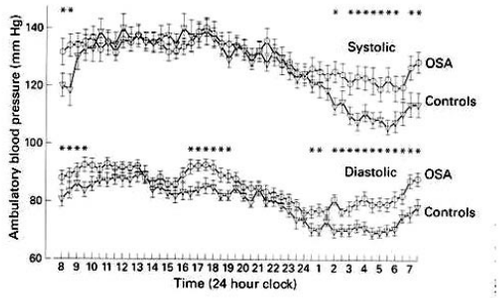
- Ultra quiet
- Integrated humidifier available
- REMstar CPAP family available through MOST® – Management of Sleep Therapy

CPAP*range*

Profile Respiratory Systems Ltd Heath Place, Bognor Regis, West Sussex PO22 9SL
Tel: 0870 770 3434 Fax: 0870 770 3437 www.profilehs.com/prs Email: hospitals@profilehs.com

Profile Respiratory Systems Ltd, a Profile Therapeutics plc Group Company

Figure. 1



CPAP instituted. It may be that the future development of less obtrusive therapy is easier for this often disabled group of patients to use and may make it feasible to treat OSAHS in this patient group. At present, the consensus is they are a very challenging group of patients to convince to use CPAP regularly and the benefits of therapy are unclear. Secondly, do these apnoeas and hypopnoeas and the associated blood pressure surges predispose to further strokes and thus a poorer prognosis? Again, there are no convincing data thus far, with studies underway. Thirdly, are these events purely irrelevant epi-phenomena?

It is important to recognise that there are normal subjects who are not sleepy who have irregular breathing during sleep[1] and that such irregular breathing is more common in elderly populations. There is no evidence that treating asymptomatic individuals with apnoeas and hypopnoeas is of any benefit to them[27], and thus there is no merit in screening all stroke patients for sleep breathing irregularities. However, at present, it would seem reasonable that patients with stroke who are sleepy and who are noted to snore loudly should be screened for OSAHS and treated with CPAP where appropriate and feasible.

Further reading

Douglas NJ. *Clinicians' Guide to Sleep Medicine*. London: Arnold, 2002.
ISBN 0340 742054.
See news item on page 35 for more deails.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. (1993). *The occurrence of sleep-disordered breathing among middle-aged adults*. N. Engl. J. Med. 328: 1230-1235.
2. Douglas NJ. *Clinicians' Guide to Sleep Medicine*. (2002). London: Arnold.
3. Norton PG, Dunn EV. (1985). *Snoring as a risk factor for disease: an epidemiological survey*. Br. Med. J. (Clin. Res. Ed.) 291: 630-632.
4. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkila K. (1985). *Snoring as a risk factor for hypertension and angina pectoris*. Lancet 1: 893-896.
5. Lavie P, Ben Yosef R, Rubin AE. (1984). *Prevalence of sleep apnea syndrome among patients with essential hypertension*. Am. Heart J. 108: 373-376.
6. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. (1997). *Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model*. J. Clin. Invest. 99: 106-109.
7. Fletcher EC, Lesske J, Qian W, Miller CC3, Unger T. (1992). *Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats*. Hypertension 19: 555-561.
8. Hla KM, Young TB, Bidwell T, Palta M, Skatrud JB, Dempsey J. (1994). *Sleep apnea and hypertension. A population-based study*. Ann. Intern. Med. 120: 382-388.
9. Peppard PE, Young T, Palta M, Skatrud J. (2000). *Prospective study of the association between sleep-disordered breathing and hypertension*. N. Engl. J. Med. 342: 1378-1384.
10. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S *et al.* (2000). *Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study*. Sleep Heart Health Study. J.A.M.A. 283: 1829-1836.
11. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A *et al.* (2000). *Association of hypertension and sleep-disordered breathing*. Arch. Intern. Med. 160: 2289-2295.
12. Lavie P, Yoffe N, Berger I, Peled R. (1993). *The relationship between the severity of sleep apnea syndrome and 24-h blood pressure values in patients with obstructive sleep apnea*. Chest 103: 717-721.
13. Davies CW, Crosby JH, Mullins RL, Barbour C, Davies RJ, Stradling JR. (2000). *Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects*. Thorax 55: 736-740.
14. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. (2001). *Randomized Placebo-controlled Trial of Continuous Positive Airway Pressure on Blood Pressure in the Sleep Apnea-Hypopnea Syndrome*. Am. J. Respir. Crit. Care Med. 163: 344-348.
15. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR *et al.* (2002). *Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial*. Lancet 359: 204-210.
16. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA *et al.* (1990). *Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context*. Lancet 335: 827-838.
17. Palomaki H, Partinen M, Juvela S, Kaste M. (1989). *Snoring as a risk factor for sleep-related brain infarction*. Stroke 20: 1311-1315.
18. Spriggs DA, French JM, Murdy JM, Curless RH, Bates D, James OF. (1992). *Snoring increases the risk of stroke and adversely affects prognosis*. Q. J. Med. 83: 555-562.
19. Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikkila K, Sarna S. (1987). *Snoring as a risk factor for ischaemic heart disease and stroke in men*. Br. Med. J. (Clin. Res. Ed.) 294: 16-19.
20. McArdle N, Vennelle M, Coleman EL, Dennis MS, Warlow CP, Douglas NJ. (2001). *Matched control comparison of sleep disordered breathing in TIA*. Am. J. Respir. Crit. Care Med. 163: A36.
21. Bassetti C, Aldrich M. *Night time versus daytime transient ischaemic attack and ischaemic stroke: a prospective study of 110 patients*. 1999. J. Neurol. Neurosurg. Psychiatry 67: 463-467.
22. Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB. 1996. *Investigating the relationship between stroke and obstructive sleep apnea*. Stroke 27: 401-407.
23. Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S. 1996. *Sleep-disordered breathing and poor functional outcome after stroke*. Stroke 27: 252-259.
24. Parra O, Arboix A, Bechich S, Garcia-Eroles L, Montserrat JM, Lopez JA *et al.* 2000. *Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack*. Am. J. Respir. Crit. Care Med. 161: 375-380.
25. Sandberg O, Franklin KA, Bucht G, Eriksson S, Gustafson Y. 2001. *Nasal continuous positive airway pressure in stroke patients with sleep apnoea: a randomized treatment study*. Eur. Respir. J. 18: 630-634.
26. Wessendorf TE, Wang YM, Thilmann AF, Sorgenfrei U, Konietzko N, Teschler H. 2001. *Treatment of obstructive sleep apnoea with nasal continuous positive airway pressure in stroke*. Eur. Respir. J. 18: 623-629.
27. Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM *et al.* 2001. *Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial*. Ann. Intern. Med. 134: 1015-1023.

Correspondence Address

Prof Neil Douglas, Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW, UK
Tel. 0131 536 3252, Fax. 0131 536 3255, E.Mail. n.j.douglas@ed.ac.uk

Would you fall asleep at a time like this?

Someone with excessive daytime sleepiness could.

Obstructive sleep apnoea (OSA) is a serious, chronic disorder that affects around 2 to 4% of middle-aged adults.[1]

Despite the use of CPAP (Continuous Positive Airway Pressure) therapy, many patients still suffer from daytime sleepiness.[2,3]

For them, the excessive daytime sleepiness (EDS) resulting from OSA can have a devastating impact on quality of life, with profound sleepiness, reduced levels of concentration, vigilance and cognitive function, and changes in personality leading to long term effects on employment and social function.[4-6]

However, since the motor accident rate in patients with OSA is 5-10 times the normal rate,[7-9] the consequences can be much more immediate.

Provigil® - effective treatment of EDS associated with OSA.

Provigil® (modafinil), an effective and well tolerated treatment for EDS associated with narcolepsy,[10-13] is now also indicated for the treatment of EDS associated with OSA.

Provigil® can significantly reduce daytime sleepiness, allowing patients to function more normally during the day and thereby improving their quality of life.[10,11,14]

Prescribing information can be found on opposite page

PROVIGIL®
MODAFINIL

Helping to bring normality back to life

For further information on Provigil's treatment of EDS associated with narcolepsy and obstructive sleep apnoea/hypopnoea syndrome, please visit our website at www.cephalon.co.uk

UK ABBREVIATED PRESCRIBING INFORMATION: PROVIGIL® 100 mg/200 mg Tablets
Please refer to UK Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** White to off-white tablets containing modafinil 100 mg or modafinil 200 mg (indicated by '100' or '200' debossed on one side). **Indication:** Excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnoea. **Dosage:** *Adults:* 200 - 400 mg daily either as two divided doses in the morning and at noon or as a single morning dose according to response. *Elderly:* Treatment should start at 100 mg daily, which may be increased subsequently to the maximum adult daily dose in the absence of renal or hepatic impairment. *Severe renal or hepatic impairment:* Reduce dose by half (100 - 200 mg daily). *Children:* See contra-indications. **Contra-indications:** Use in pregnancy and lactation, children, uncontrolled moderate to severe hypertension, arrhythmia, hypersensitivity to modafinil or any excipients used in Provigil. **Warnings and precautions:** Patients with major anxiety should only receive Provigil treatment in a specialist unit. Sexually active women of childbearing potential should be established on a contraceptive programme before taking Provigil. Blood pressure and heart rate should be monitored in hypertensive patients. In patients with obstructive sleep apnoea, the underlying condition (and any associated cardiovascular pathology) should be monitored. Provigil is not recommended in patients with a history of left ventricular hypertrophy nor in patients who have experienced mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia. Studies of modafinil have demonstrated a low potential for dependence, although the possibility of this occurring with long - term use cannot be entirely excluded. **Drug interactions:** Modafinil is known to induce CYP3A4/5 (and to a lesser extent, other) enzymes and so may cause clinically significant effects on other drugs metabolised via the same pathways. The effectiveness of oral contraceptives may be impaired through this mechanism. When these are used for contraception, a product containing at least 50 mcg ethinyloestradiol should be taken. Certain tricyclic antidepressants and selective serotonin reuptake inhibitors are largely metabolised by CYP2D6. In patients deficient in CYP2D6 (approximately 10% of the population) a normally ancillary metabolic pathway involving CYP2C19 becomes more important. As modafinil may inhibit CYP2C19 lower doses of antidepressants may be required in such patients. Care should also be observed with co-administration of other drugs with a narrow therapeutic window, such as anti-convulsant or anticoagulant drugs. **Side effects:** *Very common (>10%)* – headache, nervousness. *Common (>1%)* – insomnia, anxiety, dizziness, somnolence, depression, abnormal thinking, confusion, paraesthesia, hypertonia, nausea, dry mouth, diarrhoea, decreased appetite, dyspepsia, constipation, tachycardia, palpitation, vasodilatation, asthenia, chest pain, abdominal pain and blurred vision. Dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed. (See SmPC for uncommon side effects). **Basic NHS Cost:** Pack of 30 blister packed 100 mg tablets: £60.00. Pack of 30 blister packed 200 mg tablets: £120.00 **Marketing authorisation numbers:** PL 16260/0001 Provigil 100 mg Tablets; PL 16260/0002 Provigil 200 mg Tablets. **Marketing authorisation holder:** Cephalon UK Limited. **Legal category:** POM. **Date of preparation:** November 2002. Provigil 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 Infomation Freefone 0800 783 4869 (ukmedinfo@cephalon.com).

References:
1. Young T *et al. N Engl J Med* 1993; **328**: 1230-1235.
2. Sforza E and Krieger J. *Journal of the Neurological Sciences* 1992; **110**: 21-26.
3. Guilleminault C and Philip P. *Sleep* 1996; **19**(9): S117-S122.
4. Strollo PJ *et al. N Engl J Med* 1996; **334**: 99-104.
5. Bedard M-A *et al. J Clin Exp Neuropsychol* 1993; **15**: 330-341.
6. Kales A *et al. J Chron Dis* 1985; **38**(5): 427-434.
7. George C *et al. Lancet* 1987; **2**: 447.
8. Findley LJ *et al. Am Rev Respir Dis* 1988; **138**: 337-340.
9. Haraldsson PO *et al. J Otorhinolaryngol Relat Spec* 1990; **52**: 57-62.
10. US Modafinil in Narcolepsy Multicenter Study Group. *Neurology* 2000; **54**: 1166-1175.
11. US Modafinil in Narcolepsy Multicenter Study Group. *Ann Neurol* 1998; **43**: 88-97.
12. Broughton RJ *et al. Neurology* 1997; **49**: 444-451.
13. Hirshkowitz M *et al. Sleep* 2001; **24** (Ab Suppl): A239.
14. Provigil in OSAHS Study Group (5545).

Cephalon®

© Cephalon UK Limited, 11/13 Frederick Sanger Road, Surrey Research Park, Guildford, Surrey GU2 7YD. All rights reserved. December 2002.

PRO511/Dec 02

Web Browser

Web Address	Details
PRODUCT INFORMATION	
ambion.com	**Ambion (Europe) Ltd**: The RNA resource from the RNA company. Information, research papers, developments, technologies, protocols, products, and manuals for RNA manipulations.
camb-labs.com	**Cambridge Laboratories**: Information on our range of neurology products and useful backgrounders on various neurological disorders. Links to key neurological organisations and patient associations are provided.
therapy.com/international	**Cyberonics Europe**:Up to date information on Vagus Nerve Stimulation Therapy - the effective and tolerable treatment for refractory epilepsy, includes clinician and patient resources plus contact details of Cyberonics.
PUBLISHERS	
dunitz.co.uk	**Martin Dunitz Ltd:** Part of the Taylor & Francis Group, Martin Dunitz publishes top quality, high level medical books in areas such as cardiology, neurology, psychiatry, oncology and urology.
acnr.co.uk	**ACNR magazine:** Download free PDF's of articles past and present and link to other sites of interest.
CONFERENCES	
epdaconferences.org	**European Parkinson's Disease Association**: 5th European PD Association meeting.
bnpa.fsnet.co.uk	**British Neuropsychiatry Association**:information on the 2003 Annual meeting.
dcn.ed.ac.uk/ectmc	**Edinburgh Clinical Trial Management Course:** information and booking for the meeting.

To list your web site in the Web Browser call Rachael on 0131 477 2335.

New for 2003!

We are delighted to announce the launch of ACNR's web site
www.acnr.co.uk

- Download free PDFs of current/previous issues, as well as individual articles.
- Join our e-mail newsletter list, to receive site update information
- Send us your comments and suggestions

"For those of you who struggle with the concept of paper, you can now go back to your computer!"

Roger Barker, Co-editor

Clinical Anatomy of the Median Nerve

Author

Brian McNamara is Consultant Neurophyisologist at Cork University Hospital. He was SHO and Registrar at Cork University Hospital, and SpR at Addenbrooke's Hospital in Cambridge. His interests include magnetic stimulation, cellular electrophysiology all aspects of clinical neurophysiology.

