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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

INSIDE > Special Preview – ABN Annual Meeting
(See Pages 32 34).

In this issue

Win a FREE place at ACNR's Neurology Digest Meeting
Turn to page 39 for details

NEWS REVIEW > CONFERENCE REPORTS > JOURNAL REVIEWS > BOOK REVIEWS > EVENTS DIARY

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Peter Rothwell wins Outstanding Achievement award

Solvay Healthcare recently sponsored the Outstanding Achievement in Evidence Based Healthcare Award at the inaugural BMJ Group awards. Those who have improved patient care through the use of evidence based medicine were recognised at the event.

The winning clinician was Peter Rothwell, Professor of Clinical Neurology at the University of Oxford, for his remarkable contributions in stroke treatment and prevention. The award was presented by Solvay's Chief Executive Officer, Dr Thomas Weidauer.

Professor Rothwell has pioneered developments in stroke prevention throughout his career. This award recognises his work in demonstrating the need for acute preventative treatment and how such treatment reduces the early risk of major strokes by 80%. The evidence based results from his team in Oxford have led to a national and international change in clinical practice, backed now by official guidelines from NICE.

For more information E. edickinson@bmj.com

UCLan Professor's Boost for Health and Social Care Research

Caroline Watkins, Professor of Stroke & Older People's Care, at the University of Central Lancashire (UCLan), has been appointed as NIHR Senior Investigator. She has been recognised for her outstanding contribution to patient-focused research and research leadership, and has been commended for her strong interactions with patients and the public, as well as policy makers.

For more information about UCLan, please visit www.uclan.ac.uk

New Chair of Headache UK

The Chief Executive of The Migraine Trust, Wendy Thomas, has been appointed Chair of Headache UK, an alliance of professional health organisations. Headache UK aims to raise awareness of chronic headaches as a major public health problem. It also promotes understanding of the significant impact headaches can have on people's lives and tries to ensure speedy diagnosis and better treatment for people who live with chronic headaches.

Wendy Thomas said, "Every day 190,000 people in the UK suffer a migraine attack and many more suffer from serious headaches. Migraine and headache are a major public health issue, which has been estimated to cost the UK £7 billion a year in absenteeism and reduced productivity. We need to do everything we can to push headache disorders up the health agenda." Headache UK supports the All Party Parliamentary Group on Primary Headache Disorders (APPGPHD), which carries out high-level briefings for parliamentarians on topics such as the economic cost of migraine and the role of specialist general practitioners in diagnosing headache.

Briefings from the APPGPHDs can be found at www.headacheuk.org

Second round of NIHR Senior Investigators announced

Professor Nick Fox, Professor Andrew Lees and Professor David Miller have been appointed as NIHR Senior Investigators. The NIHR has appointed sixty-three new members of the NIHR College of Senior Investigators as the outcome of the second annual competition. Senior Investigators are recognised for their outstanding contribution to health and social care research. The second set of appointments augment the existing 100 Senior Investigators who were appointed in April 2008.

Andrew Lees

David Miller

Nick Fox

For more information see: www.ion.ucl.ac.uk

MS Society wins AMRC award

The MS Society received recognition of its work at the Association of Medical Research Charities (AMRC) Awards. The charity's research team won the award for Best Patient and Public Involvement for its Research Network - a group of around 300 people affected by multiple sclerosis (MS) closely involved in the Society's research programme. The volunteers lie at the heart of the programme and are involved every step of the way; shaping overall research strategy, influencing funding decisions, and overseeing research grants.

Judges on the panel unanimously praised the scheme for its integration, describing it as 'outstanding' and 'impressive' and demonstrating 'real involvement'. Jayne Spink, Director of Policy and Research, said, "This award is a real credit to the hard work of our volunteer Research Network members, and that of Public Involvement Officer, Gabby Ansems, whose leadership has revitalised and evolved the programme to the success it is today." The Society was also runner up for Best Use of Design for the recently re-launched flagship research publication Research Matters.

For more information see www.mssociety.org.uk

MND Association wins award for successful Research Foundation campaign Care Research

The Motor Neurone Disease (MND) Association has received an award for its successful Research Foundation campaign which secured multi-million pound Government funding for MND research.

The MND Association Research Foundation campaign won in the campaigning and public affairs category of the 2009 Science Communication awards, organised by the Association of Medical Research Charities (AMRC). The MND Association set up the Research Foundation in 2006 with the aim of raising £15 million for MND research. They put together a business case and lobbied in Parliament for half of this funding to be provided by the Government. They were delighted when, in 2007, this was secured through the setting up of a funding partnership with the Medical Research Council.

The awards are held every two years and are designed to celebrate AMRC members' excellence in communicating science and to recognise and reward best practice in science communication.

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CONTENTS

MAY/JUNE 2009

Web Content

Case Report: Progressive Subcortical Gliosis of Neumann: Does MRI/MRS Permit Ante Mortem Diagnosis?
AJ Larner, ETS Smith, M Doran

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Cover shows the Liverpool Arena and Conference Centre, venue for the ABN 2009 Annual Meeting.
See page 32 for more details.

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It is now over 15 years since the first gene linked to familial ALS was described. Since then, much has been done in the lab with the resultant transgenic animals, although sadly little from this research has made an impact in the natural history of this condition in patients. However, recently a number of new genes have been discovered in ALS and with this comes renewed hope that disease modifying therapies may be soon in the clinic. In this issue of ACNR we are extremely fortunate to have this work summarised for us by Jemeen Sreedharan and Chris Shaw, part of a team who have made a substantial contribution to this area of ALS research.

Sarah Creer and colleagues in the Rehabilitation article discuss "voice banking". This is storing your voice early in the course of a neurodegenerative process, so that it can be used later in the course to help fashion and aid communication. The article describes how this process can be done and how it will evolve in the years to come.

The article by the ABNT discusses the results of a new survey of trainees and concludes "Despite some difficulties, most neurology registrar posts continue to offer excellent training opportunities. However, registrars with any concerns about their training programme should certainly raise these with their Programme Director and, failing that, with the ABNT. Only with active trainee involvement will the high standard of neurology training be maintained in the face of the pressures of service delivery."

Mal de Debarquement Syndrome is a rare condition that many will not have heard about. As a consequence it is often hard to diagnose and Jane Houghton describes her own experiences with this condition in our Personal perspectives article.

Since the introduction of L-dopa for the treatment of PD in the late 1960s, the use of this drug has always caused debate. In our sponsored article, Murat Emre and colleagues discuss how best to employ this agent in the management of PD, including which formulation.

The next article in the series from the UAE, by Khalid Mohamed and Sabahat Wasti, takes as its theme the topic of spasticity in cerebral palsy. They describe the current management of this condition and how this is changing as the health care system in UAE evolves.

In the neuroliterature series, Andrew Larner explores further the works of Charles Dickens, highlighting the author's acute powers of observation. Heather Angus-Leppan has written a short viewpoint on the vexed issue of integrating paediatric-adolescent and adult services, in this case in the context of neurological care. This interesting article is thought provoking and does raise issues about how best to integrate young patients with more advanced cases of the same condition.

We have our usual collection of reviews, and in addition we have two meetings to highlight: the annual ENS meeting in Milan in June, and the first of the new style ABN meetings which is taking place in Liverpool, also in June. Professor Alastair Compston offers an invitation to attend the ABN, and you can also see details of the programme on pages 33 and 34.

Finally don't forget our planned ACNR digest event which is advertised in this issue of the ACNR. See page 39 for further information. We look forward to seeing many of you there. ◆

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

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Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** *Tablets*: None. *Syrup*: Do not store above 30°C. Use within 4 weeks of first opening. *Solution for infusion*: Do not store above 25°C. 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Email: medicalinformation@ucb-group.com. **Date of Revision:** January 2009 (08VPE0353) Vimpat is a registered trade name. **References:** 1. VIMPAT® Summary of Product Characteristics. 2. Beyreuther BK *et al. CNS Drug Rev* 2007; **13**(1): 21–42. 3. UCB Data on file. **Date of preparation:** February 2009. 09VPE0029

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Editorial board and contributors

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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 our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.

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Heather Angus-Leppan is ACNR's ABN representative on the Editorial Board. She is Head of the Neurology Department at Barnet Hospital and Consultant Neurologist, Honorary Senior Lecturer and Epilepsy Lead at the Royal Free Hospital, London, UK. She is the Honorary Assistant Secretary of the Association of British Neurologists, Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and current Chair of the Map of Medicine Epilepsy Group, UK.

