ISSN 1473-9348 Volume 4 Issue 3 July/August 2004

ACNR

Advances in Clinical Neuroscience & Rehabilitation

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

Review Articles: The Impact of Systemic Inflammation on Brain Inflammation; Genetics of Learning Disability
Management Topic: Aneurysmal Subarachnoid Haemorrhage
Rehabilitation Article: Progression and Correction of Deformities in Adults with Cerebral Palsy

www.acnr.co.uk

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. He has recently been appointed to the new position of University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

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 Reader 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.

Alastair Wilkins is Specialist Registrar in Neurology in East Anglia. He trained in Cambridge, Sheffield and London, and has just finished a PhD investigating potential mechanisms of axon loss in multiple sclerosis.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Professor Soffietti is Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital, Torino, Italy. He is President of the Italian Association of Neuro-Oncology, member of the Panel of Neuro-Oncology of the EFNS and EORTC Brain Tumour Group, and Founding member of the EANO (European Association for Neuro-Oncology). He has written more than 300 scientific papers.

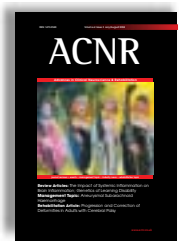
Professor Klaus Berek, Austria: Since 1999, Dr Berek has been Head of the Neurological Department of the KH Kufstein in Austria. He is a member of the Austrian Societies of Neurology, Clinical Neurophysiology, Neurological and Neurosurgical Intensive Care Medicine, Internal and General Intensive Care Medicine, Ulrasound in Medicine, and the ENS.

Professor Hermann Stefan, Germany: Professor Stefan trained in neurology, psychiatry, neuropathology, and epileptology at the University Bonn. He is Professor of Neurology/Epileptology in the Department of Neurology, University Erlangen-Nürnberg, and specialises in the treatment of epilepsies, especially difficult to treat types of epilepsy and presurgical evaluation, including Magnetic source imaging (MEG/EEG) and MR-Spectroscopy.

Professor Nils Erik Gilhus, Norway: Professor Gilhus has been Professor of Neurology at the University of Bergen and Haukeland University Hospital since 1987. He is Research Dean at the medical faculty, and Chairman for the Research Committee of the Norwegian Medical Association. He chairs the scientist panel of neuroimmunology, European Federation of Neurological Societies (EFNS), is a member of the EFNS scientific committee, the World Federation of Neurorehabilitation council, and the European School of Neuroimmunology board. His main research interests are in neuroimmunology and neurorehabilitation.

contents

july/august 2004



The Royal Hospital of Neuro-disability is holding an 'Exhibition of Celebration' to mark it's 150th anniversary. This will take place at the Air Gallery in London from 20-24th September. One of the featured artists is Rosa Sepple, whose work appears on the front cover of this issue. The Royal Hospital is the UK's leading centre for rehabilitation and care of people with acquired brain injury and neurological illness.
For further details about the exhibition of celebration and the Royal Hospital for Neuro-disability please see www.rhn.org.uk or call 020 8780 4561.

Features

Regulars

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.

Neuroscience Events from Elsevier
REGISTER NOW

ISDN 2004

15TH BIENNIAL MEETING OF THE INTERNATIONAL SOCIETY FOR DEVELOPMENTAL NEUROSCIENCE

AUGUST 4–7, 2004
EDINBURGH, UK

Join international speakers and delegates for a complete review of the latest thinking on cell-cell interactions in the developing nervous system and disease correlates of perturbed development. Organized by the **International Society of Developmental Neuroscience** with administration provided by Elsevier.

Register online at **www.isdn-conference.com**

Satellite events prior to the 2004 Meeting of the Society for Neuroscience ● San Diego, CA, USA

Neurons and memory

The 2nd **Neuron** Satellite Meeting

October 21–22, 2004

Review recent advances in memory research, including molecular, cellular, and systems level studies at this second meeting organized by the editors of *Neuron*.

Speakers: Ron Davis, Yadin Dudai, Eric Kandel, Joe LeDoux, Earl Miller, Brenda Milner, Roger Nicoll, Larry Squire, Wendy Suzuki, Susumu Tonegawa and Gina Turrigiano.

For further information visit: **www.neuron-meeting.com**

6 Decades of GABA

October 21–22, 2004

Hear from eminent scientists on the role of GABA in a topical and comprehensive review of the significance of this important neuro-transmitter over the past 60 years and in the future.

Organized in association with *Biochemical Pharmacology*.

Chairs: NG Bowery, *UK*, SJ Enna, *USA*, H Möhler, *Switzerland*, RW Olsen, *USA*

For further information visit: **www.gaba-conference.elsevier.com**

Protein misfolding in Alzheimer's and other age-related neurodegenerative diseases

The 5th *Neurobiology of Aging* Conference

October 21–22, 2004

This timely conference will bring together specialists in protein folding with Alzheimer's disease (AD) researchers whose work emphasizes cell biological aspects related to protein processing in AD. Topics will be of interest to all those concerned with early events in the pathological cascade of AD.

Organized in association with *Neurobiology of Aging*. **Chair:** P Coleman, *USA*

For further information visit: **www.nba-conference.elsevier.com**

THE CYTOSKELETON AND SYNAPTIC FUNCTION

14th *Neuropharmacology* Conference

October 20–22, 2004

Join leading experts from the neurosciences and cell biology to discuss cytoskeletal influences on neuronal function, stability and plasticity of neuronal morphology and the molecular mechanisms that regulate pre- and post-synaptic structure.

Organized in association with *Neuropharmacology*.

Chairs: Al Matus, *Switzerland*, S Halpain, *USA*, M Sheng, *USA*

For further information visit: **www.neuropharmacology-conference.elsevier.com**

Elsevier Conferences
Tel: +44 (0) 1865 843095
Fax: +44 (0) 1865 843958
Email: conferenceinfo@elsevier.com

ELSEVIER

Editorial

Welcome to the third issue of ACNR this year. You may be interested to know that the journal is currently receiving over 1500 visitors to its website every month, which is very encouraging to all of us involved.

In this issue we have review articles that focus on the X-linked mental retardation and the interplay between systemic and brain inflammation. We are also pleased to announce the launch of two new series of articles, one on neuropathology edited by Professor Roy Weller and the other on neurosurgery edited by Peter Whitfield, which forms our new management topic.

In his article, Professor Hugh Perry provides us with a thought provoking and far-reaching article on the role of brain inflammation in neurological diseases and how this may be affected by systemic inflammation. This is of great interest, as in neurological practice the relationship between intercurrent illnesses and neurological deterioration in conditions such as MS and Parkinson's disease is well recognised, if poorly understood. Hugh helps us understand why this may occur, and by so doing how in future we may be able to better control CNS disease progression through modulating inflammatory processes.

The genetics of learning disability is often regarded as difficult and of minimal interest to neuroscientists and neurologists, but in her article Dr Lucy Raymond shows just how wrong this perception has become. The realisation that the genes underlying these disorders are becoming better defined has led to a re-evaluation of the investigation of such children. In this article Lucy Raymond takes us through this rapidly emerging field, highlighting where it is going and what insights this will reveal on our understanding of CNS development and maturation. This is truly a fast moving field with wide reaching implications to neurologists, geneticists and neuroscientists.

Roy Weller and Dr Mazanti begin the series of articles on neuropathology with an overview of the pathology of encephalitis - a condition which is not uncommon in neurology, wherever it is practised. This article presents a succinct and accessible account on the aetiological agents underlying encephalitis, and how this translates into pathological processes. In addition they discuss the difficult issues of primary infection, versus ADEM and how these can be distinguished pathologically.

The new management topic of neurosurgery starts in this issue and follows on from our series on epilepsy, nerve and muscle disease and movement disorders (all freely available to read and download on our website). Peter Whitfield, who has kindly taken on organising this series of articles, presents his approach to the management of aneurysmal subarachnoid haemorrhage (SAH) (see also Journal reviews on new recommendations for CSF examination in SAH). These articles, as with the others in these series, are designed to navigate the non-specialist through an area that will impinge - if not directly- on their clinical practice, and needless to say Peter does this superbly in his account.

Whilst we are on the topic of vascular disease, we also have a very useful update on thrombolysis for acute ischaemic stroke by Dr Michael Power, which is particularly apt given the recent Lancet article on this very topic by Hacke *et al.*

The rehabilitation article in this issue tackles cerebral palsy (CP), and Mark Paterson delivers a beautifully written account on the progression and management of deformities in adults suffering with CP. This is a very sensible account on this topic and clearly comes from great experience, and is one of the best accounts I have ever read on this subject.

We also have all our other usual articles - Alex Leff appropriately takes on alexia in the cognitive primer series with an acknowledgement to the contribution and comments from Professor Elizabeth Warrington. In our historical section Andrew Larner discusses the neurological contributions of Caleb Hillier Parry. We also have two conference reports and a range of journal and book reviews, some of which can only be found on the web - so do go and have a visit.

Once more thanks for your continued support and do continue to feed back to us on what can be improved.

Roger Barker, Co-editor
E-Mail.AdvancesinCNR@aol.com

For adjunctive treatment of partial onset seizures in adults with epilepsy.

One to build with.

Strong.

- Significant long-term seizure freedom[1]

Simple.

- No known pharmacokinetic interactions[2,3]

Solid.

- Excellent tolerability[4]

Keppra® levetiracetam

Building powerful AED therapy

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: £52.30. 1,000 mg x 60 tablets: £101.10. **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:** February 2004.

References: 1. Krakow K, Walker M, Otoul C, Sander JWAS. Long-term continuation of Levetiracetam in patients with refractory epilepsy. *Neurology.* 2001;56:1772-1774. **2.** Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomised clinical trial. *Neurology.* 2000;55:236-242. **3.** Patsalos PN. Pharmacokinetic profile of Levetiracetam: toward ideal characteristics. *Pharmacol Ther.* 2000;85:77-85. **4.** French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. *Epilepsy Res.* 2001;47:77-90.

ucb Pharma CNS INNOVATORS™

The Impact of Systemic Inflammation on Brain Inflammation

We have all at one time or another experienced the consequences of a systemic infection – we feel unwell or sick. As formalised by Hart (1988)[1] systemic infections have a profound effect on behaviour giving rise to the spectrum of changes known as "sickness behaviour". Sickness behaviour is characterised by changes such as fever, reduced appetite, reduced activity and reduced social interaction (see figure). Sickness behaviour is part of our normal homeostasis and evolved not only as a mechanism to fight infections, but also as a possible mechanism to protect individuals, or the group, from spread of infection[2]. This short review summarises what we know about how systemic inflammation is communicated to the brain, and highlights how these pathways may have a significant impact on ongoing brain inflammation associated with neurological disease.

Systemic inflammation communicates with the brain

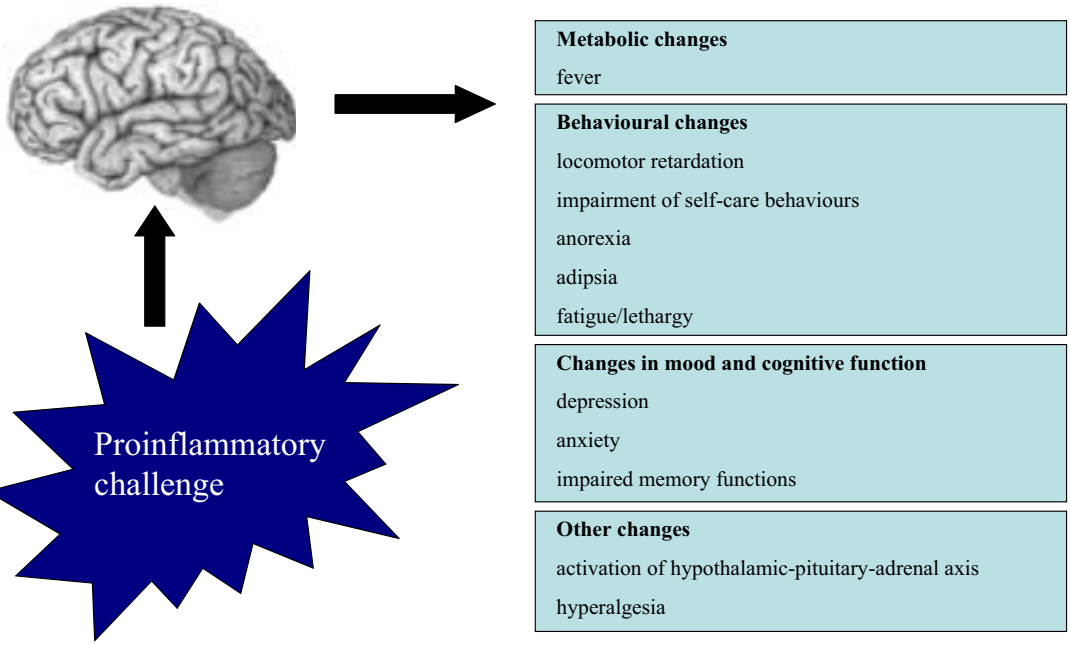
In response to an infection inflammatory cytokines such as interleukin-1€ (IL-1€) tumour necrosis factor-✓ (TNF-✓) and interleukin-6 (IL-6) are generated at the site of infection. These cytokines circulate in the blood and communicate with neurons in the brain. There are at least four different pathways by which inflammation in peripheral tissues communicate with the brain[3]. Firstly, the cytokines may by-pass the blood-brain barrier at the circumventricular organs, and there bind to receptors on macrophages within these organs and activate them. Secondly, the circulating cytokines may activate the cerebral endothelial cells, which in turn activate the perivascular macrophages, that signal to the microglia within the parenchyma. Thirdly, cytokines may activate the sensory afferents of the vagus nerve within the abdominal and thoracic cavity, which communicate with neuronal populations within the brainstem. Finally, there is evidence that cytokines may be actively transported by the endothelium across the blood-brain barrier.

A major component of this signalling by systemic cytokines to the brain is the macrophage populations of the brain the perivascular macrophages and the microglia. These macrophage populations signal the presence of systemic inflammation to neurons by synthesising inflammatory mediators, including some of the same inflammatory cytokines as are induced peripherally. Microinjection of inflammatory cytokines such as IL-1€ into the appropriate regions of the brain will evoke components of sickness behaviour.

Since the macrophage populations in the brain play an important role in the transduction of signals from the peripheral immune system to neuronal populations in the brain it is clear that they will also play a key role in determining the gain, or amplitude, of the signal that is generated in the brain. It is well established that the resident populations of macrophages in the brain are relatively down regulated or switched off when compared to other tissue macrophages. However, if the perivascular macrophages and microglia in the brain are already activated or "primed" by ongoing pathology in the brain we might expect a systemic inflammatory response to now have a rather different effect from that seen in a normal healthy young brain[4].

Inflammation in the brain

Multiple sclerosis is an inflammatory disease of the central nervous system with well-defined neuropathology. T-cells and macrophages invade the CNS, they damage the blood-brain barrier, cause demyelination and axon injury[5]. The macrophage populations within the focal plaques, and distal to the plaques, are more activated than those in the normal brain. In chronic neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) there is also an ongoing inflammatory response, albeit highly atypical[6]. In these chronic neurodegenerative diseases the inflammation is dominated by cells of the mononuclear phagocyte/macrophage lin-



Professor V.Hugh Perry is Professor of Experimental Neuropathology and Director of Southampton Neuroscience Group at the University of Southampton. He has a particular interest in the contribution of inflammatory processes to neurological disease.

eage. Macrophages and microglia in the brains of AD and PD patients are morphologically and phenotypically activated and express, or synthesise de novo, a number of cell surface or cytoplasmic antigens not present on resting or quiescent microglia[7]. The contribution of this atypical inflammatory response to disease onset and progression is a matter of interest and debate.

In the ageing brain it is also apparent that the resident macrophage populations are no longer as down regulated as that found in the brains of younger persons[8]. Indeed in a recent community based neuropathology study, it was found that in the brains of at least 30% of elderly persons who were cognitively normal, there was significant neuropathology comparable with that seen in the demented cohort[9], and this is likely to be associated with microglia activation.

Thus, in diverse disease states, and also as a part of ageing, the resident macrophage populations of the central nervous system "escape" from the mechanisms that normally control their highly down regulated phenotype. However the fact that the macrophages/microglia in these circumstances are morphologically activated does not imply that they synthesise the entire plethora of pro-inflammatory molecules that macrophages are capable of making[6]. Indeed these macrophages appear to be "primed" and thus susceptible to a secondary stimulus. The primed or activated macrophage populations in the diseased or aged brain are likely to amplify signals that pass from the immune system to the brain during the course of a systemic inflammatory insult or infection.

Interactions between systemic and brain inflammation

It has been shown in a number of studies that at least 30% of all relapses that take place in patients with multiple sclerosis are preceded by a systemic infection, commonly an upper respiratory infection[10]. In the animal model of multiple sclerosis, experimental allergic encephalomyelitis (EAE), animals challenged systemically with agents that reactivate the immune system, results in relapse or exacerbation of clinical disease[11].

The impact of systemic infections on cognition and other aspects of behaviour in the elderly and demented is clinically well known: a systemic infection may lead to delirium, a state characterised by confusion, loss of cognition and hallucinations. Delirium in the demented has a poor prognosis and carries a significant risk factor for rapid decline and an early death[12]. The cellular and molecular events underlying delirium have not been extensively investigated and the state of delirium may represent only the most extreme aspect of the impact of a systemic infection.

Experimental evidence that systemic inflammation may impact on ongoing brain inflammation comes from studies of mouse models of prion disease and Alzheimer's disease. In these models the microglia become activated by the presence of the ongoing pathology. Following a peripheral challenge with endotoxin, to mimic aspects of a systemic infection, cytokine synthesis in the brain is exaggerated[13,14] and so too are the behavioural consequences[14]. In a study on a small number of patients with Alzheimer's disease it has been shown that infections in a two month period lead to a more rapid cognitive decline in the subsequent two month period, in the absence of delirium[15]. It is not yet known whether these recurrent infections have an impact on the long-term rate of cognition decline. However, it should be noted that activation of blood monocytes and raised blood cytokine levels occur more readily in aged than in younger subjects[16]. Thus infections, surgery, or injuries in the elderly may generate a more pronounced systemic inflammatory cytokine synthesis even before these effects are amplified within the brain.

Conclusion

The evidence available suggests that if the macrophage populations in the brain are activated by ongoing neuropathology, or as a consequence of ageing, the signals from a systemic inflammatory condition may lead to these brain macrophage populations generating excess cytokines which in turn leads to exacerbation of a clinical condition. The extent to which systemic inflammation or disease may accelerate the rates of neuronal degeneration, cognitive decline and other permanent behavioural deficits remains to be studied.

References

1. Hart BL. *Biological basis of the behavior of sick animals.* Neurosci Biobehav Rev. 1988:12(2):123-37.
2. Kiesecker JM, Skelly DK, Beard KH, Preisser E. *Behavioral reduction of infection risk.* Proc Natl Acad Sci U S A. 1999;96(16):9165-8.
3. Konsman JP, Parnet P, Dantzer R. *Cytokine-induced sickness behaviour: mechanisms and implications.* Trends Neurosci. 2002;25(3):154-9.
4. Perry VH, Newman TA, Cunningham C. *The impact of systemic infection on the progression of neurodegenerative disease.* Nat Rev Neurosci. 2003;4(2):103-12.
5. Compston A, Coles A. *Multiple sclerosis.* Lancet. 2002 6;359(9313):1221-31.
6. Perry VH, Cunningham C, Boche D. *Atypical inflammation in the central nervous system in prion disease.* Curr Opin Neurol. 2002;15(3):349-54
7. McGeer PL, McGeer EG. *Inflammation, autotoxicity and Alzheimer disease.* Neurobiol Aging. 2001;22(6):799-809.
8. Sheng JG, Mrak RE, Griffin WS. *Enlarged and phagocytic, but not primed, interleukin-1 alpha-immunoreactive microglia increase with age in normal human brain.* Acta Neuropathol (Berl). 1998;95(3):229-34.
9. Neuropathology Group MRC CFAS *Pathological correlate of late-onset dementia in a multicentre, community-based population in England and Wales.* Lancet 2001: 357: 169-75.
10. Buljevac D, Flach HZ, Hop WC, Hijdra D, Laman JD, Savelkoul HF, van Der Meche FG, van Doorn PA, Hintzen RQ.*Prospective study on the relationship between infections and multiple sclerosis exacerbations.* Brain. 2002;125(Pt 5):952-60.
11. Crisi GM, Santambrogio L, Hochwald GM, Smith SR, Carlino JA, Thorbecke GJ. *Staphylococcal enterotoxin B and tumor-necrosis factor-alpha-induced relapses of experimental allergic encephalomyelitis: protection by transforming growth factor-beta and interleukin-10.* Eur J Immunol. 1995;25(11):3035-40.
12. George J, Bleasdale S, Singleton SJ. *Causes and prognosis of delirium in elderly patients admitted to a district general hospital.* Age Ageing. 1997;26(6):423-7.
13. Sly LM, Krzesicki RF, Brashler JR, Buhl AE, McKinley DD, Carter DB, Chin JE. *Endogenous brain cytokine mRNA and inflammatory responses to lipopolysaccharide are elevated in the Tg2576 transgenic mouse model of Alzheimer's disease.* Brain Res Bull. 2001;56(6):581-8.
14. Combrinck MI, Perry VH, Cunningham C. *Peripheral infection evokes exaggerated sickness behaviour in pre-clinical murine prion disease.* Neuroscience. 2002;112(1):7-11.
15. Holmes C, El-Okl M, Williams AL, Cunningham C, Wilcockson D, Perry VH. *Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease.* J Neurol Neurosurg Psychiatry. 2003 Jun;74(6):788-9.
16. Grimble RF. *Inflammatory response in the elderly.* Curr Opin Clin Nutr Metab Care. 2003 Jan;6(1):21-9.

Correspondence to:
Professor V Hugh Perry, School of Biological Sciences, Biomedical Sciences Building, Southampton, SO16 7PX
E-Mail. v.h.perry@soton.ac.uk

Genetics of Learning Disability

Lucy Raymond is a university lecturer and honorary consultant in medical genetics, University of Cambridge. She has a special interest in the genetics of learning disability and has established an international collaborative study (GOLD study) that aims to identify abnormalities in novel genes that cause mental retardation.

Definition of mental retardation

The definition of Mental Retardation (MR) requires there to be significant subaverage general intellectual functioning (Criterion A) that is accompanied by limitations in adaptive functioning in at least 2 of the following skill areas: communication, self care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health and safety (Criterion B). The onset must occur before age 18 years (Criterion C). General intellectual functioning is defined by the intelligence quotient, IQ. Adaptive functioning refers to how effectively individuals cope with common life demands. These are less objective measures and rely on information gathered from independent sources e.g. teacher evaluation and educational, developmental and medical history, nevertheless these assessments are extremely useful. In the UK, the ICD-10 Classification of Mental and Behavioural Disorders, WHO, Geneva 1992 is used whilst in the USA the DSM-IV diagnostic classification is used which is broadly similar to the WHO classification[1,2].

IQ across the population is normally distributed and is set at 100 and an IQ <70 is classified as intellectual impairment or mental retardation. In approximately 0.5-1% of the population mental retardation is severe, defined as an IQ<50, and in 2-3 % of the population the mental retardation is mild to moderate (IQ 50-70) which defines them as having special needs.

Etiology of mental retardation

In many cases (40%) the underlying aetiology remains unknown but with improved technology and understanding this figure is gradually reducing. Both environmental and genetic causes lead to MR and frequently coexist in an individual. *Environmental* exposure divides into pre-, peri- and postnatal exposure. The longterm consequences of extreme prematurity and the associated medical complications accounts for an increasingly significant proportion of children with mental retardation whereas the proportion of children suffering from post natal infections is diminishing. Perinatal injury due to birth problems remains common as does prenatal exposure to teratogens during pregnancy. These include fetal exposure to sodium valproate, anticoagulants, alcohol and high levels of blood glucose in diabetic mothers. A small proportion of children also suffer from accidents or infections beyond the postnatal period that results in mental retardation.

The *genetic* contribution to severe MR is high as empiric recurrence risks for siblings of severely affected individuals are 5-8% if a single case is observed and 12-15% if 2 siblings are affected [3]. This includes both chromosomal abnormalities and single gene defects. The relative excess of males in the population with severe mental retardation (1.3-1.7:1) suggests that X-linked disease genes are a significant contribution to the overall genetic aetiology[4]. Recent studies using modern cytogenetic techniques, to exclude chromosome abnormalities, suggest that where 2 male siblings are severely retarded, in the absence of a chromosome abnormality, the likelihood of this being due to an X-linked gene abnormality is as high as 80%[5].

Investigation of the patient with mental retardation

The assessment of an individual with mental retardation relies heavily on a good clinical history and examination. A detailed 3 generation pedigree may reveal histories of fetal loss, miscarriage or a history of medical problems in other family members which may provide clues to the underlying aetiology. Details of maternal health, pregnancy history and birth history noting birth weight, height and head circumference are invaluable. A profile of developmental milestones and education history will help to distinguish the individual with slow development from those with developmental regression associated with neurodegenerative conditions. There have been several consensus papers recently recommending base line investigations for a developmentally delayed child (see table 1)[6].

Chromosomal abnormalities associated with mental retardation

Routine Karyotype

This is in effect a visual inspection of the whole genome at the resolution of approx 5-10 Mb. This will detect large gain or loss of chromosome material and rearrangements which are almost always of clinical significance. Although the technique is ultimately limited by the resolution of the microscope the quality of the chromosome preparations have gradually improved over the last 10 years and re-evaluation of a patient's chromosomes where a chromosome abnormality is suspected is well worthwhile.

Table 1
Investigation of a child with developmental delay based on Shevell *et al* 2003

Investigation of the child with developmental delay
● 3 generation pedigree and details of development of all possibly affected individuals
● Obtain a detailed clinical history of maternal health pre-pregnancy
● Pregnancy history
● Birth history and birth height, weight and head circumference
● Developmental milestones
● Educational history (special schools and IQ)
● Neonatal PKU and hypothyroidism
● Karyotype (550 G banded resolution)
● Fragile X
● Telomere screen
● MRI of brain
● EEG if epilepsy present
● Metabolic screen if clinically indicated

Peaks and troughs of levodopa therapy have put limits on patient function.