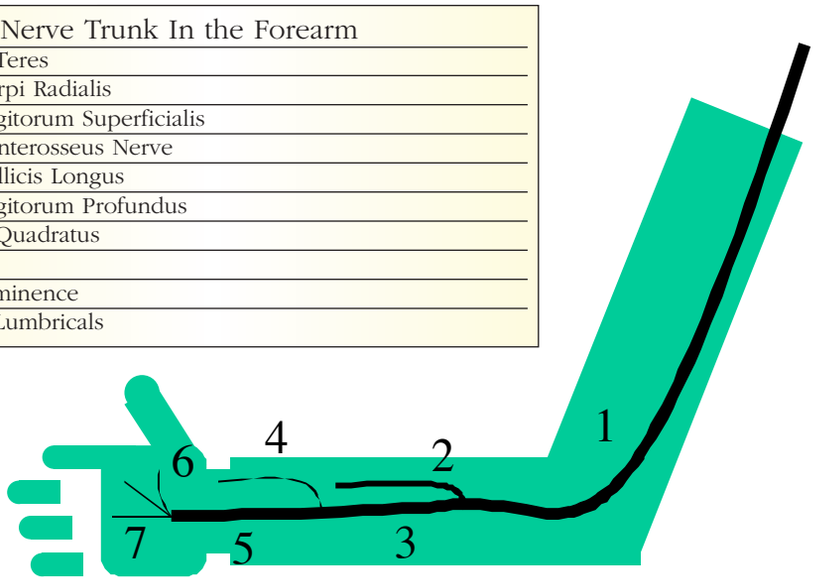
I realise that save for all but the most ardent afficionado an inch by inch discussion of the components of the peripheral nervous system can rapidly induce somnolence. To avoid raking up memories of afternoon snoozes in the back seats of the anatomy lecture theatre I will focus on those nerves that commonly present with entrapment syndromes or as a result of trauma. In any discussion of the clinical anatomy of the peripheral nervous system it is hard to avoid dwelling a great deal on the median nerve. Carpal tunnel syndrome is by far the commonest peripheral entrapment neuropathy, roughly 3% of women and 1% of men will develop carpal tunnel syndrome at some stage. In the catchment area for our neurophysiology service that is roughly 10,000 patients.

Anatomy

The median receives fibres from C6, C7, C8 and T1 roots. It may sometimes contain C5 fibres. It is formed in the axilla by a branch each from the medial and lateral chords of the brachial plexus, which arise on either side of the axillary artery and fuse to form the nerve anterior to the artery. In the arm it is closely related to the brachial artery. (ACNR vol1, issue 2, pp24-25). There is not much action in the arm otherwise as the median nerve has no branches above the cubital fossa. The nerve enters the cubital fossa lateral to the brachialis tendon and passes between the two heads of the pronator teres. In pronator teres it gives off the anterior interosseus branch. The nerve continues in the forearm sandwiched between flexor digitorum profundus and flexor digitorum superficialis. Just above the wrist the nerve emerges to lie between the flexor digitourm superficialis and flexor carpi ulnaris muscles. Here the nerve gives off the palmar cutaneous branch that supplies the skin of the central portion of the palm. Unfortunately the nerve then passes through the carpal tunnel into the hand, lying in the carpal tunnel anterior and lateral to the tendons of flexor digitorum superficialis, in the hand the nerve divides into a muscular branch and palmar digital branches. The muscular branch supplies the thenar eminence, the palmar digital branch supplies sensation to the palmar aspect of the lateral 3 1/2 digits and the lateral two lumbricals. The muscles supplied by the median nerve are summarised in table 1, the course of the nerve is summarised in figure 1.

Table 1

Median Nerve Trunk In the Forearm
Pronator Teres
Flexor Carpi Radialis
Flexor Digitorum Superficialis
Anterior Interosseus Nerve
Flexor Pollicis Longus
Flexor Digitorum Profundus
Pronator Quadratus
Hand
Thenar Eminence
Lateral 2 Lumbricals



Branches of the Median Nerve

1. Branches to Pronator Teres, Palmaris Longus, Flexor Carpi Radialis, Flexor Digitorum, Superficialis
2. Anterior Interosseus
3. Nerve passes between flexor digitorum superficialis and flexor digitorum profundus.
4. Palmar cutaneous branch
5. Nerve in carpal tunnel
6. Branch to thenar eminence
7. Branches to lumbrical and cutaneous branches to 3 1/2 digits.

Entrapment syndromes

There are three well described entrapment syndromes involving the median nerve or its branches, namely carpal tunnel syndrome, pronator teres syndrome and anterior interosseous syndrome.

Carpal Tunnel Syndrome

Carpal tunnel syndrome due to compression of the median nerve in the carpal tunnel syndrome, commonly presents with sensory disturbance and pain in the hand. I have found that one of the most useful diagnostic clues is the presence of sensory symptoms at night time relieved by changing hand posture. It is also worth remembering that carpal tunnel syndrome can sometimes present with symptoms in an ulnar or radial nerve distribution. In my opinion clinical testing with Tinel's sign adds little to a good history. There are as many ways of testing electrophysiogically for carpal tunnel syndrome as there are neurophysiologists, my own preference is to compare median sensory conduction velocity across wrist with ulnar velocity. This should be supported by measurement of motor conduction across the wrist and motor conduction in the forearm segment.

Anterior Interosseus Nerve Palsy

There are a number of causes described for anterior interosseus nerve palsy. These include fractures of the radius midshaft, excessive exercise or penetrating injuries to the forearm although many cases may be idiopathic. Selective involvement of the anterior interosseus nerve may be seen in brachial neuritis. It presents principally as weakness of the index finger and thumb. On clinical examination this is best observed by observing the pinch attitude of the thumb and index finger. Neurophysiological evaluation should include motor and sensory studies of the median nerve to exclude median nerve trunk involvement. Needle EMG should be performed on flexor pollicis longus and compared with a muscle innervated in the forearm by the median nerve trunk, flexor digitorum superficialis is usually the easiest.

Pronator Syndrome

This is due to compression of the median nerve as it passes through pronator teres. Classically it presents with pain on the

volar surface of the forearm following prolonged pronation of the forearm. Often there are no signs and neurophysiological evaluation is normal. It may also be difficult to distinguish from carpal tunnel syndrome. Useful clues however are dyaesthesia in the 'palmar triangle' and replication of symptoms by prolonged pronation. Sometimes nerve conduction studies in severe cases may demonstrate focal slowing of median motor conduction in the forearm segment.

Other Causes of Median Neuropathy

Compression of the median nerve at the elbow can result from a supracondylar ligament (Ligament of Struthers), compression in the forearm can occur in the proximal arch of the flexor digitorum superficialis. Trauma can obviously occur to the nerve anywhere along its course. Types of injury can include penetrating injuries in the axilla and fracture to the shaft of the humerus. Acute compression can occur as a result of bleeding into the forearm or the placement of A/V fistulas in dialysis. Neurophysiologically these are confirmed by demonstrating slowing of conduction across the site of injury or compression and neuropathic features on EMG on those muscles supplied by branches given off below the site of injury or compression.

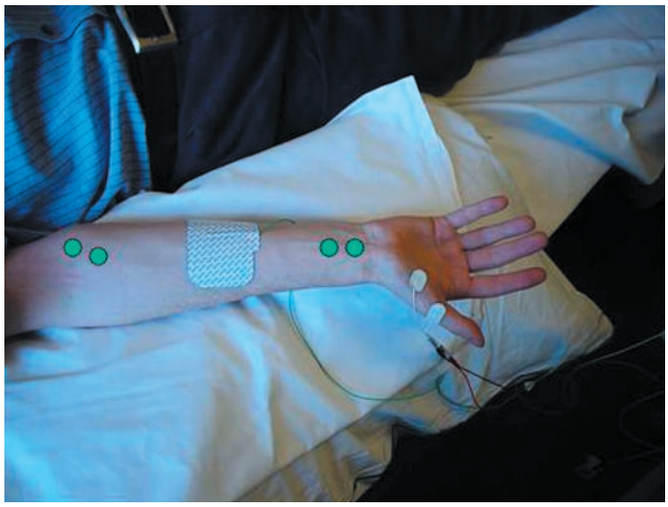


Figure 1: Set up for Median motor study, electrodes are placed over the abductor pollicis brevis (APB), the nerve is stimulated at the wrist and elbow (green markers).

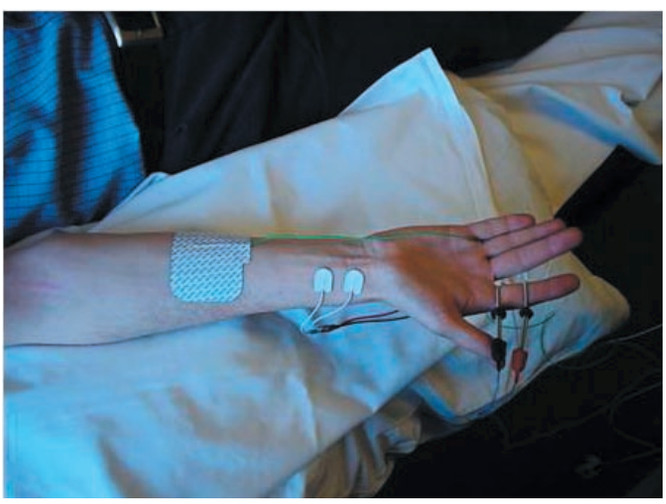


Figure 2: Set up for median sensory study, digital nerves are stimulated with ring electrodes and the response is recorded radial to the palmaris tendon.

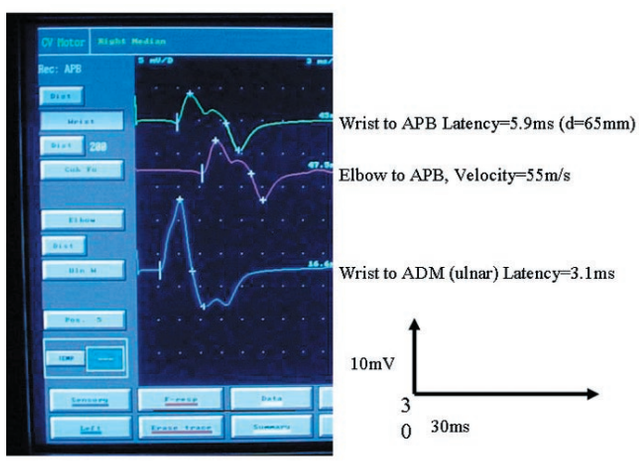


Figure 3: Median motor study in carpal tunnel syndrome, median motor conduction is delayed across the carpal tunnel, note the difference in latency between the distal median motor study and the normal distal ulnar study, median conduction in the forearm is within normal limits.

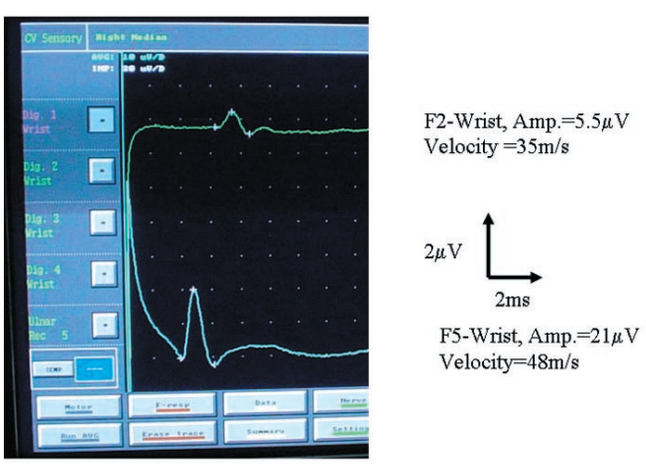


Figure 4: Median sensory study in carpal tunnel syndrome, note the slowing and the reduction in amplitude in the median sensory action potential compared with the normal ulnar sensory action potential.

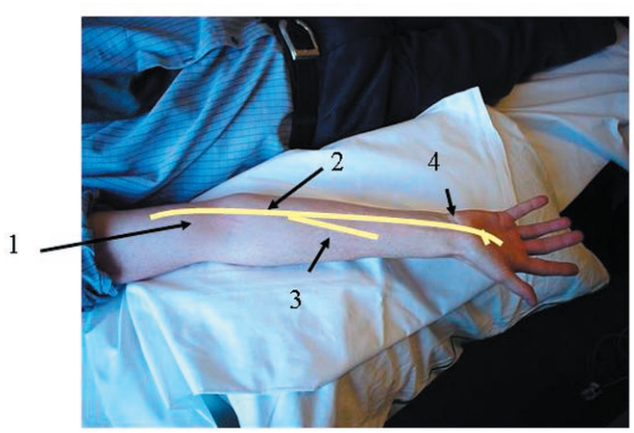


Figure 5: Four sites of median nerve entrapment, 1 Ligament of Struthers, 2 Pronator Teres, 3 Anterior interosseus nerve, 4 Carpal Tunnel.

Surgical treatment of Parkinson's Disease

The surgical treatment of movement disorders is over a century old but went into a steep decline in the 1970's with the introduction of effective drug therapies such as levo-dopa. However, about a decade ago Laitinen reported on the success of pallidotomy for the treatment of advanced Parkinson's disease, which led to a resurgence of interest in functional neurosurgery for movement disorders. This coupled to an increased understanding of the underlying neural mechanisms and circuitry involved in basal ganglia disorders with improved surgical techniques and the development of deep brain stimulation (DBS) technology has paved the way for major advances in the treatment of Parkinson's Disease (PD).

HISTORICAL BACKGROUND

Surgery for PD has passed through several phases during its evolution, of which three major stages can be identified - (1) Non-basal ganglia procedures, (2) Open basal ganglia procedures and (3) Stereotactic basal ganglia procedures.

The recognition that in some cases of stroke, contralateral loss of tremor occurred, prompted Horsley in 1909 to perform excision of the motor cortex in a case of athetosis with good effect. However, at least two decades passed before this work was extended to patients with PD by surgeons such as Bucy (1939). Tremor was reduced with some hemiparesis but the technique was not adopted widely as identification of the motor strip was difficult, rigidity and akinesia remained and post-operative epilepsy was a common problem.

At around this time other procedures which were explored including cervical dorsal rhizotomy, cord section, cerebellar dentatectomy and bilateral cortico-spinal tractotomies but all were later discarded because of their ineffectiveness.

In the 1940s and 1950s Meyers focused attention on the basal ganglia and reported a 60% improvement in rigidity and tremor following the combined section of pallido-fugal fibres, resection of the caudate head and anterior capsulotomy. Subsequently an anecdotal observation by Cooper (1953) led to a new approach. In a case of attempted pedunculotomy for parkinsonism, the procedure had to be abandoned because of bleeding which was controlled by clipping the anterior choroidal artery. The patient not only survived, but had good amelioration of symptoms and no deficit despite infarction of the globus pallidus. Procedures such as these led the way for modern stereotactic neurosurgery.

By the early 1950s a small area of the basal ganglia was defined as the optimal target in surgery for Parkinsonism, comprising the medial pallidum and the ansa lenticularis. The tools capable of reaching these targets without causing damage along the approach were available in concept from the late 19th century and are described by Harting of Utrecht (1861) who designed the "kephalograph" to make directed intracranial lesions in the experimental animal and Zernov (1889) who developed the "encephalometer", successfully used to treat superficial brain lesions.

The breakthrough in the development of human stereotactic surgery came in 1947 when Speigel and Wycis, who by extending the original frame designed by Horsley and Clarke (1908), introduced the stereo-encephalotome, which used landmarks within the brain, rather than the skull. Parkinsonism could now be treated by thermal lesion or injection of alcohol (chemo-pallidectomy) in the thalamus, ansa lenticularis and pallidum. Lesions in the thalamus more reliably abolished tremor, so that by the late 1950s this had become the preferred target, particularly the ventrointermediate (Vim) nucleus.