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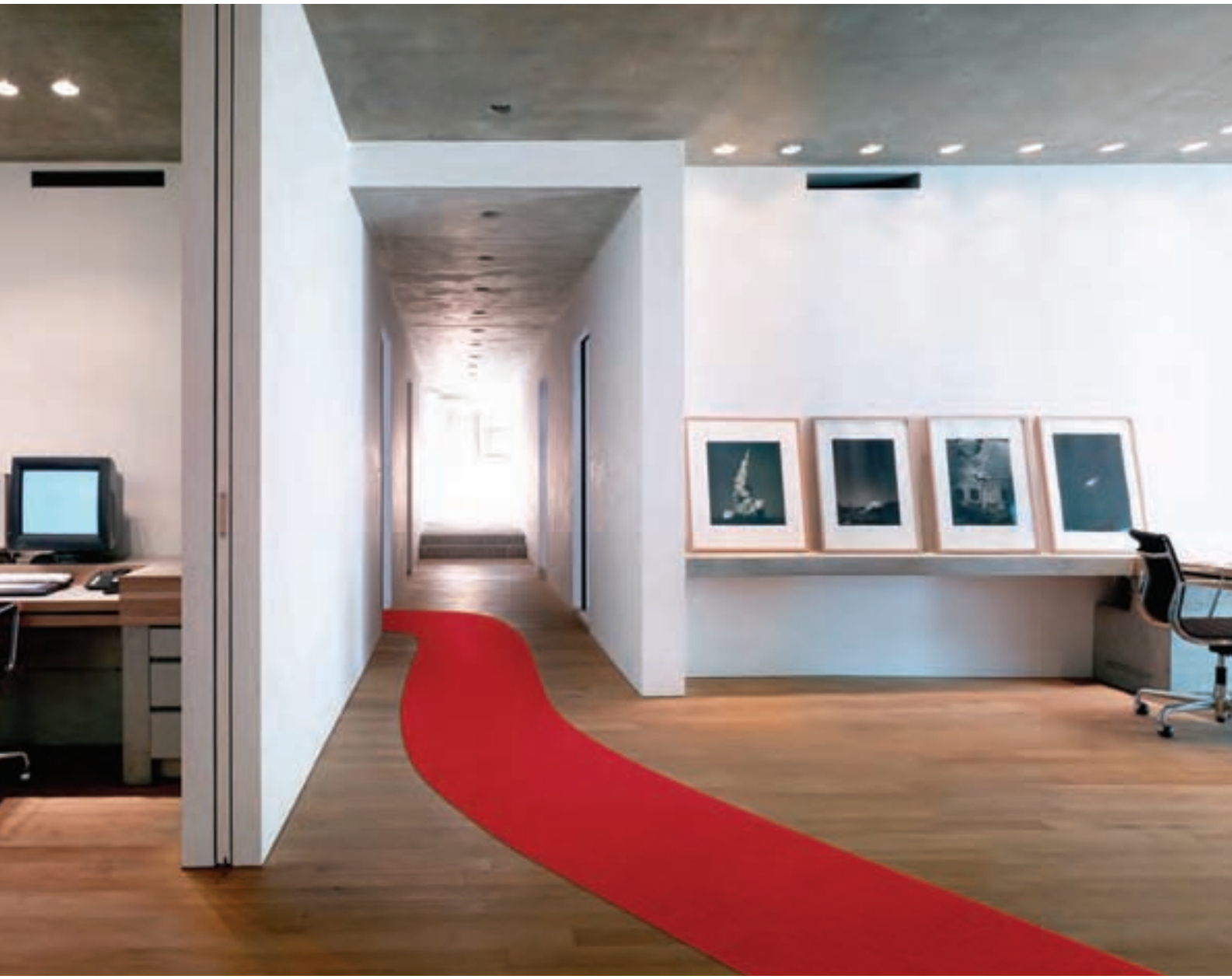

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The Genetics of Amyotrophic Lateral Sclerosis

Jemeen Sreedharan,
Jemeen Sreedharan has an interest in neurodegenerative diseases and carried out research into the genetics of familial ALS in Chris Shaw's laboratory at the Institute of Psychiatry. He is currently a neurology registrar in the East Kent Hospitals NHS Trust.

Christopher E Shaw
is Professor of Neurology and Neurogenetics, at the Institute of Psychiatry, King's College London. He is also an Honorary Consultant Neurologist at King's College and Guy's Hospitals. His early training in General Medicine and Neurology was conducted in New Zealand. He came to the UK in 1992 on a Wellcome Trust Fellowship to study Neurobiology at Cambridge. His clinical and research focus is the genetic and molecular basis of motor neurone disease (MND). He has run a clinic for patients with MND at King's College Hospital and another for people with a variety of inherited neurological disorders at Guy's Hospital since 1995. He is Head of the Department of Clinical Neuroscience and Director of the Medical Research Councils Centre for Neurodegeneration Research.

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Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive, age-dependent neurodegenerative disorder of motor neurons. It causes paralysis, bulbar dysfunction and respiratory failure and is invariably fatal within 2-5 years of onset. Riluzole, the only disease modifying agent used in ALS, has only a modest effect on survival.[1] Treatment is essentially supportive and palliative and ~1200 people die of ALS annually in the UK. ALS is challenging to study as it is mostly sporadic, rapidly progressive and clinically heterogeneous. Significantly, a family history of ALS is seen in 5-10% of cases (FALS), usually with autosomal dominant inheritance.[2] FALS is essentially indistinguishable from the more common sporadic ALS (SALS). Identification of FALS genes offers a direct approach to elucidating common mechanisms of disease in ALS and potentially identifying therapeutic targets.

Classical Mendelian inheritance in FALS kindreds is complicated by a variable age of onset, phenotypic heterogeneity and incomplete penetrance. There is also growing evidence that SALS has a genetic basis. Environmental factors interacting with genetic variants of small effect may predispose to SALS and may also explain the heterogeneity of FALS. ALS is a complex genetic disease with sporadic and familial ALS existing at opposite ends of a genetic spectrum. Ten forms of FALS linked to separate genetic loci have been classified, six of which cause typical ALS (Table 1). Two loci linked to ALS with frontotemporal dementia (ALS-FTD) have also been characterised. ALS and FTD are recognised to be part of a clinicopathological spectrum. Up to half of ALS patients may have clinical features of FTD,[3] and both conditions demonstrate characteristic pathological inclusions containing ubiqutinated TAR DNA-binding protein (TDP-43).[4,5]

In this review we will discuss the major genetic causes of ALS, starting with genes identified by linkage analysis of FALS kindreds. The most significant genes associated with sporadic disease will also be highlighted.

FALS genes causing typical ALS

ALS1- SOD1

Autosomal dominant FALS was first linked to chromosome 21q22, and mutations in Cu/Zn superoxide dismutase *(SOD1)*, an antioxidant enzyme, were subsequently identified.[6,7] Over 120 SOD1 mutations in all five exons affecting all functional domains are recognised. SOD1 mutations are the commonest cause of FALS accounting for ~20% of cases. The pathogenicity of mutant SOD1 is not fully understood but is probably due to a toxic gain of function affecting many cellular processes, including mitochondrial function and axonal transport.[8] SOD1 mutations are also seen in 1-7% of SALS cases.[81]

ALS6-FUS

Linkage of ALS to chromosome 16p (ALS6) was originally described in several families in 2003.[9,10,11] The mean age of onset is ~45 years with disease duration ~33 months and lower motor neuron predominance. Mutations in fusion *(FUS)* have recently been found in these kindreds.[12,13] FUS has roles in gene transcription and RNA processing. Although a predominantly nuclear protein, mutations result in cytoplasmic sequestration. *FUS* mutations cluster at the c-terminus and may account for as many as ~7% of FALS cases, though more studies are needed to accurately determine their frequency. FUS mutations have not been found in SALS cases.

ALS10-TARDBP

Mutations in *TARDBP*, which encodes TDP-43, have been found in FALS and SALS cases. This demonstrates a mechanistic role in neurodegeneration for TDP-43, the hallmark protein of ALS.[14] Around 30 *TARDBP* mutations, mostly c-terminal, have been described by various groups in ALS (Table 2). The mean age of disease onset is ~55 years with survival ~54 months. There is little evidence of cognitive dysfunction, which is surprising given that TDP-43 inclusions are also a hallmark of FTD. *TARDBP* mutations account for ~3% of FALS and ~1% of SALS, though these values vary between populations.

Genes causing rare ALS variants

ALS2-Alsin

ALS2 is a rare, recessively inherited, juvenile-onset disease characterised by slowly progressive spasticity beginning in the lower limbs and spreading to the upper limbs and bulbar musculature. Truncation mutations in the *ALS2* gene (coding for alsin) were found in Tunisian and Arab kindreds.[15,16] Alsin has roles in cellular trafficking and the cytoskeleton.[17,18,19] Alsin may also protect neurons against mutant SOD1-mediated toxicity and promote neurite outgrowth.[20,21] Mutations are thought to result in loss of function.

ALS4-Senataxin

ALS4 is a rare, non-fatal, autosomal dominant, juvenile-onset distal hereditary motor neuropathy characterised by limb weakness, muscle wasting and pyramidal involvement. Bulbar and respiratory muscles are spared. Missense mutations in

Table 1 Genes and loci linked with ALS

Disorder	OMIM	Locus	Gene (protein) function	Inheritance	Onset	References
Typical ALS						
ALS1	105400	21q22.1	SOD1 (Cu/Zn superoxide dismutase 1) Converts superoxide to water or hydrogen peroxde	Dominant	Adult	Siddique et al., 1991 Rosen et al., 1993
ALS3	606640	18q21	?	Dominant	Adult	Hand et al., 2002
ALS6	608030	16q12	TLS/FUS (TLS/FUS) Gene transcription, RNA processing	Dominant	Adult	Ruddy et al., 2003 Sapp et al., 2003 Vance et al., 2009
ALS7	608031	20ptel-p13	?	Dominant	Adult	Sapp et al., 2003
ALS9	611895	14q11	ANG (Angiogenin) Angiogenesis	Dominant	Adult	Greenway et. al., 2006 Wu et. al., 2007 Gellera et. al., 2008
ALS10	612069	1p36.2	TARDBP (TDP-43) DNA/ RNA binding, splicing, transcriptional regulation	Dominant	Adult	Sreedharan et. al.,2008 Kabashi et. al., 2008
ALS with frontotemporal dementia						
ALS-FTD1	105550	9q21-22	?	Dominant	Adult ALS with FTD	Hosler et al., 2000 Ostojic et al., 2003
ALS-FTD2	611454	9p21-13	?	Dominant	Adult ALS with FTD	Vance et al., 2006 Morita et al., 2006 Valdmanis et al., 2007
Atypical ALS						
ALS2	205100	2q33	ALS2 (ALS2/Alsin) Endosomal dynamics. Guanine exchange factor for Rab5 and Rac1. Neuronal survival factor	Recessive	Juvenile – predominantly UMN (PLS, infantile-onset ascending HSP)	Hadano et al., 2001 Hentati et al., 1994 Yamanaka et al., 2006 Yang et al., 2001
ALS4	602433	9q34	SETX (Senataxin) Putative DNA /RNA helicase, RNA metabolism	Dominant	Juvenile – recessive mutations Cause ataxia-oculomotor apraxia type 2	Chance et al., 1998 Chen et al., 2004
ALS5	602099	15q15.1-21.1	?	Recessive	Juvenile	Hentati et al., 1998
ALS8	608627	20q13.3	VAPB (VAMP associated membrane protein B) Endosomal trafficking, calcium metabolism	Dominant	Adult – causes slowly progressive SMA phenotype, tremor or typical ALS	Nishimura et al., 2004 Nishimura et al., 2004b atypical ALS with

SETX (coding for senataxin) have been found in three Caucasian kindreds.[22,23] The function of senataxin is unknown, but it is notable that recessive *SETX* mutations (mostly truncations) cause ataxia-oculomotor apraxia 2 (AOA2).[24] This suggests that a toxic gain of senataxin function may be responsible for ALS4, while loss of function may lead to AOA2.