When symptoms develop due to shortening of levodopa/DDCI dose effectiveness switch to Stalevo and stay in control.[1,2]

New STALEVO

Stalevo (levodopa / carbidopa / entacapone) Brief Prescribing Information Indication: Treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment. **Dosage and administration:** Orally with or without food. One tablet contains one treatment dose and may only be administered as whole tablets. Optimum daily dosage must be determined by careful titration of levodopa in each patient preferably using one of the three tablet strengths. Patients receiving less than 70-100mg carbidopa a day are more likely to experience nausea and vomiting. The maximum Stalevo dose is 10 tablets per day. Usually Stalevo is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone. See SPC for details of how to transfer these patients and those not currently treated with entacapone. *Children and adolescents:* Not recommended. *Elderly:* No dosage adjustment required. *Mild to moderate hepatic impairment, severe renal impairment (including dialysis):* Caution advised. **Contraindications:** Hypersensitivity to active substances or excipients. Severe hepatic impairment. Narrow-angle glaucoma. Pheochromocytoma. Concomitant use of non-selective monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine). Concomitant use of a selective MAO-A inhibitor and a selective MAO-B inhibitor. Previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis. **Warnings and precautions:** Not recommended for treatment of drug-induced extrapyramidal reactions. Administer with caution to: patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions, or past or current psychosis; patients receiving concomitant antipsychotics with dopamine receptor-blocking properties, particularly D2 receptor antagonists; patients receiving other medicinal products which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias, monitor cardiac function carefully during initial dosage adjustments. Monitor all patients for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully. Caution when driving or operating machines. Doses of other antiparkinsonian treatments may need to be adjusted when Stalevo is substituted for a patient currently not treated with entacapone. Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dosage reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy. **Undesirable effects:** *Levodopa / carbidopa* – Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, depression, cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence. *Entacapone* – Most frequently relate to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and urine discolouration. Common: insomnia, hallucination, confusion and paroniria, Parkinsonism aggravated, dizziness, dystonia, hyperkinesias, diarrhoea, abdominal pain, dry mouth constipation, vomiting, fatigue, increased sweating and falls. See SPC for details of laboratory abnormalities, uncommon and rare events. **Legal category:** POM. **Presentations, basic NHS costs and marketing authorization numbers:** Stalevo 50mg/12.5mg/200mg, 30 tablet bottle £24.00, 100 tablet bottle £80.00, MA numbers: EU/1/03/260/002-003; Stalevo 100mg/25mg/200mg, 30 tablet bottle £24.00, 100 tablet bottle £80.00, MA numbers: EU/1/03/260/006-007; Stalevo 150mg/37.5mg/200mg, 30 tablet bottle £24.00, 100 tablet bottle £80.00 MA numbers: EU/1/03/260/010-011. **Distributed in the UK by:** Orion Pharma (UK) Ltd. Leat House, Overbridge Square, Hambridge Lane, Newbury, Berkshire, RG14 5UX, England. **In Ireland information is available from:** Orion Pharma (Ireland) Ltd, c/o Allphar Services Ltd, Belgard Road, Tallaght, Dublin 24. Tel 01-4041600. Fax: 01-4041699. Full prescribing information is available on request. Stalevo is a registered trademark. Updated November 2003.

New Stalevo® ▼
levodopa, carbidopa, entacapone

Enhance the benefits of levodopa

References
1. Larsen JP *et al. Eur J Neur* 2003;**10**:137-146.
2. Rinne UK *et al. Neurology* 1998;**51**:1309-1314.

Date of preparation:
December 2003
STA1016

Microdeletion syndromes and subtelomeric deletion analysis

There are recurrent small microdeletions of the genome that are associated with characteristic syndromes. Routine chromosome analysis would appear normal as these microdeletions are too small to be detected by G banding and light microscopy and would only be detected using specific genomic DNA fluorescent probes which fail to bind where there is deletion. The common deletion syndromes are Wolf-Hirshhorn, Cri du Chat, Williams, Prader-Willi, Angelman, Rubinstein-Taybi, Miller-Dieker lissencephaly, Smith-Magenis, Alagille, DiGeorge or 22q11 deletion syndrome (see table 2 for the chromosomal location).

In 1995 Flint *et al.* extended this technique to develop a strategy to screen for the abnormal inheritance of subtelomeric DNA polymorphisms in individuals with mental retardation[7]. They found 3/99 patients had an abnormality at the end of one of the chromosomes. Since then the technology has been developed to provide this as a clinical service for suitably selected patients. The range of diagnostic yield is approximately 3.5 to 11%[8].

Genomic Microarrays

The principle is therefore well established that small deletions or duplications of chromosome material can lead to mental retardation. The recent challenge has been to identify small deletions and duplications in the whole genome in a single or few procedures. The use of multiple probes simultaneously is now possible using probes of known location on the genome 1 Mb apart[14]. Recent publications have established that a further 10% of patients with mental retardation carry deletions or duplications[9,10]. Although this technique is not yet in routine clinical practice it is likely to be soon.

Single gene disorders associated with mental retardation

There are 3 broad phenotypic groups of diseases where mental retardation is a significant feature: progressive neurodegenerative conditions; syndromic mental retardation where the mental retardation accompanies other physical features and non-syndromic mental retardation where the mental impairment is the only significant and constant feature. Research to identify the causes of non-syndromic mental retardation has been predominantly confined to characterising disease causing genes on the X chromosome. This has been due to the relative excess of males in the population with severe mental retardation[4], the availability of large kindreds with X linked disease and the relative experimental ease of identifying recessive genes on the X chromosome.

Fragile X syndrome was the first single gene in this category to be identified and since 1991 a further 16 X-linked genes have been associated with a non-syndromic mental retardation phenotype although some of these genes are also associated with a specific syndromic diagnosis: *FMR2*, *PAK3*, *OPHN1*, *GDI*, *IL1RAPL1*, *RSK2*, *ATRX*, *ARHGEF6*, *MECP2*, *TM4SF2*, *SLC6A8*, *FACL4*, *ARX*, *AGTR2*, *PQBP1*, *DLG3*. All the genes identified to date are rare causes of X-linked mental retardation as only a small number of families have ever been found to carry mutations in the same X linked gene and there remains a large number of X linked families where the causative mutation have not yet been identified. To account for the remaining unresolved X linked families, it has been estimated that as many as 75 additional genes on the X chromosome remain to be assigned to a mental retardation phenotype[11].The provision of a molecular genetics service for all these rare X linked genes is indeed a challenge and currently relies on research groups with a special interest.

Future work

The identification and characterisation of many more genes responsible for mental retardation over the coming few years is likely with the development of large-scale corroborative research endeavours. This means that for many families more appropriate diagnostic investigations will be available and families will have the possibility of understanding the basis of the disability in their child. This knowledge will also ensure that accurate and appropriate genetic information is available to the family. Over the next 10 years, it is hoped that many of the 40% of children where a diagnosis is not yet achieved will have the benefit of an accurate diagnosis.

References

1. WHO. *The ICD-10 classification of mental and behavioural disorders:* WHO, 1992.
2. Assoc AP. *Diagnostic and statistical manual of mental disorders DSM-IV:* American Psychiatric Association, 1994.
3. Crow YJ, Tolmie JL. *Recurrence risks in mental retardation.* J Med Genet 1998;35(3):177-82.
4. Penrose LS. *A clinical and genetic study of 1280 cases of mental defect.* Vol 229. London: HMSO, 1938.

Table 2
Common microdeletion syndromes identified by FISH at specific chromosome locations.

Syndrome	Chromosome location
Wolf-Hirschhorn	4p16.3
Cri du chat	5p15.2-p15.3
Williams	7q11.23
Prader-Willi	15q11-q13(paternal)
Angelman	15q11-q13 (maternal)
Rubinstein-Taybi	16p13.3
Miller-Dieker lissencephaly	17p13.3
Smith-Magenis	17p11.2
Alagille	20q12.1-p11.23
Di George, 22q11 syndrome	22q11.21-q11.23

5. Turner G, Partington M. *Recurrence risks in undiagnosed mental retardation.* J Med Genet 2000;37(12):E45.
6. M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, Majnemer A, Noetzel M, Sheth RD. *Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. Neurology* 2003;60(3):367-80.
7. Flint J, Wilkie AO, Buckle VJ, Winter RM, Holland AJ, McDermid HE. *The detection of subtelomeric chromosomal rearrangements in idiopathic mental retardation.* Nat Genet 1995;9(2):132-40.
8. Flint J, Knight S. *The use of telomere probes to investigate submicroscopic rearrangements associated with mental retardation.* Curr Opin Genet Dev 2003;13(3):310-6.
9. Vissers LE, de Vries BB, Osoegawa K, Janssen IM, Feuth T, Choy CO, Straatman H, van der Vliet W, Huys EH, van Rijk A, Smeets D, van Ravenswaaij-Arts CM, Knoers NV, van der Burgt I, de Jong PJ, Brunner HG, van Kessel AG, Schoenmakers EF, Veltman JA. *Array-based comparative genomic hybridization for the genomewide detection of submicroscopic chromosomal abnormalities.* Am J Hum Genet 2003;73(6):1261-70.
10. Shaw-Smith C, Redon R, Rickman L, Rio M, Willatt L, Fiegler H, Firth H, Sanlaville D, Winter R, Colleaux L, Bobrow M, Carter NP. *Microarray based comparative genomic hybridisation (array-CGH) detects submicroscopic chromosomal deletions and duplications in patients with learning disability/mental retardation and dysmorphic features.* J Med Genet 2004;41(4):241-8.
11. Ropers HH, Hoeltzenbein M, Kalscheuer V, Yntema H, Hamel B, Fryns JP, Chelly J, Partington M, Gecz J, Moraine C. *Nonsyndromic X-linked mental retardation: where are the missing mutations?* Trends Genet 2003;19(6):316-20.

Correspondence to:
Dr. F Lucy Raymond
Cambridge Institute for Medical Research, University of Cambridge, Cambridge, CB2 2XY
E-Mail: flr24@cam.ac.uk

GOLD study details see http//:goldstudy.cimr.cam.ac.uk

Aneurysmal Subarachnoid Haemorrhage

Population based studies indicate that the incidence of SAH in the UK is around 10 per 100,000 of the population per annum with a median age at presentation of 61 years and a female preponderance (64%)[1]. Aneurysmal SAH is associated with smoking and hypertension. Early diagnosis and treatment is the key to reducing the high morbidity and mortality that is associated with this disorder[2].

Diagnosis and grading

The classical presentation of SAH is with a sudden severe headache accompanied by vomiting, photophobia and neck stiffness. Other less obvious cases of sudden severe headache with resolution over 24-48 hours may lead to a missed or delayed diagnosis and therefore a high index of clinical suspicion is required when taking a history. Some patients present in coma.

All patients with a suspected SAH require an urgent CT brain scan to demonstrate haemorrhage. The sensitivity of this investigation exceeds 95% if performed within 24h of the ictus. CT angiography is often utilised in specialised units to help delineate any aneurysms at this stage and this may even replace invasive cerebral angiography. If the initial CT scan is normal a lumbar puncture should be performed without delay, since uniformly blood stained CSF supports a diagnosis of a Sylvian Fissure Haematomas and warrants further investigation regardless of the presence of xanthochromia.

Patients with a SAH can be graded according to their clinical status[3]. Poor grade patients (not obeying commands) require airway protection and are best ventilated for transfer to a regional centre.

Early management (figure 1)

The principal causes of deterioration and death in patients with a SAH are severe primary haemorrhage, rebleed, delayed cerebral ischaemia, hydrocephalus and general medical complications and so the early management is directed at minimising the overall risk of such complications.

A severe haemorrhage contributes to a cycle of elevated intracranial pressure, cerebral ischaemia and catastrophic cerebral oedema. Respiratory and circulatory support may improve the situation. Patients with clinical signs of dehydration are at an increased risk of developing delayed cerebral ischaemia and so early fluid administration of saline alternating with colloid supplemented by oral intake should be established in good grade patients[4]. Central venous pressure monitoring to titrate fluid administration in poor grade patients is essential.

Nimodipine is a selective calcium channel antagonist that should be administered to all patients. It is proven to reduce the incidence of a poor outcome from delayed cerebral ischaemia[5]. Anticonvulsants are only recommended if seizure activity has occurred.

Referral

All patients except those with fixed dilated pupils from a catastrophic presentation haemorrhage should be urgently referred to the regional neurosurgical service. Patients who do not obey commands should be ventilated for transfer.

Specialist management (figure 1)

Specialists need to recognise and treat hydrocephalus and cerebral ischaemia in addition to providing definitive aneurysm treatment. The insertion of an external ventricular drainage in patients who do not obey commands where the CT scan reveals ventricular dilatation can improve the clinical grade. Patients who obey commands do not require CSF drainage unless their neurological state deteriorates. External ventricular drains should be tunnelled posteriorly to minimise encroachment upon any subsequent craniotomy site.

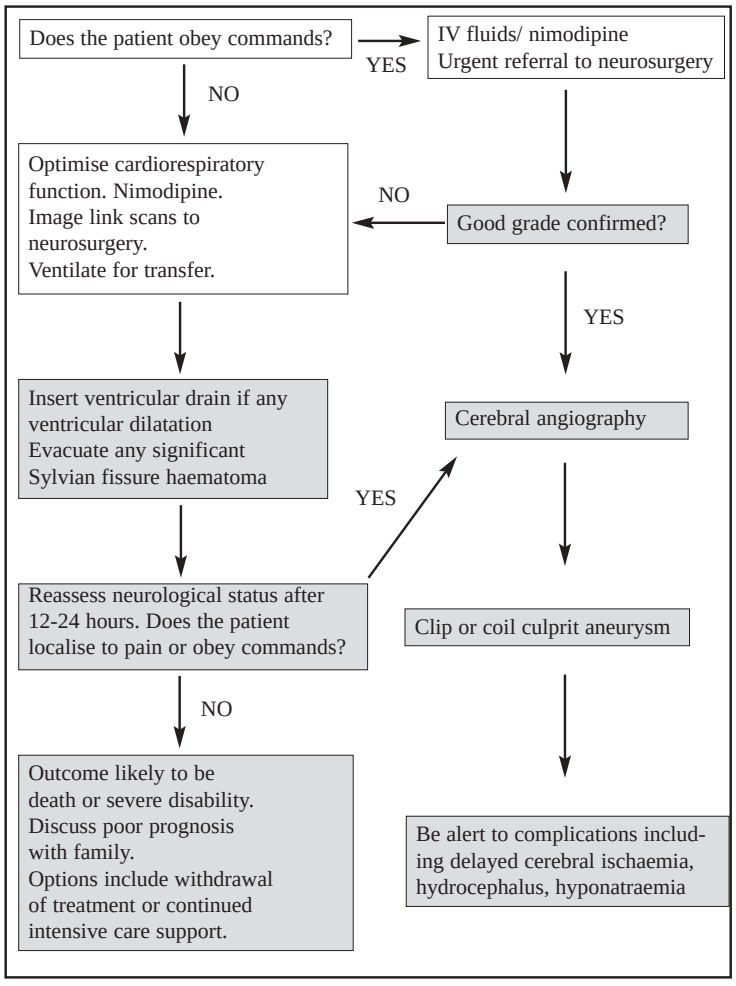
Four-vessel cerebral angiography is performed in good grade patients within 24-48 hours of transfer. Ventilated poor grade patients are assessed neurologically after treatment of hydrocephalus and stabilisation on the critical care unit. If they localise to pain, or better, after cessation of sedation, angiography is undertaken. Whilst the CT scan appearances help to determine the likely location of the culprit aneurysm the entire intracranial circulation is inspected to determine the presence of multiple aneurysms (which occur in around 20% of cases). The advent of 3-D reconstruction technology has improved angiographic interpretation and aids both endovascular and surgical approaches.

Endovascular management

Over the past decade endovascular techniques have become the treatment of choice for ruptured posterior

Peter Whitfield is a consultant neurosurgeon at the South West Neurosurgical Centre in Plymouth. He has previously worked in Glasgow and Aberdeen in addition to his higher surgical training in Cambridge. Peter has a PhD in the molecular biology of cerebral ischaemia. His clinical interests include vascular neurosurgery, image guided tumour surgery and microsurgical spinal surgery. He has a practical interest in medical education and is involved in implementation of the Phase 2 teaching in neurosciences at the Peninsula Medical School.

Figure 1: Management algorithm for patients with a subarachnoid haemorrhage. Shaded boxes indicate specialist neurosurgical management.



DR. ALOIS ALZHEIMER

BEFORE HIM, THE DISEASE DIDN'T HAVE A NAME

BEFORE ARICEPT, IT DIDN'T HAVE A REALISTIC TREATMENT

Aricept®
donepezil hydrochloride

CONTINUING COMMITMENT TO ALZHEIMER'S

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

Eisai Pfizer

A577-ARI236-12-02

fossa aneurysms. Publication of the interim results of the International Subarachnoid Aneurysm Trial (ISAT) has supported the development of aneurysm coiling for anterior circulation aneurysms[6]. Although the long term durability of coils has not yet been adequately determined, the absolute difference of 6.9% in poor outcome at 12 months has led to a large increase in the number of coiling procedures undertaken nationwide. Coiling is performed under general anaesthetic and close liaison between radiologist and surgeon is recommended to discuss optimal management. A sub-optimal coiling may be appropriate in elderly and/or poor grade patients whereas significant aneurysm remnants are less acceptable in younger, good grade patients (figure 2). If coiling is not appropriate open surgery is undertaken provided the patient localises to command.

Surgical management

Aneurysm surgery is usually performed within 72 hours of the ictus to minimise the re-bleed risk and enable aggressive treatment of any subsequent delayed ischaemic deficit.

Technical aspects of surgery

Most anterior circulation aneurysms are approached through an ipsilateral pterional craniotomy. The scalp is opened as a single layer and a Z-shaped incision is made in the temporalis fascia and frontal periosteum permitting exposure of the pterion. A single burrhole in the posterior temporal region is incorporated into a low pterional craniotomy. A cresenteric dura flap is opened in a dry operative field with a halo retractor system in place. The brain can appear very swollen at this stage. However, placement of a subfrontal 8mm retractor with microscope assistance enables visualisation of the optic nerve. The chiasmatic, carotid and lamina terminalis cisterns are then opened and brain decompression is achieved. The temporal bridging veins are divided before placing a 6mm retractor on the temporal lobe to expose the Sylvian fissure. This is opened to provide direct access to the internal carotid artery and the bifurcation. Sub-pial resection of brain adjacent to the middle or anterior cerebral arteries minimises traction on the subarachnoid vessels as the aneurysm complex is encountered (figure 3). Great care is taken to identify the anatomy of the aneurysm. With anterior communicating artery aneurysms the contralateral A1 and A2 vessels can usually be identified by inspection across the chiasm. With large MCA aneurysms the sac may need to be retracted to identify the more medially placed M2 efferent vessels. Time spent dissecting around the aneurysm neck minimises the risk of tearing the arachnoid causing an intraoperative rupture during clip placement. Cauterisation of the aneurysm sac may enable moulding of the aneurysm permitting better placement of a clip. Clip placement is frequently more safely achieved with a short period of parent vessel temporary clipping to reduce the tension in the aneurysm sac. Clip blades should be placed parallel to the parent vessel to prevent kinking or occlusion of parent and distal vessels. The dome of the clipped aneurysm is punctured to ensure that it has been satisfactorily secured. If an intraoperative rupture occurs, aspirate blood without increasing the size of the rent in the aneurysm. Often a small bleed will cease with suction, irrigation, precise coagulation and pressure. Fenestrated and encircling clips can be used to effectively rescue a tense situation should the rent be near the aneurysm neck. Once the aneurysm is secure the dura is closed, the bone flap replaced, the temporalis reconstructed and the scalp closed.

Sylvian fissure haematomas

Patients presenting with a Sylvian fissure haematoma, depressed consciousness and a fixed dilated pupil require urgent intervention if any chance of a reasonable outcome is to be offered. A dilemma occurs between delaying treatment for investigation and undertaking surgery without knowledge of the underlying pathology. If a CT angiogram can be performed at presentation, valuable information can be gained without undue delay but in the emergency situation formal cerebral angiography is not warranted. The surgical tactics are determined by the experience of the operator. In non-expert hands partial haematoma evacuation with removal of the bone flap is reasonable pending a delayed definitive procedure to secure the aneurysm. In expert hands an extended pterional flap and subfrontal exposure of the optic nerve is recommended. The aneurysm (which is usually a laterally projecting middle cerebral aneurysm or an internal carotid bifurcation aneurysm) can then be dissected and a final clip placed usually under the protection of a proximal temporary clip.

Post-clipping/coiling management

The principal causes of post-treatment deterioration are distal vessel compromise as a result of treatment, delayed ischaemic deficit and hydrocephalus. The former is minimised by careful attention during the procedure. Aspirin or heparin may be beneficial to minimise the risk of an early intraluminal thrombosis in patients who have undergone endovascular treatment where the coil projects into the parent vessel.

Vasospasm should be managed prophylactically and therapeutically. A target systolic blood pressure of around 160 mmHg and CVP of 8-10 cm are achieved using fluids and inotropes as required. Should clinical features of vasospasm become evident the blood pressure is further augmented to evaluate whether improvement occurs. Careful monitoring of electrolytes is mandatory at this stage. Hyponatraemia should not be managed with fluid restriction since this is associated with a high incidence of cerebral infarction.[4] The value of angioplasty or papaverine injection in patients with symptomatic vasospasm requires further evaluation in the setting of a randomised controlled clinical trial. Hydrocephalus is treated with ventricular or lumbar drainage of CSF. A shunt can transform the outcome for a small number of patients.

Prognosis

A 1992-96 population based study in the UK showed that 16% of patients with a SAH died without receiving medical attention – presumably due to a catastrophic sudden presentation. A further 5% of patients died within 24h of ictus. By day 3 the case fatality rate was 30%.[1] A recent National SAH audit indicated that about 30% of catastrophic SAH cases suffer from rebleeds, about 30% develop cerebral ischaemia and about 30% deteriorate from hydrocephalus. By day 30 the case fatality rate increased steadily to 44%, probably due to the high morbidity of delayed cerebral ischaemia and the prevalence of medical problems in patients with SAH.[1] Natural history studies indicate that without treatment approximately 20% of aneurysms will re-rupture within 2 weeks of the first bleed[7].

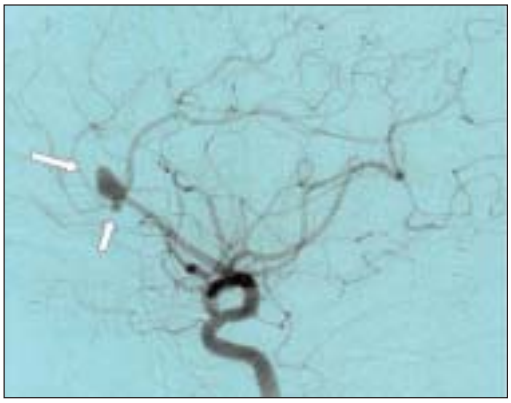


Figure 2. Lateral carotid angiogram showing a 12mm bi-lobed pericallosal artery aneurysm in a patient with a history of a SAH (arrowheads). Whilst coiling of the large superior sac was thought to be readily achievable, endovascular occlusion of the inferior lobule was considered to be difficult and uncertain due to anatomical factors. Clipping was therefore performed as the treatment of choice in this patient who made a complete recovery.

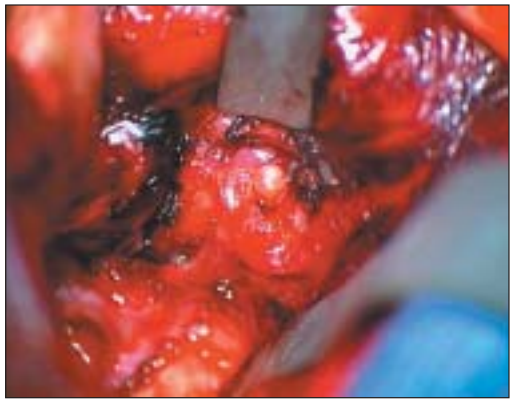


Figure 3. Anatomical dissection of a middle cerebral artery aneurysm during surgery.

Non-specific symptoms associated with SAH include headaches, lethargy, poor concentration and short-term memory deficits. Such cognitive problems can be the source of major disability[8].

The prognostic factors predictive of a poor outcome are increasing age, poor grade, presence of extensive intraventricular haemorrhage and the development of delayed cerebral ischaemia. In good grade patients a favourable outcome is achieved in 90% of patients with death and severe disability occurring in a minority[9]. However, the prognosis in poor grade patients is generally poor with only a minority achieving a favourable outcome[10].

Summary

The management of SAH is now multidisciplinary from the outset. Neurosurgeons, radiologists and intensivists all provide significant contributions to early patient care. Whilst coil technology and intracranial angioplasty evolve, surgery becomes less commonplace. However, surgery for intracranial aneurysms provides a major challenge that requires skill, dedication and attention to detail. The young ambitious neurosurgeon will find great satisfaction from aspiring to treat this cohort of patients.

Reference List

1. Pobereskin L.H. *Incidence and outcome of subarachnoid haemorrhage: a retrospective population based study.* Journal of Neurology, Neurosurgery and Psychiatry 2001;70:340-343.
2. Kassell NF, Torner JC, Haley ECJ, Jane JA, Adams HP, Kongable GL. *The International Cooperative Study on the Timing of Aneurysm Surgery.* Part 1: Overall management results. Journal of Neurosurgery 1990;73:18-36.
3. Teasdale G, Drake C.G., Hunt W, *et al. A universal subarachnoid haemorrhage scale: report of a committee on the World Federation of Neurosurgical Societies.* Journal of Neurology, Neurosurgery and Psychiatry 1988;51:1457-1457.
4. Wijdicks EFM, Vermeulen M, ten Haaf J.A., Hijdra A., Bakker W.H., van Gijn J. *Volume depletion and natriuresis in patients with a ruptured intracranial aneurysm.* Ann Neurol 1985;18:211-216.
5. Pickard JD, Murray GD, Illingworth R, *et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial.* BMJ 1989;298:636-642.
6. International Subarachnoid aneurysm trial (ISAT) collaborative group. *International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial.* Lancet 2003;360:1267-1274.
7. Locksley HB. *Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations. Based on 6368 cases in the Cooperative Study.* Journal of Neurosurgery 1966;25:321-368.
8. Mavaddat N, Sahakian BJ, Hutchinson PA, Kirkpatrick PJ. *Cognition following subarachnoid hemorrhage from anterior communicating artery aneurysm: Relation to timing of surgery.* Journal of Neurosurgery 1999;91:402-407.
9. Whitfield PC, Moss H, O'Hare D, *et al. An audit of aneurysmal subarachnoid haemorrhage: earlier resuscitation and surgery reduces inpatient stay and deaths from rebleeding.* Journal of Neurology, Neurosurgery & Psychiatry 1996;60:301-306.
10. Hutchinson PJ, Power DM, Tripathi P, Kirkpatrick PJ. *Outcome from poor grade aneurysmal subarachnoid haemorrhage - which poor grade subarachnoid haemorrhage patients benefit from aneurysm clipping?* British Journal of Neurosurgery 2000;14:105-109.