Interest in stereotactic surgery for Parkinson's disease all but disappeared following the introduction of levodopa in 1968. However, the increasing numbers of PD patients with dyskinesias and motor fluctuations that ensued prompted pursuit of a surgical solution. Interest in Pallidotomy was renewed in the 1980s, and by the mid 1990s its effectiveness had been confirmed by many groups, particularly in the alleviation of levodopa induced dyskinesias. Unpredictable results with the transplantation of foetal dopamine cells and adrenal medullary grafts into the striatum, furthered the cause in favour of lesional surgery but concern remained regarding high complication rates, particularly following bilateral procedures.

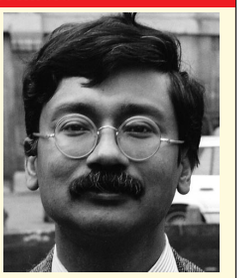
DEEP BRAIN STIMULATION (DBS)

By the 1960s, the use of intraoperative stimulation of brain targets in preparation for ablative surgery had established the concept that high frequency Vim stimulation suppressed tremor. This technique was initially used to identify the optimal site for thalamic lesioning. However by the late 1970s and early 1980s, therapeutic rather than diagnostic uses of DBS for PD were occurring. High frequency electrical DBS is thought to work by providing an adjustable inhibitory effect on the target site. It has the advantages over lesional surgery of being reversible, adaptable and avoids concern about the adverse cognitive and bulbar effects observed following bilateral lesions. Though effective, DBS requires careful postoperative adjustment, averaging 40 hours of adjustment for optimum benefit and maintenance of effect in certain patient groups. The replacement of equipment when hardware failure occurs (wires moving, breaking or becoming infected) is a further consideration with estimates in the region of 20%. The stimulation battery unit also requires replacement every three to five years depending on target and parameter settings. Occasionally this entails emergency admission following dramatic rebound symptoms that have been observed following acute stimulator failure. DBS therefore necessitates considerable long-term commitment from the team looking after the patient. Consequently there remains a place for "palliative" thalamotomy or pallidotomy in certain situations.

Although results following DBS can be impressive, they are dependent on careful patient selection. With the exception of tremor, successful surgical treatment of Parkinsonian symptoms is reliant upon the presence of a dopaminergic responsive system. "Burned out" cases, with no useful "on" periods, will not respond to surgery. Similarly non-dopa responsive parkinsonian diseases, such as multiple system atrophy, will not significantly benefit from surgery. It is crucial that patients with significant cognitive or psychiatric difficulties are avoided.

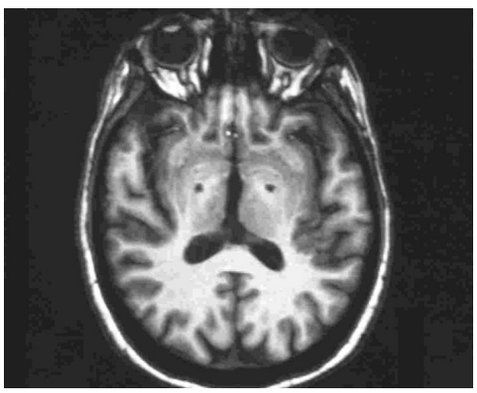
Drug induced hallucinations, postural instability and dysphonia, particularly in the "on" state are further poor prognostic signs. Although the temptation is to offer surgery because little else can be done, it must be considered that surgery carries with it at least a 3% risk of significant morbidity or mortality resulting from intra-cerebral haemorrhage. This makes the trade off between possible risks and potential benefit not sufficiently favourable to recommend surgery in these patients.

Authors

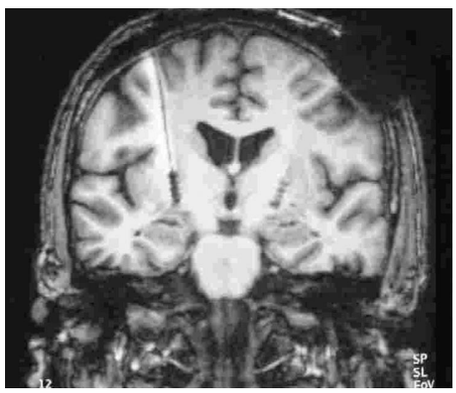


Professor Aziz studied physiology at University College London graduating in 1978. During this time he developed his keen interest in the role of the basal ganglia in movement disorders. He studied medicine at King's College London (1978-1983) and obtained his surgical fellowship in 1987 following which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

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



Lesional Surgery. Post-operative axial MRI scan of patient following bilateral pallidotomy for PD.



DBS. Coronal MRI scan of a patient following implantation of bilateral electrodes into the GPi.

TARGETS FOR DBS IN TREATMENT OF PARKINSON'S DISEASE

Thalamus

Historically, chronic thalamic stimulation had already been used for the treatment of chronic pain. However because the thalamus is the final common outflow pathway for all tremors, contralateral tremor is reliably suppressed with DBS in the region of Vim. The majority of studies that have evaluated thalamic stimulation have reported approximately 90% improvement in tremor of the contralateral limb, whilst avoiding the adverse effects on speech and cognitive function related to thalamotomy. Although tremor is markedly improved in PD, there is sometimes no significant improvement in activities of daily living as there is no effect on bradykinesia and although dyskinesia is occasionally helped, this is not a reliable observation. Even patients with tremor predominant Parkinson's disease will normally develop bradykinesia in time, so it is now recommended that such patients should have STN rather than thalamic stimulation, reserving thalamic surgery for non-Parkinson's disease tremor.

Pallidum

Based on the success of DBS for tremor and of pallidotomy for parkinsonian symptoms, Siegfried and Lippitz (1994) used the technology of DBS for continuous stimulation of the posteroventral globus pallidus internus (GPi). Posteroventral pallidal stimulation will reliably abolish contralateral dyskinesias. This includes biphasic and peak dose dyskinesia, and "off" state dystonias. The improvement in "off" state bradykinesia also occurs, as does contralateral tremor but this is not a reliable effect. Medication remains unaltered following the procedure. Axial symptoms, including dyskinesias, non-dopaminergic gait and bulbar function do not improve, whilst "on" state postural instability and freezing may be worsened. Other potential side effects include visual field defects (optic tract), hemiparesis and dysarthria (internal capsule). Weight gain is also frequently observed, probably resulting from reduction in dyskinesias as well as functional improvements that may aid feeding.

Subthalamus

Bilateral subthalamic stimulation alleviates all the principal symptoms of tremor, rigidity and badykinesia. In 1993 Benebid reported stimulation of the subthalamic nucleus (STN), which improved almost all parkinsonian symptoms allowing substantial reduction of dopaminergic medication. Drug induced dyskinesias are also reduced, although unlike pallidal surgery, this occurs by the resultant reduction of medication postoperatively. On stimulation or lesioning of the pallidum or STN, transient dyskinesias may ensue, which are usually a predictor of successful outcome. Unilateral surgery can be offered to patients with very asymmetric disease, but most require bilateral surgery to avoid problems with variable medication requirements on the two sides. Adverse effects are very frequent during electrical stimulation of the subthalamic area and include dystonic symptoms, paraesthesia and oculomotor effects. There is also concern about the frequency of psychiatric side effects, particularly depression that probably arises as a result of the inhibition of STN limbic areas. As this can occur in the absence of any previous history of mental disorder, patients with a history of significant depression should not be offered STN surgery, since the observed rate of suicide has been high in some series.

SUMMARY

In summary, there is no doubt that there remains a definite role for neurosurgical intervention in the treatment of PD. Particularly with reference to DBS, dramatic benefits with a relatively small risk of adverse effects, are acheivable in experienced hands. Robust comparative trials are however urgently required, not only to validate the effectiveness of DBS but also to help determine the cost effectiveness of this relatively expensive treatment. Confirming the mechanisms by which these systems exert their effect also carries considerable importance as this could potentially provide new insights for the development of future neuroprotective therapies.

Further Reading

Benabid A. *et al. Chronic Stimulation for Parkinson's Disease and Other Movement Disorders.* in: Textbook of Strereotactic and Functional Neurosurgery, Edited by Gildenburg P. and Tasker R. McGraw-Hill 1998, pp 1199-1212

Gabriel EM, Nashold BS Jr. *Evolution of neuroablative surgery for involuntary movement disorders: an historical review.* Neurosurgery 1998; 42: 575-90; discussion 590-1.

Gildenburg P. *The History of Stereotactic and Functional Neurosurgery,* in: Textbook of Strereotactic and Functional Neurosurgery, Edited by Gildenburg P. and Tasker. McGraw-Hill 1998, pp 5-20

Guridi J, Lozano AM. *A brief history of pallidotomy.* Neurosurgery 1997; 41: 1169-80; discussion 1180-3.

Laitinen LV, Bergenheim AT, Hariz MI. *Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease.* J Neurosurg 1992; 76: 53-61.

Limousin P, Krack P, Pollak P *et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease.* N Engl J Med 1998; 339: 1105-11.

Surgical Treatment of Parkinson's Disease and Other Movement Disorders, Edited by Tarsy D, Vitek J, Lozano A. Humana Press 2002.

Correspondence Address

Mr. John Yianni[1] and Prof. Tipu Aziz[1,2]
[1]The Oxford Movement Disorder Group, Department of Neurological Surgery, The Radcliffe Infirmary, Oxford
[2]University Department of Physiology, Oxford University, Oxford
Correspondence to: Prof. T. Aziz, Department of Neurological Surgery, The Radcliffe Infirmary, Oxford OX2 6HE, UK.
E-Mail. tipu.aziz@physiol.ox.ac.uk, Fax:01865 224786

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

Contact details are -
Mr. Clive Woodard, UK Manager - Activa Therapy, Medtronic (UK) Ltd,
Suite One, Sherbourne House, Croxley Business Centre,
Watford, Herts WD1 8YE
Tel: 01923 212213
Email: clive.woodard@medtronic.com

Medtronic
When Life Depends on Medical Technology

Association of British Neurologists Autumn Meeting Jointly with British Neuropsychiatry Association

2-4 October, 2002
At the Royal College of Physicians, London

The juxtaposition of two societies with similar, but sometimes different angles on brain function and mis-function, had by its very nature, clear potential to both excite or disappoint. Either side might fail to appreciate the nuances of the argument from the opposite standpoint, perhaps translated into failure to attend sessions not thought to be directly relevant to their field. Happily, this was far from the case for this meeting, and the end of conference consensus was that this had been an inspiring and friendly meeting, with large amounts of ground shared, and knowledge gained, which would be of great use in tackling the clinical problems common to both.

The meeting was enlivened by two controversial debates: 'that neither neurologists nor psychiatrists are competent to manage conversion disorder' and 'published trials provide sufficient evidence to warrant the use of aspirin for the secondary prevention of ischaemic stroke'. A fine tour of frontal lobology was provided by Professors Robbins, Neary and David.

We were proud to have two senior guests of honour: Lord Owen who described to us, from first hand experience, how serious illness had impacted on Heads of Government, and indeed had on occasion changed history. The next day Lord Walton received the ABN Medal and recalled an imposing career in both neuroscience and politics.

Great thanks must also be paid to Professor McDonald as Harveian Librarian, who delighted us with a fantastic display of neuroscience documents from the College Library over the centuries.

The eight mini-reports below provide some of the flavour of the conference, but full credit must be paid to all those who talked and provided posters for this meeting.

1. **The 12 year prognosis of unilateral functional weakness and sensory disturbance.** Stone, Edinburgh and Oxford: 60 patients who had received a diagnosis of unilateral functional weakness or sensory disturbance between 1985-1992 were reviewed, with a mean duration of follow-up of 12 years. Over 80% still reported weakness or sensory disturbance, with self reported limitation of function common. Only one had developed a neurological disorder to explain the symptoms.

2. **Corticosteroids do not prevent optic nerve atrophy following optic neuritis.** Hickman, London: the central question was whether pulsed high dose steroid reduced optic nerve atrophy in optic neuritis. Analysing optic nerve images from a recent trial of steroid versus placebo, no evidence of a preventive effect was found.

3. **The accuracy of the pulvinar sign on MRI in the diagnosis of vCJD.** Collie, Edinburgh: the MRI scans of the available 92/100 cases of vCJD were reviewed independently by two neuroradiologists. Despite variation in scan protocol, hyperintensity of the posterior thalamus relative to the anterior putamen (the 'pulvinar' sign) was positive in 85% of cases. Using FLAIR imaging the current sensitivity of this sign is 95% - the most acccurate non-invasive diagnositic test for vCJD.

4. **Cognitive and behavioural profile of atypical Parkinsonian syndromes.** Bak, Cambridge: applying a variety of cognitive tests to four extra-pyramidal syndromes, characteristic profiles of impairment were found. Progressive supranuclear palsy (PSP) had the greatest impact on verbal fluency, dementia with lewy bodies (DLB) on orientation, and corticobasal degeneration (CBD) on language; psychiatric symptoms were more frequent in CBD and DLB. Multiple system atrophy emerged relatively unscathed.

Lord Walton of Detchant, who received the ABN medal at the meeting.

5. **Long term outcome in children born to mothers with epilepsy.** Adab, Liverpool and Manchester: approximately 250 children born to mothers with epilepsy were assessed in terms of their verbal IQ. 80 were unexposed to anticonvulsants, the remainder to a variety of drugs. Mean VIQ was significantly lower in the valproate group compared to both non-exposed and other monotherapy groups.

"In patients with epilepsy, déjà vu occurred significantly more often, lasted longer, and was associated with more physical features and dissociation than in controls."

6. **A study of déjà vu in patients with temporal lobe epilepsy, students and neurology outpatients.** Warren-Gash, Edinburgh: in patients with epilepsy, déjà vu occurred significantly more often, lasted longer, and was associated with more physical features and dissociation than in controls. 88% of controls had experienced déjà vu sensations.

7. **Homocysteine and cerebral small vessel disease.** Hassan, London and Leeds: homocysteine is postulated to be toxic to endothelium. In this study, mean levels were higher in lacunar stroke (>2 months after last event) than in matched controls. The risk increased with increasing levels of homocysteine.

8. **Do rates of cerebral atrophy in Alzheimer's disease accelerate?** Janssen, London: patients with early onset Alzheimer's disease were imaged longitudinally to determine the rates of atrophy. There was considerable variation in the inter-patient rate of progression, however the intra-patient rate remained relatively constant with a gradual acceleration over time.

Jeremy Chataway,Consultant Neurologist
St Mary's Hospital, London and
National Hospital for Neurology and Neurosurgery,
Queen Square, London

7th International Congress of Parkinson's Disease and Movement Disorders

10-14 November, 2002
Miami, Florida

The 7th International Congress on Parkinson's disease and Movement Disorders was held in the Fountainebleau Hilton Resort and Towers, Miami Beach, between the 10th and the 14th November. The surroundings were beautiful and the sight of sun, surf and sand were a welcome break for the numerous UK delegates.

The meeting itself was of the highest calibre, with a mixed programme, generally well paced, comprising plenary sessions (11 in total) and poster sessions (seven in total). A minor criticism was that with over 1180 posters on display, the time available for viewing was somewhat restricted, necessitating some homework before each session and a clear focus.

When writing a report from such a large meeting, it is impossible not to "cherry pick", clearly reflecting one's own preferences (and sometimes attendance!). I will not comment upon the posters, since the space available would make this virtually meaningless (interested readers may refer to the Movement Disorders Journal Supplement 5, 2002 for a full list of abstracts anyway). There was, however, the usual eclectic mix of work, ranging from the nature of Ravel's neurodegenerative illness and the effect of golf upon Parkinson's disease, to leading edge genetic and therapeutic studies.