ALS8-VAPB

Following linkage of a large Portuguese Brazilian kindred with dominantly inherited atypical ALS to chromosome 20q13.3 (ALS8), a mutation in the *VAMP/synaptobrevin-associated membrane protein B gene (VAPB)* was identified.[25,26,27] The same mutation was found in seven more Brazilian families with an ancient common founder.[28] Three distinct phenotypes are seen: late-onset SMA, typical ALS and slowly-progressive ALS with tremor. VAPB can associate with microtubules and is implicated in axonal and intracellular transport, and may also be important as a motor neuronal survival factor.[29,30,31] Mutant VAPB may have excitotoxic properties.[32,33,34]

Dynactin (OMIM 601143)

A large kindred with a slowly progressive ALS-like syndrome was linked to chromosome 2p13.[35] The phenotype was predominantly lower motor neuron, involving the limbs and face and causing vocal cord paresis. A mutation of the axonal motor protein dynactin was identified, and further mutations found in one SALS, two FALS cases and one ALS-FTD kindred.[36,37] Dynactin mutations have not been formally classified as an ALS subtype.

SALS genes: candidate approaches

The search for SALS genes has frequently involved a candidate-gene approach. This has demonstrated a role for FALS genes, most notably *SOD1* and *TARDBP*, in a minority of sporadic cases. Numerous candidate-gene studies in ALS have produced conflicting results. The most significant of candidates are discussed below.

VEGF (OMIM 192240)

Vascular endothelial growth factor (VEGF) was identified as a candidate for ALS on the

Table 2 TARDBP genetic screens in ALS

Reference	Index FALS screened (mutations)	SALS screened (mutations)	Mutation Frequency (FALS, SALS)	Ethnic origin
Sreedharan et al., 2008	154 (1)	372 (2)	0.65%, 0.54%	UK & Australian Caucasian
Gitcho et al., 2008	8 (1)	0	12.5%, -	European
Kabashi et al., 2008	80 (3)	120 (6)	3.75%, 5%	France/Quebec
Van Deerlin et al., 2008	65 (2)	86 (0)	3%, 0%	Eastern Europe, China
Yokoseki et al., 2008	16 (1)	112 typed for mutation only (0)	6.25%, -	Japan
Kuhnlein et al., 2008	31 (2)	134 (0)	6.25%, 0%	German
Rutherford et al., 2008	92 (3)	24 (0)	3.26%, 0%	Caucasian
Daoud et al., 2008	0	285 (6)	- 2.1%	French
Lemmens et al., 2009	20 (1)	0	5%, -	Belgian
Corrado et al., 2009	125 (6)	541 (12)	4.8%, 2.2%	Italian
Gijselinck et al., 2008	0	237 (0)	- 0%	Belgian
Guerreiro et al., 2008	0	297 (0)	0%, 0%	Caucasian & African

basis of a mouse model displaying motor neuron degeneration following deletion of the hypoxia response element of the *VEGF* promotor.[80] However, *VEGF* mutations have not been found in ALS cases and association studies have generated conflicting results.[40,41,42,43]

ALS9- ANG

Angiogenin is functionally similar to VEGF. Significant association between SALS and the angiogenin gene *(ANG)* was identified in Irish and Scottish populations.[44] Coding mutations were subsequently found in sporadic and familial cases and shown to impair the angiogenic properties of angiogenin.[45,46] Although ANG mutations are a rare cause of FALS, they are classified as ALS9.

Paraoxonase (OMIM 168820, 602447)

Paraoxonases have antioxidant and detoxifying roles.[47,48] Their candidacy in ALS stems from evidence that chemical exposure may increase the risk of ALS.[49,50] Functional polymorphisms in the *PON* genes on chromosome 7q have been associated with susceptibility to Alzheimer's disease (AD)[51] and Parkinson's disease (PD).[52] Evidence from several groups supports an association with susceptibility to ALS, though reports are conflicting.[53]

Neurofilaments (OMIM 162280, 162230)

Neurofilamentous aggregates within motor neurons are a neuropathological hallmark of ALS. Neurofilaments are composed of heteropolymers of light, medium and heavy subunits (NF-L, -M and -H) and are involved in maintenance of cytoskeletal and axonal architecture.[54] Rare deletions and insertions within the multi-KSP phosphorylation domain of NF-H have been found in ~1% of SALS cases and one FALS case[55,56,57], although functional studies of NF-H KSP variants is lacking. NF-H variants are unlikely to be a significant cause of ALS.

Peripherin (OMIM 602447)

Peripherin is another intermediate filament protein expressed in neuronal projections and is upregulated in the CNS in injury.[58] Rare mutations of peripherin have been found in ALS[59,60] and are associated with abnormal NF assembly in vitro and marked peripherin aggregation in anterior horn cells in vivo. These data suggest that peripherin variants may play a small role in the pathogenesis of ALS.

SMN (OMIM 600354, 601627)

Spinal muscular atrophy (SMA) is an autosomal recessive lower motor neuron disorder of neonates and children usually caused by deletion of the *Survival Motor Neuron 1 (SMN1)* gene.[61] Two copies of SMN exist at the chromosome 5 locus in humans, with deletions in SMN1 causing disease. *SMN2* is only partially functional due to splice variation, but an increase in *SMN2* copy number can ameliorate the severity of SMA.[62] SMA may result from a loss of motor neuron-specific functions of SMN, including processing and transport of RNAs.[63,64] Although studies have not demonstrated a direct role for *SMN1* variants in ALS, copy number analysis demonstrates that ALS patients may have reduced SMN protein levels, or deletions of *SMN2*, although, reports are conflicting.[65,66,7,68,69]

SALS genes: Genome-wide association studies

Unlike candidate approaches, genome-wide association (GWA) studies can be used to identify susceptibility genes without making assumptions about the likely disease mechanisms. They have the potential to identify new mechanistic pathways. Early GWA studies did not identify polymorphisms linked to ALS, probably because they were underpowered, reporting on only a few hundred ALS individuals and controls. Evidence from other so-called complex diseases such as Type II diabetes suggests that ~2-3000 cases and controls are required to generate reliable results, when one accounts for the stringent corrections required for multiple analyses on the same data set. More recent GWA studies in ALS have been large-scale studies analyzing thousands of cases and controls using high-density mapping techniques such as DNA microarrays. These approaches have led to the identification of four significant genetic associations in SALS: *FLJ10986*[75], the inositol 1,45-triphosphate receptor 2 gene, *ITPR2*[76], the dipeptidyl peptidase 6 gene, *DPP6*[77] and the elongator protein 3 gene, *ELP3*[78]. FLJ10986 is expressed in brain, but its function and the effects of the ALS variants are unknown. ITPR2 is involved in glutamate-mediated neurotransmission, regulation of intracellular calcium and has an important role in apoptosis. All these roles have previously been linked with ALS pathogenesis. DPP6 is expressed predominantly in the brain, regulates neuropeptide activity and modulates voltage-gated potassium channels. ELP3 is involved in RNA processing and gene expression, which are increasingly recognised to be important in ALS pathobiology. ELP3 may additionally be neuroprotective.[78]

Although these GWA studies suggest that there may be a significant genetic component to sporadic ALS, they have used relatively common polymorphic markers. Thus, if rarer polymorphisms account for much of the susceptibility in ALS these will be unlikely to be picked up even if several thousands of patient samples are screened.

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Genetic links between ALS and FTD

A genetic link between ALS and FTD is strongly suggested by linkage of families displaying inheritance of both ALS and FTD to loci on chromosome 9p[70] and 9q[71,72,73] (Table 1). No mutations have been identified as yet. There is little evidence that pure FTD genes (*Progranulin*, *MAPT* and *CHMP2B*) are a significant cause of ALS.[74]

Conclusions

The identification of SOD1 mutations in 20% of FALS kindreds and the use of SOD1 models of disease have enhanced our knowledge of motor neuron degeneration[79], but therapeutic developments have been disappointing. Several new genes have recently been identified, notably *TARDBP*, *FUS* and *ANG*, and suggest a significant role for RNA-processing abnormalities in ALS. ELP3 variants add further weight to this hypothesis. SOD1 screening has been available as a clinical test for some years. *TARDBP* and *FUS* screening should prove cost effective as most mutations cluster within a single exon. The identification of gene mutations in the remaining ~75% of FALS cases, and the characterisation of genes that contribute to SALS will add further pieces to the jigsaw puzzle that is ALS. ◆

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Voice Banking

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Degenerative diseases such as Parkinson's (PD) or motor neurone disease (MND) can lead to the partial or complete loss of speech. The time from diagnosis to a deterioration of the individual's control of their musculature varies but can be short and, as one of the first symptoms to present, speech deterioration frequently coincides, with or quickly follows, diagnosis. At diagnosis, thoughts about the future without speech or with speech that is no longer recognisable as your own can be difficult to focus on. This is a time, however, to take steps to make recordings of the voice (ahead of the deterioration) for later use in a prosthesis. This `banking' process makes it possible to produce a speech synthesiser that does not sound like someone with a different geographical, social, ethnic background or someone of a different age or gender, but can provide a voice with which the individual can identify and be recognised. This article examines the options available for voice banking; the current research in this area and also will provide some guidelines on making your own recordings.

The most basic type of speech synthesis is to store and playback pre-recorded phrases. Most communication aids can store digitised phrases for easy and quick access. This approach is limited in what can be said and how much can be stored.

A slightly different approach can be taken in banking a voice to create a fully synthesised output that can produce any utterance. High quality voices are currently available on communication aids such as the Toby Churchill Lightwriter (**http://www.toby-churchill.com/**). The quality of Acapela (**http://www.acapela-group.com/**) concatenative synthesis voices, for example, is due to a very large database of recordings produced by a professional speaker with high quality recording equipment, good recording conditions and consistent voice quality. This technique requires a dataset to be recorded that contains all the sounds in the target language so that it can produce any required output. The database is segmented into smaller units which can then be recombined to produce new utterances. Recording these sounds in context captures the variation in production depending on the surrounding speech making the speech more natural sounding and intelligible. Producing this quality of output is unlikely to be achieved by a non-professional speaker but as a trade-off of quality against a degree of personalisation, options are available for people wanting to bank their own voices using a smaller amount of data and in their own homes.