Correspondence to:
Peter Whitfield, BM (Distinction) PhD FRCS Eng FRCS (Surgical Neurology), consultant neurosurgeon and honorary university fellow
South West Neurosurgery Centre
Derriford Hospital
Plymouth PL6 8DH
E-Mail.
Peter.Whitfield@phnt.swest.nhs.uk

Alexia

Dr Alexander Leff is a specialist registrar at the Royal Free Hospital and National Hospital for Neurology and Neurosurgery. He trained at University College London where he studied history of Medicine as part of an intercalated BSc. His main research interests include functional imaging and the recovery of language, and the rehabilitation of hemianopic alexia.

Introduction

The term alexia denotes the presence of an acquired reading disorder that prevents comprehension or production of written language[1]. Although the word "dyslexia" is equivalent, it is often used to refer to a range of disorders seen in people who fail to develop normal reading skills in childhood.

Normal people can read single words as quickly as single letters. Thus, the letters of a word are perceived in parallel, and no eye movements are made within a word unless it is long or unfamiliar. Reading text requires the reader, in addition, to direct their eyes along the array of words. Therefore, during fixation on a word embedded in text, two processes occur in parallel: word recognition, and the planning of the eye movement onto the viewing point of the next word. Specific regions throughout both cerebral hemispheres are involved in supporting the interdependent processes required to achieve effortless text reading (high visual acuity, letter and word recognition, central language processing, directed visuo-spatial attention and oculomotor control)[2]. Any disease process that affects oculomotor control will be likely to impinge on reading ability, but these disorders are beyond the scope of this article; I will instead concentrate on the syndromes caused by disruption to visual processing of word forms or of those neural regions that support central language processing.

The high visual acuity required to discern word forms is in part due to the preferential representation of foveal and parafoveal vision (having radii of 1° and 5° around fixation, respectively) in the primary visual cortex. Bilateral extra-striate cortices are also involved in reading, but the first cortical region to exhibit asymmetric activity to word forms is left ventro-lateral occipito-temporal cortex (VLOT – see figure). This region, along with an area of cortex that extends medially and anteriorly, is often referred to as the 'visual word-form area' as damage to it, or its connections, can lead to the isolated alexic syndrome first recorded by Jules Dejerine in 1892 - 'alexia without agraphia' also known as 'pure' alexia[3,4]. This syndrome is characterised by the breakdown of the patient's ability to process word forms as a whole unit. As letter identification is often spared, patients tend to read using a letter-by-letter strategy which is laborious and error prone, especially for longer words. There is still debate as to whether this region solely or even predominantly supports reading function[5], but a patient with pure alexia who writes at a normal pace and then fails to read back to you what they have just written is one of the more striking signs in clinical neurology.

Classification

Neurologists and psychologists differ in the terminology they use to describe alexic syndromes[6,7]; however, both recognise the importance of identifying whether the syndrome occurs as part of a generalised language disorder (alexia in the context of aphasia; alexia with agraphia; 'central' alexia) or in an isolated form (alexia without agraphia; 'peripheral' alexia). The neuropsychological classification of central alexia is based around the relative impairment of two functionally distinct reading routes: reading by sound and reading by sight. Normal readers can pronounce unfamiliar words by applying the common rules of correspondence between spelling and sound in their language. These rules work for the majority of English words, but there is a sizable minority of irregular words (e.g. yacht, blood, two and mauve) which cannot be read in this way and rely on the reader having built up a "sight" vocabulary, whereby words can be read without recourse to "sounding out". Patients who can only read by the sight route typically have only minor reading deficits, but are unable to read non-words such as "mune" as these words will not be present in their 'sight' vocabulary: so-called 'phonological dyslexics'[8]. Patients who can only read by sound can manage non-words but have problems with irregular words, pronouncing pint as if to rhyme with mint: so-called 'surface' dyslexics[9]. Regularisation errors are often seen early in patients presenting with a temporal variant of fronto-temporal dementia (FTD), allowing this condition to be differentiated from both frontal forms of FTD and Alzheimer's disease[10]. Patients are also described who have a double deficit, affecting, to different degrees, both the sight and sound reading routes; such patients are deemed to have 'deep' dyslexia[9,11]. As well as producing error patterns consistent with the two conditions just mentioned, these patients have additional problems reading function words (it, and, when), and often make semantic errors; e.g. a patient with this syndrome read "inn" as "*pub*", but was unable to read the word "in" at all (Prof. Richard Wise – personal communication). Patients with central alexia often have their reading disorder ignored by clinicians as comprehension and speech output impairments tend to overshadow any disability caused by the alexia; however, occasionally the aphasic and alexic components dissociate to some degree resulting in grossly aphasic patients being able to read quite well, thus allowing communication to continue though this modality[12].

In contrast, patients with a peripheral alexia have preserved central language function (although specific anomic deficits have been noted, the commonest being colour anomia, an impairment of naming in the context of normal colour perception). Patients with pure alexia may initially present with global alexia, being unable to recognise and name letters[13]. In hemianopic alexia, word recognition is intact, but the presence of a right homonymous hemianopia leads to disruption of the visuomotor co-ordination of eye movements during text reading[2]. Patients with neglect alexia consistently make errors on either the initial or final letters of a word (e.g. clock read as *b*lock)[14]. Another form of peripheral alexia is attentional alexia, where patients complain of letter crowding, sometimes blending elements of two words into one; they perform better when word stimuli are presented in isolation rather than flanked by other words and letters[15].

When central alexic disorders are due to focal pathology such as stroke, they are almost always associated with damage to the dominant hemisphere in the territory of the middle cerebral artery (MCA). If peripheral alexia is due to focal pathology, then this is usually in the territory of the posterior cerebral artery (PCA) or in the border-zone between MCA and PCA, potentially causing additional 'parietal' (perceptual) or 'temporal' (associative) agnosias as well as other neuropsychological deficits associated with damage to or disconnection of occipital cortical regions.

Clinical examination

The general neurological examination may provide clues as to the lesion site and thus the type of alexia that may be expected. If a patient is aphasic then it is important the examiner gets a feel for their speech output, evaluating spontaneous speech (open questions), automatic speech (counting, days of the week) and repetition (single words

Initiating therapy with Mirapexin quickly and effectively controls the symptoms of Parkinson's disease.[1]

Using Mirapexin as initial therapy can delay the introduction of levodopa for at least four years[2] and help to delay the troublesome motor complications associated with long-term levodopa use.[3]

Mirapexin™
pramipexole

Act today for an active tomorrow

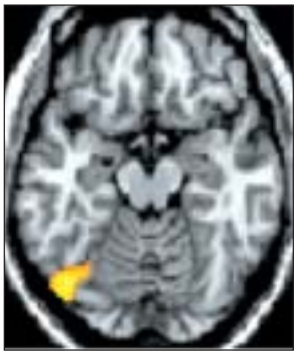
MIRAPEXIN™ (pramipexole) Abbreviated Prescribing Information. Before prescribing see Summary of Product Characteristics. **Presentation:** Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing 0.125mg, 0.25mg and 1mg respectively of pramipexole salt [dihydrochloride monohydrate]. **Uses:** The treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa. **Dosage and Administration:** Adults and Elderly Patients: *Administration:* The daily dosage is administered orally with water in equally divided doses three times per day. *Initial treatment:* Titration of dose from 0.264mg base (0.375mg of salt) per day, doubling the dose every 5-7 days, to a daily dose of 1.08mg base (1.5mg salt). If a further dose increase is necessary the daily dose should be increased by 0.54mg base (0.75mg salt) at weekly intervals up to a maximum dose of 3.3mg base (4.5mg salt) per day. NB The incidence of somnolence is increased at doses higher than 1.5mg (salt)/day. *Maintenance treatment:* The individual dose should be in the range from 0.264mg base (0.375mg salt) to a maximum of 3.3mg base (4.5mg salt) per day. It is recommended that the dosage of levodopa is reduced during both the escalation and the maintenance treatment with Mirapexin, dependent upon individual response. *Treatment discontinuation:* Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.54mg of base (0.75mg of salt) per day until the daily dose has been reduced to 0.54mg of base (0.75mg of salt). Thereafter, the dose should be reduced by 0.264mg of base (0.375mg of salt) per day. *Renal impairment:* Consult the Summary of Product Characteristics for information on revised dosage schedules. *Hepatic impairment:* Dose adjustment in patients with hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications, Warnings etc.: Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings:** In patients with renal impairment a reduced dose is recommended (see above). Hallucinations are a known side-effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur. Mirapexin has been associated with somnolence and, uncommonly, sudden sleep onset. Patients who have experienced somnolence and/or an episode of sudden onset of sleep must refrain from driving or operating machines, until such recurrent episodes and somnolence have resolved. Futhermore a reduction of dosage or termination of therapy may be considered. In advanced Parkinson's disease, in combination with levodopa, dyskinesias can occur during the initial titration of Mirapexin. If they occur, the dose of levodopa should be decreased. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In cases of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. **Drug Interactions:** There is no pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules, such as cimetidine and amantadine, may interact with pramipexole resulting in reduced clearance of either or both drugs. Reduction of the pramipexole dose should be considered when these drugs are administered concomitantly with Mirapexin. While increasing the dose of Mirapexin it is recommended that the dosage of levodopa is reduced and the dosage of other anti-Parkinsonian medication is kept constant. Due to possible additive effects, caution is advised when patients are co-prescribed Mirapexin with other sedating medication or alcohol. Co-administration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** The effect on pregnancy and lactation has not been investigated in humans. Therefore, Mirapexin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Similarly, Mirapexin should not be used during breast-feeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, dizziness and peripheral oedema occurred more often than with placebo. More frequent adverse reactions in combination with levodopa were dyskinesias. These adverse events tend to decrease or disappear with continued therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin is titrated too fast. Mirapexin has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. **Overdose:** There is no clinical experience with massive overdosage. Expected adverse events include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive/emetic measures may be required. **Basic NHS Cost:** 0.088mg x 30 £10.00, 0.18mg x 30 £20.00, 0.18mg x 100 £66.67, 0.7mg x 30 £63.67, 0.7mg x 100 £212.24. **Legal Category:** POM. **Marketing Authorisation Holder:** Pharmacia Enterprises S.A., 6, Circuit de la Foire Internationale, L-1347 Luxembourg, G.D. Luxembourg. **Marketing Authorisation Number:** Mirapexin 0.088mg x 30 tablets EU/1/97/051/001; Mirapexin 0.18mg x 30 tablets EU/1/97/051/003; Mirapexin 0.18mg x 100 tablets EU/1/97/051/004; Mirapexin 0.7mg x 30 tablets EU/1/97/051/005; Mirapexin 0.7mg x 100 tablets EU/1/97/051/006. Further information is available from Pharmacia Ltd, Davy Avenue, Milton Keynes, MK5 8PH, UK. Tel: 01908 661101. **Date of preparation:** April 2003.

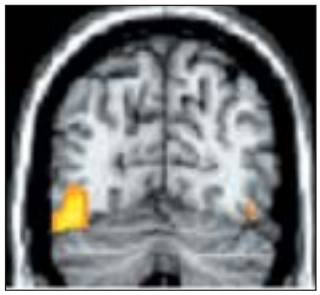
References: 1. Shannon KM, Bennett JP Jr, Friedman JH *et al*. Neurology 1997; 49: 724-728. 2. Barone P, Bressman S. Poster presented at 53rd Annual American Academy of Neurology; May 5-11, 2001 Philadelphia, Pa. 3. Parkinson's Study Group. JAMA 2000: Vol 284, No.15: 1931-1938.

Pfizer

Alexia sub-type	Error patterns (specific test material)	Usual lesion site
Central:	**Alexia part of a general language disorder**	
Reads by sound (surface dyslexia)	Regularisation errors, can read non-words (Irregular words, non-words).	Left medial +/- lateral temporal lobe (FTD).
Reads by sight (phonological dyslexia)	Difficulties with suffixes, unable to read non-words (non-words).	Left temporo-parietal lobe.
Both routes damaged (deep dyslexia)	As above plus: semantic errors, frequency/ imageability effects, poor with function words.	Extensive left temporo-parietal lobe.
Peripheral:	**Other language functions usually spared**	
Global	Very slow or inaccurate letter naming but can recognise letters (number naming may be spared).	Left VLOT or connections and splenium of CC[13].
Pure	Slow and inaccurate reading, short words easier, may use a "letter-by-letter" strategy.	Left VLOT or connections.
Hemianopic	Slow but accurate text reading, may miss prefix/ suffix depending on side of hemianopia, left HH usually more disabling than right HH (fields).	Any cause of a HH, often macular-splitting, often post-geniculate.
Neglect	Errors on prefix more common than suffix.	Right parietal lobe.
Attentional	Merged words, letter crowding (better with isolated words).	Left parietal lobe.

The main sub-types of alexia are tabulated along with their commonly associated error patterns and lesion sites. Recommended specific test material outside that found in ordinary printed material is bracketed. CC = corpus callosum; HH = homonymous hemianopia; VLOT = Ventro-lateral occipito-temporal cortex





Axial and coronal views of left VLOT cortex activated during an H_2O15 PET study. Subjects viewed single words at increasing rates. The group PET data are displayed on a canonical single-subject T1 MRI image[18]. Damage to or disconnection of this region usually causes pure alexia.

and sentences), before testing reading as the main aim in this scenario is to look for relative differences in language function between aural and graphic probes. If an isolated reading disorder is identified, then writing should also be tested (spontaneous and to dictation).

Although a variety of psychological test batteries are available for detailed assessment of reading, (e.g. the PALPA[16]) most clinicians can get a feel for the broad types of alexia with just a pen and paper and some non-specialist reading material (a newspaper or magazine is often to hand and tends to contain different font sizes, simple sentences and pictures; the latter can be used to screen for anomia, hemi-neglect, simultanagnosia, and colour anomia).

Visual acuity and fields need to be checked first. If a hemianopia is present with > 5 degrees of vision preserved to the right of fixation then it is unlikely that there will be a hemianopic contribution to the reading deficit. Patients should read a simple passage of print out loud with the examiner recording their errors. Errors are usually categorised along two principle axes according to the type of speech error made and the class of word (in terms of grammar and orthography) that the error is made on. Errors of speech output usually fall into two groups: semantic or phonological e.g. "cat" misread as "*dog*" or "c*a*b" respectively. Phonological errors are responses where the phoneme (speech sound) structure differs from the target enough for a word to have either its meaning changed or lost, and are usually due to phonemic substitutions, insertions or omissions which can occur at the beginning, middle or end of a word. Some patients will tend to make errors on certain grammatical classes of words (nouns, verbs, modifiers or function words), while others will have problems along other descriptive axes

PARKINSON'S DISEASE
Specialist care from Pfizer

Continuous control

Twenty-four hour symptom control – one dose a day

Cabaser® CABERGOLINE
The once-daily dopamine agonist

As adjuvant therapy to levodopa

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

April 2004

CAB 117

such as the commonness (frequency), concreteness (imageability), or letter or syllable length of a word.

Treatment

There are no generally agreed specific therapies for either the central or peripheral alexias, although there is a plethora of case reports detailing successful, uncontrolled, bespoke behavioural interventions. In hemianopic alexia, where the neural representations of written word forms have been spared, the emphasis has been on retraining the oculomotor system in order to improve reading scanpaths[17]. There is an ongoing randomised, controlled study aimed at assessing different oculomotor interventions in this condition (please contact the author for details).

Acknowledgement

Many thanks to Elizabeth Warrington for applying her usual clarity of thought to this manuscript.

References

1. Damasio AR. *Varieties and significance of the alexias.* Arch Neurol 1977;34:325-326.
2. Leff AP, Scott SK, Crewes H, Hodgson TL, Cowey A, Howard D, Wise RJ. *Impaired reading in patients with right hemianopia.* Ann Neurol 2000;47:171-178.
3. Dejerine J. *Contribution a l'étude anatomo-pathologique et clinique des differentes variétés de cécité-verbale.* Memoires Societé Biologique 1892;4:61-90.
4. Warrington EK, Shallice T. (1980) *Word form dyslexia.* Brain 1980;103:99-112.
5. Behrmann M, Nelson J, Sekuler EB. *Visual complexity in letter-by-letter reading: "pure" alexia is not pure.* Neuropsychologia 1998;36:1115-1132.
6. Benson DF, Geschwind N. *The alexias.* In: Vinken PJ, Bruyn GW (eds.). Handbook of clinical neurology, Vol 4. Amsterdam: North Holland, 1969:112-140.
7. Shallice T. *From neuropsychology to mental structure.* Cambridge: Cambridge University Press, 1988.
8. Beauvois M-F, Derouesne J. *Phonological alexia: three dissociations.* J Neurol Neurosurg Psychiatry 1979;42:1115-1124.
9. Marshall JC, Newcombe F. *Patterns of paralexia: a psycholinguistic approach.* J Psycholinguist Res 1973;2:175-199.
10. Hodges JR, Patterson K, Ward R, Garrard P, Bak T, Perry R, Gregory C. *The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study.* Neuropsychology 1999;13:31-40.
11. Low AA. *A case of agrammatism in the English language.* Arch Neurol Psychiat 1931;25:556-597.
12. Warrington EK, Leff AP. *Jargon dyslexia: a single case study of intact reading comprehension in a jargon dysphasic.* Neurocase 2000;6:499-507.
13. Binder JR, Mohr JP. *Topography of callosal reading pathways.* Brain 1992;115:1807-1826.
14. Costello AD, Warrington EK. *The dissociation of visuospatial neglect and neglect dyslexia.* J Neurol Neurosurg Psychiatry 1987;50:1110-1116.
15. Warrington EK, Cipolotti L, McNeil J. *Attentional dyslexia: a single case study.* Neuropsychologia 1993;31:871-885.
16. Kay J, Lesser R, Coltheart M. *Psycholinguistic assessments of language processing in aphasia (PALPA): reading and spelling.* Hove: Lawrence Erlbaum Associates, 1992.
17. Zihl J. *Eye movement patterns in hemianopic dyslexia.* Brain 1995;118:891-912.
18. Leff AP, Crewes H, Plant GT, Scott SK, Kennard C, Wise RJ. *The functional anatomy of single-word reading in patients with hemianopic and pure alexia.* Brain 2001;124:510-521.

Correspondence to:
Alexander Leff,
The Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG.
E-Mail.
alexander.leff@imperial.ac.uk

Inflammatory Diseases of the CNS I: Encephalitis

Neuropathology Articles in ACNR

A series of neuropathology articles will be published in the next few issues of ACNR with the aim of fostering interdisciplinary team discussion. The number of team meetings is increasing, bringing together all the disciplines involved in the diagnosis, management and treatment of patients with neurological disease. An essential part of this process is education. The more we understand the basic principles in each other's discipline, the better the communication and care of patients.

In the first three articles we shall deal with Inflammatory Diseases of the CNS, not as extensive reviews but as short accounts of the basic pathological principles used by neuropathologists to establish diagnoses and to plan research.

Inflammatory Diseases of the CNS I: Encephalitis by Dr Ingrid Mazanti and Professor Roy Weller, Southampton
Inflammatory Diseases of the CNS II: Meningitis and Cerebral Abscess by Dr Susan Robinson and Dr William Stewart, Glasgow
Inflammatory Diseases of the CNS III: Sarcoidosis and Non-Metastatic Diseases associated with Neoplasia by Professor Francesco Scaravilli, London

Professor Roy O. Weller, Series Editor

Introduction

Intracranial infections involving the bones of the skull or spine (osteomyelitis), the extradural compartments, the pachymeninges (dura), subdural space, leptomeninges and subarachnoid space are mainly caused by bacteria and occasionally by fungi and viruses (leptomeningitis). The organisms that infect the CNS itself (the brain and the spinal cord) are mainly viruses and bacteria, but fungi and protozoa, such as Toxoplasma and amoebae, do occasionally invade the CNS.

Encephalitis can be defined as diffuse inflammation of brain tissue, or spinal cord (encephalomyelitis or just myelitis). Two major forms of encephalitis occur: those due to virus infections and those due to autoimmune inflammation - Acute Disseminated Encephalomyelitis (ADEM).

Viruses responsible for encephalitis

The table lists the main viruses involved in encephalitis and encephalomyelitis. Many are enteroviruses; encephalitis caused by respiratory viruses appears to be less common[1]. In many parts of the world encephalitides are seasonal due to the spread of viruses by insects (arboviruses)[2]. New virus infections of the CNS, such as West Nile Fever[3] and Nipah[4], continue to evolve. Immunosuppression is an important predisposing factor for infections of the central nervous system by viruses such as the wart virus (papova virus). Viruses mainly gain access to the body via the respiratory, gastrointestinal or genitourinary mucosae and through insect bites. From the site of inoculation, viruses spread to lymph nodes and then enter the brain via the blood. Certain viruses, e.g. rabies, enter the CNS by retrograde axoplasmic transport along nerves from peripheral wounds. Other viruses, such as human immunodeficiency virus (HIV), are thought to enter the CNS within infected mononuclear cells/macrophages. DNA viruses (eg herpes simplex) and RNA viruses (eg measles) enter neurons and glia by attaching to receptors on the cell surfaces and then replicate within the cell. New virus particles may bud from the surfaces of cells or are released through lysis of the infected cells. In autoimmune encephalomyelitis (ADEM) there is no causative virus in the CNS, although the inflammatory changes of perivenous inflammation and perivenous demyelination may be widespread and are thought to result from an autoimmune reaction, frequently in response to a previous systemic virus infection.

Pathology

The pathology of the various viral infections listed in the

Dr Ingrid Mazanti trained in medicine at the Copenhagen University. After specialisation in histopathology and a consultant histo-/neuropathology position in Glostrup Hospital, Copenhagen, she is now a consultant neuropathologist to the Wessex Neurological Centre in Southampton.

Professor Roy O. Weller has wide experience in providing a regional diagnostic neuropathology service in Southern Britain and has published a number of text-books. His research fields have been in peripheral neuropathies, hydrocephalus and tumours, and more recently in Neuroimmunology and Alzheimer's Disease.

Table: Viruses causing encephalitis in various regions of the CNS (modified from (1)

Viruses infecting the central nervous system and its coverings	
Meningitis	Virus affecting mainly the white matter (leukoencephalitis or leukoencephalopathy)
Echovirus Coxackieviruses Other enteroviruses Herpes simplex virus 2 Mumps Human immunodeficiency virus Lymphocytic choriomeningitis virus	Papovavirus (JC virus) Human immunodeficiency virus
Virus affecting mainly grey matter (polioencephalitis/poliomyelitis)	Virus affecting mainly both grey and white matter (panencephalitis/panmyelitis)
Poliovirus Coxackievirus A4, A7 or B3 Echovirus 2 or 9 Enteroviruses 70 and 71 Rabies Arboviruses (especially Japanese encephalitis virus and Tick-borne encephaltitis viruses)	Herpes simplex virus 1, Herpes simplex virus 2 Varicella-zoster virus Cytomegalovirus Human immunodeficiency virus Measles Arboviruses (insect borne) Early herpes simplex virus infection Atypical herpes simplex encephalitis

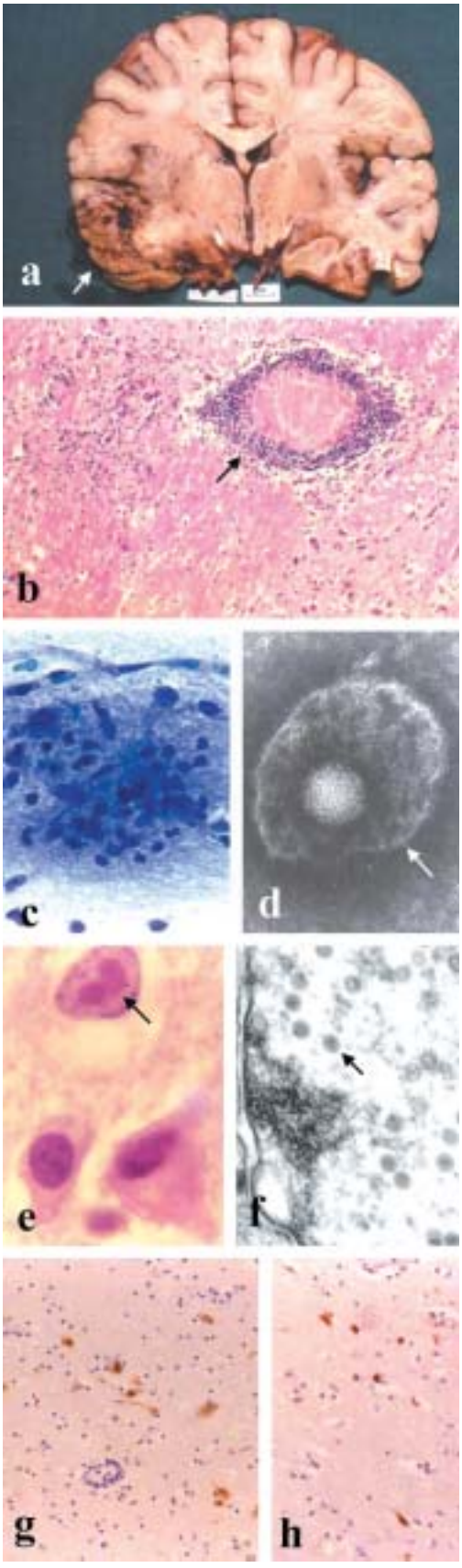


table varies, depending upon the causative virus, the location in the brain or cord affected and upon the acute or chronic nature of the disease. For example, poliomyelitis classically infects and destroys spinal and bulbar motor neurons, whereas herpes simplex infection (HSV-1) is localised to the temporal lobes. Nevertheless, the major pathological reactions within the CNS are very similar throughout a whole range of virus infections. As an example of an acute encephalitis, the pathology of herpes simplex encephalitis is described in some detail below.

Herpes simplex (HSV-1) encephalitis is probably the most common acute necrotising encephalitis in the UK. Patients present with headache, fever, seizures and decreasing levels of consciousness. CT and MRI reveal swelling and necrosis of the temporal lobes that is often bilateral. In patients who survive for many years, there is cystic change and atrophy of the temporal lobes. HSV is present in cold sores on the lips and in the trigeminal ganglia; but whether the close anatomical relationship between the trigeminal ganglia and the temporal lobes plays a role in the spread of infection to the brain remains unresolved.

Macroscopically, the brain at autopsy in a patient dying with acute herpes simplex encephalitis shows haemorrhage, swelling and necrosis of the temporal lobes (figure 1a), often with atrophy and cystic change.