Three reports particularly attracted my attention in the plenary sessions. Vincenzo Bonifati (Italy) described the clinical features of recessive Parkinson's disease (PD). Notably, however, he announced the gene, DJ-1, believed to underpin the PARK 7 phenotype (onset < 40 years of age, slowly progressive, dystonic features and psychiatric manifestations). This gene is located on chromosome 1p36. Its seven exons encode a ubiquitous 189 amino acid protein thought to modulate transcription and to be involved in the oxidative stress response. The elegant studies described put another tantalising piece into the jigsaw of PD pathogenesis and will undoubtedly spawn important work in other parkinsonian genotypes and phenotypes.

Stanley Fahn (USA) described the results of the ELLDOPA study. This multicentre, randomised, placebo-controlled study examined the effects of levodopa in early PD. Three hundred and sixty-one drug-naïve patients were randomised at a time when they did not require anti-parkinsonian treatment to either placebo or one of three doses of levodopa (150mg, 300mg or 600mg per day). Study duration was 40 weeks and the majority of patients were then re-examined after a two-week washout period (the washout period was later extended in some patients). Fifty six per cent of 361 patients underwent b-CIT SPECT at baseline and 95% of these subjects were re-scanned at 40 weeks. Primary end-point was the change in Unified Parkinson's Disease Rating Scale (UPDRS) between baseline and after 40 week washout.

Unsurprisingly, dyskinesias occurred more frequently in the higher dose L-dopa group (16%) and wearing-off was also more common in these patients. After washout, the total and motor UPDRS scores were improved (-1.4 and -1.3, respectively) in the 600mg/day L-dopa group, compared with baseline, while there was also a highly significant improvement in quality of life on this dose. Patients allocated placebo deteriorated by 7.8 and 5.2 points in the total and motor UPDRS scores, respectively. Professor Fahn discussed the possibility that L-dopa might actually be neuroprotective, although there is an obvious clinical price to pay in terms of motor complications. Furthermore, the results of the SPECT study showed a significantly greater loss of striatal tracer uptake in the higher L-dopa group (-1.4% versus -7.2%). These values were comparable to those previously reported in the CALM-PD study, which also used SPECT. It is interesting that greater emphasis was put on the clinical output from the ELLDOPA study, despite the "contrary" SPECT correlate. Eleven per cent of subjects had normal SPECT scans; a new term to describe these patients was coined "SWEDDs" (subjects without evidence of dopaminergic deficits). The more cynical observer might call these patients essential tremor!

Warren Olanow (USA) presented the results from a two-year double-blind controlled trial of foetal nigral transplantation in PD. Thirty-four patients with advanced disease (aged 35-75) were allocated to either bilateral transplantation with one donor per side, four donors per side or bilateral placebo surgical procedures (the inner cranial vault and dura mater were not penetrated). Some jaws dropped in the audience when they heard that the placebo patients, like those in the active treatment groups, also took cyclosporine A for six months. The primary endpoint for the study was the change in motor UPDRS score in a practically defined "off" state. Two deaths, unrelated to the transplant procedure, occurred during the study. A post-mortem in one subject (who had received four doors per side) indicated approximately 100,000 tyrosine hydroxylase-positive surviving cells per striatum. Despite this, and the fact that 18F-dopa PET scans showed a significantly increased tracer uptake in transplanted patient groups, the study was "negative" as clinical (primary and also secondary) endpoints did not show a significant improvement ($p=0.24$ for primary endpoint). There was no benefit in younger versus older patients, but patients with less severe disease (motor UPDRS < 49 at study entry) did show a greater improvement. Furthermore, and consistent with the earlier Freed study, 13 of the 23 patients receiving transplants showed "off" medication dyskinesias (so-called "runaway" dyskinesias). Three of these patients were so disabled by their dyskinesias, they required "additional surgery". Olanow presented the data beautifully, but it is impossible not to feel deflated by another negative transplantation study. No doubt the media will go to town and suggest that this is the last nail in the coffin for this procedure. Certainly a more measured approach, as advocated by workers in this area in the UK, with greater emphasis on underlying neurobiological mechanisms and more exhaustive initial use of animal models, is indicated if this treatment is to be resurrected.

In terms of "all round education and enjoyment" the plenary session on tauopathies took the biscuit for me. Perhaps it was the more clinically-based approach, supplemented by video and case studies that got this off to such a good start. David Neary's talk, concerning the phenotypic and pathological correlates of frontotemporal dementias, was outstanding and of particular help to those clinicians, including myself, who do not (knowingly) see these patients very often. This was followed by Peter Heutink (Netherlands) who gave an accessible state of the art dissection of the molecular genetics of the tauopathies.

Other high spots included a debate between Professor Andrew Lees (UK) and Charles Duyckaerts (France) with the title "Is Parkinson's disease with dementia and dementia with Lewy bodies the same disease?". Professor Lees argued they were and with the use of a well-practised debating style, humour and no little substance, carried the day for me (even though no "official" vote was taken).

David Brooks (UK) gave the Stanley Fahn lecture (yes, it is possible in the USA to still be alive and have a lecture named after you!). There is no auditorium too large to cramp his inimitable style, laced with humorous interjections, in clearly getting across complex imaging paradigms and results. He briefly described the outcome of the REAL-PET study in showing that patients receiving the dopamine agonist ropinirole displayed significantly less progression in their 18F-dopa scans when compared with patients allocated levodopa. His talk also, however, touched upon a wide range of other topics including the application of PET to non-motor complications of PD such as depression (reduced noradrenergic function in limbic areas) and dementia (potential use of the amyloid-binding tracer 11C-PIB).

In conclusion, I found that attendance at this meeting was extremely rewarding from a professional perspective. This seems to have been the view of the majority of UK colleagues who I saw during the five days in Miami. Furthermore, I also managed to keep my sun-tan to a respectable shade!

David J Burn,
Newcastle upon Tyne

XENAZINE™ 25 ABBREVIATED PRESCRIBING INFORMATION: Please refer to Summary of Product Characteristics before prescribing Xenazine™ 25. Each tablet contains 25mg tetrabenazine. **USES**: Movement disorders associated with organic central nervous system conditions, e.g. Huntington's chorea, hemiballismus, and senile chorea. Moderate to severe tardive dyskinesia, which is disabling and/or socially embarrassing, and persistent despite withdrawal, switching or reduction of the dose of antipsychotic medication, or where withdrawal of the medication is not a realistic option. **DOSAGE**: Organic Movement disorders: Dosage and administration are variable and only a guide is given. An initial starting dose of 25mg three times a day is recommended. This can be increased by 25mg a day every three or four days until 200mg a day is being given or the limit of tolerance, as dictated by unwanted effects, is reached, whichever is the lower dose. If there is no improvement at the maximum dose in seven days, it is unlikely that Xenazine™ 25 will be of benefit to the patient. Tardive Dyskinesia: An initial starting dose of 12.5mg a day is recommended, subsequently titrated to response. Again medication should be discontinued if there is no clear benefit or side effects cannot be tolerated. Children & Elderly: No specific dosage recommendations are made for the administration of Xenazine™ 25 to children or the elderly. **CONTRA-INDICATIONS, WARNINGS, ETC.** Contra-indications: Xenazine™ 25 blocks the action of reserpine. Precautions: Xenazine™ 25 may cause drowsiness and could interfere with activities requiring mental alertness. Patients should be advised not to drive or operate machinery until their individual susceptibility is known. For use in tardive dyskinesia the condition should be persistent despite withdrawal, reduction in dose or alteration of antipsychotic medication, or where withdrawal of the medication is not a realistic option. Pregnancy and Lactation: There is inadequate evidence of safety of the drug in human pregnancy and no evidence from animal work. Xenazine™ 25 should be avoided in breast-feeding mothers. Interactions: Levodopa should be administered with caution in the presence of Xenazine™ 25. **Side effects:** Side effects are usually mild with little hypotensive action and few digestive disorders. The main unwanted effect reported to date has been drowsiness, which occurs with higher doses. If depression occurs, it can be controlled by reducing the dose or by giving antidepressant treatments. Xenazine™ 25 should not be given immediately after a course of any of the monoamine oxidase inhibitors as such treatment may lead to a state of restlessness, disorientation and confusion. A parkinsonian-like syndrome has been reported on rare occasions, usually in doses above 200mg per day, but this disappears on reducing the dose. Neuroleptic malignant syndrome (NMS) has been reported rarely. This may occur soon after initiation of therapy, following an increase in dosage or after prolonged treatment. The clinical features usually include hyperthermia and severe extrapyramidal symptoms. Skeletal muscle damage may occur. If NMS is suspected Xenazine™ 25 should be withdrawn and appropriate supportive therapy instituted, treatment with dantrolene and bromocriptine may be effective. **Overdosage**: Signs and symptoms of overdosage may include drowsiness, sweating, hypotension and hypothermia. Treatment is symptomatic. **PHARMACEUTICAL PRECAUTIONS**: Store below 30ºC **LEGAL CATEGORY** POM **PRESENTATION, PACK SIZE, PRODUCT LICENCE NUMBER & BASIC NHS COST:** Round yellowish buff tablets, printed with CL25 containing 25mg of tetrabenazine in packs of 112. PL 14576/0005 £100.00 **FURTHER INFORMATION IS AVAILABLE FROM THE PRODUCT LICENCE HOLDER**: Lifehealth Limited, 23 Winkfield Rd, Windsor, Berkshire, SL4 4BA. Date of preparation: October 2002. © Cambridge Laboratories. **Reference:** 1. Jankovic J, Beach J. Neurology 1997; 48: 358-362.

Many movement disorders. *One* treatment choice.

Only Xenazine 25 is proven and licensed for use in all these hyperkinetic movement disorders

Restoring movement through choice, restoring confidence

Long term therapy with Xenazine 25 demonstrates sustained benefits and is generally well tolerated[1]

Xenazine™ 25
tetrabenazine
movement through choice

Cambridge Laboratories Ltd., Deltic House, Kingfisher Way, Silverlink Business Park, Wallsend, Tyne and Wear NE28 9NX. Tel: 0191 296 9369 Fax: 0191 296 9368 www.camb-labs.com

Cambridge LABORATORIES
Building Partnerships in Healthcare

CL/TET024

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 February 7th, 2003.

2003

January

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

Neuroendoscopy
21-22 January, 2003; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335,
Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

British Association of Stroke Physicians Annual Conference
22 January, 2003; Keele, UK
www.basp.ac.uk/baspconference2003.htm

Neuromuscular Conference & EMG Workshop
25-26 January, 2003; London, Canada
E. betsy.thoth@lhsc.on.ca

ABN Joint Meeting with the Neurology Association of South Africa
29 January-1 February, 2003;
E. selliott@curie.uct.ac.za

Chicago Review Course ini Neurological Surgery
31 Jan-9 February, 2003; Chicago, US
Tel. 001 773 296 6666,
Fax. 001 773 296 9999,
E. Dkeegan@chicagoreviewcourse.com

February

Improving Stroke Rehabilitation
3 February, 2003; London, UK
Tel. 020 7017 5668,
E. rhiannon.clayton@informa.com,
www.healthcare-info.co.uk/LH1195

Quantitative Neurosciences: Models, Algorithms, Diagnostics, and Therapeutic Applications
5-7 February, 2003; Florida, US
E. Dr Panos Pardalos, pardalos@ufl.edu or Dr J Chris Sackellares, sackellares@epilepsy.health.ufl.edu

Gordon Holmes Prize for Trainees in Neurology, Neurosurgery, Neurophysiology, Neuropathology or Neuroradiology
6 February, 2003; London, UK
RSM, Tel. 020 7290 2984,
E. cns@rsm.ac.uk

Neurological Anatomy
10-12 February, 2003; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Stepping Out After Brain Injury
12 February, 2003; London, UK
Gwen Cutmore, Tel/Fax. 01621 843334,
E. gwen.cutmore@lineone.net

28th International Stroke Conference
13-15 February, 2003; Phoenix, US
Tel. LaRita Edwards, 001 214 706 1100,
Fax. 001 214 706 5262,
E. strokeconference@ heart.org

Neuroradiology
13 February, 2003; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Approaches for Intracranial Surgery
14 February, London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Recovering From Head Injury, Medico-legal Aspects of Neuropsychiatry
13-14 February, 2003; London, UK
Gwen Cutmore, Tel/Fax. 01621 843334,
E. gwen.cutmore@lineone.net

Atypical Parkinsonian Disorders; From Protein Dysfunction to Therapeutic Intervention
19-21 February, 2003; Innsbruck, Austria
http://apd2003.neuro-uibk.info/

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

2nd International Meeting on Steroids and Nervous System
22-26 February, 2003; Torino, Italy
Fax. 0039 0 116 707 732,
E. giancarlo.panzica@unito.it

Relevance of Cell Death in Development of Disease of the Brain
24-25 February, 2003; Berlin, Germany
Sonia Waiczies, Tel. 0049 30 450 539 051,
Fax. 0049 30 450 539 906,
E. sonia.waiczies@charite.de

Annual Conference on Acute Medical Emergencies
24-25 February, 2003; London, UK
Jayne Wesley-Smith, Tel. 0207 7200 600,
Fax. 0207 7207 177,
E. ame@confcomm.co.uk

Dementia 2003
24-25 February, 2003; London, UK
Gemma Dines, Tel. 0208 678 5322

Edinburgh Clinical Trial Management Course (ECTMC) 2003
26-28 February, 2003; Edinburgh, UK
Anne Williamson, Tel. 0131 537 2913,
Fax. 0131 332 5150,
E. ectmc@skull.dcn.ed.ac.uk

1st International Conference on Cytokine Medicine
27-28 February, 2003; Manchester, UK
Jacinta Scannell,
Tel. 020 897 70011,
E. cyto@hamptonmedical.com

March

Back Pain
6 March, 2003; London, UK
RSM, Tel. 020 7290 2984,
E. cns@rsm.ac.uk

Faculty of Old Age Psychiatry Residential Meeting
6-7 March, 2003; London, UK
Tel. 0207 2352 351 x 142,
Fax. 0207 2596 507, E.
pcornell@rcpsych.ac.uk

Goal Planning in Acute and Community Settings
7 March, 2003; Ely, UK
Alison Gamble, Tel. 01353 652173,
Fax. 01353 652164, E-Mail.
alison.gamble@pow.lifespan-tr.anglox.nhs.uk

Preventive Pharmacotherapy of Headache Disorders
7-9 March, 2003; Copenhagen, Denmark
Hanne Aggergaard, Tel. +45 43 233 291,
Fax. 45 43 233 926,
E. hagn@glostruphosp.kbhant.dk

Heart & Brain, 6th International Stroke Conference and 3rd Conference of the Mediterranean Stroke Society
12-15 March, 2003; Monte Carlo, Monaco
Tel. +972 3 5140018/9, Fax. +972 3 5172484, E. Stroke6@kenes.com

Innovative Therapies in Autoimmune Disease Conference
13-16 March, 2003; Washington, US
Tel. 001 404 633 3777,
E. acr@rheumatology.org

Transcranial Magnetic Stimulation in Movement Disorders
Santa Margherita Ligure, Genova
14-15 March, 2003
Tel. +39 010 583 224, Fax. +39 010 553 1,
E. aristea@aristea.com