Festvox, (http://festvox.org/), from Carnegie Mellon University, Pittsburgh, is a voice building tool for researchers and as such, is not designed to be easy for someone without specialist phonetic and computational knowledge to use. A reasonable synthesised voice can be produced with around 1200 sentences or 1hr 20 mins of continuous speech. With minimal data input, however, it can be inconsistent and sometimes unintelligible. Examples of my own voice built with the Festvox tool and around 600 sentences (40 mins of speech) are available on the ACNR website (**www.acnr.co.uk/rehabfiles**) (fest_cultural, fest_cupoftea), with an example of the original recorded speech (original_smc).

More specifically aimed at people with progressive speech loss, ModelTalker, developed by the Nemours Speech Research Laboratory at the Alfred I. duPont Hospital for Children in Wilmington, Delaware, USA, is a free voice building service which can be used on any home computer (**www.modeltalker.com**). The data collection tool, ModelTalker Voice Recorder (MTVR), requires around 1800 utterances to be recorded. MTVR prompts the individual to produce an utterance, screening it for consistency of pitch, loudness and pronunciation, aiming to collect only good quality usable data. The system is optimised for US English and results have been shown to be mixed for British English speakers, particularly as the pronunciation check may have to be switched off for UK speakers. Examples of my ModelTalker voice are on the ACNR webpage (mt_cultural, mt_cupoftea). The user can upload the recordings to the developers and within a short time, the voice becomes available to download. The interface is easy to use and the voice building process is done entirely by the developers. The voice can be used on any home computer and is portable onto other communication aids that support SAPI 5.1 voices.

Commercially, voice building has been reserved for providing a service for companies due to the high cost. Cereproc (**http://www.cereproc.com/**), based in Edinburgh, estimate a voice built specifically for a company would cost upward of £20k, making it non-viable for individuals. However, Cereproc are currently looking for investment for production of software for voice banking and voice building for text to speech synthesis for individuals with progressive speech loss, so the market is becoming aware of the need for personalised synthesised voices.

On the research front, Hidden Markov Models (HMMs) are being used to create robust statistical representations of speech which can then be adapted towards an individual's speech. The HTS toolkit (http://hts.sp.nitech.ac.jp/) has been developed by Nagoya and Tokyo Institutes of Technology, Japan. The amount of data required for this technique is significantly reduced to around 100 sentences, or approximately 6-7 minutes of continuous speech. These models can generate speech for any utterance in a consistent way that sounds similar to the person's speech to which it has been adapted. The speech has a slightly more robotic quality to it but is much more consistent than concatenative techniques. It is easier to manipulate in terms of prosody and speed, making it easier to tailor the speech output to the individual's own needs. Using 500 sentences as adaptation data, examples (hts_cultural,

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hts_cupoftea) are available to hear made from my own voice.

Current research in progress in the CAST (Clinical Applications of Speech Technology) group at the University of Sheffield (**http://www.shef.ac.uk/cast/**) is using HTS to bank and recreate voices where deterioration has begun. Where voices have started to deteriorate, features of the voice that hold the speaker's characteristics are retained and those features that are affected by the speech disorder, such as energy or duration, are substituted from the robust statistical model. This work is showing promise as a potential for voice banking pre- and post-deterioration for eventual use in personalised voice output communication aids.

For voice banking, steps can be taken to ensure that recordings could be used in the future when new technologies become available, as well as for currently available sources and techniques. If an individual wishes to make recordings onto their own computer, here are some guidelines to ensure that the quality is high and the output is as usable as possible.

1. The recordings should be as high quality as possible using a non-compressed format, i.e. WAV files not mp3. Successful voices have been built using recordings done on a home computer in a quiet room, which is usually of sufficient quality. You could also contact your local university Linguistics or Speech Science department as they may have suitable facilities or equipment that they may be willing to offer.

2. Recordings should be done either in one sitting or at the same time of day over a short period of time. Do not record if you have a cold or are fatigued and keep the recording conditions as consistent as possible. A head-mounted microphone usually improves consistency.

3. Record phrases that you use frequently, including names and places. Record tokens such as "yes", "no" and "mm" so these can be used directly as recorded for social interaction. Apart from these tokens, avoid recording isolated words; it is more useful for the voice building process to put them into contexts in longer phrases. Record favourite songs or phrases in different tones of voice as these are difficult to reconstruct with a synthesiser. Other useful phrases could be recorded such as this list devised by Beukelman and Gutmann in 1999 (http://aac.unl.edu/vocabulary.html) on which part of the ModelTalker inventory is based. Another suggestion is to spend a few days becoming aware of your own communications and note down what you might need to access quickly or say well. Talk to family and friends as they may be more aware of your idioms and care providers about what you may find useful as your condition progresses.

4. Try also to record a set of data that has a wide phonetic coverage of English. The ModelTalker database is balanced for the phonetic coverage of US English. Once downloaded, it provides a useful interface for collecting recordings, which are stored on the computer once the recordings are uploaded. It provides a recorded database whether or not the final synthesised voice from ModelTalker provides a good result. Another suggestion is to record set A of the Arctic database which is around 600 sentences. This was designed to have full coverage of the sounds of English specifically for a speech synthesis task. This can be found at http://festvox.org/cmu_arctic/.

5. Try and sound as natural as possible.

The synthesised voice end result will not be able to recreate your own voice exactly but banking as much data as possible will at least provide a starting point for a prosthetic voice to retain some of your own characteristics in that speech, either now or when the technology becomes available. ◆

Some More Dickensian Diagnoses

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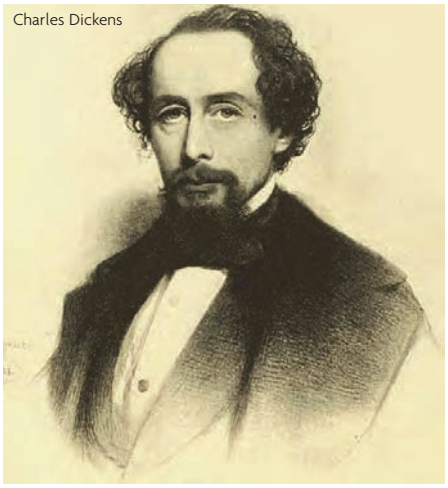
There is a tradition of distinguished clinical neurologists attempting to explain some of the vivid character descriptions in the works of Charles Dickens (1812-1870) in terms of neurological diagnoses: Lord Brain,[1] Macdonald Critchley,[2] David Perkin.[3] Less distinguished figures have also dabbled in the field.[4] Here we tentatively suggest some further possible Dickensian diagnoses, our justification for doing so being Critchley's statement that "Both as a stylist, and as a recorder of the *comédie humaine*, Charles Dickens is still insufficiently acclaimed".[2] To be sure, some of his insights have been acknowledged, for example this account from *David Copperfield* (1850) which may describe the phenomenon of *déjà vu*:[5,6]

> We have all some experience of a feeling which comes over us occasionally, of what we are saying and doing having been said or done before, in a remote time – of our having been surrounded dim ages ago, by the same faces, objects, and circumstances – of our knowing perfectly what will be said next, as if we suddenly remembered it.

Both Grandfather Smallweed (*Bleak House*, 1853), who needs to be carried everywhere, and Mrs Clennam (*Little Dorrit*, 1857), who is confined to a chair in her room, have been cited as examples of paraplegia by Lord Brain.[1] As regards the latter, there is an interesting description following her dramatic recovery of the ability to walk at the end of the novel (chapter 31):

> There Mrs Clennam dropped upon the stones; and she never from that hour moved so much as a finger again, or had the power to speak one word. For upwards of three years she reclined in her wheeled chair, looking attentively at those about her, and appearing to understand what they said; but, the rigid silence she had so long held was evermore enforced upon her, and, except that she could move her eyes and faintly express a negative and affirmative with her head, she lived and died a stone.

This description may call to the neurologist's mind the locked-in syndrome (de-efferentation) following a ventral brainstem stroke, which typically leaves patients alert and able to perceive sensory stimuli, but unable to move other than some preservation of eyelid and sometimes ocular movements; the head movements apparent in Mrs Clennam would be unusual. Bauby, a famous sufferer of locked-in syndrome (and now the subject of a motion picture), cited a possible literary case of this condition in Alexandre Dumas's


Charles Dickens

novel *The Count of Monte Cristo* (1894),[7] but not this possible, and prior, case report by Dickens.

The Smallweeds (*Bleak House*) are a peculiar clan. Mrs Smallweed, wife of Grandfather, is "weak in her intellect" and accordingly has been identified as suffering from dementia.[1] Macdonald Critchley cites two fragments of her speech as examples of senile verbigeration (inappropriate recurrent utterances, speech iteration).[8] And what can one make of young Mr Bartholemew Smallweed, aka Small, or Chick Weed?

> Whether Young Smallweed … was ever a boy , is much doubted .. of small stature and weazen features … he is a weird changeling, to whom years are nothing … a kind of fossil Imp (Chapter 20)

> There has been only one child in the Smallweed family for several generations. Little old men and women there have been, but no child … until grandmother … became weak in her intellect, and fell (for the first time) into a childish state (Chapter 21).

This early appearance of features typically associated with ageing in the apparent absence of cognitive impairment may suggest a diagnosis of progeria (Hutchinson-Gilford progeria syndrome, HGPS). Short stature, skin changes, facial features that resemble aged persons, but with normal cognitive development are typical of this syndrome. Classical HGPS follows an autosomal dominant pattern of inheritance, although almost all cases represent spontaneous mutations.[9]

Krook (*Bleak House*), brother of Mrs Smallweed, is famed for his untimely demise by means of spontaneous combustion, a storyline which involved Dickens in some controversy, not all his readers wishing to suspend disbelief. But a

possible pre-mortem diagnosis may be suggested by this description of Krook:

> He was short, cadaverous, and withered, with his head sunk sideways between his shoulders, and the breath issuing in visible smoke from his mouth, as he were on fire within. His throat, chin and eyebrows were so frosted with white hairs, and so gnarled with veins and puckered skin, that he looked from his breast upwards, like some old root in a fall of snow.

Dilatation or engorgement of neck and face veins is one of the characteristic physical findings in superior vena cava obstruction.