The diagnostic features of encephalitis are seen microscopically. They consist of death of neurons and other cells, inflammation and the presence of the infecting virus. Dying neurons are recognised by their shrunken (pyknotic) nuclei, and pale, pink cytoplasm in haematoxylin and eosin (H&E) stained sections. The major inflammatory cells are lymphocytes; they enter the brain via post-capillary venules, accumulate around veins and spread diffusely into the infected brain tissue (Figure 1b). Microglial cells become activated, proliferate and may form small collections (microglial stars) around dead virus-infected neurons that they ingest (neuronophagia) (figure 1c). A small number of neutrophil polymorphonuclear leukocytes may be present in the early stages of the disease whereas reactive astrocytosis and macrophages are seen in the more advanced stages of the encephalitis. Identification of HSV-1 in the tissue allows a definitive diagnosis to be made. This may entail the culture of virus or the detection of antibodies to HSV in the CSF; more commonly now, viral DNA is detected by PCR.

Viruses are detected in biopsy or autopsy brain tissue

Figure 1: Herpes simplex encephalitis:
(a) Coronal section of the cerebral hemispheres showing haemorrhagic necrosis in both temporal lobes; the left temporal lobe (arrow) is more affected than the right. (b) Histology of a haematoxylin and eosin (H&E) stained section showing lymphocytes around a vein (arrow) and spreading into the surrounding brain tissue. (c) A collection of microglial cells (microglial star) with rod-shaped nuclei, around an infected neuron (smear preparation stained with toluidine blue) (d) A herpes virus particle isolated from brain, showing the central icosohedral nucleocapsid and the outer membrane (arrow) derived from the cell membrane. (Negatively stained PTA Transmission Electron Micrograph (TEM) x 114,000) (e) High magnification photomicrograph of an intranuclear viral inclusion (arrow); the nucleus bottom left shows diffuse hyperchromasia also indicating the presence of virus (H&E). (f) Herpes virus particles (arrow) in a nucleus. (TEM x 30,000) (g) HSV protein within brain cells is stained brown by immunocytochemistry. (h) HSV DNA in brain cells is stained brown by in situ hybridisation. (Reproduced by kind permission of Prof JAR Nicoll (Figs a, b, e, g, h.) Dr PJ Gallagher (Figure f) and Ms Sue Cox (Figure d). The plate of figures was kindly prepared by Anton Page and Roger Alston)

UK ABBREVIATED PRESCRIBING INFORMATION: PROVIGIL® 100mg/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 (debossed with "Provigil" on one side and "100 mg" or "200 mg" on the other). **Indication:** Excessive sleepiness associated with chronic pathological conditions, including, narcolepsy, obstructive sleep apnoea/hypopnoea syndrome and moderate to severe chronic shift work sleep disorder. **Dosage:** *Adults: Narcolepsy and Obstructive Sleep Apnoea/Hypopnoea Syndrome:* 200 – 400 mg daily either as two divided doses in the morning and at noon or as a single morning dose according to response; *Shift Work Sleep Disorder:* 200 mg daily taken as a single dose approximately 1 hour prior to the start of the work shift. *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:* Not recommended. **Contra-indications:** Use in pregnancy and lactation, 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 child-bearing 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. Patients should be advised that Provigil is not a replacement for sleep and good sleep hygiene should be maintained. Provigil is not recommended in patients with a history of left ventricular hypertrophy, cor pulmonale, or 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. Provigil tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption. **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 ethinylestradiol 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 Caucasian 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 anticonvulsant or anticoagulant drugs. **Side effects:** *Very common* (>10%) – headache. *Common* (>1%) – nervousness, insomnia, anxiety, dizziness, somnolence, depression, abnormal thinking, confusion, paraesthesia, blurred vision, nausea, dry mouth, diarrhoea, decreased appetite, dyspepsia, constipation, tachycardia, palpitation, vasodilatation, asthenia, chest pain, abdominal pain and abnormal liver function tests. 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:** PL16260/0001 Provigil 100 mg Tablets, PL 16260/0002 Provigil 200 mg Tablets. **Marketing authorisation holder:** Cephalon UK Limited. **Legal category:** POM. **Date of preparation:** March 2004. 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 Information Freefone 0800 783 4869 (ukmedinfo@cephalon.com). PRO809/Mar 04

Cephalon
deliver more>

in a variety of ways. Virus particles can be isolated by homogenising fresh tissue in glutaraldehyde, centrifuging and negatively staining the virus in the supernatant with phosphotungstate (figure 1d); this was a major diagnostic technique before the introduction of immunocytochemistry and PCR, and remains a key investigation for the characterisation of novel virus infections. In H&E stained sections of brain tissue, viral inclusions may be seen in the nuclei of infected cells, or the virus may be spread more diffusely through the nucleus (figure 1e). Viral particles in the nuclei lack the outer membrane of the intact virus (compare electron micrographs figure 1d and f). Viral proteins within cells are detected by immunocytochemistry (figure 1g), provided the antibodies are available, and viral DNA by *in situ* hybridisation (figure 1h).

The pathological features illustrated in figures 1 b & c are characteristic of the body's defences against virus infections. Infected cells produce interferons (IFN). IFN-/ and € induce other cells to resist infection by the virus; IFN-*y* acts as a potent pro-inflammatory factor that activates NK cells, monocytes and macrophages. NK lymphocytes are rapid response cells that kill cells infected by virus although the mechanism of such killing is unclear. Specific antibodies to viral glycoproteins are produced by B lymphocytes/plasma cells and together with complement, they neutralise free virus especially in the blood. T lymphocytes play a key role in encephalitis as MHC Class I–restricted $CD8^+$ cytotoxic T lymphocytes destroy cells infected with virus. Immunosuppression interferes with these defence mechanisms; as a consequence, viruses that do not normally infect the CNS, such as cytomegalovirus (CMV) and papova virus, may proliferate in the CNS causing CMV-encephalitis and progressive multifocal leukoencephalopathy respectively.

Differential diagnoses

One major differential diagnosis at biopsy or autopsy is between virus infection and autoimmune encephalomyelitis (ADEM)[5]. The regional specificity of many virus infections within the CNS may suggest a diagnosis of viral encephalitis as may the intense lymphocyte infiltration and presence of viral protein or nucleic acid by histology, immunocytochemistry and *in situ* hybridisation. PCR or antibody studies of CSF may identify a virus. However, in more than 50% of cases no virus is identified by these techniques even though it is suspected[2]. ADEM is usually preceded by a systemic viral illness some 2-3 weeks previously, such as measles in the developing world or a wide variety of pulmonary or gastrointestinal infections in Europe and USA. Although often centred on the cerebral white matter, ADEM may affect many areas of the CNS including the spinal cord. Distinction from a virus infection may be difficult and may depend upon the history and the lack of evidence of a virus infection in the CNS. Bacterial and fungal infections mainly result in neutrophil polymorphonuclear leukocyte infiltration and focal necrosis associated with the presence of bacteria or fungi. Differentiating these diseases from the lymphocyte-dominated inflammation of viral encephalitis and ADEM is, therefore, relatively straight-forward. The other major differential diagnosis is multiple sclerosis (MS). MS appears to be an autoimmune disorder and is characterised by demyelination, perivenous lymphocytes, microglial activation, monocyte/macrophage invasion reactive astrocytosis, and varying degrees of axonal degeneration. However, MS plaques are usually focal and well-demarcated areas that lack overt evidence of infecting virus. Confusion occurs most often between MS and ADEM, although mostly the MS plaques are well circumscribed whereas the areas of demyelination seen in ADEM are frequently confined to narrow areas around veins[5].

References

1. Love S, Wiley CA. *Viral diseases.* In: Graham DI, Lantos PL, eds. Greenfield's Neuropathology. London: Arnold, 2002:1-105.

2. Boos J, Esiri MM. *Viral Encephalitis in Humans.* Washington: ASM Press, 2003.

3. Beasley DW, Davis CT, Whiteman M, Granwehr B, Kinney RM, Barrett AD. *Molecular determinants of virulence of West Nile virus in North America.* Arch Virol Suppl 2004,18:35-41.

4. Johnson RT. *Emerging viral infections of the nervous system.* J Neuovirol 2003,9:140-147.

5. Prineas JW, McDonald WI, Franklin JM. *Demyelinating diseases.* In: Graham DI, Lantos PL, eds. Greenfield's Neuropathology. London: Arnold, 2002:471-550.

Correspondence to:
Dr Ingrid Mazanti
Department of Cellular Pathology,
Division of Neuropathology,
Southampton University Hospitals
NHS Trust, Southampton
SO16 6YD, UK
E-Mail.
Ingrid.Mazanti@suht.swest.nhs.uk

Progression and Correction of Deformities in Adults with Cerebral Palsy

Mark Paterson is a paediatric orthopaedic consultant in London with a particular interest in cerebral palsy and neurodisability. He is Secretary to the British Society for Surgery in Cerebral Palsy and is the Orthopaedic Representative for Scope.

Introduction

Cerebral palsy (CP) is a lifelong condition, and although the neurological lesion may be static, the musculoskeletal sequelae change significantly throughout life.

The effect of spasticity upon the musculoskeletal system is summarised in Figure 1.

The childhood years are spent in a constant attempt to maintain functional muscle length and joint ranges as the skeleton grows. Management - stretches, serial casting, orthotics, myoneural blockade and muscle-tendon surgery - reflects this ongoing battle against threatened muscle contracture and consequent joint deformity.

In adult life, growth is clearly no longer a deforming force. However, it is replaced by a number of other potential general problems, such as stiffness, weakness and fatigue. These will affect individuals to a varying extent depending on their level of disability. Furthermore, there are specific problems related to individual joint segments that are again associated with particular levels of disability. These general and specific features will be described below, together with strategies for coping with them.

With the exception of hip reconstruction and spinal surgery, there is nothing technically difficult about the actual operative procedures described. The skill, such as it is, lies in the assessment of these patients and their problems and in determining an appropriate plan of management. It follows that one should refer to an orthopaedic surgeon with an interest in cerebral palsy who will be sensitive to the needs and priorities of their patients, who will be able to analyse movement, and who will have close links with physiotherapists, occupational therapists and seating specialists.

Spectrum of disability

The spectrum of disability following skeletal maturity is very wide. Any consideration of orthopaedic problems in the adult with CP has to take into account the following groups:

1. walking adults leading independent lives
2. obligatory chair users
3. severely involved adults requiring constant care
4. a small number of adults with isolated upper limb problems.

Some adults with mild spastic diplegia will have few or no problems with daily life as an adult. More severely affected adults will experience increasing problems as the abnormal muscle forces take their toll on the joints of the limbs and on the spine.

1. Spasticity – the sequence of events.

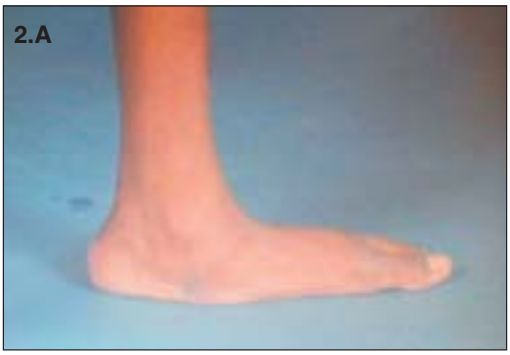
The walking adult with CP

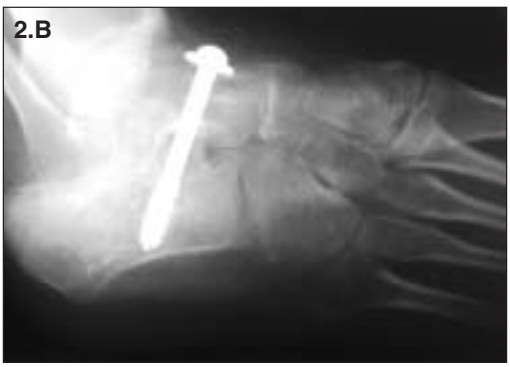
Weakness and fatigue

The importance of muscle weakness is often not recognised. In cerebral palsy, the fundamental problem is one of muscle imbalance, but although the deforming muscle group may be relatively powerful compared with its antagonists, its absolute power is often significantly lower than normal[1,2]. In the presence of spasticity or fixed contracture it may be difficult to demonstrate weakness. Indeed, there are some CP patients who depend on their spasticity to maintain an upright position. The fact that their muscles may be weak often comes as a surprise to the young adult. There is an understandable tendency for the owners of these troublesome tight muscles to assume that because they are stiff and resisting stretch, they must be strong muscles, but in many cases, nothing could be further from the truth. In practice, this situation tends to be well tolerated by the teenager and young adult, but often by the late twenties and early thirties, there is a definite reduction in walking distance and complaints of fatigue on carrying out tasks previously performed with ease[3]. In many ways this is similar to the experience of those with lower motor neurone disease such as polio or spina bifida. There is little the orthopaedic surgeon can do here in terms of intervention, but a full explanation of the phenomenon is invaluable, even if the message is hard to take.

Stiffness

Loss of movement range is a common problem once CP patients move away from the care of paediatric physiotherapists and enter a busy independent life on their own. The reduction in availability of physiotherapy in adult life is dramatic and appears to be a universal problem[4]. Much can be done by the patients themselves, but some joint





2. A. Marked valgus deformity causing pain on medial border of foot
B. Lateral radiograph showing subtalar fusion.

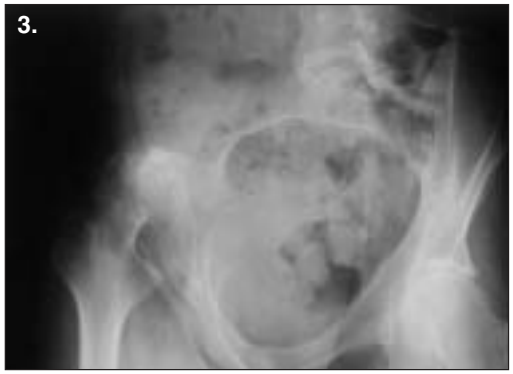
ranging exercises do require help from another individual, and there is undoubtedly the "personal trainer" factor of encouragement and motivation. Although the literature is split on the value of stretching and strengthening exercises in adult CP[5,6] my experience is that patients do benefit from short intensive "top-up" blocks of physiotherapy once or possibly twice a year. The best advice that can be given to the diplegic patient leading an independent life is to sign on with a gym (preferably one with a pool). It is often possible to find someone in these places who is willing to help out with a few hamstring stretches once a week.

There is probably little role for muscle-tendon lengthening surgery in the adult diplegic patient because of the risk of creating unacceptable weakness. Use of tone-reduction techniques such as myoneural blockade with botulinum A or ethanol also have limited effect because the contractures in adults are largely structural in nature rather than dynamic. One exception to this is the patient (usually hemiplegic) with a dystonic component to their motor disorder, as these often respond well to botulinum.

Specific problems

Persistent flexed knee gait is the commonest pattern in the adult walking patient and represents a continuing imbalance between a weak quadriceps mechanism and more powerful and contracted hamstrings. This crouch position may have been exacerbated by inappropriate heel cord lengthening in childhood. It will also be worsened by increased body weight. Patellofemoral compression forces in the weight-bearing flexed knee are high, and can give rise to painful degenerative arthritis in relatively early adult life. Contracture of the quadriceps can give rise to an additional complication at the knee in the form of a high-riding patella (patella alta). Loss of the normal articular relationship with the femur may further exacerbate discomfort. This is a very difficult problem to manage and there is no easy surgical solution. Lengthening of the hamstrings will serve no useful purpose if the quadriceps are too weak to maintain knee extension. Repositioning of the high patella in its normal groove involves lengthening the quadriceps mechanism and reefing the stretched patellar tendon, and runs the risk of further weakening an already compromised quadriceps mechanism. One alternative may be to avoid excessive soft tissue surgery and instead perform a shortening extension femoral osteotomy with reefing of the patellar tendon. The problem is far from solved.

Low back pain is very common in the walking adult with CP. This is purely mechanical in nature and occurs as a result of the excessive pelvic movements which are characteristic in this condition. Treatment is symptomatic.



3. Neglected but painless dislocation of the right hip in a 51 year old man.

Foot deformities established in childhood tend to become more troublesome in adult life. These may be simple hallux valgus and claw toe deformities or they may represent more fundamental hindfoot valgus or varus malalignments. Many minor problems can be dealt with adequately by appropriate in-shoe orthotics, but surgical correction should be seriously considered to re-establish a comfortable and stable base for walking (figure 2).

In late adult life, the problems of degenerative arthritic change become dominant. There is no reason why someone with spastic diplegia or hemiplegia should not be offered a total hip replacement. It used to be said that there was an unacceptably high risk of implant dislocation due to the spasticity, but more recent studies have shown that this is not the case[7].

The obligatory chair-user with CP

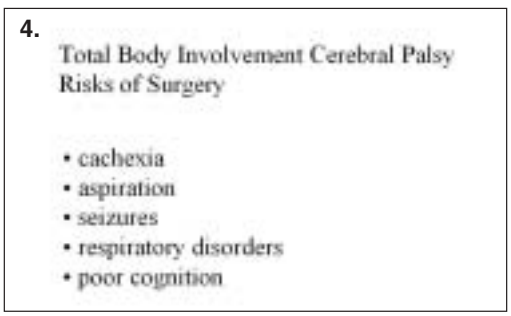
These patients will either be more severely affected diplegic patients who have lost useful walking function or, more commonly, patients with total body involvement CP.

The orthopaedic priorities in the non-walking patient with total body involvement centre around the spine and pelvis. The aim is to achieve and maintain symmetry as far as possible. Loss of symmetry resulting from, say, unilateral hip dislocation and the associated pelvic obliquity, leads inexorably to seating problems and will exacerbate any pre-existing scoliosis.

The management of the subluxing and dislocating hip will be dealt with in the next section on the severely involved adult requiring constant care.

Scoliosis may continue to deteriorate well into adult life[8]. The best opportunity to correct and stabilise this surgically has been missed by the time patients reach skeletal maturity. Bracing with a spinal orthosis is neither practical nor effective in the majority of adults with spinal deformity. Thus, the importance of good specialist seating cannot be overstated. Without such seating, a patient with an unbalanced spinal curve will not be able to use his or her upper limbs to their optimum effect. They will either be slumped to one side or will be using one hand constantly as a support to prevent such a posture. It is unrealistic to expect such seating to achieve any corrective function; this is accommodative seating designed to support in a functional position.

Occasionally the scoliosis is so severe that there is intractable pain from impingement of the lower ribs on the iliac crest. There is also a risk of decubitus ulceration. By this stage surgical correction may then be necessary, but the risks of surgery are high and the degree of correction achieved is likely to be disappointing.



4. Total body involvement cerebral palsy – risks of surgery.

Frequency matters!

Don't just prescribe Mestinon: personalise it!

Mestinon®
pyridostigmine bromide

Personalised therapy

Because every Myasthenia Gravis patient is individual

To get the most out of Mestinon, the most widely prescribed 1st-line treatment for Myasthenia Gravis (MG)[1,2,3,] **it has to be taken at frequent intervals:**

- ***A half-life of 3-4 hours means that a dose frequency of around every 4 hrs is necessary for continuous cover***
- ***Frequency may be increased to every 3 hrs when awake[4]***
- ***Dosage should be tailored to the needs of the patient***

Don't just prescribe Mestinon: personalise it. Make sure every patient gets the most out of Mestinon – 5-6 times a day!

Prescribing Information:

Presentation: Each tablet contains 62.5mg pyridostigmine bromide (equivalent to 60.0mg of the base). **Indications:** Myasthenia Gravis, paralytic ileus and post-operative urinary retention. **Dosage and Administration:** *Myasthenia Gravis – Adults* – Doses of 30 to 120mg are given at intervals throughout the day. The total daily dose is usually in the range of 5-20 tablets. *Children* – Children under 6 years old should receive an initial dose of half a tablet (30mg) of Mestinon; children 6-12 years old should receive one tablet (60mg). Dosage should be increased gradually, in increments of 15-30mg daily, until maximum improvement is obtained. Total daily requirements are usually in the range of 30-360mg. The requirement for Mestinon is usually markedly decreased after thymectomy or when additional therapy is given. When relatively large doses of Mestinon are taken by myasthenic patients, it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects. It should be noted that the slower gastro-intestinal motility caused by these drugs may affect the absorption of Mestinon. In all patients the possibility of "cholinergic crisis", due to overdose of Mestinon, and its differentiation from "myasthenic crisis" due to increased severity of the disease, must be borne in mind. *Other indications: Adults* – The usual dose is 1 to 4 tablets (60-240mg). *Children* – 15-60mg. The frequency of these doses may be varied according to the needs of the patient. *Elderly* – No specific dosage recommendations. **Contra-indications, Warnings etc:** *Contra-indications* – Gastro-intestinal or urinary obstruction, known hypersensitivity to the drug and to bromides. Extreme caution is required when administering Mestinon to patients with bronchial asthma. *Warnings* – care should also be taken in patients with bradycardia, recent coronary occlusion, hypotension, vagotonia, peptic ulcer, epilepsy or Parkinsonism. Lower doses may be required in patients with renal disease. *Use in pregnancy:* The safety of Mestinon during pregnancy or lactation has not been established. Experience with Mestinon in pregnant patients with Myasthenia Gravis has revealed no untoward effects. Negligible amounts of Mestinon are excreted in breast milk but due regard should be paid to possible effects on the breast-feeding infant. *Side effects:* These may include nausea and vomiting, increased salivation, diarrhoea and abdominal cramps. *Drug interactions* – None known. **Pharmaceutical Precautions:** *Storage* – Recommend maximum storage temperature 25ºC. Protect from light and moisture. **Legal Category:** POM. **Package Quantities:** Amber glass bottles with aluminium screw caps and desiccant, containing 200 tablets. **Basic NHS Price:** £50.15. **Product Licence Number:** PL 15142/0006. **Product Licence Holder:** ICN Pharmaceuticals Ltd, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire. RG24 8WD.

References:

1. Sharma KR. Myasthenia Gravis: a critical review. *IM Intern Med* 1996; August: 47-69
2. Drachman DB. Myasthenia Gravis. *N Eng J Med* 1994; **330:** 1797-1810
3. Buckley C. Diagnosis and treatment of Myasthenia Gravis. *Prescriber* 2000; **11**(Issue 22); 107-113
4. Vincent A and Drachman DB. Myasthenia Gravis. *Neuromuscular disorders* 2001; **11:** 159-188

Date of Preparation: May 2003

VP006/0504

VALEANT Pharmaceuticals Ltd.

There is much discussion between orthopaedic and spinal surgeons over the respective roles of hip subluxation and scoliosis in the genesis of the ultimate deformity, and which to correct first. Some maintain that the scoliosis is the primary deforming factor, causing pelvic obliquity and encouraging the uncovering of the femoral head, whereas others take the opposite view, stating that the dislocation and pelvic obliquity cause the spinal curve to develop. It is a somewhat sterile and unhelpful argument, and it is probably more useful simply to regard the spinal and hip deformities as interactive, and to take steps to prevent these deformities developing in the first place.

There is a tendency to ignore hamstring contractures in the obligatory chair-user as there is no walking ability that requires knee extension. This is a mistake. The hamstrings not only flex the knees but due to their origin from the pelvis also pull on the pelvis at the back. Hamstring contractures therefore result in a posterior tilt of the pelvis so that the patient is sitting on their sacrum rather than their ischial tuberosities. Not only does this create problems with pressure areas, but it gives rise to a compensatory thoracic kyphosis which is frequently marked and very disabling. This is one situation where soft tissue surgery in adults with CP can be extremely beneficial. Hamstring lengthening will result in a more upright spinal posture and easier and more comfortable sitting.

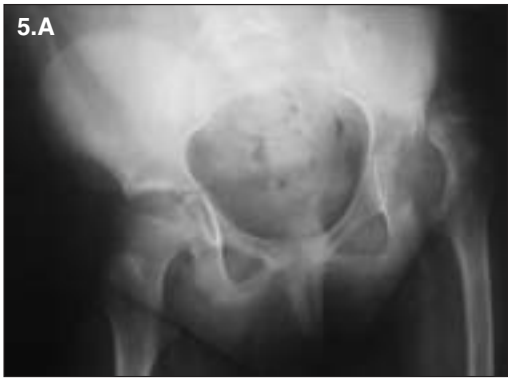
The severely affected adult with total body involvement CP

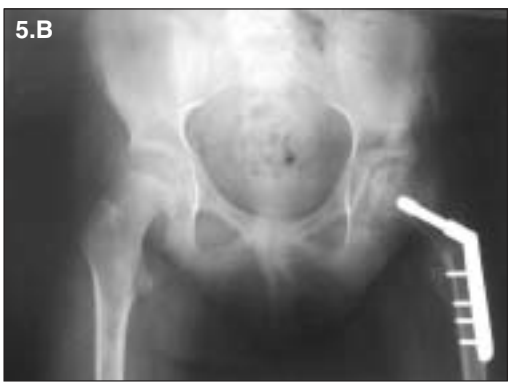
The major orthopaedic problem in this group is that of hip dislocation (figure 3). Subluxation of one or both hips may continue to progress through growth into adult life. This may be a silent event, but it is likely that we underestimate the level of discomfort and disability associated with dislocated hips[9]. There may be problems with cleaning and dressing because of the associated adduction and flexion contracture. As discussed above, a unilateral dislocation will result in asymmetric sitting and lying posture, and exacerbation of any pre-existing scoliosis. Occasionally, in an apparently painless bilateral dislocation symmetry may be maintained and there may be no sequelae in terms of seating, lying or care problems.

However, surgery in this group of patients is a major undertaking as can be seen from figure 4. Perioperative mortality rates for hip reconstruction surgery may be as high as 4%[10]. If the dislocation is apparently asymptomatic, it is tempting to leave well alone.

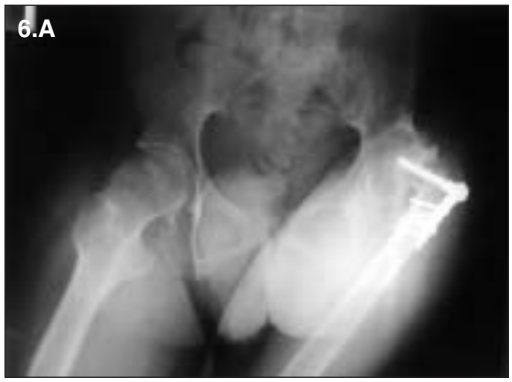
If pain, posture or caring difficulties conspire to make hip surgery necessary, a decision has to be made with respect to the condition of the femoral head. If the progression of subluxation has been brisk, the femoral head may still be in good condition and it is reasonable to plan a full reconstruction of the hip joint. This will involve soft tissue releases of the adductors and hip flexor muscles, osteotomy of the proximal femur to correct rotational and valgus deformity, and possibly also a pelvic osteotomy to realign or reshape the acetabular roof (figure 5). If however the head has been out of the acetabulum for a long time, the articular surface will have become worn and ulcerated from pressure against the capsule of the joint. If such a hip is reconstructed to produce a reduced femoral head, it may continue to be painful due to this articular damage. In the adult patient this is likely to be the case, and under these circumstances, an alternative to reducing the dislocated head is required.