3rd Advanced Prosthetic and Amputee Rehabilitation Course
17-19 March, 2003; London, UK
Mrs Sandy Weatherhead, BSRM, Tel. 01992 638865, E-Mail. admin@bsrm.co.uk

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

American Academy of Neurology 55th Annual Meeting
29 March-5 April, 2003; Honolulu, Hawaii
Tel. 001 651 695 1940,
Fax. 001 651 695 2791

April

British Society for Rheumatology 20th AGM
1 April, 2003; Manchester, UK
Tel. Caroline Pembroke, 0207 242 3313,
Fax. 0207 242 3277,
E. caroline@rheumatology.org.uk

IPA European Regional Meeting
1-4 April, 2003; Geneva, Switzerland
E. ipa@ipa-online.org

36th Annual Scientific Meeting of The Pain Society
1-4 April, 2003; Glasgow, UK
Tel. 0207 6318 870, Fax. 0207 323 2015,
E. meetings@painsociety.org

See the Bigger Picture - Learning Difficulties, ADHD, DAMP, Dyslexia
2-3 April, 2003; Edinburgh, Scotland
Tel. 0046 31 818 200, Fax. 0046 31 818 226, E. congrex@gbg.congrex.se

ABN Spring Scientific Meeting
2-4 April, 2003; Cardiff, UK
E. abn@abnoffice.demon.co.uk

Annual Meeting of the American Academy of Neurology
5-12 April, 2003; Nashville, US
Tel. +1 651 695 1940

Cannabis
7 April, 2003; London, UK
RSM, Tel. 020 7290 2984, E. cns@rsm.ac.uk

Neurology for Neuroscientists IX
7-8 April, 2003; Oxford, UK
Prof. J B Clark, E. nneurosc@ion.ucl.ac.uk,
www.ionlucl.ac.uk/neurochemistry/N4N/programme.html

British Geriatric Society Spring Meeting
10-12 April, 2003; Aberdeen, UK
BHM Ltd. Tel. 01825 768 902, Fax. 01825 768 902, E. contact@bhm.co.uk

2nd Emirates Neuroscience Conference
12-17 April, 2003; Dubai, United Arab Emirates
Dr Javaid Iqbal, Tel. 0097 142 666 416/0097 142 711 221, Fax. 0097 142 711 221,
E. jiqbal49@emirates.net.ae

17th National Meeting of the British Neuroscience Association
13-16 April, 2003; Harrogate, UK
Tel. 0151 794 5449,
E. harrogate2003@bna.org.uk

Approaches to the Lumbar & Thoracic Spine
14-16 April, 2003
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

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

Annual Meeting of the American Association of Neurological Surgeons
26 April-1 May, 2003; San Diego, US
www.neurosurgery.org

May

Pain
1 May, 2003; London, UK
RSM, Tel. 020 7290 2984, E. cns@rsm.ac.uk

6th International Conference AD/PD
8-12 May, 2003; Seville, Spain
Kenes International, 17 Rue du cendrier, PO ox 1726, CH-1211 Geneva, Switzerland.
Tel. +41 22 908 -488, Fax. +41 22 7322850, E. adpd@kenes.com

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

The Society of Neurological Surgeons 2003 Annual Meeting
18-20 May, 2003; Cincinnati, US
David G Peipgras, Tel. 001 507 284 2254,
Fax. 001 507 284 5206,
piepgras.david@mayo.edu

2nd World Congress of Physical & Rehabilitation Medicine - ISPRM
18-22 May, 2003; Prague, Czech Republic
Congress Secretariat
Tel. +972 3 9727500, Fax. +972 3 9727555, E. physical@kenes.com

Basic Neurophysiology
19 May, 2003; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Clinical Neurophysiology
20 May, 2003; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Neuropathology
21-22 May, 2003; London, UK
Neurosurgery Courses Assistant, RCSE,
Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

8th Euroacademia Multidisciplinaria Neurotraumatologica
21-24 May, 2003; Graz, Austria
E. hans.tritthart@klinikum-graz.at

Neurology for Neurosurgeons
22-23 May, 2003; London, UK
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

5th World Congress on Brain Injury
23-26 May 2003; Stockholm, Sweden
E. info@internationalbrain.org. or
Tel. 001 703 683 8400 ext 101

The Spectrum of Multiple Sclerosis Care
28 May - 1 June, 2003; San Diego, US
Tel. 001 201 837 0727 x 120,
E. info@mscare.org

Brain Awareness Week: 10-16 March 2003
International public programme of brain related events
Contact Lisa Cokayne-Naylor on Tel: 020 7937 8771,
Email: edab@which.net or see www.edab.net

BRAIN AWARENESS WEEK
JUST USE IT
THE EUROPEAN DANA ALLIANCE FOR THE BRAIN

ATYPICAL PARKINSONIAN DISORDERS

From protein dysfunction to therapeutic intervention

International Meeting

Invited Faculty

- D Caparros-Lefebvre, FRENCH WEST INDIES
- G Dechant, Innsbruck, AUSTRIA
- D Dickson, Jacksonville, USA
- M Goedert, Cambridge, UK
- J Hardy, Jacksonville, USA
- M Hutton, Jacksonville, USA
- S Kuzuhara, Mie-ken, JAPAN
- AE Lang, Toronto, CANADA
- A Lees, London, UK
- N Leigh, London, UK
- I Litvan, Bethesda, USA
- E Mandelkow, Hamburg, GERMANY
- I McKeith, Newcastle, UK
- W Poewe, Innsbruck, AUSTRIA
- N Quinn, London, UK
- M Reindl, Innsbruck, AUSTRIA
- M Spillantini, Cambridge, UK
- J Steele, GUAM
- N Stefanova, Innsbruck, AUSTRIA
- F Tison, Bordeaux, FRANCE
- E Tolosa, Barcelona, SPAIN
- J Trojanowski, Philadelphia, USA

sponsored by

The Movement Disorder Society

February 19-21, 2003, Innsbruck, Austria

Congress Organiser

Prof. Gregor Wenning, MD PhD
Department of Neurology, University of Innsbruck,
Anichstrasse 35, 6020 Innsbruck / Austria
Tel.: ++43/512/504-3920, Fax: ++43/512/504-3852
Email: gregor.wenning@uibk.ac.at

Meeting Homepage:
http://apd2003.neuro-uibk.info

EDINBURGH CLINICAL TRIAL MANAGEMENT COURSE (ECTMC) 2003

26th February - 28th February 2003

This 3-day course focuses on managing randomised controlled trials (RCTs), but also covers some aspects of trial design. It is designed for people who are: a) working as a trial manager or coordinator; b) have taken part in controlled trials and wish to run their own trial (or broaden their knowledge) c) who have no trials experience, but intend to play a part in running RCTs in the future. The knowledge gained is often relevant to people working on other types of research design (cohort studies, surveys, etc). The course is recognised by the UK Medical Research Council, and is a mixture of lectures and small group workshops. Its practical approach takes participants through all stages of undertaking a well-run trial. Topics will include:

- Rationale for doing RCTs
- Starting up a trial
- Regulatory requirements
- Involving consumers
- Designing trial materials
- Methods of randomisation
- Maximising recruitment
- Managing data effectively
- Managing a realistic budget

Fees: The course fee is £450 per delegate, which includes lunches, refreshments, an evening reception and the course dinner.
For further details, including the draft programme, see www.dcn.ed.ac.uk/ectmc.
You can register provisionally at this site; confirmation of your place will be issued when your payment is received. Places are limited, so please book early to avoid disappointment.

For other enquiries about the course, please contact Anne Williamson, The Edinburgh Clinical Trial Management Course,.Dept. Clinical Neurosciences, Western General Hospital Crewe Road, Edinburgh EH4 2XU.Tel: 0131 537 2913, Fax: 0131 332 5150, Email: ectmc@skull.dcn.ed.ac.uk

The British Neuropsychiatry Association 2003 Annual Meeting

13-14 February, 2003, Institute of Child Health, London

Topics to be covered include:

- Recovering from Head Injury
- Medico-Legal Aspects of Neuropsychiatry
- The Neuropsychiatry of Love

The meeting includes keynote addresses from prominent international/UK speakers, and a session for members' contributions.

In addition: On 12 February BNPA is holding a Conference on "Stepping out after Brain Injury"; this will be linked to the BNPA conference session on "Recovering from Head Injury"

For further information contact:
Gwen Cutmore, BNPA Conference Secretary, Landbreach Boatyard, Chelmer Terrace, Maldon, Essex. CM9 5HT, Tel/Fax: 01621 843334; email: gwen.cutmore@lineone.net, website: www.bnpa.fsnet.co.uk.

For details of membership to the BNPA, open to medical practitioners in psychiatry, neurology and related clinical neurosciences, contact:
The Secretary, Professor A S David, Department of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF.

FREE EFNS ABSTRACTS CD

Special offer for ACNR readers - free CD of EFNS abstracts courtesy of Janssen-Cilag

Did you miss the EFNS? To receive a free CD of abstracts, simply complete your details below and post to ACNR , 7 Alderbank Terrace, Edinburgh EH11 1SX, fax to 0131 313 1110, or e-mail your details to AdvancesinCNR@aol.com, putting 'EFNS Abstracts CD' in the subject line:

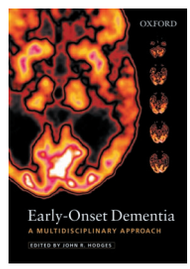
Name .....

Mailing Address: .....

..... Post Code .....

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o AdvancesinCNR@aol.com

Early-onset dementia: A multidisciplinary approach



Edited by: John R. Hodges
Publisher: Oxford University Press 2001
Pages: 478 pp
ISBN: 0-19-263034-2
Price: £75

Reading some textbooks of dementia one might easily gain the impression that neurologists have no part to play in the assessment, diagnosis, and management of patients with this condition, it falling entirely within the remit of old age psychiatrists and geriatricians. However, as has been recognised since Alzheimer's original case, many patients with dementia are in the presenile age group (however "presenile" might be defined), and hence fit awkwardly into such a schema. Furthermore, it is well recognised that services for younger demented patients are less well developed than for the elderly. Hence there is a clear need for a book looking specifically at early-onset dementia.

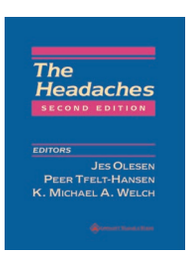
Chapters in this book follow a traditional pathway, covering clinical, neuropsychological and neuropsychiatric assessment of cognitively impaired individuals, followed by structural and functional imaging studies, then pathology at the molecular, biochemical and histological levels. Diagnoses meriting their own chapters include: Alzheimer's disease, with a particular emphasis on familial cases and the consequences of deterministic mutations in the genes encoding amyloid precursor protein and the presenilins; frontotemporal dementia; dementia with Lewy bodies; vascular dementia; Huntington's disease; prion diseases; and inflammatory and infective causes of dementia. The prion disease chapter includes a number of interesting case vignettes, including one (case 7) suggesting that the typical phenotype of variant Creutzfeldt-Jakob disease had been encountered prior to the UK epidemic. Drug treatment for both the cognitive and behavioural/psychiatric symptoms of dementia is covered.

Most of these aforementioned chapters would sit very easily in any textbook of dementia, without the "early-onset" qualification. Three chapters stand out as particularly germane to the theme of the book. Chapter 1 deals with the epidemiology of early-onset dementia, critical for planning service provision (regrettably this chapter is inexplicably shorn of at least half its references). Chapter 20 covers practical issues, such as driving and legal matters, which are similar in all age groups, and also financial and benefit arrangements which differ for those still in employment as compared with the retired. But perhaps of greatest relevance to the neurologist is chapter 18 which addresses causes of dementia in young adults with a particular emphasis on the wide variety of inherited metabolic disorders (Doran M, Br J Hosp Med 1997; 58: 105-10), many very unusual, but which are proportionally more frequent in this age group and necessitate specialist diagnostic skills, presumably best provided by a neurologist.

This book contains a wealth of useful information, much of it presented in easily accessible format. Such is the breadth of coverage that it may be recommended to anyone involved in the diagnosis and management of patients with dementia, not only those with early-onset.

M Doran, AJ Larner; Cognitive Function Clinic, WCNN, Liverpool

The Headaches, 2nd Edition



Edited by: Jes Olesen MD, PhD, Peer Tfelt-Hansen MD and K. Michael A. Welch, MD
Publisher: Lippincott Williams and Wilkins, 2000
Pages: 254
ISBN No: 0-7817-1597-0
Price: £140

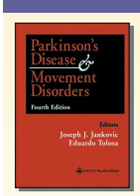
This edition of The Headaches, like the first, is a comprehensive review of the subject. Everything from the history of headache to ethical issues in headache research is covered in depth. The aim of this book is to be "an encyclopedia of headaches", and it is just that. In the preface to this edition, the editors state the hope that "the present volume will contribute to further manifest headache as a core discipline of neurology and that it will be a stimulus to develop better service for headache patients." The target audience for this book, although not clearly stated in the preface, would seem to be anyone who sees headache patients on a frequent basis.

The book is divided into six large topic areas including: 1) General aspects of the headaches, 2) basic science aspects of the headaches, 3) the migraines, 4) tension-type headache, cluster headache and miscellaneous primary headaches, 5) the secondary headaches, and 6) special problems in the headaches and their management. There are 132 chapters written by approximately 130 authors from around the world. Extensive references accompany each chapter. Many individual chapters have been authored by experts from different countries, helping to assure a balanced and international treatment of the topic. There are contributors from North America, Europe, Asia, and Australia. The book adheres to the International Headache Society classification and diagnostic criteria for headaches, thus giving continuity from chapter to chapter.

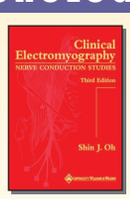
As the authors point out in the preface, this text has established itself as the primary source of reference in the headache field. This book would be worth buying by any person who takes care of headache patients on a regular basis. It should be on the shelf of every serious headache clinician and researcher.

Christopher J. Boes MD, Mayo Clinic Department of Neurology, US

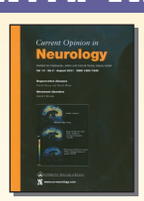
SAVE ON NEUROLOGY BOOK PRICES WITH LWW & ACNR



Parkinson's Disease and Movement Disorders, Fourth Edition
Joseph J. Jankovic, MD & Eduardo Tolosa, MD.
This multi-authored textbook gives detailed information about the basic science and clinical factors affecting diagnosis and management of Parkinson's and other movement disorders. Now in it's Fourth Edition, the book continues to provide an internationally renowned array of expert contributors along with reliable and clinically essential perspectives.
FEATURES: - Addresses common and rare movement disorders
- Includes basic science and clinical information.
ISBN • 0-7817-3515-7 • October 2002 • Hardback
Normal Retail Price: £81.00
ACNR Price: £71.00



Clinical Electromyography Nerve Conduction Studies, Third Edition
Shin J. Oh MD.
Established as a staple reference in the EMG laboratory, this book (now in its revised and updated Third Edition) gives encyclopaedic coverage of current nerve conduction techniques and their clinical uses.
Written by a world-renowned authority, the book includes a new chapter on special nerve conduction techniques, coverage of recent developments (such as electromyographic diagnosis of immunologically mediated neuropathies) and over 500 illustrations.
ISBN • 0-7817-3681-1 • November 2002 • Paperback
Normal Retail Price: £100.00
ACNR Price: £90.00



Current Opinion in Neurology
www.co-neurology.com
Editor: Richard SJ Frackowiak
Deputy Editor: Anne B Young
Current Opinion distills the massive amount of primary literature into reliable, concise and thoughtful analyses written by respected opinion leaders. The entire discipline is covered within structured sections so that you receive a full update on all aspects of neurology every year.
Visit **www.co-neurology.com** for further information and to check out a sample issue.
- ISSN – 1350-7540
- individual subscription $280 (6 issues per year) includes online access.