Richard Carstone (*Bleak House*) rejects several career opportunities, including medicine, before becoming embroiled in the legal case of Jarndyce and Jarndyce, all the proceeds of which are consumed by lawyers' fees before judgement is finally given, during which time Carstone's health fails leading to his untimely death. Perhaps unwittingly, Dickens, familiar as he was with the workings of the law from his time at Doctors Commons as a young man, may be reporting here a case of "Chancery cachexia", described as such by the nineteenth century Irish physician Jonathan Osborne (Chancery was formerly one of the courts of justice, presided over by the Lord High Chancellor).[10] In his paper on the subject,[11] Osborne described a clergyman whose fatal wasting was "occasioned by the delays and vexations in legal proceedings" in much the same way that Richard Carstone fades away having pursued his suit against the advice of John Jarndyce, and preyed upon by the venal lawyer Mr Vholes who makes much money at Carstone's expense.

This description may call to the neurologist's mind the locked-in syndrome

Miss Havisham (*Great Expectations*, 1861) merits an eponymous syndrome in the writings of Macdonald Critchley,[2] as the prototype of comparable cases of young women, usually of aristocratic or well-to-do parentage, who suffer a major shock or rebuff and who then become reclusive, opt out of life, and try to make time stand still. Queen Victoria's behaviour after the death of Prince Albert is cited as a possible example. ◆

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Living with Mal de Debarquement Syndrome

Jane Houghton
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"Life on the ocean wave" a phrase that conjures up images of thrilling and exciting times, but imagine for one moment quite literally feeling that you are on the high seas every waking minute of your life, believe me, then it becomes a living hell.

This all started for me over seven years ago. It was Friday 13th July, 2001 (maybe I should have taken that as an omen). I and five other family members spent a long weekend aboard a luxury pleasure boat in Palma Spain. It was a lovely break; we would wake up each day to blue skies and crystal clear calm waters. After breakfast we would set sail to discover yet another perfect place to drop anchor and go for a swim, often returning at full throttle crashing over the waves, it was exhilarating, idyllic. Only one thing marred it, once back on dry land I continued to feel 'all at sea' - the sink in the marina wash rooms would float up to meet me, in a restaurant the table would bob and weave about. I asked the others in my party if they were experiencing the same feelings they looked at me as if I was mad.

Back home after a week the feelings hadn't subsided. I decided to visit my GP. He said that I hadn't found my 'land-legs' yet and prescribed some anti-motion sickness tablets. They didn't work, nor did any of the others that he went on to prescribe. The sensation of being on a rough sea was constant, no let up, even when lying down in bed. Everyday tasks that we take for granted became so difficult; using a computer, ironing, vacuuming etc all increased the level of motion I felt.

My GP decided to send me for an MRI scan. By now I was frantic, believing that I had a brain tumour (what else could be affecting my vision?) Thankfully it came back negative, but still no clue as to what was wrong with me. Then came a series of visits to both neurologists and ENT consultants, numerous hearing and visual tests and still no positive findings. It was now Christmas, the ENT consultant apologised saying that although he firmly believed there was something wrong with me, he just didn't know what, especially with not having any positive test results to work from. I remember leaving the hospital in floods of tears. Was it all in my mind; was I going mad or having a break-down?

By the end of January 2002 I was suicidal, no quality of life left. My GP, relieved that I had something he could actually treat, put me on anti-depressants. The rocking and swaying sensation was far worse than it had been on the boat, I felt constantly nauseous. Also I had developed tinnitus in both ears (never even had so much as an ear ache before this, was never travel sick) I couldn't believe this was it, no concrete diagnosis, just labelled under the vast umbrella of a 'balance disorder.' I started to surf the internet for clues/answers.

In February 2002 just over six long months after that fateful boat trip I got a reply to an email I had sent to the American Vestibular Disorders Association (VEDA) explaining my symptoms and how they came about. They said from my description it pointed to a condition called Mal de Debarquement Syndrome, French for quite literally 'disembarking sickness' (MdDS for short). They told me where to find further information (www.mddsfoundation.org). Now I had to set about being medically and professionally diagnosed. Once again I turned to the internet for help. Eventually I came across the National Hospital of Neurology and Neurosurgery in London who had actually seen cases of MdDS before. I had my first appointment with them in September 2002.

Now over seven years later there is no improvement, if anything I am worse, other problems have appeared, all linked and tied up in the mystery and misery of MdDS. I see the world as constantly moving. This illusion of movement has got worse over time, a type of gaze instability/visual disturbance whereby objects jump and shimmer in front of you, often like looking at things through a heat haze. As well as 'seeing' the world move I also 'feel' it as well. Again, for someone who isn't living with MdDS it is difficult to describe but imagine when you are in a plane and you can feel inside your head when the plane changes altitude or banks to the left or right, all very dis-orientating. I live my life 'like constantly trying to walk on a mattress or trampoline.' However, I must stress at this point that there is no rotational or 'spinning' vertigo with this condition. Also, it is not 'attack' based with periods of normality. Weirdly enough the only relief a MdDS sufferer gets is when they are back in motion.

Back then I naively thought there would be a miracle cure, some tablet I could take to make it all go away. Quite simply there isn't. The best 'treatment' on offer are vestibular exercises which do help if you have an actual balance problem with your MdDS (fortunately I don't) but they do nothing to help the 'moving illusions and sensations' of the condition. In June 2004 I decided to seek a second opinion, I went to the Leicester Balance Centre. They are more brutally honest with me (which I appreciate) and basically say that at present there is no effective treatment for MdDS. I still remain a patient of theirs.

To help turn something with such a huge negative impact in ones life into a positive I try to raise awareness. Probably because of my determined 'doggedness' I am one of the few lucky ones who has actually been diagnosed. Raising awareness is crucial in helping suffers know that it 'isn't all in their head'. For me it just helps to feel that I am doing something positive by 'spreading the word' and raising its profile. I set up a UK basic website for help and support to others who find themselves with this little known and little understood disorder. (www.mdds.org.uk)

Over the years the contact and feedback that I have had makes me question just how 'rare' it is. Travel is available to everyone these days, we are all aware of the risks of DVT and flying, why isn't this the same for MdDS? I am not trying to 'harm' the travel industry in any way or sensationalise the problem. It's merely about being informed. ◆

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Beacon

Quality Control: neurology training in 2009

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The structure of medical training is undergoing major changes, from the advent of Modernising Medical Careers (MMC) to the proposed implementation of the European Working Time Directive and the drive to expand acute neurological services. There has also been a significant expansion in the number of neurology trainees in the last two years. What impact have these changes had on the quality of neurology training?

To address this question, the Association of British Neurologists Trainees committee (ABNT) decided to repeat its national survey of training posts. The questionnaire previously used in our 2007 survey was updated to incorporate these new issues. As before, the survey was distributed by ABNT regional representatives to trainees in all hospitals in their region.

Replies were received from 74 trainees (40 SpRs, 34 STs), representing 48 hospitals and covering most deaneries. It is encouraging to see that educational content of posts remains high, with all departments delivering a regular academic meeting, the majority of which are weekly. Trainees on average had 3 hours per week for private study, although this was variable. Most trainees had no problems obtaining time or funding for study leave. Whilst it may have been anticipated that with greater numbers of trainees appraisal may have suffered, in fact most trainees knew who their educational supervisor was and had an appraisal at the start and end of the post. However a proportion of trainees had difficulty obtaining the required number of formal assessments for their Record of In-Training Assessment/Annual Review of Competence Progression, often due to time constraints.

A major problem highlighted by the survey was lack of junior support. There was a strong feeling that insufficient numbers of experienced junior staff has resulted in trainees having to do additional ward-based duties and inappropriate tasks. Registrars described staying behind late to do jobs normally done by juniors. In some cases this has also led to cancellation of trainees' clinics. These problems seem to stem from poor rota planning and unfilled posts following MMC. Some trainees voiced concern that morale is low because of chronic understaffing and lack of continuity of care. Stretched junior staff may be less likely to consider pursuing a career in neurology. It is concerning that some trusts are failing in their duty to protect registrars' training by not recruiting sufficient junior staff to run the rotas.

As noted in the 2007 trainees survey, provision of office facilities remains poor. Currently there are on average 5 trainees per office and 5 trainees per desk, with a small number of trainees having no office facilities at all or sharing with their consultant or other specialties.

The survey also revealed that many trainees were expected to do clinics without supervision when their consultant was away. We suggest this may become more problematic, both for training and for patient care, as less experienced trainees begin to take up registrar posts.

With regards to on-call duties, many trainees now participate in a stroke thrombolysis rota. Although this can provide a useful training opportunity, increasing volumes of calls present challenges to rota design. Some trainees described the difficulties in providing a thrombolysis service when on a nominally non-resident rota, often with no access to an on-call room. However, a move towards full shift rotas could have significant detrimental effects on training.

Since the Postgraduate Medical Education and Training Board (PMETB) assumed its responsibilities for regulating specialty training, there have been important changes to the way in which the quality of training programmes is monitored. Although PMETB visits deaneries to assess their "quality management" there are no longer specialty-specific visits to individual training schemes. The evaluation of neurology training therefore relies on an annual report from the SAC (which is national, rather than deanery specific) and PMETBs national trainees survey. Importantly, a number of the key issues identified by our study (including junior support and office facilities) are not covered at all in the national survey. In addition, the PMETB survey provides very limited opportunities for free text comments. The ABNT will argue for improvements to next year's national survey.

Despite some difficulties, most neurology registrar posts continue to offer excellent training opportunities. However, registrars with any concerns about their training programme should certainly raise these with their Programme Director and, failing that, with the ABNT. Only with active trainee involvement will the high standard of neurology training be maintained in the face of the pressures of service delivery. ◆

Key points identified in the 2008/9 ABNT trainees survey

- 100% of departments have a regular academic meeting, 94% of which are weekly
- 66% of trainees have problems with junior support
- 89% of trainees feel they have ample opportunity for careers advice
- 51% of trainees are expected to do clinics without supervision when their consultant is away
- 77% of trainees have no problems obtaining study leave or funding
- 45% of trainees are not always able to attend regional training days
- 52% of posts participate in thrombolysis, half of which provide a 24-hour service
- 37% of trainees have problems obtaining the required number of formal assessments

Transitions in Neurology

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We face many passages in life, some of them in Neurology. There is currently discussion on the movement from paediatrics to adult neurology care for those with long term or ongoing neurological conditions. The buzz word is transition, not transfer, and the goal is seamless gliding of young people between services rather than a crash landing into adult clinics. The need for education, preparation and a smooth landing for adolescents in the world of adult medicine was the subject of a recent Royal College of Physicians workshop on transitional care.