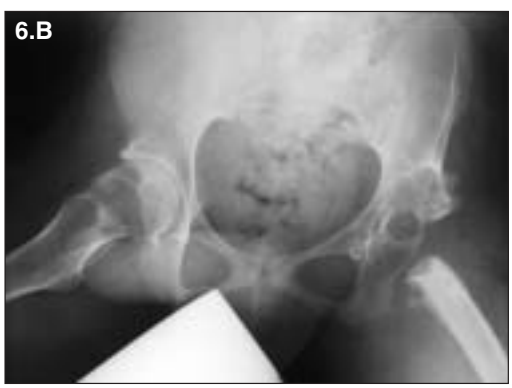
Longstanding painful hip dislocations in the adult may



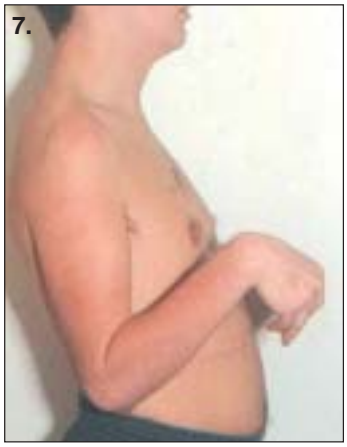


5. A. Preoperative radiograph showing dislocated left hip
B. Postoperative radiograph after soft tissue releases and both femoral and pelvic osteotomies





6. A. Failed surgery for recurrent spastic dislocation of left hip
B. Radiograph showing good abduction and level pelvis following proximal femoral resection.



7. 18 year old lad who was turned down at countless job interviews because of the appearance of his upper limb. He had little useful function in this limb and simply wanted it out of the way. Tendon lengthening at the elbow and wrist enabled him to keep his hand in a pocket and prevent excessive posturing. He got a job six weeks after surgery.

be treated by proximal femoral excision. In this procedure, the upper third of the femur is removed and the muscles around the hip fashioned into a cushion between the femoral bone end and the empty acetabulum (figure 6). This is a salvage procedure that, if performed correctly, gives a good chance of providing a comfortable and mobile "hip"[11]. It is not indicated for anyone who relies on bearing weight to effect transfers, as no guarantee can be given that this would be possible after such surgery. The procedure has suffered from a bad press in the past, largely because it has not been executed properly. It is sometimes confused with the Girdlestone procedure in which only the femoral head and neck are removed. In CP this is an inadequate resection and will lead to poor results. The formation of heterotopic bone may also impair the outcome, but this can be minimised by the administration of either preoperative radiation or postoperative indomethacin. One should expect 70-80% success rate from this procedure in terms of pain relief and improvement in ease of care.

Upper limb problems in the adult with CP

In a younger age group, carefully selected patients will achieve improved function from tendon transfer and tendon lengthening surgery. In the adult patient it is unlikely that surgical intervention in the upper limb will improve function, with the single exception of wrist fusion for the athetoid or dystonic extremity[12]. In this situation painful posturing can prevent otherwise reasonably useful function, for example, switch control or keyboard use.

Surgery is more likely to be indicated for cosmetic reasons or in extreme deformity to improve access and hygiene (figure 7). The severely involved patient may have severe thumb-in-palm or clenched-fist deformities that lead to skin maceration and infection. Simple wrist and finger flexor tenotomies can make a huge difference to the patient's and carer's life.

Summary

It will be seen that there is relatively limited scope for the orthopaedic surgeon to address established deformities in adult life, and nothing that can be done to prevent the natural history of weakness and fatigue. It is therefore essential that every opportunity is taken during the growing years to ensure that everything has been done to prevent deformity so that the patient with cerebral palsy, regardless of level of disability, faces the onset of adult life with optimised function.

References

1. Ross SA, Engsberg JR. (2002) *Relation between spasticity and strength in individuals with spastic cerebral palsy.* Dev Med Child Neurol Mar;44(3):148-57
2. Maruishi M, Mano Y, Sasaki T, Shinmyo N, Sato H, Ogawa T (2001) *Cerebral palsy in adults: independent effects of muscle strength and muscle tone.* Arch Phys Med Rehabil May;82(5):637-41
3. Jahnsen R, Villien L, Stanghelle JK, Holm I. (2003) *Fatigue in adults with cerebral palsy in Norway compared with the general population.* Dev Med Child Neurol May;45(5): 296-303
4. Bottos M, Feliciangeli A, Sciuto L, Gericke C, Vianello A. (2001) *Functional status of adults with cerebral palsy and implications for treatment of children.* Dev Med Child Neurol Aug;43(8):516-28
5. Andersson C, Grooten W, Hellsten M, Kaping K, Mattsson E. (2003) *Adults with cerebral palsy: walking ability after progressive strength training.* Dev Med Child Neurol Apr;45(4):220-8
6. Cadenhead SL, McEwen IR, Thompson DM. (2002) *Effect of passive range of motion exercises on lower-extremity goniometric measurements of adults with cerebral palsy: a single-subject design.* Phys Ther Jul;82(7)658-69
7. Weber M, Cabanela ME. (1999) *Total hip arthroplasty in patients with cerebral palsy.* Orthopedics Apr;22(4):425-7
8. Majd ME, Muldowny DS, Holt RT. (1997) *Natural history of scoliosis in the institutionalised adult cerebral palsy population.* Spine Jul 1;22(13):1461-6
9. Cooperman DR, Bartucci E, Dietrick E, Millar EA. (1987) *Hip dislocation in spastic cerebral palsy: long-term consequences.* J Pediatr Orthop May-Jun;7(3):268-76
10. Stasikelis PJ, Lee DD, Sullivan CM. (1999) *Complications of osteotomies in severe cerebral palsy.* J Pediatr Orthop Mar-Apr;19(2):207-10
11. Widmann RF, Do TT, Doyle SM, Burke SW, Root L. (1999) *Resection arthroplasty of the hips for patients with cerebral palsy: an outcome study.* J Pediatr Orthop Nov-Dec;19(6):805-10
12. Rayan GM, Young BT. (1999) *Arthrodesis of the spastic wrist.* J Hand Surg [Am] Sep;24(5):944-52

Correspondence to:
J Mark H Paterson FRCS
consultant orthopaedic surgeon
Barts and the London NHS Trust
E-Mail. jmhp@blueyonder.co.uk

Events Diary

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by August 6th, 2004. An extended listing of events is available on our website at www.acnr.co.uk

2004

July

Latin American Congress on Epilepsy
2-5 July, 2004; Mexico City, Mexico
www.epilepsiamexico2004.org

Neurogenetics Symposium
6 July, 2004; Cardiff, UK
E. jacqui.carrington@suht.swest.nhs.uk

Australian Society for the Study of Brain Impairment (ASSBI) & International Neuropsychological Society (INS) Annual Meeting
7-10 July, 2004; Brisbane, Australia
Fax. 00 61 292 480 894,
E. neuropsych@tourhosts.com.au

FENS 2004 Satellite meeting of the European Chapter of the Molecular & Cellular Cognition Society
8-9 July, 2004; Lisbon, Portugal
www.molcellcog.org

4th Forum of European Neuroscience
10-14 July, 2004: Lisbon, Portugal
http://fensforum.neurosciences.asso.fr/

Techniques and Applications of Molecular Biology: A course for medical practitioners
12-15 July, 2004; Warwick, UK
Tel. 024 7652 3540,
E. charlotte.moonan@warwick.ac.uk

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

XV meeting of the International Neuro-Opthalmology Society
18-22 July, 2004; Geneva, Switzerland
Fax. 00 41 22 839 8484,
E. info@symporg.ch

6th World Congress on Myofascial Pain and Fibromyalgia
18-22 July, 2004; Munich, Germany
Fax. 001 210 567 6964,
E. duncan@uthscsa.edu

BioScience2004 - from molecules to organisms
18-22 July, Glasgow, UK
www.BioScience2004.org,
E. erica.hammond@portlandpress.com

Assessment and Management of Children with Physical Disabilities
19-21 July, 2004; Institute of Child Health, London, UK
Tel. 020 78298692
E. courses@ich.ucl.ac.uk,

August

International Society for Developmental Neuroscience - ISDN 2004
4-7 August, 2004; Edinburgh. UK
Tel. 001 604 822 2673,
E. steeves@icord.org

Rehabilitation International Assembly and World Congress
9-14 August, 2004; Oslo, Norway
E. grete@ri-norway.no

The Neurochemical Monitoring System
16 August, 2004; Hong Kong
Fax. 00 852 2647-3074,
E. icp2003@cuhk.edu.hk

12th International Symposium on Intracranial Pressure and Brain Monitoring
17-21 August, 2004; Hong Kong
E. icp2003@cuhk.edu.hk,
Fax. 00 852 2647 3074

Edinburgh Summer School in neuroinformatics Simulation tools
23-27 August, 2004; Edinburgh, UK
www.anc.ed.ac.uk/school

22nd Conference of European Comparative Endocrinologists
24-28 August, 2004; Uppsala, Sweden
Fax. 00 46-18-13-4050,
E. kongress@ukkab.se

International Journal of Therapy and Rehabilitation Conference: 'Towards global partnerships: working together for effective clinical practice'
25-27 August, 2004; Malta
E. tania@markallengroup.com

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

September

9th International Congress of the World Muscle Society
1-4 September, 2004; Gothenburg, Sweden
Tel. 0046 3 170 860 000, Fax. 0046 317 086b 025

8th Congress of the European Federation of Neurological Societies
4-7 September, 2004; Paris, France
Tel. 0043 1 880 00 270, Fax. 0043 1 88 92 581, E. Headoffice@efns.org

The 8th Triennial Meeting of the International Basal Ganglia Society
5-9 September, 2004; Perthshire, Scotland
Tel. 0131 556 9245,
E. katy@in-conference.org.uk

ECTRIMS 2004 - European Congress for Treatment and Research in Multiple Sclerosis
6-9 September, 2004; Vienna, Austria
Fax. +41 61 686 77 88, E. info@akm.ch

9th Annual Meeting of the International Functional Electrical Stimulation Society
6-9 September, 2004; Bournemouth, UK
Tel. 01722 429066, Fax. 01722 425263, www.ifessnet2004.tk, E. i.swain@salisbury.nhs.com

BSN Annual Meeting - Neuroendocrinology
7-9 September, 2004; Glasgow, UK
E. fran.ebling@nottingham.ac.uk

Microelectrode Techniques for Cell Physiology
8-22 September, 2004; Plymouth, UK
E. dogden@nimr.mrc.ac.uk,
www.ba.ac.uk/education/courses

Developments in the Service Provision for People with Epilepsy
9 September, 2004; Cardiff, UK
Tel. 0113 210 8800, E. redgar@epilepsy.org.uk

2004 American Congress of Rehabilitation Scoiety/American Society of Neurorehabilitation
9-12 September, 2004; Florida, US
www.asnr.comr or www.acrm.org

25th Anniversary Conference of Headway, the brain injury association
9-10 September, 2004; Stratford upon Avon, UK
E. eventsandconferences@headway.org.uk

International Pharmaco-EEG Meeting
10-12 September, 2004; Antwerp, Belgium
Fax. +31 412 662 506, E. ge.ruigt@organon.com

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

1st North American / 5th National Conference on Shaken Baby Syndrome
12-15 September, 2004; Montreal, Canada
Fax. 001 801 627 3321,
E. sefranks@mindspring.com

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

12th European Symposium - European Society for Neurogastroenterology & Motility
Dr Robin Spiller, Tel. 01159 249 924,
Fax. 01159 422 232,
E. robin.spiller@nottingham.ac.uk

The British Aphasiology Society Therapy Symposium Conference
13-14 September, 2004; Liverpool, UK
Tel. 0151 529 4986,
E. alex.stirling@thewaltoncentre.nhs.uk

9th European Federation of Neurological Societies Congress
17-21 September, 2004; Athens, Greece
Fax. 00 43 1 88 92 581,
E. headoffice@efns.org

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

Part-time Postgraduate Certifice in Evidence Based Health Care
20 September 2004 - 30 September, 2005
Tel. 01865 286 941,
Fax. 01865 286 934,
E. cpdhealth@conted.ox.ac.uk

15th Migraine Trust International Symposium
20-23 September, 2004; London, UK
Tel. 02 089 770 011,
E. mtis@hamptonmedical.com

II International Congress on Neuroregeneration
20-24 September, 2004; Rio, Brazil
E. icn@congrex.com.br

2nd International Conference on Cognitive Disabilities
21-25 September, 2004; Medellin, Colombia
Fax. +57 42 794 833,
E. losalamos@epm.net.co

3rd World Congress World Institute of Pain
21-25 September, 2004; Barcelona, Spain
Fax. 00-34-934-172-279,
E. wipcongress@meet2.net

ABN Autumn Scientific Meeting
22-24 September, 2004; Blackpool, UK
Tel. 020 7405 4060,
E. abn@abnoffice.demon.co.uk

Dutch Rehabilitation Society & British Society of Rehabilitation Medicine
23-24 September, 2004; Edinburgh, UK
Tel. +31 30 2739696 or 01992 638865
E. vra@revalidatiegeneeskunde.nl or admin@bsrm.co.uk

VII Congress of the International Society of Neuroimmunology
28 September-2 October, 2004; Venice, Italy
Tel. 0039 06 519 3499,
E. eem@eemservices.com

Evidence-Based Medicine in Neurorehabilitation: 1st European Regional Meeting of the World Federation of Neurorehabilitation
29 September - 2 October, 2004; Zurich, Switzerland
Fax. 00 41 13 861 609,
E. caroline.kunz@balgrist.ch

October

Assessment and Management of Children with High Functioning Autism and Asperger Syndrome
1 October, 2004; London, UK
E. courses@ich.ucl.ac.uk

129th Annual Meeting of the American Neurological Association
3 - 6 October, 2004; Toronto, Canada
Fax. 001 952 545 6073,
E. lorijanderson@msn.com

17th Congress of the European Sleep Research Society
5-9 October, 2004; Prague, Czech Republic
Fax. +420 224 261 703,
E. esrs@conference.cz

Joint Annual Meeting of ECTRIMS and RIMS
6-10 October, 2004; Vienna, Austria
Fax. +41 61 686 77 88,
E. info@akm.ch

8th Asian & Oceanian Congress of Child Neurology
7-10 October, 2004; Delhi, India
E. kalra_veena@hotmail.com,
www.8thaoccn2004.com

17th Congress of the European College of Neuropsychopharmacology
9 - 13 October, 2004;
E. secretariat@ecnp.nl

6th Congress of the European Assoication for Neuro-Oncology EANO VI
10-14 October, 2004; Jerusalem, Israel
Fax. 00 972 3 638 4455,
E. info@ortra.com

Randomised Controlled Trials
11/13 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Qualitative Research Methods
12/13 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Ethics in Healthcare
14 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Randomised Controlled Trials
15 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

20th International Conference of the Alzheimer's Disease International
15 - 17 October, 2004; Kyoto, Japan
Fax. 00 81 75 811 8195,
E. adiconference@alzheimer.or.jp

Congress of Neurological Surgeons 54th Annual Meeting
16 - 21 October, 2004; San Francisco, US
Fax. 001 847 240 0804,
E. info@1cns.org

Health Status Measurement
18 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Randomised Controlled Trials
18/20 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Qualitative Research Methods
19/20 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

BSCN Scientific Meeting: Motor Control & AGM
20-21 October, 2004; UK
E. bscn@secretariat.freeserve.co.uk

3rd International Workshop on the CCN Family of Genes
20-24 October, 2004; St Malo, France
Fax. +33 144 276 043,
E. annick.perbal@wanadoo.fr

Ethics in Healthcare
21 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Health Status Measurement
21 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Systematic Reviews
22 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Altered Haemodynamics - A new concept in manual therapy
23-24 October, 2004; Manchester, UK
E. ACNRevents@aol.com

34th Annual Meeting of the Society for Neuroscience
23 - 28 October, 2004; San Diego, US
E. info@sfn.org

Mental Dysfunctions in Parkinson's Disease
24 - 27 October, 2004; Salzburg, Austria, Fax. 0847 127 5678,
E. PDment2004@kenes.com

Health Status Measurement
25/27 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Qualitative Research Methods
26 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Standardised Assessment in Occupational Therapy with special emphasis on Dementia, Part 1
27-29 October, 2004, London, UK
Tel. 020 7834 3181

Developments in the Service Provision for People with Epilepsy
28 October, 2004; Birmingham, UK
Tel. 0113 210 8800,
E. redgar@epilepsy.org.uk

Ethics in Healthcare
28 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Systematic Reviews
29 October, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

November

Systematic Reviews
1 November, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Ethics in Healthcare
2 & 4 November, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Systematic Reviews
3 November, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Association of British Neurologists, Spring Meeting

14-16 April, 2004; London, UK

The ABN spring meeting 2004 was held at the impressive Church House Conference Centre, tucked away near Westminster, London. The opening lecture was from Professor Pamela Shaw on the latest developments in Motor Neurone Disease. In a nicely structured talk, Professor Shaw beautifully encapsulated how genetic advances and animal models may improve our understanding and treatment of this devastating disorder, "sandwiched" between a focused and relevant clinical overview.

The remainder of the conference comprised scientific sessions and posters, covering a wide variety of specialist areas. The first afternoon session was dedicated to epilepsy, myasthenia gravis and motor neurone disease. An interesting trial of a novel therapeutic compound in myasthenia gravis was presented by D McKee (Manchester). The antisense oligodeoxynucleotide, EN101, binds to acetycholinesterase mRNA to prevent its translation into protein. The agent appeared to improve symptoms with few side effects in 14 of 16 patients with myasthenia gravis, in whom pyridostigmine had been discontinued for the trial. This drug obviously needs further testing in a randomised controlled trial to evaluate its role in the management of myasthenia but early data seem promising.

Thursday morning presentations covered multiple sclerosis (MS) and movement disorders. Interferon and glatiramer are available on the NHS, conditional on long-term data collection by the MS monitoring study. Currently 4,000 people with MS in the UK are prescribed disease modifying therapies (approximately 10% of patients), although there is significant variability between centres. 3,500 of these are in the current study. Issues that have arisen from the initial clinical and demographic data were presented (C Cooper). The development of antibodies to interferon reduces the efficacy of the drug and occurs in approximately 10-15% of treated patients. Inter- and intra-rater reliability for the EDSS was assessed and showed moderately good consistency. There are no natural history controls in the study and it would be unethical to deny suitable patients this treatment, so unfortunately historical controls will be used. More data is needed on cost effectiveness and progress post-treatment. These drugs are effective against the inflammatory component which causes acute events in MS. Axonal degeneration also causes significant disability and to date has been resistant to treatment. Some research was presented from Kings College, London (DA Bechtold) looking at the effects of anticonvulsants on axonal protection in rats with experimental autoimmune encephalomyelitis (an animal model of MS). Carbamazepine showed no positive effects and phenytion caused only a modest improvement, while lamotrigine appeared to show significant protection from axonal degeneration. Clearly, these promising results need to replicated in human subjects. On a related theme, E Lim (London) presented her work in MS patients, suggesting that the release of neurofilament heavy chains in the CSF associates with axonal loss, while higher levels of neurofilament following an acute relapse may be predictive of a poor outcome in clinically definite MS cases. Dr L Teare (Plymouth) also presented intriguing preliminary data in this session to hypothesise that cannabinoids may have neuroprotective effects in MS.

The second session covered movement disorders and included a fascinating presentation on punding in Parkinson's disease (PD) (A Evans, London). Punding is a prolonged complex purposeless stereotyped behaviour, originally described in chronic amphetamine users. Punding PD patients were more likely to be taking higher doses of dopaminergic treatment, suffer from insomnia, and take nocturnal doses of medication, compared with non-punders, suggesting a relationship with the dopamine dysregulation syndrome. The pathophysiology underpinning dyskinesias in PD was elegantly discussed by M Silverdale (Manchester), who proposed a central role for over-activity of AMPA receptors in mediating this motor complication, via increased receptor trafficking into the post-synaptic membrane. Other interesting developments included the prospect of diffusion tensor MRI being of diagnostic utility in differentiating PSP and MSA (C Blain, London) and the intriguing observation of a very high frequency of anti-basal ganglia antibodies in adults with atypical dystonia and tics, when compared with a number of control groups, including primary torsion dystonia (M Edwards, London).

The afternoon session was short to allow time for the annual general meeting (or shopping, in the case of those drawn in by the bright lights and big city). The proposal of intradetrusor botulinum toxin injections to treat the symptoms of severe detrusor muscle instability may be a promising therapeutic option (C Fowler, London). The Leeds study of dementia in PD, impressive for its lengthy follow up of the original cohort, emphasised that the main predictors for cognitive decline are age at entry to the study, lack of tremor and presence of gait disorder (E Dunn, Leeds).

Those who managed to drag themselves out of bed on the morning of the last day, after the excesses of the multi course dinner at the Savoy, were treated to some interesting talks on vascular disease, including the identification that treating TIA as a medical emergency is an economically viable consideration, with medical therapy administered within 14 days proving highly cost effective (S Allder, Sheffield). The proposal that endovascular carotid artery stenosis treatment is as safe as surgical intervention (L Coward, London) requires further supportive evidence, on the basis of a Cochrane review. Anti-phospholipid antibodies can cause a variety of movement disorders, including chorea, often affecting the mouth, tics and myoclonus. Two of six patients improved with oral anticoagulation, which should be considered in the treatment of this disorder (D Martino, London).

A study of the effectiveness of liaison neurology in an acute medical admissions unit (R Forbes, Belfast) identified benefit in terms of shorter hospital stays, while significant changes in diagnosis were made in 34% of cases assessed by the neurologist. The importance of recognising tetanus in intravenous drug abusers was highlighted (K Gormley, Devon & Exeter). Phil Smith (Cardiff) gave an entertaining resume of that elusive strategy to be adopted in creating an award winning poster at scientific meetings (Blackpool here we come!).

An extra presentation was included, documenting a mitochondrial mutation responsible for PARK 6, a hereditary form of Parkinson's Disease described in a large consanguineous family from Sicily (M Muqit, London). The PINK 1 gene encodes for a mitochondrial protein, thought to protect against stress-induced mitochondrial dysfunction. A causative mutation has been found in this gene which leads to disruption of this protective effect. PINK 1 is the first mitochondrial gene to be directly implicated in the pathogenesis of PD.

Overall the meeting was well attended and the standard of presentations was very high. It was useful to catch up, not only with colleagues, but also with the wide range of interesting research being undertaken in the UK. The organisation was superb, and thanks must go to the local organisers, headed by Professor LJ Findley.

Dr NM Warren & Dr S Molloy, Newcastle

Church House Conference Centre, Westminster, London.

14th European Congress of Physical and Rehabilitation Medicine "Advances in PRM - Traditional and Modern Concepts"

12-15 May, 2004; Vienna, Austria

Since the ECPRM in Brighton had been such a great experience, I was looking forward to the next European Congress, which again was dedicated to the broad clinical topics of our speciality. The programme offered educational seminars, hands-on workshops and scientific sessions, thus providing an overview on the state-of-the-art as well as the most recent findings in our field. Special attention was brought to topics such as Outcome Assessment, Pain, Neurological, Musculo-Skeletal and Paediatric Rehabilitation. I particularly enjoyed the Trans European Scientific Contest. This was a session with a large jury, as in the Eurovision Song Contest, where one trainee representative of each country was given the chance to present his or her work. In addition to the plenary sessions there was also a good selection of excellent poster presentations.

The Austrian Society of Physical Medicine and Rehabilitation and its committed president, Professor Quittan, were able to attract the 14th ECPRM to Vienna. With its location in the heart of Europe, Vienna was once again able to be the bridge between East and West. Many colleagues from the South/Eastern part of Europe were able to attend such a meeting for the first time. The city also provided its well-known rich cultural life, the opera, its famous museums and from the start of the congress the Wiener Mozart-Quartett spoilt us with music of Haydn and Strauß!

During the session on Physical and Rehabilitation Medicine (PRM) within Europe, Dr Ward pointed out that our speciality is small, fairly new and not very sexy. Linking PRM within all EU countries and harmonising training and medical practise is therefore the way forward. The benefits of European links are: international exchange, networking, research opportunities and help with EU funding/partnership. The UEMS (Union Européenne des Médecins Spécialistes) section of PRM functions through three major committees namely: Education and Training, Clinical Affairs and Professional Practice. Dr McNamara explained that the Education and Training responsibilities rest with the European Board of Physical and Rehabilitation Medicine, which was established in 1990. This includes certification and re-certification of specialists, trainers and training centres in PRM together with CME/CPD. The board aims to improve the quality of patient care by insuring that PRM doctors have acquired the knowledge, skills and attitudes that are essential for this care. Performance is assessed throughout training and evaluation together with the Board's examination.

The session on International Classification of Functioning, Disability and Health (ICF) pointed out that an important step in the process of rehabilitation is to determine the functional abilities of an individual. ICF, presented by WHO, is a multi-classification scheme to describe health status and the experience of disability, using a non-categorical approach. This may open up new doors to the future of PRM by providing a common language to all professionals in the field. It uses functioning as an umbrella term for body functions, body structures, activities and participation whilst denoting the positive aspects of an individual's environment. However, Professor Bullinger from Hamburg explained the transfer however into measurement approaches has only recently been initiated. The quality of life concept, which also taps into an individual's experience of health, is less theoretical. To understand health and the consequences of disease both approaches should be brought together and further development of assessment tools for ICF is necessary.

The quality of presentations in the "Trans European Scientific Contest" was excellent. I particularly enjoyed the talk by Dr Groleger from Ljubljana. She aimed to adapt the Boston Paediatric Evaluation of Disability Inventory (PEDI) to evaluate functional performance of chronically ill and disabled children in Slovenia. PEDI has been validated to discriminate between non-disabled and disabled children and proven to be sensitive to changes in functional skills. The purpose of her study was to determine whether a cross-cultural adaptation and validation procedure of PEDI is needed before using the instrument in Slovenia and to ascertain which demographic factors might influence children's functional skills level. Statistically significant differences between children in American and Slovene samples were found. A very high internal consistency of the scales was also found. The Slovene sample, in contrast to the American one, revealed that functional skills are related to demographic characteristics such as gender and the presence of older siblings in a family. The education level of parents, on the contrary, had no influence on development of functional skills in both groups. The existence of inter-cultural differences therefore is a strong argument to re-norm the PEDI before introducing the instrument into practice. Dr Groleger won the first prize of the contest.