To order any of the above publications or any other Lippincott Williams & Wilkins publications email ACNR Bookservice at ACNRbooks@aol.com or fax 0131 313 1110

EDITOR'S CHOICE

Vaccination for Alzheimer's disease

The death of neurones in Alzheimer's disease is probably caused -at least in part- by aggregates of a peptide called amyloid β peptide that form the characteristic "amyloid plaques". Perhaps the strongest evidence for this comes from work in experimental animals made transgenic for those mutations in the amyloid precursor protein that lead to the rare familial forms of Alzheimer's disease. In 1999 and 2000, it was reported that vaccination of such animals with aggregated amyloid β protein not only reduced the number of amyloid plaques, but also improved the animals' cognitive deficits.

It seemed to good to be true….. and in some ways it was. With great excitement the first patients were vaccinated with amyloid β peptide aggregates; only for disappointment to descend when the phase II trial was stopped early because of several cases of aseptic meningo-encephalitis. Now two papers in the latest issue of Nature Medicine restore some hope for the strategy.

Roger Nitsch's group in Zurich studied 24 patients who had taken part in the trial, one of whom had developed the meningo-encephalitis. They showed that sera from these patients after vaccination bound selectively to amyloid plaques and diffuse β-amyloid, both in brains from transgenic animals and Alzheimer's disease postmortem brains. Three out of six patients tested also had antibodies in the CSF that bound to amyloid plaques. Importantly, neither the CSF nor sera bound to the normal full-length amyloid precursor protein or the soluble form of β-amyloid, $A\beta_{42}$. So it seems that the vaccinations induced the response that was asked of them. The critical issue is, of course, whether this impacts on the course of their dementia; we will have to wait for the answer to that. There was no difference in the staining of the sera from the one meningo-encephalitis patient, so we are none the wiser as to the mechanism of this serious adverse effect.

More encouragement still comes from a report from St George-Hyslop's group in Toronto, Canada. They have characterised the specificity and function of the antibodies induced by vaccination of transgenic animals using amyloid β peptide aggregates. They showed that the antibody response invoked was largely against the 4-10 amino acids of $A\beta_{42}$. The immune sera inhibited Aβ cytotoxicity in a tissue culture assay and prevented the formation of Aβ fibrils. Even more exciting though, the sera disassembled aggregates that had already formed. The implication, if this could be paralleled in man, is that vaccination might actually lead to the resorbtion of amyloid plaques. Whether as a result there would be any recovery of cognitive function is obviously another matter. Nonetheless these studies will bring therapeutic vaccination back into the frame for the treatment of Alzheimer's disease. ***-AJC***

Generation of antibodies specific for beta-amyloid by vaccination of patients with Alzheimer disease.
Hock C, Konietzko U, Papassotiropoulos A, Wollmer A, Streffer J, Von Rotz RC, Davey G, Moritz E, Nitsch RM.
NATURE MEDICINE
2002 Nov;8(11):1270-5.

Therapeutically effective antibodies against amyloid-beta peptide target amyloid-beta residues 4-10 and inhibit cytotoxicity and fibrillogenesis.
McLaurin J, Cecal R, Kierstead ME, Tian X, Phinney AL, Manea M, French JE, Lambermon MH, Darabie AA, Brown ME, Janus C, Chishti MA, Horne P, Westaway D,Fraser PE, Mount HT, Przybylski M, St George-Hyslop P.
NATURE MEDICINE
2002 Nov;8(11):1263-9.

Panel of Reviewers

Roger Barker, Honorary Consultant in Neurology, Cambridge Centre of Brain Repair
Patrick F Chinnery, Senior Lecturer in Neurogenetics and Honorary Consultant Neurologist, University of Newcastle upon Tyne and Newcastle Hospitals NHS Trust
Alasdair Coles, Wellcome Advanced Fellow, Dunn School of Pathology, Oxford and Dept of Neurology, Cambridge
Amanda Cox, Research Registrar, Addenbrooke's Hospital, Cambridge
Tom Foltynie, Neurology Research Registrar, Cambridge
Richard Hardie, Consultant Neurologist and Director of Neurorehabilitation, Headley Court Medical Rehab Unit
Tim Harrower, Wellcome Clinical Research Fellow and Honorary Neurology Clinical Fellow, Addenbrooke's Hospital
Lucy Anne Jones, Research Associate (Cognitive Neuroscience)
Andrew Larner, Consultant Neurologist, Walton Centre for Neurology & Neurosurgery, Liverpool
Simon J G Lewis, Honorary Clinical Research Fellow, Cambridge Centre for Brain Repair
Mark Manford, Consultant Neurologist, Addenbrooke's Hospital, Cambridge, and Bedford Hospital
Peter Martin, Consultant Neurologist, Addenbrooke's Hospital, Cambridge
Brian McNamara, SpR in Clinical Neurophysiology, Addenbrooke's Hospital, Cambridge
Wojtek Rakowicz, SpR Neurology, National Hospital for Neurology and Neurosurgery, London
Julian Ray, Neurophysiology SpR, Addenbrooke's Hospital, Cambridge
Robert Redfern, Consultant Neurosurgeon, Morriston Hospital, Swansea.
John Thorpe, Addenbrooke's Hospital, Cambridge, and Peterborough
Ailie Turton, Research Fellow, Burden Neurological Institute, Bristol
Andrew Worthington, Brain Injury Rehabilitation Trust, Birmingham
For more information on joining our panel of reviewers, E-Mail AdvancesinCNR@aol.com or Tel. Rachael Hansford on 0131 477 2335.

★★★ RECOMMENDED

A neural network model for object-based visual neglect

Brain damage to the right parietal cortex can lead to people displaying "neglect" for objects presented in half the visual space, in this case on the *left*. Such "hemineglect" is prominent when there is competition between two objects in space. The object in the right visual field is typically "seen", while the object in the left visual field is typically neglected. Deco's attention-based computational model (2001) represents these effects. The current paper builds upon this account to investigate another neglect occurring in some patients with right parietal damage. This "object-based visual neglect" occurs when the *left side of each* object in a horizontal array within the visual field is neglected. The right side of each object is often detected even when some objects appear to the left of others. For example if two flowers are presented side by side some distance apart, only the right-sided petals on each flower would be "seen".

Mean field equations are used to specify the model. Three dynamic neural modules are involved. These include V1 (primary visual cortex), inferior temporal cortex (object) and posterior parietal cortex (spatial) components. Deco's original model was modified to include lateral inhibition between neurons in V1 and the posterior parietal cortex (PP) acting over a short range. The PP module is "lesioned" mathematically to simulate specific brain damage. The model accounts for visual object-based neglect following right parietal damage because high contrast at the edges of objects, resulting from local lateral inhibition, interacts with increasing damage towards the left visual field.

This paper offers a thought-provoking instance of computational neuroscience helping to understand brain function and may

potentially help to describe clinical phenomena.***-LAJ***

Deco G, Rolls E T
Object-based visual neglect: a computational hypothesis.
EUROPEAN JOURNAL OF NEUROSCIENCE
2002: 16: 1994-2000

MULTIPLE SCLEROSIS

Regulating models of multiple sclerosis

A population of lymphocytes have been identified in animal models, the depletion of which allows autoimmune diseases to emerge. However, it has been shown that the same lymphocyte population can halt autoimmunity if replenished in these animals. These lymphocytes can be identified by their cell surface antigens CD4 and CD25. CD4+CD25+ T cell populations are now referred to as T regulatory cells as they appear to be able to regulate autoreactive T cells that have the potential to cause autoimmune diseases.

In this paper, Kohm *et al* explore whether T regulatory cells influence the course of a model of central nervous system autoimmunity – experimental autoimmune encephalomyelitis (EAE) - in which autoreactive cells against CNS proteins cause inflammation in the CNS, comparable to that seen in multiple sclerosis.

The group demonstrate a reduction in disease severity when mice receive regulatory T cells rather than non-regulatory T cells three days prior to induction of EAE. There was no reduction in the number of mice that developed the disease. Therefore it appears that in the presence of an increased number of regulatory T cells, autoreactive cells are still activated on induction of EAE, but their ability to cause disease is reduced. The group went on to assess the cytokine profile of T cells from mice that had received the regulatory T cell infusion. On stimulation of these cells in vitro, there was a shift in the cytokine profile to that of a Th2, rather than the more typical EAE Th1 pattern. On histological examination of the CNS a reduction in inflammatory cell infiltrate was observed in the mice that had received regulatory T cells.

This is the first series of experiments looking at the effect of T regulatory cells in an animal model of multiple sclerosis; further experiments assessing the effect of these cells in established disease are eagerly awaited as this may reveal a novel therapeutic tool to explore in the treatment of multiple sclerosis. ***-ALC***

CD4+CD25+ Regulatory T Cells Suppress Antigen-Specific Autoreactive Immune Responses and Central Nervous System Inflammation During Active Experimental Autoimmune Encephalomyelitis.
Kohm AP, Carpentier PA, Anger HA, Miller SD.
THE JOURNAL OF IMMUNOLOGY
2002, 169;4712 – 4716.

What is optic-spinal multiple sclerosis?

The optic-spinal form of multiple sclerosis (OSMS), otherwise known as Devic's syndrome or neuromyelitis optica (NMO), is said to be particularly common in Japan. This retrospective study from a university hospital in Sendai in north-east Japan attempts to define the characteristics of "pure OSMS".

From the case records of 118 MS patients seen between 1988-1999, 36 were found to have "clinical OSMS", that is recurrent attacks of optic neuritis and myelitis as the only clinical features. Of these, only 10 (8.5% of the original sample) had persistently normal MRI brain scans (3-10 scans, over a ≥ 5 year period), and hence "pure OSMS".

There was a female preponderance in the pure OSMS cases (9:1), and all were CSF oligoclonal band negative. Despite this, clinical heterogeneity was apparent, in that 7 cases were mildly affected, with predominantly spinal sensory symptoms (as in so called "benign sensory" classical MS), whereas 3 with later onset disease were severely affected (as often noted in European and American cohorts of Devic/NMO patients). Spinal MR imaging in this latter group showed signal change and cavity-like structures extending longitudinally over several segments (not illustrated).

What does all this mean? Does "pure OSMS" represent a distinct demyelinating disorder, or is it simply one pattern of the protean manifestations of MS? The answer to these questions perhaps depends on whether the observer adopts the "splitting" or "lumping" point of view. From the data in this paper, there seems to be no prognostic (far less any therapeutic) implication from establishing a diagnosis of "pure OSMS".***-AJL***

Pure optic-spinal form of multiple sclerosis in Japan.
Misu T, Fujihara K, Nakashima I, Miyazawa I, Okita N, Takase S, Itoyama Y.
BRAIN
2002;125(11):2460-2468

A drug for all diseases?

Simvastatin is a 3-hydroxy-3-mthylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. It was originally developed and licensed as a drug effective at reducing total body cholesterol and low density lipoprotein. Its main indications currently are the secondary prevention and treatment of coronary artery disease and more recently cerebral vascular disease. However, it was through its use in patients receiving cardiac transplants that it emerged that the drug has other perhaps more important effects in reducing inflammation and, in this situation episodes of rejection of the transplanted organ compared to transplanted recipients not treated with a statin. Its mechanism for reducing cardiovascular disease is now called into question and a wide variety of possible indications for the drug family is currently under investigation.

These papers focus on the drug's possible use in multiple sclerosis. The first paper, by O. Neuhaus, et al, examines the in vitro effect of three HMG CoA reductase inhibitors simvastatin, lovastatin and mevastatin on T cell function, and compare this effect with that seen with Interferon beta. The second paper, published in Nature, assesses the effect of atorvastatin on experimental autoimmune encephalomyelitis (EAE) – an animal model of multiple sclerosis.

In vitro, statins were shown to reduce the capacity of T cells to proliferate when stimulated. The effect was equivalent to that seen with Interferon beta, and in combination the effect of these drugs was additive. The statins also reduced expression of chemokine receptors including ICAM-1 and matrix metalloproteinases, although not always to the extent achieved by the interferons. Youssef *et al* performed a series of experiments in which atorvastatin was given to mice both prior to and following induction of EAE. They demonstrated that oral atorvastatin prevented or reversed disease activity. This effect was maintained over six different models of EAE, including both chronic and relapsing remitting patterns, ruling out any disease pattern or species specific effect. A shift in cytokine secretion from a Th1 to a Th2 pattern was seen along with an increase in TGF beta production, a cytokine recently suspected of being involved in the regulation of autoimmunity. There was also a reduction in inflammatory infiltrate in the CNS of these mice.

The results published in these two papers taken together make a powerful argument for the further exploration of the use of HMG CoA reductase inhibitors in multiple sclerosis.

Clearly, although informative, in vitro studies sometimes poorly predict the effect of a drug in vivo, and similarly no animal model can truly predict the effect of a drug in humans. We wait with interest for the results of the ongoing phase II trial assessing the effect of statins on patients with multiple sclerosis. Given its many other proven and postulated indications this may be a tonic to add

to the tap water! ***-ALC***

Statins as immunomodulators: comparison with interferon-beta 1b in MS.
Neuhaus O, Strasser-Fuchs S, Fazekas F, Kieseier BC, Niederwieser G, Hartung HP, Archelos JJ.
NEUROLOGY
2002 Oct 8;59(7):990-7.

The HMG CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease.
Youssef S, Stuve O, Patarroyo JC, Ruiz PJ, Radosevich JL, Hur EM, Bravo M, Mitchell DJ, Sobel RA, Steinman L, Zamvil SS.
NATURE
2002 Nov 7;420(6911):78-84

REHABILITATION

Dynamic imaging in mild traumatic brain injury reveals temporal lobe abnormalities.

Most cases of mild head injury are completely recovered within 3 months. However there is a proportion of cases who experience persistent cognitive deficits. Memory and learning disturbances are frequently reported. Although these deficits are measurable by neuropsychological testing, explanation for the deficits remains questionable since images from CT and static MRI are often normal in this group of patients.

Dynamic imaging using PET and SPECT has been shown to have prognostic value in patients suffering from mild traumatic brain injury. Now a study in the USA has demonstrated its value towards explaining the persistent cognitive deficits that can develop in mild head injury patients.

20 patients who sought medical treatment for persistent cognitive and somatic complaints after a mild head injury were identified retrospectively from the register of an outpatient rehabilitation centre. All met the definition of mild traumatic brain injury proposed by the American Congress of Rehabilitation Medicine: That is they had a period of loss of consciousness or alteration of mental status lasting not greater than 30 minutes, memory loss for events immediately before or after injury and posttraumatic amnesia lasting not greater than 24 hours.

The patients' cognitive function was assessed by clinical neuropsychologists using recognised published tests. They were scanned with PET or SPECT depending on the terms of their insurance schemes. Experienced nuclear medicine physicians who did not have access to the findings of neuropsychological tests interpreted the scans.