The stereotype of paediatrics is a cloistered world full of teddy bears, smiling doctors with oodles of time and a kind if patronising devotion to their patients and families. Adult neurology is the big bad world inhabited by gruff consultants, a world of choice and responsibility.

Why has this issue come to the fore? The good reasons are the attempts to improve standards for those with long term conditions as laid out in the, sadly toothless, National Service Framework. No one would argue against clear handover letters, accurate summaries of previous and past investigations and management, and most importantly, accurate records of current treatment.

At the Royal College meeting, it was horrifying to hear from a young man who had major complications when he moved from school to university and it took months for his summaries and notes to follow him. That is bad, but you do not need transition medicine to prevent that. Clear communication must occur at all interfaces in medicine for it to be good, or even adequate.

The idea of transition medicine or adolescent medicine comes with the possible extension that health care would be further age stratified. It could be worrying for a 17 year old with diabetes to sit next to a man in outpatients who is 78 with an amputation resulting from poor diabetic control. So perhaps clinics attended by younger people should be kept separate.

This is not how life is. Most of us are not twenty and have a few wrinkles and scars to show for the passing years. Do we really want an apartheid system which shields the young from this, reinforcing the celebrity cult of young is beautiful and nothing else counts. I reject the idea that age defines people, any more than their illness, their sex or their occupation does. The same 17 year old in clinic may have chatted with his neighbour and been finally convinced that the hard work of good diabetic control was worth it.

The evidence which supporters of transition medicine point to is highly subjective. Attempts at research in this area are hampered enormously by this and by the bias of their questioning. The provision of joint clinics with paediatric and adult doctors is extremely expensive. There are few additional resources at this stage to cover the cost of these joint clinics.

Surely these needs must be individualised. That will require a shift in thinking, as many Trusts in the United Kingdom forbid adult neurologists from seeing people younger than 16. My paediatric colleagues cannot ask their 15 year old patient to be seen, or to visit, my clinic, no matter how mature. This inflexibility is a real barrier to good communication. We are all aware of the reasons there are separate wards for little children and adults, but there is room in outpatients for an intelligent and individual approach to transitions.

Even with a sample size of two teenage children, it is clear that adolescence is no more homogeneous than any other facet of human behaviour. The idea that we need separate training in communicating with teenagers, separate clinics and separate guidelines for teenagers is quite prevalent. Its worth thinking about, as there is no good evidence either way on this. If you have a view on this I urge you to make your opinion heard before another set of guidelines on this matter are cast in stone. ◆

Practical Guidance for the Management of Parkinson's Disease with Levodopa – Proceedings of the Neuronet-PD Working Group

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Introduction

Despite being the most efficacious dopaminergic treatment, there is still debate as to how best to use levodopa for the treatment of Parkinson's disease (PD). There are large amounts of data on levodopa obtained from clinical trials; however, practical guidance on how to use levodopa optimally throughout the course of the disease is scarce. In order to capture the various clinical experiences and practices of a group of experts working in the field of PD, a workshop was held at a meeting of the Neuronet-PD working group in August 2008. Neuronet-PD is an Advisory Committee on PD composed of European experts and is supported by Novartis Pharmaceuticals AG (see Acknowledgements). The objective of the meeting was to gain practical recommendations on the optimal use of levodopa, in its various standard (levodopa/dopa decarboxylase inhibitor) and combination (levodopa/dopa decarboxylase inhibitor/catechol-*O*-methyltransferse inhibitor) formulations, based on the personal experiences of the working group. Specifically, the role of the combination formulation, levodopa/carbidopa/entacapone (LCE; Stalevo®, Orion Pharma, Espoo, Finland) was discussed. This article aims to capture the recommendations that resulted from these discussions on such issues as initiation and optimisation of levodopa therapy, management of side effects and optimising compliance. The recommendations, practices and guidance described here are all experience- rather than evidence-based and, thus, instead of having a consensus on all issues, the purpose of this review is to reflect all the individual experiences and strategies being used by the different experts.

Since its introduction in the 1960s, levodopa has transformed the treatment of PD, resulting in dramatic improvements in patient quality of life and reductions in disability, and has remained unrivalled in its symptomatic control.[1-4] However, despite its superior symptomatic benefits, long-term use of the drug is associated with the development of motor complications, such as wearing-off and dyskinesia,[5] which can occur as early as 6 months after the initiation of levodopa.[6] In the past, fear of these complications has often led physicians to delay the initiation of levodopa, giving priority to dopamine agonists, and to prescribe suboptimal doses once initiated. Regardless of which therapy is initially given, as the disease progresses the majority of patients will require levodopa, either as a supplemental therapy or a monotherapy.[3,4,7] Recent studies have also demonstrated that, in the long term, the choice of initial treatment may not alter the ultimate risk of developing troublesome dyskinesias once levodopa is initiated,[8] or the incidences of motor complications.[9,10]

Initiation of levodopa therapy

Background

Levodopa is administered with a dopa-decarboxylase inhibitor (DDCI), such as benserazide (Madopar® and Prolopa®, Roche Products Ltd, Welwyn Garden City, UK) or carbidopa (Sinemet®, Merck, Sharp & Dohme, Haarlem, The Netherlands and Parcopa®, Schwarz Pharma, Monheim, Germany; Figure 1). Inhibition of dopa decarboxylase (DDC), one of the major routes of peripheral levodopa metabolism, helps to increase the half-life and bioavailability of levodopa.[11-16] Despite an improvement in the pharmacokinetic profile of levodopa through this combination, it is still characterised by fluctuations and deep troughs in plasma levodopa levels. Thus, a third, pharmacokinetically enhanced formulation of levodopa, LCE (levodopa/carbidopa/entacapone), has recently been developed, which provides dual-enzyme inhibition of both DDC and catechol-*O*-methyltransferase (COMT), the second enzyme involved in the peripheral metabolism of levodopa.[17]

Recommendations of the Neuronet-PD members

Levodopa can be initiated in various ways and will differ between individuals. In general, patients should start on low doses of levodopa and titrate up until an efficacious dose is reached. The two most common strategies for initiating levodopa therapy are at doses of 50 or 100 mg, with variations of these summarised below. Age is an important consideration when deciding on the best strategy to initiate levodopa. In elderly patients (aged >65 years) levodopa may be used as first-line therapy. In contrast, the first-line therapy in young-onset patients is predominantly dopamine agonists with levodopa often only initiated as an adjunct when symptomatic control becomes insufficient. As such, lower initial

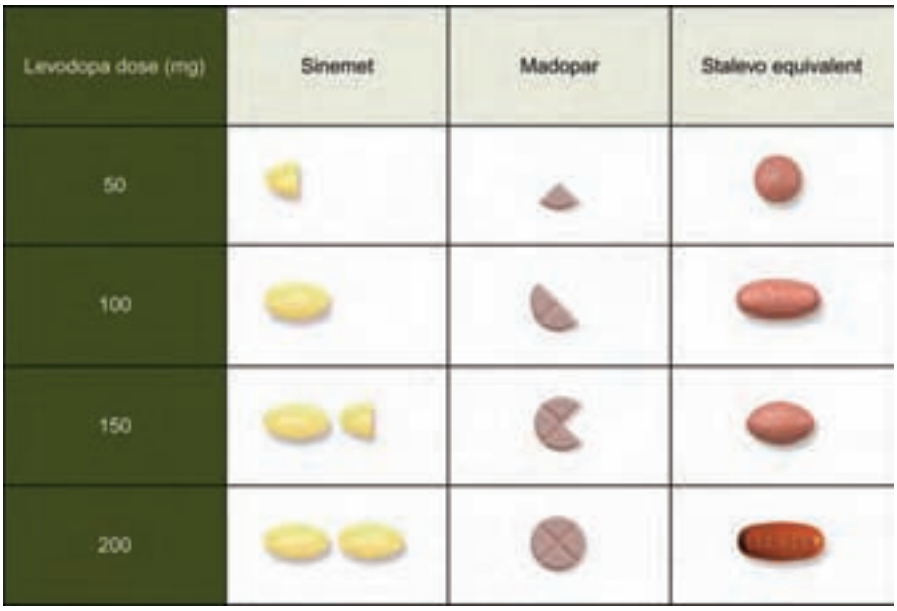

Figure 1: Levodopa formulations and their currently available dosing strengths.

doses of levodopa should be employed (i.e. 50 mg unit dose may be preferable to 100 mg). However, levodopa may be initiated as first-line therapy in younger patients if they suffer from disabling side effects with dopamine agonists.

Direct initiation of 100 mg levodopa three times daily

This is a common strategy for the initiation of levodopa in patients who are not experiencing motor fluctuations and who are at a low risk of developing dyskinesia. A three times daily (tid) dosing regimen may be the most convenient for patients as doses can be scheduled around mealtimes, and 100 mg levodopa allows most patients greater symptom control than if they were initiated at lower doses.

Initiation of 50 mg levodopa four times daily

Initiating patients on a four times daily (qid) regimen may allow for a better coverage throughout the day compared with a three times daily regimen. The additional benefit of this strategy is the use of lower individual doses of levodopa in patients who may be at risk of developing adverse events. This strategy is mainly used in order to reduce possible adverse events seen with 100 mg levodopa and to reduce the fluctuations in plasma levels, which may, in the long term, lead to the pulsatile stimulation of striatal dopamine receptors. However, 100 mg levodopa qid should also be considered if 50 mg levodopa doses provide insufficient symptom control. There are limitations to this strategy; namely, patients may have greater difficulty adhering to a four times daily dosing regimen, as it does not revolve around mealtimes. Thus, unless the patient is awake long hours, this strategy may be difficult to adhere to. Additionally, there is still a lack of clinical data to support the superiority of this strategy over a three times daily regimen.

Slow, gradual titration to levodopa three times daily

Further variations of the gradual titration up to 100 mg levodopa include starting at 50 mg levodopa once daily and adding another 50 mg dose every 3 days until 50 mg tid is reached, and starting with a 100 mg levodopa dose in the morning and two additional 50 mg doses that would gradually be replaced by two 100 mg doses over the period of a week. These strategies may aid the physician in the individual optimisation of therapy on a patient-by-patient basis, as therapy can be stabilised at any stage depending on the patient's response to each step. In addition, these strategies may be more suitable for patients at risk of poor drug tolerance and could also incorporate an intermediate step of 75 mg levodopa.