Professor Turner-Stokes gave a very interesting presentation on the relationship between reduced spasticity and improved arm function after botulinum toxin treatment for upper limb spasticity in stroke patients. The treatment usually targets specific muscles without affecting others. Focal functional gains are therefore not detectable with standardised global measures like the Barthel score, hence different outcome measures were used. In her first study a retrospective meta-analytic approach was adopted, selecting items from standardised scales most relevant to the intervention. A clear relationship between maximal change in spasticity and function was demonstrated. Change in spasticity frequently preceded change in function. Preliminary results of a second small multiple single case study were also presented. Goal Attainment Scaling (GAS) was used to enhance detection of functional gains as compared with simple rating of percentage goals achieved. In GAS tasks are individually set. The individual's current and expected performance after the intervention is taken into account and the team defines and agrees with the patient and the family what a "successful" outcome is. A five-point scale then measures the degree of attainment for each goal. Goals are also weighed to take account of the importance of the goal and the difficulty of achievement. The sum of attainment levels and relative weights for each goal is then transformed into a standardised measure. Simple rating of percentage goals showed poor specificity for identifying successful clinical outcomes. GAS scored 100% positive predictive value for clinical success. GAS therefore appeared to be superior to generic measures.

Four days in Vienna flew by thanks to a wonderful atmosphere where not only vivid exchange of up-to-date information was being offered, but also where many cultural and social highlights were being enjoyed in a city where hospitality is not only a word. After all, quoting the final comments of Professor Stam from Amsterdam at the closure of the meeting… "rehabilitation medicine IS a sexy speciality".

Dr Bénédicte Mancel,
Norwich

UNITED IN CARE

THE 1ST NATIONAL CONFERENCE

1st December 2004
Royal College of Physicians, London

This conference aims to identify ways to improve inter-disciplinary collaboration among the health professionals providing health care for older people. The morning topics will include:
● Understanding syncope and falls ● Parkinson's disease
● Treatment update on the dementias ● Stroke

The afternoon will provide an opportunity for a discussion led by a panel to examine the team approach to feeding issues in hospital, led by a well-known 'personality' in the field and representatives from the multi-disciplinary teams.
Full participation of the audience will be encouraged to make this as interactive as possible.

For more information or to register for the conference, please call MEP Ltd on 020 7561 5400 or email info@mepltd.co.uk

Chartered physiotherapists working with older people

Nutrition Advisory Group for the Elderly

Medical society for health in old age

OCTEP

City University London

St Bartholomew School of Nursing & Midwifery

North East London

The Scientific Basis of Neurology & Neuroscience for Clinicians 12

Sponsored by the Guarantors of Brain

Wellcome Trust Conference Centre
Wellcome Trust Genome Campus, Cambridge

November 1st and 2nd 2004

Neuroscience for Clinicians 12 is combined with a meeting to celebrate establishment of the Department of Clinical Neurosciences in the University of Cambridge. The full cost for early applicants (limited to 60) is £35 and includes 2 nights residence at Hinxton Hall. Preference will be given to neurologists in training. Others may attend the meeting at a cost of £25 but will need to make independent arrangements for accommodation. The lectures cover topics proving popular in previous years given by outside speakers and members of the Cambridge neuroscience community - many associated with the Department of Clinical Neurosciences. The meeting incorporates the 4th MSD - Cambridge Neurology Lecture (Professor Martin Schwab) and the 12th Gordon Holmes Lecture (Professor Colin Blakemore) sponsored by the Guarantors of Brain.

Contact Katrina Dedman
Secretary to Professor DAS Compston, Tel. 01223 217091,
E-Mail. kd203@medschl.cam.ac.uk

Thursday 18
Friday 19
November 2004

Cost
£85 + VAT

Rootstein Hopkins Space
London College of Fashion

Speakers:
Dr Loretta Giorcelli, Professor of Special Education, Australia
Dr Sam Goldstein, Neurology, Learning and Behaviour Centre, US

A fantastic opportunity for you to participate in a Master Class that will provide a good solid foundation (with cutting edge information) about learning difficulties.

For more information contact: Concorde Services Ltd, Tel. 020 8743 3160, E-Mail. masterclass@concorde-uk.com www.mindroom.org

The Royal Society *of* Medicine presents:

- **Pathways to Work - enabling rehabilitation**
  Monday 18 October 2004
  Venue: The RSM, London

- **Palliative Care: Moving the Boundaries... again**
  Tuesday-Wednesday 23-24 November 2004
  Venue: The Spa Complex, South Bay, Scarborough

- **Neuropathic Pain**
  Friday 21 January 2005
  Venue: The RSM, London

For further information please email:
jennifer.lake@rsm.ac.uk
Tel: +44 20 7290 3919
or browse our website at
www.rsm.ac.uk

The Royal Society of Medicine

An Update on Thrombolysis for Acute Ischaemic Stroke

Stroke is the third commonest cause of death and the leading cause of adult disability in the UK. Its burden is set to increase because of an ageing population. Recently the thrombolytic agent, recombinant tissue plasminogen activator (rt-PA/alteplase), received a licence for the treatment of acute ischaemic stroke, within three hours of symptom onset. It is the first thrombolytic agent to be licensed for this indication and has the potential to radically change the early management of acute ischaemic stroke and reduce resultant disability. However, its successful implementation poses a number of important challenges. This article provides an update on progress in this area.

Michael Power is consultant geriatrician and lead stroke clinician at the Ulster Hospital, Dundonald. He is Chairman of NIMAST (N. Ireland multidisciplinary association for stroke teams), formed in 1999 with the aim of improving standards of stroke care in Northern Ireland. www.nimast.org.uk

Acute ischaemic stroke

Acute ischaemic stroke accounts for approximately 80% of all strokes, and occurs when a thrombus, or embolism, blocks a cerebral blood vessel. Resulting mortality and morbidity, particularly long term disability, are high. Approximately 20% of patients will die within thirty days of stroke onset, and many are left permanently disabled. Up to now treatment has been largely restricted to supportive and rehabilitative care. Organised stroke unit care, and the use of aspirin given as soon as possible after stroke onset, have been shown to offer benefit. However, no therapies that are able to reduce brain damage and resultant disability were available for immediate administration. This changed with the licensing of rt-PA in April 2003 in the UK.

Thrombolysis for acute ischaemic stroke

The two thrombolytic agents that have to date been most studied in stroke are recombinant tissue plasminogen activator (rt-PA) and streptokinase. The trials involving streptokinase have been disappointing, reporting an early increased risk of cerebral haemorrhage and death, with no net benefit at final follow-up[1]. However, a number of large multicentre randomised placebo controlled trials have shown an overall benefit for early treatment with rt-PA, despite an increased risk of early haemorrhage[2,3,4,5,6]. For example, the National Institute of Neurological Disorders and Stroke (NINDS) trial reported in 1995 that patients were at least 30% more likely to have minimal or no disability three months after their stroke if treated with rt-PA within three hours of symptom onset. Despite the risk of symptomatic intracranial haemorrhage, mortality at three months was lower in the rt-PA group at 17%, compared with 21% in the placebo group. More recently, pooled data from the six large randomised controlled trials of rt-PA, involving 2775 patients, was analysed to gain better insight into the effect of time to treatment on efficacy. The findings reported recently confirm that the sooner the treatment is given to suitable stroke patients, the greater the benefit[7]. The odds ratio for a favourable outcome at three months is shown below. These results confirm the strong association between rapid treatment and favourable outcome.

A Cochrane review of thrombolysis for acute ischaemic stroke analysed 18 randomised controlled trials of any thrombolytic agent[8]. The review included 5727 patients given urokinase, streptokinase, recombinant pro-urokinase or rt-PA. About half of the data comes from trials testing rt-PA. There is a paucity of data from patients aged >80 years. Overall thrombolytic therapy, administered up to 6 hours after ischaemic stroke, significantly reduced the proportion of patients who were dead or dependent (modified Rankin 3 – 6) at 3 to 6 months follow up. Overall the reviewers concluded that thrombolytic therapy appears to result in a significant net reduction in the proportion of patients dead or dependent in activities of daily living, despite an increase in early symptomatic intracranial haemorrhage or death. Further trials are underway to assess if benefit extends beyond the licensed 3-hour time window. The third International Stroke Trial (IST-3) is recruiting patients of all ages up to 6 hours after stroke. The third European Cooperative Acute Stroke Study (ECASS III) is examining potential benefit for patients in the 3-4 hour time window.

The use of rt-PA following stroke

rt-PA was licensed under the brand name Actilyse for use in acute ischaemic stroke in April 2003 in the UK. It must be administered within a 3-hour time window and was launched under strict licensing guidelines. Under these it can only be used by a physician specialised in acute stroke care and with experience in the use of thrombolytic treatments and appropriate facilities to monitor its use and complications. Brain imaging must be conducted before administration, to exclude intracranial haemorrhage or early signs of major infarction. Furthermore there is a requirement, as part of the licensing agreement, to register all treated patients within the Safe Implementation of Thrombolysis in Stroke MOnitoring STudy (SITS-MOST). This is an initiative by the medical profession to confirm that rt-PA remains a safe treatment choice outside of clinical trials. Details of the registry are available at www.acutestroke.org.

Observational studies

The Standard Treatment with Alteplase to Reverse Stroke (STARS) study suggested that favourable clinical outcomes and a low rate of symptomatic intracranial haemorrhage could be achieved[9]. Further experience has come from the Canadian Activase for Stroke Effectiveness Study (CASES). This study includes over 60 active centres in Canada and has presented results on 944 patients enrolled so far. Results to date indicate a lower rate of symptomatic intracranial haemorrhage (4.7%) than that found previously, even though the level of stroke severity is similar to the NINDS study (NIHSS

Time to treatment administration (mins)	0-90	91 – 180	181 –271	271 – 360
Odds ratio for a favourable outcome	2.8 (CI 1.8-4.5)	1.6 (CI 1.1-2.2)	1.4 CI (1.1-1.9)	1.2 (0.9-1.5)

score = 15) with 30% of patients having minimal or no neurological deficit and 46% being independent at 90 days.

Potential barriers to delivery of thrombolysis

The safe introduction of thrombolytic therapy in the UK can only take place against the backdrop of an organised, efficient and integrated stroke service. However there are considerable logistical difficulties in organising services to enable thrombolysis to be delivered within the required 3-hour time window. A recent systematic review of this topic has been published and identified numerous barriers to thrombolysis[10].

Meeting the required timeframe is only achievable alongside the promotion of rapid recognition of stroke symptoms by the public at large, public education about "brain attack" and a recognition that such patients require urgent transfer to hospital as quickly as possible and prompt access to specialised acute stroke units. Paramedics – the first point of contact for most patients with acute ischaemic stroke – have a vital role in the rapid recognition of stroke and transferring patients rapidly to hospital. Although many patients do arrive in the hospital within three hours of onset, unless they are triaged as high priority (much in the same way as those with acute heart attacks are) and managed quickly, thrombolysis is unlikely to have a major impact on outcome.

Conclusion

The benefits of thrombolysis using rt-PA within three hours of stroke onset can be substantial. By promoting the rapid recognition of stroke symptoms in the community, prompt transport of patients to specialised acute stroke units for early investigation, neuro-imaging, stabilisation and treatment, there would be substantial net benefit for all patients with stroke and not just for the small proportion (currently between 2.5% and 5%) eligible for thrombolysis. Clearly, we have a long way to go before "brain attack" is given the same degree of priority and urgency as "heart attack" currently is.

Barriers to thrombolysis

- failure of patient/carer to recognise the symptoms of stroke or seek urgent help
- initial contact with GP rather than ambulance
- failure of paramedical /emergency department staff to triage stroke as an emergency
- delays in neuro-imaging
- inefficient process of in-hospital emergency stroke care,
- difficulties in obtaining informed consent
- physician uncertainty in administering rt-PA.

Contraindications to thrombolysis with rt-PA:

Patients with:

- symptoms of ischaemic attack that began more than 3 hours prior to start of infusion or when time of symptom onset is unknown
- minor neurological deficit or symptoms that are rapidly improving before start of infusion
- severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques
- seizure at onset of stroke
- evidence of intracranial haemorrhage (ICH) on the CT scan
- symptoms suggestive of subarachnoid haemorrhage, even if the CT-scan is normal
- who have had heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory
- any history of both prior stroke and concomitant diabetes
- a prior stroke within the last 3 months
- platelet count below 100,000/mm3
- systolic blood pressure >185mmHg or diastolic blood pressure >110mmHg or those on IV medication to reduce blood pressure to these limits
- blood glucose <2.8 or >22 mmol/l

Please refer to Actilyse Summary of Product Characteristics for a full list of contraindications.

References

1. Lees KR 2000 *Thrombolysis* British Medical Bulletin 56(2): 389-400.
2. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. 1995 *Tissue Plasminogen Activator for Acute Ischaemic Stroke* NEJM 333: 1581 –1587.
3. Hacke E *et al* 1995 *Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke.* The European Cooperative Acute Stroke Study (ECASS) JAMA 274:1017-1025.
4. Hacke E *et al* 1998 *Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II)* Lancet 1998;352: 1245-1251.
5. Clark WM *et al* 2000 *The rt-PA (alteplase) 0 to 6 hour acute stroke trial, Part A (A0267g): Results of a double-blind, placebo-controlled multicentre study* Stroke 31: 811-816.
6. Clark WM *et al* 1999 *Recombinant tissue-type plasminogen activator (alteplase) for ischaemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study : a randomised controlled trial* JAMA 282 (212):2019-2026.
7. Hacke W *et al* 2004 *Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials* Lancet 363(9411): 768-74.
8. Wardlaw JM *et al* 2004: *Thrombolysis for acute ischaemic stroke (Cochrane Review).* Cochrane Library, Issue 1, 2004.
9. Albers GW *et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke.* Journal of the American Medical Association 2000; 283:1145-50.
10. Kwan J *et al. A systematic review of barriers to delivery of thrombolysis for acute stroke.* Age and Ageing 2004; 33:116-121.

Correspondence to:
Dr. Michael Power
Dept Elderly Medicine
Ulster hospital
Dundonald
Belfast BT16 1RH
Michael.Power@ucht.n-i.nhs.uk

We would like to thank Boehringer Ingelheim for their support in publication of this article
The views expressed are those of the author and do not necessarily represent those of Boehringer Ingelheim

Neurological Contributions of Caleb Hillier Parry

Caleb Hillier Parry (1755-1822) was a schoolfellow of Edward Jenner during the latter's education in Cirencester between 1758 and 1761. The friendship established during these years was to be lifelong. Parry was the original dedicatee of Jenner's seminal 1798 pamphlet describing smallpox vaccination, and Parry returned the compliment in his book on rabies and tetanus published in 1814.

After qualifying in Edinburgh, Parry set up in practice in Bath in 1779, which was to be his home for the rest of his life. He was the first president of the short-lived "Gloucestershire Medical Society" (1788-1793), meeting at the Fleece Inn in Rodborough near Stroud, of which Jenner was also a member. Like Jenner, Parry was an observant clinician, and an experimentalist, and they also shared interests in other aspects of natural history, including geology.[1,2]

With the benefit of hindsight, Parry's most significant clinical contribution was probably his 1799 book on angina, the first devoted to the subject, in which he drew on Jenner's (unpublished) work showing that the symptom was associated with "malorganisation" of the coronary arteries. Parry also encountered cases of exophthalmic goitre, the first in 1786, some fifty years before the account of Graves (1835) which achieved eponymous fame for the latter. However, Sir William Osler acknowledged Parry's priority, and "Parry's disease" has found favour in some quarters. These works have attracted attention in journals devoted to cardiology and endocrinology, respectively.[3,4]

Parry believed his most important contribution was his theory of "determination of the blood", in essence that flow of blood, usually excessive, contributed to organ dysfunction. He thought this was particularly applicable to diseases of the nervous system. Although this theory is now of historical interest only, Parry did make various contributions of value to neurological practice. Long sections of two of his major works were devoted to the nervous system.[5,6] I am not aware of previous articles on Parry in journals devoted specifically to neurology (Jenner too had neurological interests[7]).

1. Carotid artery compression for seizures

Parry's studies of carotid artery compression date from the late 1780s. In addition to the observation (1799) that carotid compression slowed the heart beat, a manoeuvre still used in clinical practice for the emergency treatment of some tachyarrhythmias, he also reported the use of carotid compression to treat episodes of loss of consciousness. Motivated by his theory that nervous system disease resulted from excessive blood flow to the brain ("determination"), he reported improvement in a young woman with bizarre episodes of convulsive movements and impairment of consciousness (in retrospect it is possible that these were induced by hyperventilation) following carotid compression, although the effects were only transient.[8]

Other cases with features more suggestive of partial-onset epileptic seizures were also reported to be controlled by carotid compression.[8,9] This is of possible interest in light of current investigations of implantable vagal stimulators for the control of refractory seizures, although Parry specifically denied that his technique of carotid compression produced pressure on the vagus.[10]

Parry also had other suggestions for how to deal with "fits". Consulted by a carpenter about his 15 or 16 year-old daughter who was having fits, Parry reports that:

"… he and his wife had made it a rule never to contradict her, but uniformly indulged her in every wish ... I urged this man to change his method of proceeding and, instead of this absurd indulgence, to give her a good shaking, or else throw a bason [*sic*] of cold water in her face, immediately on the approach of the next fit."

In the event, the carpenter could not bring himself to follow these recommendations, but apparently spoke sharply to his daughter instead, and the fits ceased.[11]

2. Headache

Parry gives a clear description of his own migraine without headache (or migraine equivalent)

> "After violent fatigue, more especially when accompanied with fasting eight or ten hours, … I have frequently experienced a sudden failure of sight. The general sight did not appear affected; but when I looked at any particular object, it seemed as if something brown, and more or less opake [*sic*], was interposed between my eyes and it, so that I saw it indistinctly or sometimes not at all. Most generally it seemed to be exactly in the middle of the object, while what my sight comprehended all round it, was as distinct and clear as usual; in consequence of which, if I wished to see any thing, I was obliged to look on one side … After it had continued a few minutes, the upper or lower edge … appeared bounded by an edging of light of a zig-zag shape, and coruscating nearly at right angles to its length … they would remain for twenty minutes sometimes to half an hour … They were in me never followed by headach [*sic*] .."[12]

Parry also presents cases which are suggestive of migraine exacerbation during holiday periods,[13] and of migrainous stroke.[14]

The young woman with bizarre convulsive episodes (see above) also had "fits of delirium … preceded by a sense of fulness and throbbing pain in the head, accompanied with a great degree of heat and flushing about the head (what the common people in this country call opening and shutting) and neck", and also "an unusual sensibility with regard to light and sound". Carotid compression, as well as helping the seizures, also "nearly or totally removes the hemicrania of the side on which the compression is made; the headach [*sic, passim*] which is called nervous; that also which is intituled bilious, … " restoring the patient to "perfect use of her senses and powers of rea-

Caleb Hillier Parry (1755-1822)

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.

soning. At the same time the headach, and the undue sensibility with regard to light and sound, which had always taken place in the intervals of the paroxysms, were altogether wanting, and the patient declared that in every respect she was free from complaint". Moreover, whereas the beneficial effect on the seizures was brief, "I have, however, seen some instances in which the nervous and bilious headachs have been for a considerable time, and even permanently, relieved".[15] Modern accounts of the efficacy of carotid or superficial temporal artery compression in migraine have appeared.[16]

It was suggested by Kelly in 1948 that Parry's 1792 paper[8] contained a description of the condition known as "histaminic cephalgia",[17] which itself would now be included under the rubric of cluster headache[18] or perhaps trigeminal autonomic cephalgia.[19] However, the case contains no mention of unilaterality, pacing behaviour, nocturnal attacks, miosis, ptosis, conjunctival injection, lacrimation or nasal congestion, so it seems that the case for Parry describing cluster headache is not established. However, another patient, Mrs R., had "nervous headach [*sic*] over the forehead, eyes, and occiput … accompanied with fulness [*sic*] and stuffing of the nose like a cold, coming and going off in a short time".[20]

3. Facial hemiatrophy

> "… Miss F., aged twenty-eight, … thirteen or fourteen years ago, when at school, was rather suddenly seized with some degree of hemiplegia of the left side ... from the period of the attack the left side of the face began to grow more thin than the right, and the eye to become less prominent, and therefore to appearance smaller … from the same period, her hair on the upper part of the left side of her head, which was before of a dark brown colour, began to grow white … when she protrudes her tongue it turns to the left."[21]

This is from Parry's account of hemifacial atrophy, still sometimes known as Parry-Romberg syndrome (the German's account appeared some years later, 1846). The condition is still seen occasionally by neurologists, sometimes associated with ipsilateral brain atrophy, vascular malformations, and partial-onset seizures, as well as various ophthalmological and dermatological features. There are probably various causes.[22]

4. Miscellaneous

Other neurological conditions which may be encountered in Parry's writings include:

- Visual hallucinations on alcohol withdrawal;
- Dropped hands from lead poisoning, in painters and plumbers (but never cider drinkers!);
- Tic douloureux;
- Wry neck, "suspended by attention to other objects".

He also writes (in 1815) of "shaking palsy", in which the "head and limbs shake, more especially on any muscular exertion", a description perhaps more suggestive of essential tremor than Parkinson's disease.

It is reassuring to find that, like some of his neurological successors, Parry sometimes struggled with clinical-anatomical correlation: a description of right facial weakness with involvement of taste, suggestive of a Bell's palsy, is ascribed to "affection of the second and third branches of the Trigeminus". As there was no difficulty moving the eyeball "it follows that the first (ophthalmic) branch was unaffected"![23]

Parry's medical practice was effectively ended in 1816, at the age of 61 years, by a stroke which resulted in aphasia and right hemiparesis (presumably a left middle cerebral artery territory event). Jenner reported:, "He looked at me earnestly for some time, then grasped my hand and by piteous moans and sighs expressed how strongly he felt his situation", perhaps in part from his clinical familiarity with right hemiplegia.[24] Communication remained difficult for the rest of his life but his two unmarried daughters who helped to care for him were able to interpret, and hence he was able to dictate reminiscences which they wrote down. It is also recorded that he was able to correct with his left hand a manuscript written by his son, Edward (noted for his exploration of the Arctic), an achievement perhaps reminiscent of the scientist Ernst Mach who learned to type with his left hand after a left hemisphere stroke.[25]

References

1. Glaser S. *The spirit of enquiry. Caleb Hillier Parry MD, FRS.* Stroud: Alan Sutton, 1995.
2. Larner AJ. *Caleb Hillier Parry (1755-1822); clinician, scientist, friend of Jenner.* J Med Biog (in press).
3. Fye WB. *Caleb Hillier Parry.* Clin Cardiol 1992;15:619-621.
4. Volpé R. *Caleb Hillier Parry 1755-1822.* The Endocrinologist 1994;4:157-159.
5. Parry CH. *Elements of pathology and therapeutics, being the outlines of a work, intended to ascertain the nature, causes, and most efficacious modes of prevention and cure, of the greater number of the diseases incidental to the human frame; illustrated by numerous cases and dissections.* Bath: Cruttwell, 1815:226-367 (paragraphs DXIX-DCCCLII). [Hereafter Elements.]
6. Parry CH. *Collections from the unpublished medical writings of the late Caleb Hillier Parry M.D. F.R.S.* (3 volumes). London: Underwoods, 1825: volume I:260-590. [Hereafter Collections.]
7. Larner AJ. *Jenner, on the intellect.* Advances in Clinical Neuroscience and Rehabilitation 2003;3(2):29.
8. Parry CH. *On the effects of compression of the arteries in various diseases, and particularly in those of the head; with hints towards a new mode of treating nervous disorders.* Memoirs of the Medical Society of London 1792;3:77-113. [Hereafter Memoirs.]
9. Parry CH. *On a case of nervous affection cured by pressure of the carotids; with some physiological remarks.* Philosophical Transactions of the Royal Society 1811;101:89-95; see also Elements, 1815: 315 (paragraph DCCXXXVII).
10. *Collections,* 1825; volume I:322.
11. Ibid., volume I:368.
12. Ibid., volume I:557-559.
13. Ibid., volume I:279.
14. Ibid., volume I:480-481; see also *Elements*, 1815:373 (paragraph DCCCLVIII).
15. *Memoirs,* 1792:85,82,89,86,97 respectively; see also *Elements,* 1815:305 (paragraph DCCXVI).
16. Drummond PD, Lance JW. *Extracranial vascular changes and the source of pain in migraine headaches.* Ann Neurol 1983;13:32-37.
17. Kelly EC. *Encyclopedia of medical sources.* Baltimore: Willimas & Wilkins, 1948:317.
18. Sjaastad O. *Cluster headache syndrome.* London: WB Saunders, 1992:1-34 [especially 1-18]
19. Matharu MS, Goadsby PJ. *Trigeminal autonomic cephalgias.* J Neurol Neurosurg Psychiatry 2002;72(supplII):ii19-ii26.
20. *Collections*, 1825; volume I:331.
21. Ibid., volume I:478-480. *Elements*, 1815:404 (paragraph DCCCLXXI) mentions this same case but only the eye and hair changes.
22. Larner AJ, Bennison DP. *Some observations on the aetiology of hemifacial atrophy ("Parry-Romberg syndrome").* J Neurol Neurosurg Psychiatry 1993;56:1035-1036.
23. *Collections*, 1825; volume I:545-546; see also *Elements*, 1815:254-255 (paragraph DXCII).
24. *Collections*, 1825; volume I:492-510.
25. McManus C. *Right hand, left hand. The origins of asymmetry in brains, bodies, atoms and cultures.* London: Phoenix, 2003:185-187.

Correspondence to:
AJ Larner
Walton Centre for Neurology and Neurosurgery
Lower Lane, Fazakerley
Liverpool L9 7LJ
U.K.
E.mail.
a.larner@thewaltoncentre.nhs.uk

Book Reviews

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

The Clinical Science of Neurologic Rehabilitation (2nd edition)

Edited by: Bruce H Dobkin
ISBN: 0195150643
Publisher: Oxford University Press
Price: £85 (hardback)

One of the major challenges facing a neurorehabilitationist-in-training is how to build up the breadth of knowledge necessary for the modern biopsychosocial, interdisciplinary approach to rehabilitation. The neuroscience literature has often provided indepth studies on mechanism without a clear message on rehabilitation context, whereas the rehabilitation literature examined clinical practice without a clear link to biological mechanism.

This systematic, readable and well-referenced volume, by a neurologist who specialises in neurorehabilitation, succeeds in bridging this gap. The first section summarises the current state of knowledge of nervous system structure and function, changes in response to injury, and the rationale for different medical and non-medical rehabilitation interventions. The second section, 'Common practices across disorders', spans the composition of the inter-disciplinary team, outcome measurement, gait rehabilitation and the medical management of common complications. The third section focuses on an evidence-based approach to the rehabilitation of stroke, traumatic brain injury, and acute and chronic myelopathies, with a shorter final chapter on other neurological disorders. The current state of the literature is reviewed, together with comments on the likely place of new interventions in the rehabilitation process and suggestions of directions further research is likely to take.