Static scans taken during the acute post-injury period were normal in 15 of the 20 patients, but the later dynamic scans found abnormalities in 18. Nineteen of the 20 patients were found to have cognitive deficits and memory deficits were the most frequent, occurring in all 19. All in all, 17 of the 20 (85%) patients had positive findings on both dynamic imaging and clinical psychologists tests. Although there were a few cases where the abnormalities identified on the imaging did not match the cognitive impairment inferred from the test results, a large proportion of the abnormalities in scans were in the temporal lobe. The authors of the study, Umile *et al.*, considered that the prevalence of memory problems in the patients could be explained by damage to the temporal lobes in which the hippocampus and memory related structures are located. However they did not report the prevalence of attention disorders in the patients and it is possible that reduced cerebral blood flow in the temporal lobes was the result of disuse of the memory centres that was secondary to attention deficits sustained from damage in other brain areas.

Evidence of pathology in these patients should be useful in confirming that the problems they complain of are not just psychosocial. However the reduced activity or cerebral blood flow in particular brain areas may not always reflect the primary cause of the deficit. In addition PET and facilities are not widely available and both SPECT and PET use labelled markers and are therefore not usually used for repeated measures. Sensitive and safe physiological markers that can be used to determine the effectiveness of treatment for these patients are also needed. ***–AJT***

Dynamic imaging in mild traumatic brain injury: support for the theory of medial temporal vulnerability.
Umile EM, Sandel E, Alavi A, Terry CM, Plotkin RC.
ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION
2002: 83: 1506-1513

★★★ **RECOMMENDED**

After stroke cortical space for hand recovery is pinched

Recovery of hand movement is often poorer than proximal arm movement after stroke. It has been hypothesised that this is because there is more redundancy in the motor pathways projecting to motoneurones of proximal musculature than there is in those projecting to the motor neurones of distal muscles. However a group of neuroscientists have tested and found support for another idea: that there is competition among body parts for territory in the sensorimotor cortex and that when the territory is reduced in size, due to stroke, even limited activity of the upper arm might prevent the hand from gaining more control.

Muellbacher and colleagues tested their idea in a rehabilitation experiment involving six patients who had hand weakness for over 12 months post stroke. After a single baseline measurement the six were given three intensive practice episodes in a metronome-paced pinch task. Maximum pinch force and acceleration of thumb flexion were measured after each practice episode. And as an indicator of change in cortical representation, the threshold level of transcranial magnetic stimulation intensity required to illicit EMG responses and amplitude of responses in flexor pollicis brevis were also measured at the beginning and end of the three practice episodes.

The patients improved over the first two practices but no further improvement occurred as a result of the third practice. There was no significant change in motor threshold or MEP amplitude in the flexor pollicis brevis muscle as a result of the practice. The researchers concluded that recovery with practice alone was saturated and that the practice had not resulted in measurable increase in the thumb representation in the motor cortex.

Next they selectively deafferented the patients' upper arms, but not the hands, with local anaesthetic. This was achieved by injection into the upper brachial plexus roots, using electrical stimulation for guidance. A further two practice episodes were completed. These resulted in additional improvement in pinch and acceleration performance and a significant increase in MEP amplitude. Patients showed retention of the force gains two weeks later and reported benefits in some daily living tasks. So presumably the hand space was not reinvaded by the proximal arm representation once the anaesthetic had worn off.

Deafferentation of the upper arm coupled with pinching practice appeared to reduce weakness by increasing the effectiveness of cortical connections influencing hand muscle activity. This is an interesting and novel therapeutic strategy that deserves further investigation. It will be particularly important to determine the acceptability to patients of the invasive brachial plexus injection weighed against its benefit in reducing disability. ***–AJT***

Improving hand function in chronic stroke.
Muellbacher W, Richards C, Zieman U, Wittenberg G, Weltz D, Borojerdi B, Cohen L, Hallett M.
ARCHIVES OF NEUROLOGY
2002: 59: 1278-1282

PARKINSON'S DISEASE

★★★ RECOMMENDED

Tablets for fruit flies with Parkinson's disease

Fruit flies do not get Parkinson's disease, but they can be given it……. They have dopaminergic neurones, 16-20 or so of them, in the *dorsomedial cluster*, which can be used as models of human dopaminergic nigral neurones. To investigate the mechanism of α-synuclein toxicity in dopaminergic cells, researchers from the University of Pennsylvania have directed expression of α-synuclein to *Drosophila* dopaminergic cells using the dihydroxyphenylalanine decarboxylase promoter. Using this model Pavan Auluk had previously shown that transgenic co-expression of the heat shock protein 70 (Hsp70) reduced dopaminergic cell death. In this paper, he and colleagues went one step further towards a human therapy. They fed the fruitflies a drug called geldanamycin, a naturally occurring benzoquinone ansamycin that inactivates Hsp90, which in turn suppresses Hsp70. The experiment worked like a dream: geldanamycin protected the fruitfly dopaminergic neurones from α-synuclein toxicity. This short paper is an excellent example of how the experimental versatility of insect models can be exploited for insights into human neurodegenerative diseases. ***-AJC***

Pharmacological prevention of Parkinson disease in Drosophila.
Auluck PK, Bonini NM.
NATURE MEDICINE
2002 Nov;8(11):1185-6

Non-drug therapy in Parkinson's disease – any evidence it does any good?

In the management of Parkinson's disease one often refers patients for occupational therapy, physiotherapy or speech and language therapy (SALT) with gratifying results. However one is never entirely certain what is the evidence that it works and when patients should be referred, and thus one is left basing one clinical practice on anecdote and personal experience. Now Deane *et al* have attempted to answer this question by synthesising six Cochrane sytematic reviews, and found that there is no evidence that any of these therapies work in PD – not because there is evidence to show this but because there is no proper evidence one way or the other. In their review they found 16 randomised controlled trials for physiotherapy, 2 for occupational therapy and 5 for SALT and dysarthria. However all the trials used unique methods of assessment and outcome, with problems of bias and so could not be subject to a meta-analysis. Thus no conclusions about these therapies could be made.

This is perhaps not surprising but it is a sobering thought to know that we refer many patients for this therapy based on no clinical evidence of efficacy. It therefore seems critical that we should embrace the approach now being adopted for drug therapies in PD, in the paramedical therapies especially given the limited health service resources that are available in the UK. ***– RAB***

Systematic review of paramedical therapies for Parkinson's disease.
Deane KH, Ellis-Hill C, Jones D, Whurr R, Ben-Shlomo Y, Playford ED, Clarke CE.
MOVEMENT DISORDERS
2002 17:984-991

★★★ RECOMMENDED

Novel sites to target therapy in Parkinson's disease – the peduculopontine nucleus

The pedunculopontine nucleus or PPN is a small structure found in the rostral tegmental area of the brainstem that has long been thought to be important in some of the features of Parkinson's disease. It is known to receive from the outflow nuclei of the basal ganglia and to project both rostrally to the thalamus and caudally to the spinal cord, and has long been known experimentally to have something to do with locomotion. In this recent paper from the Oxford group, they now explore the role of this nucleus in the akinesia of parkinsonian syndromes. The hypothesis being that in PD there is excessive activity in the basal ganglia outflow nuclei, which thus produces increased inhibition in the PPN resulting in akinesia and that blocking this may relieve this feature of the illness.

In this study 2 macaque monkeys were used and the parkinsonian state induced using MPTP – a toxin known to induce parkinsonism in people, although in a fashion that is distinct from PD both clinically and pathologically. Nevertheless this is a toxin that is of use and does selectively target central catecholaminergic pathways when given systemically. These monkeys were studied using a range of clinical measures, as well as the response to micro-injections of GABA antagonists and agonists studied.

In the non-parkinsonian state injection of the GABA agonist muscimol reduced their activity, whilst in the MPTP treated monkeys the injection of the GABA antagonist reversed their akinesia in an equivalent fashion to that seen with L-dopa. Thus supporting their hypothesis, although it must be stressed that the response was similar to that seen with L-dopa which raises questions as to whether targeting this structure has any advantage over using standard drug therapies. Nevertheless this paper is important in highlighting the importance of this much neglected nucleus in PD which as the authors conclude may even be a possible target for the akinesia of a whole range of parkinsonian conditions. ***–RAB***

Reversal of akinesia in experimenta; parkinsonism by GABA antagonist microinjections in the pedunculopontine nucleus.
Nandi D, Aziz TZ, Giladi N, Winter J, Stein JF.
BRAIN
2002 125:2418-2430.

PRION DISEASE

★★★ RECOMMENDED

Treating prion disease: a set back

Prusiner and colleagues reported in 2001 that lysosomotropic acridine derivatives, including the anti-malarial drug quinacrine, could rapidly eradicate the production of disease-associated (protease-resistant) isoforms of the prion protein (PrP^{Sc}) in stably infected murine neuroblastoma (N2a) cell cultures. Since quinacrine is known to cross the blood-brain barrier and has a reasonable safety profile, these observations have prompted its use in human prion disease (initially on compassionate grounds, although a trial is now underway). However, no animal model data to support its use have been reported.

Collins and colleagues inoculated Balb/c mice intracerebrally with pooled brain homogenate from mice confirmed as dying from a spongiform encephalopathy. Three groups of animals (n = 8 each) received no treatment, early treatment (5 days post-inoculation), or late treatment (65 days post-inoculation), with quinacrine hydrochloride (20 mg/kg loading dose on day 1, followed by 10 mg/kg/day, by gavage feeding). The mean survival was identical in all three groups of animals. Neuropathological examination and Western immunoblots for protease-resistant PrP showed no intergroup differences.

Hence, disappointingly, there was no concordance between the animal model findings and the earlier cell culture studies. These results do not entirely close the door on quinacrine as an antiprion therapy: it might perhaps have been more effective in animals inoculated peripherally, or receiving other prion strains. However, it does point up the considerable difficulties in extrapolating from

laboratory studies, however promising, to clinical practice. ***-AJL***
Collins SJ, Lewis V, Brazier M, Hill AF, Fletcher A, Masters CL.
Quinacrine does not prolong survival in a murine Creutzfeldt-Jakob disease model.
ANNALS OF NEUROLOGY
2002;52(4):503-506

★★★ RECOMMENDED

Sporadic CJD: anatomical substrate of myoclonus and periodic sharp wave complexes

Myoclonus and electroencephalographic periodic sharp wave complexes (PSWC) are characteristic findings in sporadic Creutzfeldt-Jakob disease (sCJD) but their pathogenesis is ill understood; there is even disagreement as to whether the two are pathophysiologically linked. The laborious, retrospective, pathological study reported in this paper from Germany attempts to correlate these features with thalamic pathology, specifically the loss of parvalbumin immunoreactive neurones. Parvalbumin (PV) is a cytosolic Ca2+ binding protein, implicated in the buffering and transport of Ca2+, predominantly expressed in inhibitory GABAergic interneurones, and for which neuroprotective roles have been suggested.

Counting PV+ neurones in various thalamic nuclei (cases n = 21; controls n = 5), the investigators found reductions in most nuclei in sCJD brains, most marked (_40% vs. controls) in the reticular nucleus. sCJD patients with PSWC on EEG had a greater reduction in reticular nucleus PV+ neurones than those without PSWC, but this did not reach statistical significance; whereas patients with myoclonus and PSWC did have a statistically significant reduction in reticular nucleus PV+ neurones compared to those with myoclonus without PSWC.

The reticular nucleus is believed to serve as a pacemaker, generating and maintaining highly synchronous electrical activity. Loss of reticular nucleus PV+ immunoreactivity, reflecting loss of GABAergic interneurones, may therefore lead to loss of intrathalamic inhibition, and hence increased synchronicity and the appearance of PSWC. This hypothesis might be tested by looking at thalamic PV immunoreactivity in other neurodegenerative diseases in which PSWC occasionally occur, such as dementia with Lewy bodies.***-AJL***
Tschampa HJ, Herms JW, Schulz-Schaeffer WJ, Maruschak B, Windl O, Jastrow U, Zerr I, Steinhoff BJ, Poser S, Kretzschmar HA.
Clinical findings in sporadic Creutzfeldt-Jakob disease correlate with thalamic pathology.
BRAIN
2002;125(11):2558-2566

NEURO-ONCOLOGY

Can we stomach nerve injury?

Following nerve transection, the chances of recovery depend on the ability of the proximal stump to sprout, and then correctly link up with distal motor endplates or sensory receptors. Axons have the potential to regenerate over short distances, usually less than 5 mm, divisions greater than this are problematic. Even when anatomical reconnection is achieved, functional recovery is not guaranteed since individual axons can lose their way and head towards the wrong target. Scar formation can also impede this rewiring mechanism and if the axons fail to cross this barrier, a neuroma can develop. Autologous nerve graft is considered as conventional surgical treatment if end-to-end repair is not possible, complications of this method include painful neuroma formation and loss of function at the donor site. Therefore the impetus to use natural or synthetic materials has driven experimental studies, including the insertion of conduit tubes with growth factors being added to the recipe. An important ingredient for success is ample vascular supply.

A novel approach has recently been adopted by Castaneda and Kinne, whereby omentum grafts were used to bridge transected sciatic nerves in the rat. The omentum has a number of advantages as a natural framework to aid axon regeneration, including a large vascularisation capacity, harvesting is relatively easy and can be performed laparoscopically, and no significant injury at the donor site. Additionally the omentum can synthesize growth factors. The study compared functional recovery in three groups of rats, all groups underwent 25-30mm transections, one group had a conventional end to end repair whilst the other had an omentum graft and the third group had no further intervention following transection. Functional recovery, measured at 2 weekly intervals, was quickest in the omentum graft group based on an objective measure of hind leg walking. Histology was also favourable at eight weeks. These are encouraging results and perhaps the next step is to compare repair rates in autologous nerve grafts and include neurophysiological assessment. ***-JR***
Omental graft improves functional recovery of transected peripheral nerve.
Castaneda F and Kinne R.
MUSCLE AND NERVE
2002:26(4):527-532

Complimentary Journals Reviewed

We would like to thank the following publishers who have provided us with complimentary review subscriptions to their journals. For subscription details please contact the relevant publisher direct.

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

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

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

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

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

Study of cholesterol drug as a potential therapy for multiple sclerosis

The MS Trust recently reacted favourably to early research reported in Nature indicating that atorvastatin, a commonly used cholesterol lowering agent, has the ability to influence the immune system and prove effective in reversing paralysis in mice infected with an experimental model of Multiple Sclerosis.

Chief Executive, Christine Jones, said: "Of course these are very early findings and results demonstrated in mice with the experimental equivalent of MS are not necessarily replicated in people with MS. However, the reported results are certainly very encouraging."

Major surgery in children with Sturge-Weber Syndrome

Researchers report that hemispherectomy – a procedure in which half the brain is removed - may reduce or eliminate severe seizures even in older children with this rare disorder associated with epilepsy.

Contrary to results of previous studies, the study at Johns Hopkins Children's Center in Baltimore found that in children with Sturge-Weber syndrome, delaying hemispherectomy even for years had no apparent effect on seizure control or learning ability. Some 80% of Sturge-Weber patients develop epilepsy.

More than 80% of patients were reported to be seizure-free following the surgery and more than half were off anticonvulsants. The type of hemispherectomy that was performed, or the amount of brain matter actually removed, did not influence the child's seizure outcome.