Optimisation of levodopa therapy

Background

Once initiated on levodopa, modifications to the dosing regimen will eventually be required to help maintain optimal symptom control and manage motor complications. Commonly employed strategies for maintaining symptom control include increasing the total daily dose and the unit dose of levodopa, increasing the number of daily doses, using controlled-release levodopa or switching to Stalevo. Increasing the dose strength or frequency of levodopa doses does not fully address the high peaks and low troughs in plasma levodopa levels, although frequent dosing can achieve higher plasma levodopa concentrations for longer periods of time.[18] In addition, high doses of levodopa are associated with an increased risk of dyskinesia.[19,20] Controlled-release formulations have an unpredictable pharmacokinetic profile with erratic absorption and delayed ON-time,[16] and do not reduce the risk of dyskinesia compared with immediate-release formulations.[21] Despite this, controlled-release formulations may be of some benefit during the night-time.

Stalevo has been shown to reduce the deep troughs in plasma levodopa levels associated with conventional levodopa in studies with both healthy subjects and patients with PD (Figure 2), as well as to increase the half-life and bioavailability of levodopa.[18,22] The improved pharmacokinetic profile associated with dual-enzyme inhibition has been demonstrated to increase ON-time, decrease OFF-time and improve motor scores in patients experiencing advanced wearing-off.[23,26] Benefits can also be seen in patients with early signs of wearing-off or who require the initiation of levodopa. In patients with early wearing-off, Stalevo provides improvements in motor function, activities of daily living, patient-assessed

Table 1: Response of wearing-off symptoms following a switch to Stalevo (SENSE trial)

Symptom	Symptom classification	Present at screening n=113, %	Improved at Week 6 n=113, %
Q1. Tremor	Motor	81	74
Q2. Any slowness of movement	Motor	91	60
Q3. Mood changes	Non-motor	43	52
Q4. Any stiffness	Motor	76	62
Q5. Pain/aching	Non-motor	50	32
Q6. Reduced dexterity	Motor	90	53
Q7. Cloudy mind/ slowness of thinking	Non-motor	54	34
Q8. Anxiety/panic attacks	Non-motor	20	30
Q9. Muscle cramping	Motor	53	60
Any motor symptom	**Motor**	**100**	**62**
Any non-motor symptom	**Non-motor**	**82**	**38**

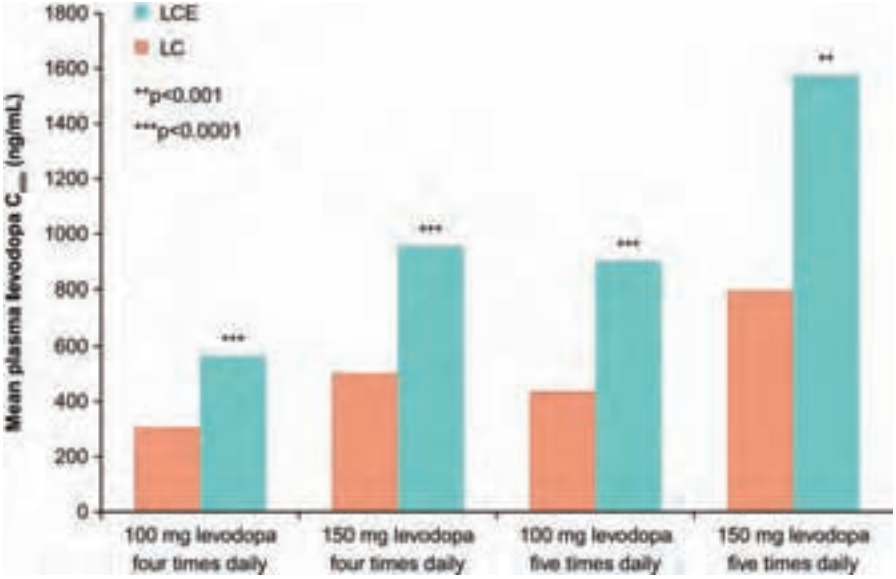

Figure 2: Minimum levodopa concentrations of Stalevo compared with conventional levodopa in healthy volunteers (the KINESTA study)[28] LCE=levodopa/carbidopa/entacapone; LC=levodopa/carbidopa; C_{min}=minimum levodopa concentration.

Clinical Global Impression of Change [CGI-C]), and motor and non-motor wearing-off symptoms, regardless of whether patients had previously received levodopa/benserazide or levodopa/carbidopa (Table 1).[27] In addition, the benefits of Stalevo compared with conventional levodopa on health-related quality of life have been demonstrated in the QUEST-AP study in patients with PD experiencing no, or minimal, non-disabling motor fluctuations.[28] Finally, the use of high doses of Stalevo (200 mg levodopa) may be of benefit for night-time use. A recent pharmacokinetic study demonstrated greater levodopa bioavailability and a longer half-life with Stalevo compared with controlled-release levodopa, commonly used at night, when given as a single night-time dose.[29]

Recommendations of the Neuronet-PD Working Group

The modification of a patient's levodopa dose is necessary to maintain symptom control and to manage motor complications. To maintain symptom control, the most common modification strategy is to increase the individual levodopa dose, either by an increase from 100 to 150 or 200 mg of conventional levodopa or an increase in dose frequency from three to four times daily dosing. Once patients begin to experience wearing-off, a switch to Stalevo is often the most beneficial strategy. The switch to Stalevo can be implemented in a number of ways, and the most efficacious switching strategy depends on the profile of the patient. In general, when switching to Stalevo, the number of doses per day should remain the same unless the patient is receiving five or six doses per day. In this case, a reduction in the number of daily doses to four or five is recommended.

Direct switch to Stalevo

The most commonly used strategy for patients experiencing predictable motor fluctuations and who are not at risk of dyskinesias is a direct overnight switch to Stalevo with equivalent levodopa dose.

Gradual switch to Stalevo

A more gradual switch using lower levodopa doses is advised for patients at risk of dyskinesia or those with severe motor fluctuations. The gradual switch can be carried out by switching from conventional levodopa dose by dose to equivalent doses of Stalevo, or by the use of entacapone. Use of entacapone means the addition of an extra tablet to each dose of conventional levodopa, which would then be replaced by a single, equivalent tablet of Stalevo. Adherence may be an issue with this strategy, as an increase in the patient's pill burden occurs in the intermediate stage of the switch. It is worth noting that although a switch to equivalent doses of Stalevo would be suitable for most patients, those receiving high daily doses of levodopa may benefit from a gradual, stepped switch to a lower Stalevo strength to minimise any dyskinesia or worsening of parkinsonian symptoms.

In Europe, Stalevo is available in three different dose strengths containing 50, 100 and 150 mg levodopa. In addition, a 200 mg levodopa dose strength, has recently become widely available throughout Europe. However, two new strengths have recently been made available in the USA containing 75 and 125 mg levodopa, and these will also soon be available in most European countries. The flexible dose range may be advantageous in the gradual switch to Stalevo, as it allows for the up- or down-titration of therapy in small levodopa increments, thus allowing the effective management of side effects without compromising efficacy. The range also allows the simplification of the dosing regimen without the need for breaking tablets.

Switch to a combination of Stalevo and Sinemet/Madopar

In countries where Stalevo 200 is not yet available, physicians may need to consider combining Stalevo with low doses of Sinemet or Madopar to provide adequate symptom control in patients requiring a high total daily levodopa dose. In addition, extra doses of levodopa (controlled- and immediate-release) to supplement Stalevo at night-time and for the first morning dose is also recommended in some cases to help maintain symptomatic control and minimise wearing-off.

Dose fractionation is generally thought to be a strategy best suited to patients at a more advanced disease stage, as a less frequent dosing regimen could be harder to maintain symptomatic control throughout the day. Although certain European countries do use controlled-release levodopa more than others, in general, the sole use of controlled-release formulations during the daytime are avoided due to their unpredictable response. However, they may be of use at night-time.

Maintaining patients on optimal therapy

Background

Adherence and compliance to medication is important in PD to maintain function and to prevent the development of motor complications.[30,31] However, studies in patients with PD have shown poor medication compliance, especially with regard to the timing of each dose of medication. With advancing disease, the increasingly complex dosing regimens have been shown to negatively impact on patient adherence.[32,33] A number of interventions have been suggested to help maintain patients on optimal therapy. These include advanced warning of side effects, the addition of an anti-emetic during the initiation or dose titration phase, PD nurse/physician follow-up visits or phone calls and computer-based patient information. Informing the patient of potential adverse events; for example, prior warning of chromaturia with Stalevo (a harmless discoloration of urine), may help increase patient compliance if they are made aware that this is a harmless chemical effect of the drug. Active counselling about therapy has been shown to improve a patient's timing adherence to treatment.[34] Similarly, a follow-up call has been demonstrated to be useful in reducing discontinuation rates of patients with PD who had begun therapy with levodopa/DDCI and entacapone. A phone call 2 weeks after therapy initiation significantly decreased discontinuations for up to 6 months of therapy.[35]

Recommendations of the Neuronet-PD Working Group

Patient contact following the initiation of levodopa is essential for patient compliance; however, its success depends on available resources and in some cases may prove impractical if physicians do not have access to adequate services. Specialist PD nurses are

available in certain countries to provide patient support and education, via follow-up calls. Alternatively, the use of a specific helpline number or a special weekly outpatient clinic, which the patients could call or visit in the event of experiencing any adverse events, may help patients to maintain their levodopa therapy. It is also worth highlighting the use of computer-based patient information, via memory sticks or web-based programs, such as Google Health, as potentially useful therapy maintenance strategies.