I would recommend this as compulsory reading for any neuro-rehabilitationist who seriously wants to integrate their everyday clinical practice with a sound knowledge of neuroscience. As a useful starting point for anyone wanting to explore the evidence for (and clinical context of) particular rehabilitation interventions, it should also have a place on library shelves beside standard neurology texts.

David Shakespeare,
Lancashire Teaching Hospitals Trust, Preston.

Vascular Cognitive Impairment. Preventable Dementia

Edited by: JV Bowler, V Hachinski
Publisher: Oxford University Press
ISBN: 0-19-263267-1
Price: £79.50

The editors of this book coined the term "vascular cognitive impairment" (VCI), to replace the concept of vascular dementia (VaD), in 1995. This book reviews the clinical, neuropsychological, neuroimaging and neuropathological aspects of VCI, as well as addressing treatment. It enters a field which has seen at least two major publications in recent years (Chui E, Gustafson L, Ames D, Folstein MF (eds.). Cerebrovascular disease and dementia. Pathology, neuropsychiatry and management. London: Martin Dunitz, 2000; and Erkinjuntti T, Gauthier S (eds.). Vascular cognitive impairment. London: Martin Dunitz, 2002).

Various themes emerge. The definition of VCI stemmed, at least in part, from a desire to identify cases at the earliest possible stage, before dementia (i.e. sufficient cognitive impairment to affect occupational or social function) was evident, the rationale being that intervention at this stage might prevent dementia (hence the subtitle of the book), in much the same way that the concept of mild cognitive impairment has been developed by researchers aiming to identify the earliest, and potentially treatable, stages of Alzheimer's disease (AD). However, the editors are at pains to point out that this conceptual change from VaD to VCI necessitates abandoning diagnostic criteria based on an Alzheimer-like neuropsychogical profile, particularly with it emphasis on memory loss (the "Alzheimerised" dementia concept). Hence VCI cases, which may manifest frontal executive dysfunction, language and motor problems, will by-and-large not be identified in "memory clinics" (certainly our experience in this centre). This also has implications for recruitment to clinical trials, selection criteria often revolving around "objective" test scores which might possibly exclude individuals who might benefit from treatment. The difficulty in trying to differentiate VCI from AD is compounded by the observation that they share risk factors, and histopathologically a mixed picture may be the most common finding in late-onsert dementia patients (MRC CFAS, Lancet 2001; 357: 169-75).

This well-produced volume summarises a great deal of information on the effects of cerebrovascular disease on cognitive function in an accessible manner, and can be unhesitatingly recommended to both cognitive neurologists and stroke physicians. Yet this remains an area where certain data are sparse, meaning that operational criteria for VCI cannot currently be proposed. This book may serve, at least in part, as a manifesto for the concept of VCI. A fuller discussion of the emerging evidence for cholinesterase inhibitors in VCI/VaD would have been desirable, but this was perhaps unavoidably occasioned by the publication schedule.

AJ Larner; Cognitive Function Clinic, WCNN, Liverpool

Cerebrovascular Ultrasound: Theory, Practice and Future Developments

Edited by: M Hennerici, S Meairs
Publisher: Cambridge University Press
ISBN: 0521632234
Price: £170

The editors have attempted to provide a definitive cerebrovascular ultrasound textbook. Previous texts on the subject have suffered from a dryness of technical prose and insufficient clinical content to inspire even the most dedicated stroke clinician. In the UK this is compounded by the absence from training of obligatory "hands-on" ultrasound exposure. This criticism cannot be levelled at our international colleagues – a fact reflected in the gallery of authors who have contributed to this book.

The target readership for this text is practising stroke clinicians but its broad coverage of the subject should find readers in vascular laboratories and in neurosurgery, vascular surgery and radiology departments. It is subdivided into three sections addressing physics and haemodynamics, clinical intra- and extracranial applications, and future developments. Non-physicists may find the early chapters mathematically intimidating and inaccessible but the excellent clinical sections more than balance this. The clinical coverage is logically set out and extends from plaque morphogenesis, characterisation and natural history, through to quantification of carotid stenosis with reference to carotid surgery trials. Intracranial applications include microemblous detection, measurement of intracranial stenosis, arteriovenous malformations, post subarachnoid vasospasm and haemodynamic reserve testing.

Inevitably there is some repetition and redundancy of text, but the editing has minimised this and it allows each chapter to stand alone sufficiently for the majority of readers approaching this as a reference text. Those of us who must interpret the significance of carotid ultrasound reports in the TIA clinic will find much of relevance to our practice.

The section on future developments is short but manages to cover multi-gated embolus detection, 3 and 4D carotid imaging, and functional Doppler testing which will interest clinicians. But the text is weighted towards the extracranial circulation. I was disappointed by the paucity of text related to intracranial 3D power Doppler to image the circle of Willis and transcranial Doppler perfusion measurement. The latter would have complemented the chapter on ultrasonic thrombolysis. One notable absence is the use of transcranial Doppler to measure cerebral autoregulation from analysis of phase shifts or rate of recovery from rapid changes in systemic blood pressure – both of which are familiar research tools for assessment of cerebrovascular pathophysiology.

This is a very wlecome addition to the cerebrovascular library and is to be recommended. It is a well-marshalled, systematic, well-illustrated and readable text, accessible to a wide variety of clinicians, radiologists and scientists dealing with cerebrovascular disease.

RP White, WCNN, Liverpool

EDITOR'S CHOICE

Presenilin 1 gene mutation causing Pick's disease

Over 100 mutations in the presenilin 1 (PS1) gene causing Alzheimer's disease (AD) have been described in the past decade (molgen-www.uia.ac.be/Admutations). Cell biological and animal models show these mutations increase production of the long variant of amyloid €-peptide (Ab42) by increasing gamma-secretase cleavage of amyloid precursor protein (APP). This report from Belgium broadens the clinical phenotype of PS1 mutations, reporting a novel mutation (G183V) associated with the clinical features of frontotemporal dementia (FTD) and, uniquely, a neuropathological substrate typical of Pick's disease.

The proband presented aged 54 with apathy, disinhibition and frontal release signs. Memory functions were intact. Brain imaging showed predominant frontotemporal atrophy. The clinical-radiological diagnosis was FTD. However, unusually for FTD, he had an abnormal EEG (slow and sharp waves in the temporal regions) and later developed dyspraxia (not further specified). He died at age 62. Brain pathology showed tau positive Pick bodies and Pick cells but no amyloid deposits. No mutation was found in the genes encoding APP, tau, PS2, or prion protein, but a novel mutation was identified in PS1, which was also found in 3 other family members, 2 with lesser degrees of cognitive and neuroradiological change.

Although the clinical phenotype of FTD has previously been reported with PS1 mutations (L113P, insR352), this is the first case with neuropathological evidence of Pick's disease. Although the neurogenetic finding might be a novel polymorphism, the cosegregation with clinical and neuroimaging abnormality suggests pathogenicity. The proposed mechanism is a dominant negative effect, resulting in loss of gamma-secretase activity; if correct, treatment of such patients with gamma-secretase inhibitors would be contraindicated. *-AJL*

Dermaut B, Kumar-Singh S, Engelborghs S, Theuns J, Rademakers R, Saerens J, Pickut BA, Peeters K, van den Broeck M, Vennekens K, Claes S, Cruts M, Cras P, Martin JJ, Van Broeckhoven C, De Deyn PP.
A novel presenilin 1 mutation associated with Pick's disease but not €-amyloid plaques.
ANNALS OF NEUROLOGY
2004;55(5):617-626

★★★ RECOMMENDED

NEUROIMMUNOLOGY: anti basal ganglia antibodies – what do they signify?

There have recently been a whole series of articles on the role of anti basal ganglia antibodies in neurological disease, in particular PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders After Streptococcal infections) and related disorders. Gavin Giavannoni and colleagues in London were one of the first groups to demonstrate antibodies against the basal ganglia in patients with a range of neurological disorders following streptococcal infections, suggesting that the humoral mediator of the condition could be isolated and act as a diagnostic test. They now extend these findings to encephalitis lethargica (EL) by describing 20 new cases of this condition in which a range of immunological abnormalities were seen including antibodies against a range of neural epitopes (but not just in the basal ganglia). In addition they demonstrated that these antibodies can be seen pathologically in brain specimens from a patient who died from this condition, and argue that they are pathogenic and thus that EL is therefore related to Sydenham's chorea and PANDAS. However, despite this convincing account, it is often difficult to prove causality with antibody mediated disorders, and a couple of recent papers in Movement Disorders take on this challenge. The first of these papers by Singer *et al* demonstrates that the striatal microinfusion of PANDAS sera (as well as that from patients with Tourettes syndrome) is without effect, suggesting that the antibodies contained within the sera are non-pathological. Indeed this group then go on to report in this same issue of Movement Disorders that their ELISA method for detecting anti basal ganglia antibodies cannot differentiate between PANDAS and controls, suggesting a "lack of major antibody changes in this disorder", a conclusion that is largely embraced by the accompanying editorial by Roger Kurlan.

So how does one reconcile all these different findings and what does it mean when one has a positive anti basal ganglia result in a patient? I think for the moment it is not clear, but it is important to remember that assays such as those employed in these studies are very operator dependent and certainly in the hands of Giavannoni *et al* they appear to have very low false positive results. Therefore results from this laboratory are probably significant, but quite how they cause disease is unclear at this stage given that the passive transfer of disease has not been achieved – analogous to the situation that is seen with most antibody associated paraneoplastic syndromes. This failure to prove causality also creates issues of treatment, in that whilst antibiotics to treat the underlying streptococcal infection are clearly important, it is not clear what, if any, immunosuppressive therapies should be advocated…..but that is the subject of future studies and I also suspect yet more controversy! *-RAB*

Dale RC, Church AJ, Surtees RAH, Lees AJ, Adcock JE, Harding B, Neville BGR, Giovannoni G (2004)
Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity.
BRAIN
2004:127:21-33

Kurlan R
The PANDAS hypothesis: losing its bite?
MOVEMENT DISORDERS
2004: 19:371-374

Loiselle CR, Lee O, Moran TH, Singer HS
Striatal microinfusions of Tourette Syndrome and PANDAS sera: Failure to induce behavioral changes.
MOVEMENT DISORDERS
2004: 19:390-396

Singer HS, Loiselle CR, Lee O, Minzer K, Swedo S, Grus FH.
Anti-basal ganglia antibodies in PANDAS.
MOVEMENT DISORDERS
2004: 19:406-415

MULTIPLE SCLEROSIS: Transplant drug helps aggressive disease

The interferon-failure era has well and truly begun. The enthusiasm for interferons as a treatment for multiple sclerosis has waned on both sides of the Atlantic and the hunt is on for more effective treatments. There are many new agents at one stage or other in the development pipeline. One of the most interesting is daclizumab, a monoclonal antibody that binds to – and blocks the function of –, CD25, the alpha chain of the IL2 receptor. IL2 is a pivotal cytokine in the survival and proliferation of T cells. This antibody has a proven track record at inhibiting rejection in organ transplantation and, like several drugs before it, translation into the autoimmune field made good sense.

Roland Martin's group at the NIH have reported a pilot study of treating just 10 patients with daclizumab, all of whom had "failed" interferon by virtue of having had one relapse, or progressing by just one EDSS point, in the previous eighteen months. (In itself, that is a provocative definition as it does not take account of pre-treatment relapse frequency). The patients were required to demonstrate a high degree of new MRI lesion formation before treatment was given as a monthly infusion over 6 months. During this time, new MRI lesion formation was reduced by 78%. So the drug is effective at reducing inflammation in the brain… as have been many novel agents.

So far, so good. But what makes this study special is that, as the trial was taking place, high expression of the CD25 molecule was discovered to be a marker of regulatory T cells, whose job it is to suppress autoimmunity. So daclizumab potentially might have exacerbated disease activity, by releasing the control of autoaggressive T cells. Almost certainly, daclizumab would be considered too dangerous if the trial were being

planned now. So, once again, the treatment of multiple sclerosis has thrown up a confusing result that sends us back to the immunological drawing board. *-AJC*

Bielekova B, Richert N, Howard T, Blevins G, Markovic-Plese S, McCartin J, Wurfel J, Ohayon J, Waldmann TA, McFarland HF, Martin R.
Humanised anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon-beta.
PROC NATL ACAD SCI U S A.
2004;101:8705-8708.

REHABILITATION: What happens to Head Bangers?

This group have published several papers in this field in recent years but this one adds significantly to the picture of short to medium term outcome in children after a head injury (HI). Their study population of nearly a thousand was identified from a comprehensive local Register linked to the trauma centre admissions. A postal questionnaire was used, based on a new outcome scale derived from the Glasgow Outcome Scale for adults, the Kings Outcome Scale for Childhood Head Injury (KOSCHI) and covering a wide variety of symptoms, behaviour, personality and performance. This was sent out to the parents of children up to six years since injury. Amazingly they were able to retrieve GCS and/or duration of loss of consciousness in all patients (as there is another ongoing study in trauma) – most studies report routine recording of GCS in only up to 60% of cases.

They formed a control group of 45 children by asking some parents of the study group to identify a child of the same age and sex but without a history of head injury (but one wonders about the possibility of parents choosing a "role model" child in their area and thus the validity of this control?) There was a nearly 60% response rate (thus over 500 children), higher in the more severe groups and no noted differences in characteristics between responders and non-responders.

Some surprising findings include that only 30% of the study group had any follow-up and only 8% received any form of therapy. Current teachers were aware of the child's head injury in only 40% of cases. Nearly half the children had moderate disability according to the KOSCHI outcome score and worryingly 43% of those with mild HI were in this group. Not surprisingly symptoms were more frequent in the more severely injured groups and worse outcome was associated with poor socio-economic status (which is already recognised as a risk factor for acquiring head injury in the first place).

As they mention, up to 3,000 children each year in the UK acquire significant new neurological or cognitive disability as a result of head injury. Clearly given their young age and impact on development there is a huge potential for improvement in quality of life with appropriate assessment and intervention. The authors suggest a postal questionnaire follow-up to identify those that may benefit from follow-up assessment. However, one wonders whether an information/advice sheet to parents on discharge with relevant contacts as has been advocated for adults might be more efficient? *-JJMACF*

CA Hawley, AB Ward, AR Magnay, J Long.
Outcomes following childhood head injury: a population study.
JOURNAL NEUROLOGY NEUROSURGERY PSYCHIATRY
2004, 75:737-742

★★★ RECOMMENDED

EPILEPSY: Telephone-induced seizures!

One of my wise teachers once said that if the history is odd, consider psychiatric causes but if it is truly bizarre then think organic. Few people could make up a story like these three patients who described typical complex partial seizures triggered by answering the phone and occurring a few seconds into the conversation. The effect was described with both land lines and mobile phones. For one patient the attacks seemed to come on most frequently when her best friend phoned her but when she was admitted for video-EEG-telemetry, it was a nurse phoning her that triggered the seizure after seven unsuccessful phone calls. The simultaneous EEG showed a right temporal seizure discharge. Recording seizures was unsuccessful in the other two patients but one had an interictal epileptiform disturbance over the right frontotemporal region and the other more non-specific changes over the left temporal lobe. Neuroimaging was normal in all three. All responded to a greater or lesser degree to carbamazepine. I see this as a strong justification to leave on my answerphone 24 hours per day.

Michelucci R, Gardella E, de Haan GJ, Bisulli F, Zaniboni A, Cantalupo G, Alberto Tassinari C, Tinuper P, Nobile C, Nichelli P, Kasteleijn-Nolst Trenite DG.
Telephone-induced seizures: a new type of reflex epilepsy.
EPILEPSIA
2004;45:280-3

★★★ RECOMMENDED

REHABILITATION: Neighbourhood Watch and the Leylandia

The two hemispheres of the brain are like a lot of neighbours; most of the time they co-operate and are quite amicable across the garden fence (corpus callosum), getting on with tasks that require involvement of both parties, but occasionally there are elements of competition and even downright antagonism! Yes I agree, a rather crass analogy but one which helps me interpret Pascual-Leone's paper on a rather surprising effect of inhibiting the motor cortex. By applying low frequency (1Hz) repetitive transcranial magnetic stimulation (rTMS) a target area of cortex can be temporarily switched off ('virtual lesioning'). This Harvard group performed this on one hemisphere and measured speed and accuracy of a motor task (index finger key tapping) pre and post rTMS of both hands. Not much happened to the execution time or accuracy in the contralateral hand, ie the hand supplied directly by M1 receiving the rTMS, however, the ipsilateral hand on performing the same motor task appeared to be significantly quicker in executing the task without compromising accuracy (same error rate) post TMS. A case of leaving the Leylandia unchecked(?). [Editor's note: this analogy defeats me].

There are various confounders that have to be taken on board but the study does seem to have controlled pretty well for these, e.g. ensuring a plateau in performance with practice of the motor task before performing the experiment. The hypothesis from this study is that a bidirectional inhibitory transcallosal pathway between motor areas can be suppressed with TMS on one side, releasing the contralateral M1 to work faster. The paper also supported this proposed mechanism by studying inhibition directly with a paired TMS study. Interestingly the effect is not equal, with the dominant hemisphere generating greater inhibition.

There is evidence from both stroke patients and rat lesioning that a paradoxical increase in function can occur in the unaffected hemisphere. If this TMS method has a long lasting effect, then a therapeutic application in rehabilitation may be possible. At the moment 600 pulses affords about 10 minutes of increased speed. Maybe I will have to give their protocol a go and see if my mobile text messaging is any quicker! *-JLR*

M.Kobayahsi, S.Hutchinson, H.Theoret, G.Schlaug, and
A. Pascual-Leone.
Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements.
NEUROLOGY
2004; 62: 91-98.

HUNTINGTON'S DISEASE: Induction of autophagy by rapamycin slows progression

Huntington's disease (HD) is an autosomal dominant inherited disorder caused by a polyglutamine tract expansion in the Huntingtin protein (Htt). HD is characterised neuropathologically by intraneuronal inclusions, which amongst other proteins, are comprised of aggregates of the N-terminal fragment of mutant Htt.

This work by Ravikumar and colleagues demonstrates that within these inclusions, mutant Htt associates with a cellular kinase, mTOR. mTOR is responsible for the regulation of cellular processes through the control of mRNA translation, such as maintenance of cellular volume and inhibition of autophagy. Sequestration of mTOR within such inclusions impairs its kinase activity and induces the autophagy process, which breaks down aggregation-prone proteins including mutant Htt. Several lines of evidence point to the cellular toxicity of intraneuronal inclusions in HD. However, there is also evidence of a possible protective role for these inclusions. This study employed rapamycin, a specific inhibitor of mTOR, to stimulate autophagy. This drug successfully

reduced mutant Htt accumulation and neurodegeneration in vitro and in vivo models of HD and improved performance in four behavioural tasks of mouse models of the disease.

It is hopeful that rapamycin will be available shortly to treat human disease since it is already used as an immunosuppressant and its ester analogue, which has fewer side effects, is undergoing evaluation in clinical trials for cancer. This pre-clinical study suggested that rapamycin loses efficacy when aggregate pathology is advanced, thus in the clinic it would be important to start therapy early to slow progression of HD. In those individuals with a genetic susceptibility, starting therapy before the onset of symptoms may stall the disease beyond normal life span and thus represent a cure.

These trials suggest a huge therapeutic potential for mTOR inhibition in the treatment not only of HD, but other neurodegenerative diseases associated with protein aggregation. *-LMS, SJT*

Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, Rubinsztein DC

Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease.

NATURE GENETICS

2004: 36 (6) ; 585-95

★★★ RECOMMENDED

STROKE: asymptomatic carotid stenosis

In 1991, the European and North American carotid surgery trials (ECST and NASCET) demonstrated a long-term net benefit of carotid endarterectomy in patients with a recent stroke and significant ipsilateral carotid stenosis. But the data was less robust for surgery for asymptomatic carotid stenosis, hence the MRC Asymptomatic Carotid Surgery trial, of which this is the 5 year report. 3120 patients were included with carotid stenosis of at least 60% on ultrasound and no attributable cerebrovascular event in the preceding 6 months. 1560 were allocated immediate surgery and 1560 randomised to deferred surgery, of which 201 patients had had an endarterectomy within the 5 year period, for one reason or other. Overall the surgical risk of perioperative stroke or death was 3.1%. It took two years before this risk was outweighed by the benefit from surgery. But, by 5 years, there was a clear benefit for early endarterectomy: a risk of 6.4% of any stroke (including peri-operative) or death in the surgical arm compared to 11.8% for medical treatment. This benefit was seen for stenoses greater than 70%. The trial will continue to run for a further 5 years, so it may be that surgery to lesser stenoses will yet prove beneficial in the long-term.

Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group.

Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial.

LANCET

2004;363:1491-502

REHABILITATION: Invasive motor cortex stimulation to help recovery from stroke

Recently it has been demonstrated that in animal models of stroke, improved function can result from subthreshold cortical stimulation when combined with motor training. This has led to a feasibility trial in human stroke patients in the US (Northstar Neuroscience). Results from the first patient in the study were published alongside reports of the preclinical studies in the December issue of Neurological Research last year. And since invasive methods of stimulation have not really been considered as an option for stroke rehabilitation in the UK, it is worth drawing attention to this article.

A 65 year old man with a subcortical infarct was recruited to the study 19 months after stroke. At the time of recruitment he was unable to move his fingers but could extend his wrist against gravity. He underwent surgery to create a cranial flap. The site, identified by fMRI, was over the cortical motor representation of wrist flexion. A plate carrying an array of electrodes was implanted and stimulation through selective electrode contacts evoked contralateral finger flexion. The flap was replaced and three days after surgery the patient began an intensive 3 week programme of occupational therapy involving the paretic hand and arm and aimed at improving activities of daily living. During these sessions an external pulse generator was worn and subthreshold cortical stimulation was delivered concurrent with Occupational Therapy. At the end of the three weeks his score on the Fugl-Meyer motor assessment was improved by 10 points and he was reported to be able to pick up a pencil and print block letters.

Of course this case report is not controlled and we cannot be sure that the reported changes would not have occurred without the stimulation. We will have to wait for the results of the trial. However, as well as the possibility that this treatment may be effective it is interesting to consider how the stimulation might have helped. The authors speculate how recovery may have occurred. The patient was unable to move the fingers voluntarily when the electrode plate was implanted but the stimulation delivered during the operation evoked individual finger flexion. This means that the corticospinal projections to the motoneurones of the finger flexors were intact but the patient could not access them. It is possible that the stimulation delivered during the patient's attempts to use the hand may have depolarised the underlying neurons to a level that allowed the movement to be executed. As the practice and stimulation continued so synaptic circuits were reinforced and voluntary movement was regained.

This invasive treatment might seem rather extreme, but if the results are good many patients might be prepared to have the surgery. However, if the cortical stimulation proves effective there may be ways in which the cortex could be stimulated by non-invasive means. *–AJT*

Brown JA, Lutsep H, Cramer SC, Weinand M.

Motor cortex stimulation for enhancement of recovery after stroke: case report.

NEUROLOGICAL RESEARCH

2003: 25: 815-818

PARKINSON'S DISEASE: Neurogenesis as a treatment for PD?

D3 receptors are widely expressed in the development and persist in neurogenic areas in adulthood (subventricular zone and hippocampus). D3 receptor activation promotes mitogenesis in vitro via G protein activation of the Ras pathway, which promotes phosphorylation of mitogen activated protein kinases (MAPK).

The authors sought to examine the role of D3 activation on precursor cells in vivo. D3 activation by 7-OH-DPAT (via intraventricular infusion for 2 weeks) increases BrdU incorporation into cells in the SVZ, RMS (rostral migratory stream, the migration path of neuroblasts to the olfactory bulb), and striatum. BrdU incorporates into dividing cells and is used as a marker for cell proliferation, and persist so cells can also be double labelled with other cell markers and thus the cell's fate can be examined. BrdU immunoreactivity in the striatum decreases as a function of the distance from the ventricle, suggesting the cells had migrated from the SVZ, or the proliferation was in response to a dose dependent effect according to the agonist gradient. The increase in BrdU was specific to D3 activation as it was not mirrored by a D1 agonist, and abolished by co-infusion of a D3 antagonist. The authors did not explore whether D3 blockade reduced basal BrdU incorporation.

Proliferation in the striatum may represent stimulation of endogenous in situ precursors. PCNA, another marker for proliferation, represents cells that are dividing only at the time of killing. PCNA immunoreactivity was increased, paralleling the BrdU increase, which suggests in situ proliferation rather than migration. Systemic, as opposed to intraventricular administration, produced uniform staining throughout the striatum. Also, BrdU labelling was increased after only 3 days of D3 stimulation, arguably, not giving the cells enough time to have migrated from the SVZ. Importantly, the majority of the newborn cells in both the RMS and the striatum co-expressed neuronal markers, indicating the new cells were new neurones. Some even expressed TH (i.e. were likely dopaminergic neurones). GFAP (astrocytic) labelling was not increased.

So, D3 stimulation increases neurogenesis in the striatum (and, in unpublished observations, in the substantia nigra). As mentioned, D3 has mitogenic properties via the MAPK system; but also through tyrosine kinase activation. TK activation is normally mediated via neurotrophins,

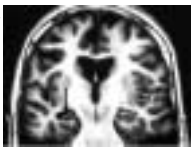
and indeed there is evidence for cross talk between D3 and BDNF (brain derived neurotrophic factor). BDNF also increases neurogenesis. Perhaps D3 activation could be harnessed to produce new neurones to replace those lost in neurodegenerative diseases like PD and HD. Perhaps this action may underlie some of the disease modifying properties of drugs such as pramipexole.

Identification of a substrate for neurogenesis in the striatum and substantia nigra offers potential for a therapeutic target for brain repair in conditions that affect these regions.-*WAR*

Van Kampen JM, Hagg T, Robertson HA.
Induction of neurogenesis in the adult rat subventricular zone and neostriatum following D3 receptor stimulation.
EUROPEAN JOURNAL OF NEUROSCIENCE
2004: 19; 2377-2387

EPILEPSY: Religiosity and the hippocampus

I clearly recall one patient coming to clinic with page upon page of closely written and perseverative text, concerning the Isle of Innisfree and its religious significance. The Geschwind syndrome triad of hypergraphia, religiosity and hyposexuality may be useful qualifications for a life in cloisters but is also thought to represent a behavioural syndrome in some patients with temporal lobe epilepsy. In this study 33 residents of the Chalfont centre with refractory epilepsy were included and underwent volumetric MRI. They were assessed on the validated and widely used neurobehavioural inventory (NBI) and divided into three groups; high or low religiosity, high or low sexuality and high or low writing behaviour. The only behaviour that was correlated with an MRI abnormality was hyper-religiosity, patients had significantly smaller right hippocampal but not amygdala volumes. The authors refer to a study of Kumagasu Minakata, apparently a Japanese genius with the Geschwind triad whose post-mortem MRI showed right hippocampal atrophy. The mechanism of these associations is unknown. - *MM*



Wuerfel J, Krishnamoorthy ES, Brown RJ, Lemieux L, Koepp M, Tebartz van Elst L, Trimble MR.
Religiosity is associated with hippocampal but not amygdala volumes in patients with refractory epilepsy.
JOURNAL NEUROLOGY NEUROSURGERY PSYCHIATRY
2004;75:640-642.