"Most interestingly, we found the child's cognitive skills were not impacted by the child's age at operation or delay of surgery. This is contrary to all other previous studies on Sturge-Weber syndrome and hemispherectomy, which emphasised early surgery to avoid cognitive decline," said Kossoff. "However, there was a trend toward poorer cognitive outcomes if seizures persisted after surgery."

Many movement disorders. One treatment choice.

Xenazine 25 (tetrabenazine) is proven and licensed for the treatment of a wide range of movement disorders associated with organic central nervous system conditions. These disorders include: Huntington's disease and other choreas, dystonia, hemiballismus, myoclonus, and Tourette's syndrome. Xenazine 25 is also indicated for moderate to severe tardive dyskinesia which is disabling and/or socially embarrassing.

Overall, Xenazine 25 is highly effective and generally well-tolerated and in contrast to conventional neuroleptics, provides a dopamine-regulating strategy without the associated risk of tardive dyskinesia. Indeed, tardive dyskinesia related to Xenazine 25 usage has never been reported. When side-effects of Xenazine 25 occur, they are usually dose-related and can be controlled by dose reduction.

Xenazine 25 has also been shown to be an appropriate choice for patients in whom other therapies have resulted in only marginal or moderate improvement, or have been associated with unacceptable side-effects.

Further information from: Cambridge Laboratories on Tel. 0191 296 9369.

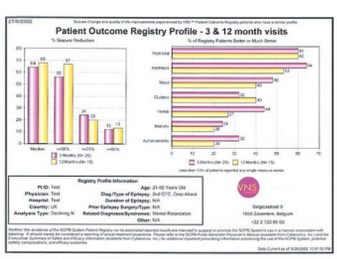
RNA from human brain sections is now available

Ambion now offers high quality FirstChoice™ Total RNA from individual regions of the human brain. Traditionally, it has been difficult for researchers to obtain high quality RNA from human brain tissue. Ambion has established relationships within the medical community to ethically obtain tissues in a manner that preserves the integrity of the RNA. They have optimised the RNA isolation procedure specifically for brain and neural tissue. A stringent Dnase treatment is included to destroy in any contaminating genomic DNA, to ensure that the RNA is ready for use in downstream applications such as RT-PCR. These efforts in conjunction with stringent quality control standards, ensure that Ambion's FirstChoice™ Brain Total RNA is intact, stable, and free of genomic DNA contamination.

For a complete listing visit www.ambion.com/prod/brain

Ambion®
THE RNA COMPANY®

Vagus Nerve Stimulation (VNS) Therapy



VNS Therapy is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalisation) or generalised seizures, which are refractory to antiepileptic medication. A positive review of VNS Therapy was carried out by The Cochrane Library earlier this year.

Naturally a commonly asked question is "Which seizure types best respond to VNS Therapy?" Cyberonics have now introduced a new service entitled "PIQ" (Patient identification and Qualification). The "PIQ" service uses the power of the VNS Patient Outcome Registry, currently with 7000 patients, to provide patient outcome data. The Registry search results are specific to individual patient criteria and are totally anonymous. The outcome data demonstrates patient outcomes in terms of % Seizure Reduction and Quality of Life benefits.

To obtain the one page PIQ form to carry out your own patient search, please contact your local Cyberonics Representative (details of the UK team at ww.vnstherapy.com/international). You can then fax your search form to 0870-1660505 and we will return the results to you in 2-3 weeks for your consideration.

Cyberonics hope this service will fulfil a need when considering VNS Therapy. Visit the website www.vns-therapy.om/international to order the new Patient and Clinician Resources.

SRS Technology – new product catalogue

The new catalogue from SRS Technology includes products aimed at making life easier for those with disabilities, including environmental control systems and devices to operate a wide range of household appliances. Also included is a range of specialist switches and joysticks, mounting systems and information on integrating wheelchairs with environmental control systems.

SRS are continually sourcing and developing new products, so they are happy to help you find any products not featured in the catalogue.

Sue, a customer with progressive MS, has found the products helpful in maintaining her independence. She says, "Previously simple tasks became real problems. Now, I no longer exhaust myself wheeling in my chair to and from the front door. I have an intercom linked to the living room and bedroom, plus an outside microphone and CCTV camera, so I can see and speak to whoever is at the front door. The door lock can also be released to admit friends."

For a free copy of the catalogue call SRS Technology on Tel. 01922 456882, E-Mail. enquiries@srstechnology.co.uk

New Neurocritical Care Society

The Neurocritical Care Society is a new international, multidisciplinary professional organisation dedicated to improving care for patients with life-threatening neurological diseases. As the first professional medical organisation exclusively devoted to the rapidly growing field of neurological intensive care, the society seeks to bring together a diverse group of physicians from different specialties who treat neurological patients in the critical care environment.

A major goal of the society is to foster the transition of neurocritical care over the next several years from the fringes of medical practice to a widely-recognised and important subspecialty of medicine. The Society is seeking to promote forceful and effective multidisciplinary collaboration to improve standards of care for critically ill neurological patients. It will do so by identifying best medical practices, providing professional education, funding research, and establishing training and certification guidelines.

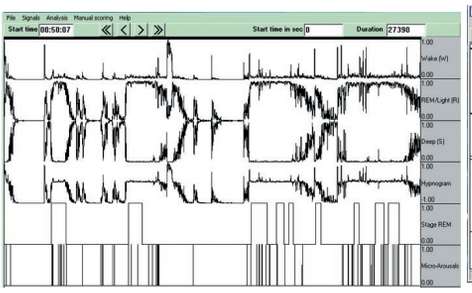
On February 15th-16th, 2003, the society holds its inaugural annual meeting in Phoenix, Arizona. In January 2004, the society will launch its official journal, Neurocritical Care. Specialists interested in joining the society or attending the meeting can visit www.neurocriticalcare.org, E-Mail. info@neurocriticalcare.org, or contact Robert G. Kowalski, Administrative Director on Tel. 001 212 305 0857.

Oxford BioSignals introduce a revolutionary tool for sleep studies

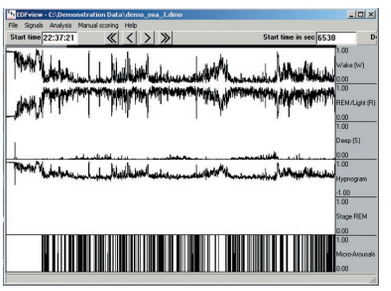
BioSleep, a system based on neural network technology, requires only a single channel of electroencephalogram (EEG). It analyses the signal automatically on a second-by-second basis, showing a night-long progression along the sleep/wake continuum. As BioSleep elucidates the macro- and microstructure of sleep, it shows rapid shifts from one stage of sleep to another and reliably detects abnormal sleep patterns, including patients with Obstructive sleep Apnoea (OSA).

It also brings into view microarousals – transient events lasting only a few seconds.

For further information contact Oxford Biosignals on Tel. 01865 336170.



BioSleep output in a healthy adult



BioSleep output in OSA patient showing increased arousals and reduced time in deep sleep

Decreasing incidence of stroke for cardiac surgery patients

Stroke and other neurological dysfunction occur in a finite number of patients who undergo cardiac operations. Dr Scott Goldman from The Lankenau Hospital and Institute for Medical Research, US, recently studied the use of Cerebral Oximetric Monitoring in cardiac surgery.

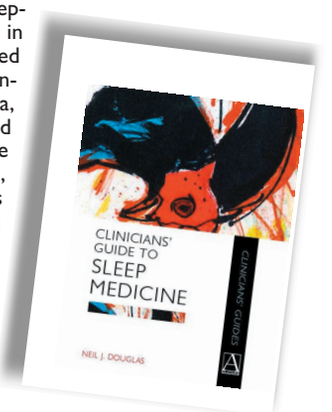
Beginning in January 2002, a percutaneous cerebral oximeter was used in all patients undergoing cardiac surgical procedures. This was done as an evaluation to determine whether monitoring and optimising cerebral oximetry values could decrease the incidence of stroke. Three hundred and sixty-two patients underwent cardiac surgical procedures using cerebral oximetric monitoring from January 1- June 30. There was one stroke in this group (0.29%). This was compared to 791 patients who underwent cardiac surgical procedures without using cerebral oximetric monitoring from January 1 - December 31, 2001. There were 14 strokes in this group (1.77%). The patient group that underwent cardiac surgical procedures using cerebral oximetric monitoring and optimised cerebral oximetry values demonstrated a marked decrease in the incidence of stroke.

For more information contact Tyco Healthcare Ltd on Tel. 01329 224226, E-Mail. marketing@tycohealth.com

Clinicians' Guide to Sleep Medicine

Neil Douglas, Professor of Respiratory and Sleep Medicine, University of Edinburgh; Director, Scottish National Sleep Laboratory, Royal Infirmary, Edinburgh, UK

Clinicians' Guide to Sleep Medicine puts the subject into context for GPs and general hospital physicians, presenting the current knowledge of sleep-related problems and their treatments in an accessible manner. Topics covered include sleep apnoea / hypopnoea syndrome, narcolepsy, snoring, insomnia, restless leg syndrome, night terrors, and sleep walking. With a balanced, readable style and clear explanatory illustrations, this book enables practising physicians to draw on the experience of an acknowledged international expert in the field and deal with the common sleep disorders with understanding and confidence.



Available now, priced £29.99. For more information or to order please contact Arnold Publishers on, Tel. 020 7873 6355, Fax. 020 7873 6299, E-Mail.healthsci.marketing@hodder.co.uk, Web: www.arnoldpublishers.com

Brain Awareness Week

Brain Awareness Week is a worldwide celebration of the brain that grows more successful every year. This exciting initiative is an opportunity to draw attention to achievements being made in scientific laboratories, and to demonstrate how they improve the diagnosis and treatment of disorders of the brain that affect millions of people.

For information about how you can organise an event during the sixth Brain Awareness Week 10 – 16 March 2003, please contact Lisa Cokayne-Naylor, European Dana Alliance for the Brain, on Tel. 020 7937 8771, E-Mail. edab@which.net or see the website www.edab.net

Siemens Medical Solutions´ operations in Sweden to be focused on IT

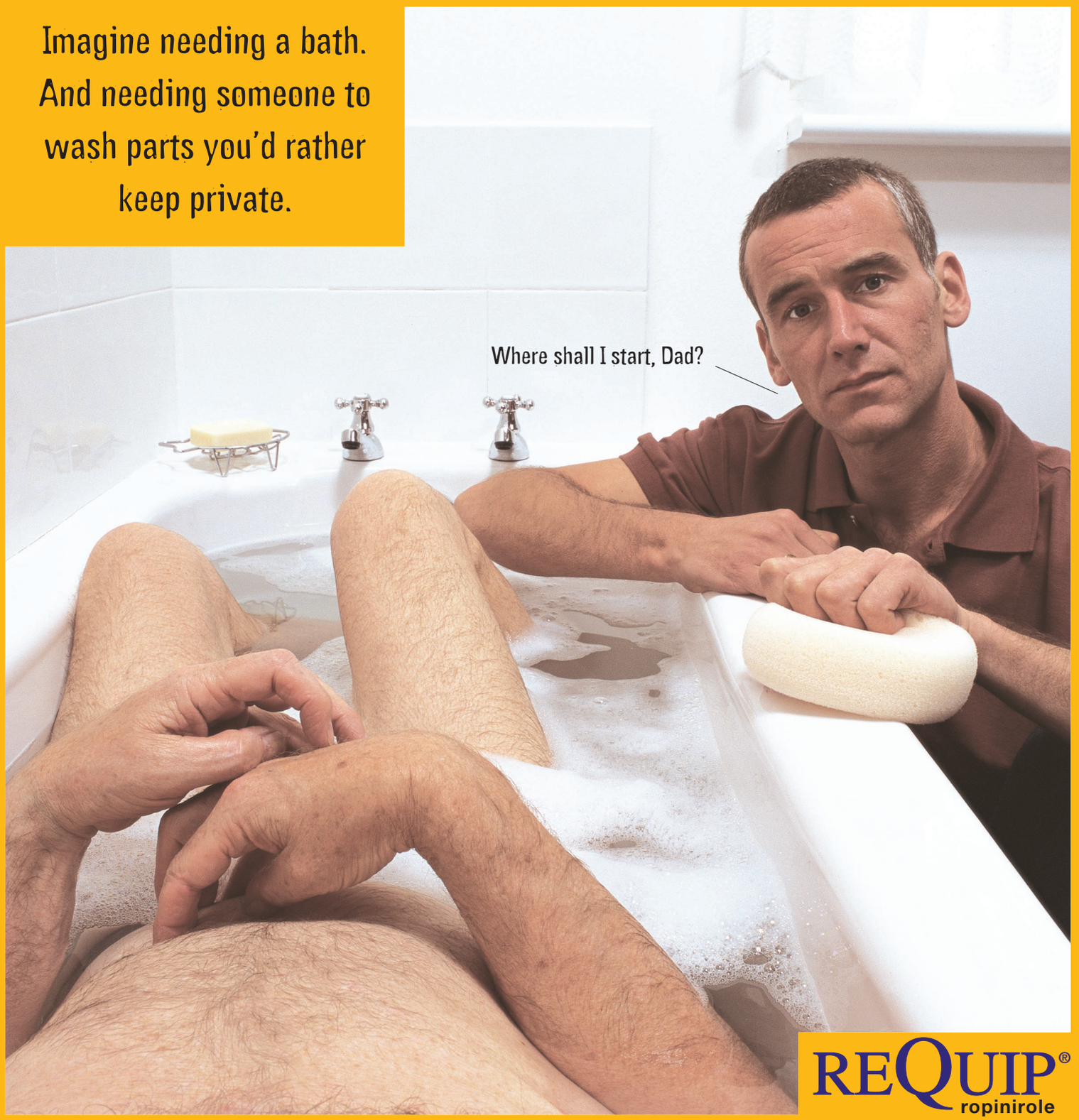
Siemens Medical Solutions (Med) proposes restructuring its Swedish operations to focus on the development of IT solutions for healthcare and to take better advantage of existing production facilities within Med. It is therefore proposed that the development and production of medical engineering hardware should be relocated from Solna to other existing facilities.

Med's Swedish operations are today mainly based in Solna and Gothenburg, where Siemens develops IT solutions for healthcare, as well as manufactures and develops certain types of X-ray equipment. Based on a strategic decision within Med, it is now proposed that the Swedish operations should focus on the development of IT solutions for healthcare.

Med is aiming to optimise its number of production facilities globally. It is therefore proposed that the development and production of medical engineering equipment should be moved from Solna to existing facilities in Germany, which have the capacity to take over Solna's production. Parts of the German production will, in turn, be moved to Siemens facilities in Asia, increasing the Group's production efficiency. Sales and marketing in Sweden and Finland, the technical services division, and the development of IT systems for healthcare, based in Gothenburg and Solna, will not be affected.

For more information please contact Mike Bell on Tel. 01344 396317.

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



REQUIP® ropinirole

FIGHTS PARKINSON'S. DEFENDS DIGNITY.

REQUIP (ropinirole) Prescribing Information

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

POM

Marketing Authorisation Holder SmithKline Beecham plc t/a GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

Further information is available from: Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; customercontactuk@gsk.com; Freephone 0800 221 441.

Requip is a Registered Trademark of the GlaxoSmithKline Group of Companies.

Date of preparation: September 2002

REQ/FRA/02/3977 - MWL

customer contact centre

Freephone **0800 221441**
Fax **020 8990 4328**
customercontactuk@gsk.com

gsk GlaxoSmithKline