Joan of Arc

ANATOMY: the oddest thing

Silas Weir Mitchell, one of America's greatest neurologists, learnt his trade – as many have done since - on the battlefield. Amongst the nerve injuries he described were several examples of the curious phenomenon of a unilateral injury leading to bilateral deficits. This paper from the Nerve Injury Unit at the Massachusetts General Hospital, explores this curious business further. In 6 rats, the left common peroneal and tibial nerves were ligated, leaving the sural intact. Then various sensory stimuli (von Frey hairs, pinprick, acetone) were applied to the rat paws. The result was long-lasting allodynia and hyperalgesia in ipsilateral sural-innervated territory only, because of unexplained mechanisms. Then the density of neurites was measured in punch skin biopsies from different nerve-innervated skin. One week later, on the lesioned side, there was 90% reduced neurite density in tibia-innervated skin, and increased neurite sprouting in the neighbouring sural area.

The remarkable finding was that there was a 50% reduction in the neurite density of the contralateral tibial-innervated skin, suggesting some anatomical connection between homologous nerves across the midline. Yet none is known to exist. In this study, there was no accompanying contralateral limb deficit, but as Weir Mitchell's cases illustrate, the same mechanism may lead to real problems in humans with unilateral injury. All very curious. *–AJC*

Oaklander AL, Brown JM.
Unilateral nerve injury produces bilateral loss of distal innervation.
ANNALS OF NEUROLOGY
2004;55:639-44.

Weir Mitchell

EPILEPSY: ictal autoscopy

Hands up those who went into neurology because they were fascinated by the insights that neuroscience can give into the workings of the human mind. I number myself among these although sadly I can now rarely understand the titles of articles in cognitive neuroscience journals, let alone their content. One of the most tantalising symptoms is autoscopy – the pathological perception of one's body or face image from an internal or external (out-of-body experience) viewpoint. The authors describe three patients with ictal autoscopy, one of whom also had other unusual ictal sensations including palinopsia, and macroasomatoagnosia, (feeling body parts were enlarged). This patient underwent video-EEG-telemetry and three seizures were recorded, each beginning with a right parietocentral discharge. She had evidence of right parietal cortical dysplasia on MRI and the other two patients, with no ictal recordings, had right parieto-occipital oligodendroglioma and scarring following a right posterior haemorrhage. Right parietal, especially inferior parietal involvement seems to be crucial for the expression of this experience.

Maillard L, Vignal JP, Anxionnat R, Taillander L, Vespignani. *-MM*
Semiologic value of ictal autoscopy.
EPILEPSIA
2004; 45:391-394

HUNTINGTON'S DISEASE: Modification of huntingtin fragments increases toxicity

Huntington's disease is caused by an autosomal dominantly inherited expanded CAG repeat in the IT15 gene on chromosome 4. The gene normally encodes for a protein of unknown function called huntingtin (htt), but in disease the protein contains an expanded glutamine (Q) stretch, encoded by the expanded CAG repeat. Fragments of the polyQ htt are believed to confer more toxicity to the cell than full-length mutant htt.

Steffan and colleagues have used cell lines transfected with a toxic fragment of htt to show that small ubiquitin-like modifier (SUMO) and ubiquitin can modify the fragment. It is known that both SUMO and ubiquitin bind to lysine residues in the fragment. The authors manipulated the fragment and transfected fragments with or without a long proline stretch, and with or without lysine mutations (thereby removing the binding site for SUMO and ubiquitin). Western blotting revealed that fragments were only modified (and thus their size altered) when lysine residues were intact, indicating that these sites were required for SUMOylation and ubiquination. Also, fragments were only ubiquitinated if they lacked the proline stretch. When SUMO was fused to the N terminus of the fragment, it accumulated and stabilised. Moreover, SUMOylation (and, independently, removal of the proline stretch) reduced aggregate formation. This may be because SUMO competes for the ubiquitin binding site (and ubiquitin is known to increase aggregation formation). Importantly, SUMO may be increasing the amount of pre-aggregation toxic oligomers.

SUMO, when co-expresssed with the htt fragment in striatal cells, represses certain gene promoters. The first 17 amino acids of htt can target proteins to the cytosol. The SUMO modification is targeted to these amino acids. The authors postulate that this cytosolic signal is reduced by SUMO, thus increasing htt nuclear localisation, such that it can influence transcription.

Mutant htt fragments were next transfected into Drosophila. Flies expressing the mutant fragment display a loss of photoreceptors. Those with a mutation in SUMO have much less photoreceptor loss; and flies with mutant ubiquitin have slightly more photoreceptor loss. Thus, SUMO contributes to neurodegeneration and ubiquitin confers slight protection.

In summary, htt can be SUMOylated; this increases htt accumulation but reduces aggregation (possibly increasing toxic oligomers), possibly

masks a cytosolic signal, represses transcription, and increases neurodegeneration in a fly model. Inhibition of SUMOylation (e.g. inhibition of E3-ligase, which normally allows SUMO to attach to htt) may be potentially therapeutic in HD. SUMO has also been implicated in the pathogenesis of other neurodegenerative diseases including SCA-1, DRPLA and Alzheimer's disease. Thus the potential therapeutic avenues may stretch far. - *WAR*

Steffan J, Agrawal N, Pallps J, Rockabrand E, Trotman LC, Slepko N, Illes K, Lukacsovich T, Zhu Y, Cattaneo E, Pandolfi P, Thompson L, Marsh J.
SUMO Modification of Huntingtin and Huntington's Disease Pathology.
SCIENCE
2004, 304, 100-104

HUNTINGTON'S DISEASE: HD mouse models are protected from excitotoxicity

Excitotoxicity, as a cause or consequence of neurodegeneration, has long been explored. Mice transgenic for the expanded HD gene have a complex response to excitotoxic injury, with different strains and different ages of mice having different levels of susceptibility to excitotoxins. Taking all these studies together, it seems that transgenic mice which express huntingtin fragments, as opposed to the full length protein, are less susceptible to excitotoxic injury. Furthermore, this effect increases as the mouse ages. Jarabek and colleagues explore this phenomenon, and possible mechanisms in the N171-82Q mouse. This is a transgenic model, with the N-terminal fragment of huntingtin inserted into the mouse genome under the prion promoter.

These mice become symptomatic between 9 and 14 weeks. Mice at 7, 15 and around 20 weeks were chosen as representing pre-symptomatic, symptomatic and hypokinetic advanced disease. When quinolinic acid was injected into the striatum, the 15 week transgenic mice showed less neuronal death than their wild type littermates. 7-week-old mice showed no difference, but, strangely, hypokinetic mice were not tested. Only in hypokinetic mice was the number of NMDA receptors reduced (NR1 subtype). So, there must be another mechanism accounting for neuroprotection in the 15 week old mice. Since phosphorylation of the NR1 subunit has been associated with increases in the NMDA receptor current, the authors conducted Western blots and quantified the protein level of phosphorylated NR1 in the two mouse groups at different ages. They demonstrated a progressive decrease in phophorylation at serine 897 in the transgenic mice. Phosphorylation at this site is protein kinase A dependent. As dopaminergic D1 receptors increase PKA levels, they were next quantified. A progressive decrease in D1 receptors was found from 15 weeks in the transgenic mice. So, the authors postulate that reduced D1 leads to reduced PKA dependent NR1 phosphorylation thus less excitotoxicity. They do, however, point out that other pathways are likely to be involved in phosphorylation, as D1 receptors were not reduced in 7 week old mice although phosphorylated NR1 was. Another effect of reduced D1 receptors is an increase in the anti-apoptotic protein, P13 kinase, which was found only in the hypokinetic mice.

nNOS is activated by NMDA mediated calcium influxes, and contributes to neurodegeneration. There was a progressive decrease in membrane associated nNOS from 15 weeks in the transgenic mice. This was not due to translocation from the cytoplasm as nNOS was not reduced in this fraction. So, presumably nNOS is being upregulated (although no mRNA was measured).

PSD-95 is a scaffolding protein, supporting both the NMDA receptor and the nNOS receptor; it is found in progressively lower levels from 7 weeks in the transgenic mouse. Citron is another protein that is supported by PSD-95, and is involved in dedritic spine formation. It too, is reduced in the transgenic mouse; fewer spines mediate less glutamatergic input and thus less excitotoxicity (dendritic spines are known to be reduced in transgenic mice).

This study has confirmed that another transgenic model is resistant to excitotoxicity and proposed some mechanisms for this (although causality has not been proven). These include reduced D1 receptor so less phosphorylation of NMDA receptors; reduced scaffolding for NMDA and nNOS; increased anti-apoptotic proteins, and reduced dendritic spine forming proteins. These protective changes may represent a protective response to chronic low-level excitotoxicity in those mice that express huntingtin fragments. It has been suggested that mice, which express full-length huntingtin, represent a much earlier stage of the disease and therefore such protective mechanisms are not yet in place. It has long been thought that neuronal dysfunction rather that cell death is the more important, certainly for fragment-expressing transgenic mice, and intriguingly such 'protective' changes may in fact be detrimental, causing or contributing to a disorder in functional neurotransmission, and so disease phenotype. -*WAR*

Jarabek B.R., Yasuda R.P., Wolfe B.B.
Regulation of proteins affecting NMDA receptor-induced excitotoxicity in a Huntington's mouse model.
BRAIN
2004: 127, 505-516

PARKINSON'S DISEASE: Placebo effects

The origins of placebo effects have always been controversial, and of late there has been interest in this effect in Parkinson's disease (PD) and the role of dopamine. However, a brief communication in Nature Neuroscience suggests that this placebo activated dopamine effect in PD is associated with decreased activity in the neurons of the subthalamic nucleus (STN). In this study, 11 patients undergoing surgery for PD were given placebo injections of subcutaneous saline (having previously been given apomorphine via this route) and the efficacy of this treatment correlated with a significant decrease in discharge in about 100 neurons recorded in the STN. Only 6 patients reported a placebo effect, whilst 5 did not, and this enabled the effect to be seen although does beg questions as to why some patients can produce this effect whilst others do not. Nevertheless this demonstration at the single unit level in the STN of the effects of placebo in PD, is of interest and once more highlights the importance of placebo in the treatment of this condition – which must be considered in any novel therapeutic trials in this condition. - *RAB*

Benedetti F, Calloca L, Torre E, Lanotte M, Melcarne A, Pesare M, Bergamasco B, Lopiano L.
Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus.
NATURE NEUROSCIENCE
2004:7:587-588.

Royal Hospital Celebrates 150th Anniversary

THIS year the Royal Hospital for Neuro-disability celebrates 150 years of providing care. To mark the occasion an 'Exhibition of Celebration' will take place at the Air Gallery in London from 20-24th September. The featured artists are Ken Paine, the late Debra Manifold and Rosa Sepple (whose work appears on the front cover of this issue of ACNR) with photography by David Maxwell and sculpture by Unus Sefardiar and A Tobias Williams, (see picture of his sculpture 'Bulletor', right). Rosa Sepple is a self-taught artist whose compositions have a powerful visual strength and refreshing spontaneity. She also suffers from trigeminal neuralgia and says, 'If just a single dysfunctional nerve has such a terrible effect it gives me a little insight into the lives of patients who have suffered substantial damage to their brain and nervous system.'

The Royal Hospital is the UK's leading centre for rehabilitation and care of people with acquired brain injury and neurological illness.

For further details about the exhibition of celebration and the Royal Hospital for Neuro-disability please see www.rhn.org.uk or call 020 8780 4561.

Advanced Medical Equipment Scan School

ADVANCED Medical Equipment are pleased to announce that they will be hosting a Scan School from 20-24 September at the Holiday Inn, Coram Street, Bloomsbury, London.

For more information Tel. 0207 923 6600, Fax. 0207 278 0989, www.ichotelsgroup.com/h/d/hi/1/en/hd/lonbl. See the location map at www.go.vicinity.com

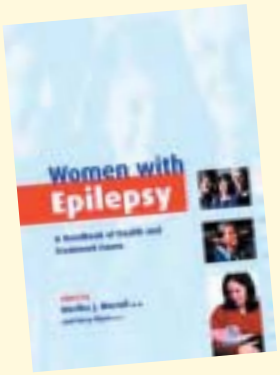
Session I will focus on EEG/ERP Acquisition & Analysis, and Session II on Curry. Register for this event at: www.neuro.com/school.sstg

Please also note that Advanced Medical Equipment have moved. Their new contact details are as follows: Advanced Medical Equipment, City Business Centre, Horsham Court, Unit 14, 6-8 Brighton Road, Horsham, West Sussex RH13 5BA. Tel. 01403 260156, Fax. 01403 260175, Web: www.advancedmedicalequipment.com

Women with Epilepsy: A Handbook of Health and Treatment Issues

EDITED by Martha J. Morrell and Kerry L. Flynn. In this handbook for sufferers, their clinicians, families and friends, a team of experts reviews the special problems faced by women with epilepsy. Hormone levels affect seizures and epilepsy treatments affect fertility, and can cause pregnancy complications and birth defects. Many health-care providers are not informed about the unique issues facing women with epilepsy. This book, published in association with the Epilepsy Foundation of America, fills that gap and provides women with epilepsy with the information they need to be effective self-advocates.

For more information contact Cambridge University Press on Tel. 01223 312393.



More Power to your Egg

THE new EP21 Current Amplifier has been introduced by Intracel. This accessory for the TSS20 Ovodyne electroporator widens the field of operation for the TSS20 ensuring that electroporation protocols hitherto impossible or difficult due to current limitation can now be effectively run. In addition to in ovo use, the amplifier will allow greater use of electroporation cuvettes for in vitro work.

The EP21 connects to the TSS20 output and whilst maintaining the square wave form and voltage allows currents of up to 1 amp to be delivered.

For more information contact Tim Scott, Intracel, Unit 4, Station Road, Shepreth, Royston, Herts SG8 6PZ. Tel. 01763 262680, E-Mail. Intracel@intracel.co.uk, www.intracel.co.uk

NICE Epilepsy Guidance

THE National Institute of Clinical Excellence has issued guidance to the NHS in England and Wales on the use of newer drugs for the treatment of epilepsy in adults.

The guidance states that Topamax (tomiramate) from Janssen-Cilag along with six other 'newer' antiepileptic drugs are recommended, within their licensed indications, for the management of epilepsy in people who have not benefited from treatment with the older AEDS, or for whom the older AEDs are unsuitable (for example because of contraindications, interactions with other drugs or where the person is a woman of childbearing potential).

The guidance further recommends that:

Adults with epilepsy should be treated with just one antiepileptic drug where possible. If the first drug doesn't prevent seizures, another can be tried; Adjunctive or combination therapy should only be considered when attempts at monotherapy have not resulted in seizure freedom; A careful assessment of the risks and benefits of treatment with individual AEDS should be undertaken, particularly in relation to women of childbearing potential; A person who has a seizure for the first time should see an epilepsy specialist as soon as possible, to find out what type of epilepsy he or she has, so that the best treatment can be started; Treatment should be reviewed at regular intervals.

For further information about Topamax contact Janssen-Cilag on Tel. 01494 567567. For information on NICE guidance, see www.nice.org.uk

Middlesex Hospital Speeds Patient Workflow

A NEW MR scanner installed at Middlesex Hospital will enable radiographers to increase patient workflow, as well as improving patient comfort. Acquired through the NHS Cancer Plan fund, the Siemens MAGNETOM Symphony scanner replaces a Siemens Open Via MR scanner previously used at the hospital. With traffic diverted for the day, the new system was successfully installed in the hospital's basement site using a massive crane to lift it into place over the main building.

The MAGNETOM Symphony scanner's compact ultra-short bore magnet system and scaleable performance covers routine to clinical research MRI. The Integrated Panoramic Array (IPA) coil technology optimises the entire patient exam process as the need to position or change coils is virtually eliminated. The system allows increased patient workflow up to 20 per cent per day compared to non-IPA systems.

"The hospital required a high field scanner that could be used for a range of cases and since receiving Siemens MAGNETOM Symphony scanner it has immediately proved popular with staff and patients alike," commented Fiona Henderson, Lead Superintendent Radiographer at Middlesex Hospital.

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

The magnet of the Siemens MAGNETOM Symphony scanner is being hoisted into the Middlesex Hospital by crane.

New Applications For The Digitimer D185 Stimulator

THE Digitimer D185 is used for spinal cord monitoring in surgical procedures including scolliosis corrections, spinal tumour re-sections and repairs of aortic aneurysms. In each case, transcranial motor evoked potentials (TceMEPs) have helped protect patients from intra-operative spinal injury. The 1000V output and brief 50 microsecond pulse also make it suitable for stimulation of spinal roots, which are difficult to activate with lower output stimulators.

Using the D185, diagnostics are possible along the whole peripheral nerve, allowing neurophysiologists to identify extremely proximal sites of conduction block. Identification of such sites is important when differentiating between treatable conditions like multifocal motor neuropathy (MMN) and motor neuron disease (MND) which is untreatable and fatal. In some cases of MMN the site of conduction block is not identified by traditional nerve conduction tests and patients are misdiagnosed with MND when they actually have a treatable condition. Stimulation with the D185 can reveal such sites and facilitate the correct diagnosis (Arunachalam et al., 2003). R. Arunachalam, A. Osei-Lah & K.R. Mills (2003) J. Neurol. Neurosurg. Psychiatry 74 1329-1331.*For more information contact Digitimer on Tel. 01707 328347, E-Mail. sales@digitimer.com*

Neurological Rehabilitation Of Parkinson's Disease

REHABILITATION comprises various forms of therapy: physical, speech and psychosocial therapy. Physical rehabilitation is used in conjunction with various antiparkinsonian agents as a non-pharmacological treatment for Parkinson's disease. The first book in the Queen Square Neurological Rehabilitation Series, Neurological Rehabilitation of Parkinson's Disease (1841842974 £26.50) edited by Diane Playford explores the approaches and processes required to ensure the comprehensive management of a patient with Parkinson's disease. This book examines what are the long-term and short-term benefits of physical therapy and the effectiveness of physical rehabilitation. The second in the series, Neurological Rehabilitation of Stroke (1841843229 £29.95) is now available. *For further information contact Taylor & Francis on Tel. 0207 7583 9855.*

Licence Extension For Provigil

THE novel wakefulness-promoting agent Provigil (modafinil) has received a significant extension to its product licence in the UK. The new indication allows Provigil to be prescribed for the treatment of excessive sleepiness associated with chronic pathological conditions, including narcolepsy, obstructive sleep apnoea / hypopnoea syndrome (OSAHS) and moderate to severe chronic shift work sleep disorder (SWSD).

Additional data in Parkinson's disease, depression, myotonic dystrophy and multiple sclerosis were supportive of showing Provigil's efficacy as a treatment for excessive sleepiness in other conditions.

"Provigil is already a first-line treatment for excessive sleepiness in narcolepsy and a useful option for the management of excessive sleepiness in obstructive sleep apnoea / hypopnoea syndrome following CPAP treatment. These new data appear to indicate that Provigil improves wakefulness regardless of the pathological condition, without any effect on sleep when this is desired," said Dr Adrian Williams, Lane Fox Respiratory Unit and Sleep Disorders Centre, St Thomas' Hospital, London.

For more information contact Cephalon on Tel. 01483 454911.

Trial Shows Increased Bleeding Risks

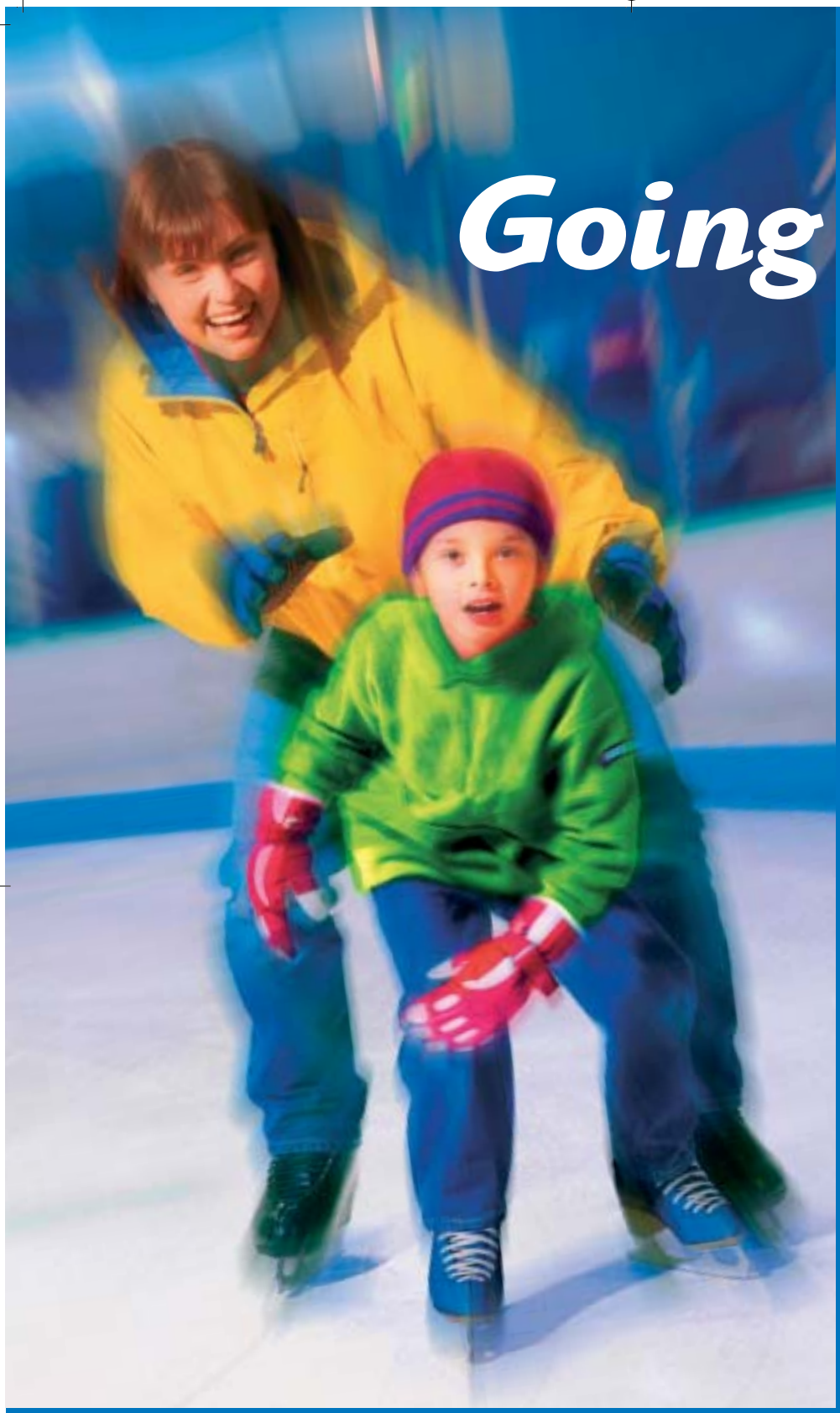
A NEW study has linked a combination of aspirin and the antiplatelet agent clopidogrel with life-threatening bleeds in high-risk stroke patients. The study also showed no additional clinical benefit with the aspirin/clopidogrel combination.

The major health threat to patients who have suffered an initial ischaemic stroke (IS) or transient ischaemic attack (TIA) is a second stroke. The risk of a recurrence is high — up to 14% annually. A stroke patient is up to fives times more likely to suffer a second stroke than a myocardial infarction.

Aspirin has long been established to reduce the risk of second stroke and the combination of aspirin with dipyridamole MR (Asasantin Retard) doubles this protective effect (compared with placebo, relative risk of second stroke is reduced by 18% with aspirin and 37% with dipyridamole MR plus low dose aspirin).

However, results of the MATCH trial (Management of AtheroThrombosis with Clopidogrel in High risk patients) reported at the 13th European Stroke Conference in Mannheim, show that in high risk patients with recent IS or TIA, the combination of aspirin 75mg daily with clopidogrel 75mg daily shows no beneficial clinical effects and doubles the risk of a life-threatening bleed (which includes intracranial bleeding).

For further information please contact KWT Public Relations Ltd, Tel. 0208 541 5999, E-Mail. enquiries.kwt@blueyonder.co.uk



Going solo

A double-blind, randomised trial has shown that Topamax 100 mg is as effective in various seizure types:

– as carbamazepine when it is predominantly selected for partial-onset seizures[1]

– as valproate when it is predominantly selected for generalised seizures.[1‡]

TOPAMAX®
TOPIRAMATE

BECAUSE LIFE WITHOUT SEIZURES IS SO MUCH BETTER*

*In a double-blind trial in newly diagnosed epilepsy, 49% of patients taking topiramate 100 mg and 63% of children on topiramate were seizure free for the last 6 months of the study[1,2] ‡Topamax is indicated as monotherapy in adults and children aged six years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. Uses: Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. Dosage and Administration: Oral: Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3 – 6 mg/kg/day (two divided doses). Initiate at 0.5 – 1 mg/kg nightly with weekly or fortnightly increments of 0.5 – 1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5 - 9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1 – 3 mg/kg. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. Contra-indications: Hypersensitivity to any component. Precautions and Warnings: Withdraw gradually. Renal impairment delays achievement of steady-state. Caution with hepatic impairment. May cause sedation; so caution if driving or operating machinery. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and requires discontinuation of Topamax and treatment of symptoms. Increased risk of renal stones. Adequate hydration is very important. Food supplement may be required. Interactions: Possible with phenytoin, carbamazepine, digoxin, oral contraceptives and metformin. Decrease in serum bicarbonate levels. Pregnancy: If benefits outweigh risks. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). Lactation: Avoid. Side Effects: Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diplopia, headache, hypoaesthesia, fatigue, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis and suicidal ideation or attempts reported rarely. Bullous skin and mucosal reactions reported very rarely. Pharmaceutical Precautions: Tablets and Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed. Legal Category: POM Package Quantities and Prices: Bottles of 60 tablets. 25 mg (PL0242/0301) = £20.02; 50 mg (PL0242/0302) = £36.17; 100 mg (PL0242/0303) = £64.80; 200 mg (PL0242/0304) = £125.83. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.88, 25 mg (PL0242/0349) = £25.32, 50 mg (PL0242/0350) = £41.60. Product licence holder: Janssen-Cilag Limited, Saunderton, High Wycombe, Buckinghamshire HP14 4HJ, UK. Date of text revision: February 2004. APIVER250204.

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

JANSSEN-CILAG Ltd

4794