Conclusions

Levodopa is still the gold standard in the medical treatment of PD. The fear of motor complications, however, has led to its delayed initiation or its suboptimal administration. Conventionally, levodopa is given with a DDCI (carbidopa [Sinemet] or benserazide [Madopar]) and more recently a combined formulation (Stalevo) has been developed that inhibits both DDCI and COMT in a single tablet. Stalevo provides an improved pharmacokinetic profile, which translates into clinical benefits compared with conventional levodopa. Strategies for the initiation of levodopa therapy vary between physicians, although initiation of either a 50 or 100 mg levodopa tid dosing regimen is most commonly used. With advancing disease, physicians commonly increase the dose or dose frequency of conventional levodopa or switch to Stalevo. Strategies for switching to Stalevo depend on the patient profile, levodopa dose and disease stage. At all stages of disease it is essential to maintain patients on optimal levodopa and to keep them informed of potential side effects. This can often be challenging, and such strategies as patient education and early follow-up may be of use to help patients gain optimal benefit from their levodopa therapy with minimum side effects. ◆

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Management of Spastic Cerebral Palsy in the UAE: An Overview

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Cerebral palsy (CP) is a diverse group of disorders caused by a static injury to the developing brain between conception and 3 years of postnatal life. CP is common, affecting roughly around 3 in a 1000, and its prevalence and aetiology is different in different parts of the world. Most children with CP will have spasticity as the main motor disorder and it can be classified either according to which body areas are affected: hemiplegia, diplegia, tetraplegia, or the movement disorder type: spastic, athetoid, ataxic and hypotonic cerebral palsy.

Most children with cerebral palsy are initially hypotonic. With time, tone changes and spasticity patterns begin to emerge and become manifest. In many children, spasticity interferes with their functional abilities and, when severe, soft tissue contractures and skeletal deformities may develop. In some extreme cases joint disarticulation and spinal malalignment results in subluxation or total dislocation of joints such as hips and / or scoliosis and kyphosis. In a minority, spasticity is useful and contributes to patients functional capabilities providing much needed strength. This is particularly true for stability provided through spasticity around the knees that in turn assists mobility.

The natural history and impact of spasticity is variable, ranging from mild functional limitation to severe disability. In many children CP can be progressive with symptom exacerbations corresponding to the periods of linear growth.

The prevalence of cerebral palsy in the United Arab Emirates

The population of the UAE is heterogeneous, comprising of nationals and expatriates. Children make up 50% of the local population. There are no available studies to indicate the prevalence of CP in the UAE. Our practice experience indicates that it is probably similar to the western populations, with some exceptions; for instance there is likely to be a higher incidence of inherited causes such as genetic microcephaly and other syndromes associated with CP, perhaps due to consanguinity and close relation marriages.[1] There is also a notable increase in multiple births and prematurity related to fertility therapy. Obstetric and neonatal care is generally well delivered and, without firm figures, perinatally acquired CP is probably comparable to the other established healthcare systems. Post natal causes for CP are relatively uncommon and include central nervous system infections in infancy and traumatic and non traumatic brain injury.

Management of spasticity:

Spasticity management requires an individualised and coordinated team effort to deliver good and efficient care; if provided well, spasticity care can improve function and reduce complications such as deformities and contractures. It may prove cost effective because of the reduction in repeated hospital admissions and reduced number of orthopaedic procedures and other interventions required. There is also the benefit of the functional gain in the affected patients. International groups have analysed the cost effectiveness of therapies used to treat spastic CP and concluded that management of spasticity is at least cost neutral if not cost effective.[2] In the UAE the provision of such a service is still in a state of evolution.

Standards of care for spasticity management:

It is internationally agreed that children with cerebral palsy require regular ongoing physical therapy;[3] this should ideally be delivered by well trained qualified paediatric neuro-physiotherapists. All CP patients require a regular follow-up by a developmental paediatrician and regular review by a paediatric neurologist, to evaluate the changing needs related to growth and the need to make necessary adjustments to the management plan in conjunction with the physical therapist.

Some patients will require more specialised interventions, such as posture management through specialised seating systems, botulinum toxin therapy or intrathecal baclofen pump. Alongside developmental paediatricians and physiotherapists, such patients must be reviewed by a whole team including specialised paediatric neurologists, occupational therapists and rehabilitation engineers. When necessary, paediatric orthopedic surgeons and neurosurgeons should be consulted.

The role of physiotherapy has been formally evaluated in CP, while newer therapies such as botulinum toxin and intrathecal baclofen have

been extensively studied. Randomised trials and systematic reviews have confirmed the short term benefit from the use of botulinum toxin.[4] Studies have, however, failed to demonstrate a persisting long term benefit. There are some long term studies that support the role of botulinum therapy in conjunction with other techniques such as abduction devices and serial casts. Botulinum toxin has also been demonstrated to reduce the risk of hip dislocation in children with CP.[5] Intrathecal baclofen delivered via a pump is gaining popularity as an effective and longer term therapy for severe lower limb spasticity.[6] These therapies require specialised expertise and should only be delivered by a trained team. They are costly and require thoughtful resource allocation and should ideally be delivered in tertiary centres.

Resource allocation and health insurance:

The UAE has recently adopted an insurance based health care system. This has introduced a western style, market place healthcare model. The insurance companies are charged by the health care providers. Patients or the employing organisation are directly charged if the insurance cover is lacking. Although private medical care has always thrived in the UAE, the new system has replaced a largely state funded system. However, healthcare provision for children with disability is still mostly state funded even for the ex-patriate population; the UK model of school health and provision of specialised care in special schools is only available in some of the state funded humanitarian projects that provide schooling and essential therapies for children with disabilities. Several non-profit organisations and private institutes also exist throughout the country and provide physical therapy, occupational therapy and speech therapy. Across the Emirates, however, service provision for children with cerebral palsy is inconsistent with some areas being better resourced than others.

The provision for spasticity management for children with CP is mainly in the large tertiary centres, such as Sheikh Khalifa Medical City in Abu Dhabi. There are four paediatric neurologists in the UAE, who provide consultations and medical treatment for spasticity. Two are trained to give botulinum toxin therapy. Whilst there are very few specialised paediatric neurophysiotherapists and occupational therapists in Abu Dhabi, children who receive the botulinum toxin therapy have access to this expertise. One hospital has a visiting developmental paediatrician who provides occasional botulinum toxin treatments.

Botulinum toxin therapy:

Botulinum toxin is well known to improve spasticity in the short term. t is now widely used for spasticity and offers best results in children with focal spasticity that is severe enough to affect function or produce symptoms or complications; an excellent review by Boyd et al[4] concluded unequivocal short term benefit from this therapy. It is now agreed that short term goals can be clearly identified and influenced by botulinum toxin. Botulinum therapy is safe and produces few and tolerable side effects. Recent studies questioned the role of this therapy in the long-term outcome of CP and spasticity. The author has researched and co-authored work[7] studying the long term effects of botulinum toxin type A. Using the Gross Motor Function Measure (GMFM) and Paediatric Disability Index (Pedi) we concluded that outcome measures may not be sensitive enough to detect the functional and symptomatic impact of botulinum therapy and a Cochrane review by our group has further confirmed the lack of evidence for long-term benefit.[8]

There is a growing body of evidence that, apart from a minority of children receiving botulinum toxin for symptomatic relief, this therapy is not effective if not accompanied by an integrated therapy and orthotic programme.

In the UAE we have been providing regular botulinum toxin therapy mainly for three groups of patients:

1. Patients with severe adductor muscle spasticity considered at high risk of hip dislocation. In this group we currently have 5 patients. The hip alignment has been maintained and the children remain free from pain and discomfort due to either continued spasticity or partial or complete dislocation. We have been successful in preventing orthopaedic intervention over the treatment period of around 3 years.
2. A second group of patients with lower limb spasticity who are ambulant. Currently we have 15 patients under treatment. They demonstrate functional improvements with botulinum therapy followed by physiotherapy and orthotics, especially in those aged between 3-10 years old.
3. Children with troublesome spasticity that causes discomfort and hinders their daily care are being treated for symptomatic relief of pain and discomfort. Currently we have around 10 children who are receiving botulinum in this category. Our experience in these children is encouraging and the parental and carer satisfaction is reflected in the fact that a close link is maintained with our service for repeated injections and follow up.

Patients are referred usually from paediatricians and rehabilitation physicians as well as treating physiotherapists; patients are accepted from all areas of the UAE. Physiotherapy is often provided locally and the physiotherapist will facilitate communication with the orthotic and occupational therapy service. Close cooperation is more feasible with the therapists working in an institution than those working in the community. The service does not have access to motion analysis or formal gait evaluation, nor is there a specialised upper limb service.

The service challenges within the UAE at the present time includes expansion and allocation of appropriate resources such as an integrated team of therapists and the availability of video equipment to undertake gait evaluations as well as access to formal motion analysis service.

Provision of a team approach to effectively manage children with upper limb spasticity requires the presence of a specialised upper limb physical and occupational therapist as well as the services of a hand surgeon; this model has been successfully developed previously by the author and colleagues in a large UK centre.

There is a large potential for further expansion and organisation of the service, especially given the current changes in the health service and the interest shown by various agencies in developing services for children with neurological disorders. Many new centres have been developed in the field of autism and learning disability, the field of physical disability is likely to follow suit and develop.

Intrathecal baclofen (ITB):

Intrathecal baclofen has been gaining popularity over the last 2 decades and the use of baclofen pumps is part of the standard care offered in many tertiary centres for children with severe spasticity. Delivery of baclofen to the intrathecal space produces dramatic improvement in the spasticity and reduces the risk of undesired central adverse effects that are known to limit the use of oral baclofen in the treatment of generalised spasticity.

The convenience of having an adjustable delivery system offers the potential for adjusting the dose depending on the patient's symptoms. Although many studies confirmed a benefit in walking patients with severe spasticity, non walkers with severe spasticity are the usual target group for ITB therapy. There is no service, to the author's knowledge, that offers ITB for children in the UAE although a small number of patients did receive this therapy abroad; none of those attends our tertiary spasticity service. Presently we are working with the neurosurgeons to set up this service.

Selective dorsal rhyzotomy:

This therapy is particularly useful for children with severe diplegia where spasticity is the main barrier to walking. Dissection of carefully selected afferent nerve fibres at the spinal level breaks the reflex arc and reduces spasticity. Studies have demonstrated much improved spasticity and functional gains, however the procedure is very specialised and irreversible. The author is not aware of rhyzotomy being undertaken anywhere in UAE.

Specialised seating service:

Historically the specialised seating service had been provided in the UAE via therapy

services and assessment conducted in conjunction with manufacturers. The author[2] is in the process of developing a multi-disciplinary seating assessment service. Around 10 patients have already been assessed in this relatively new service and parents and carers are being instructed in correct use of the equipment. The notion that systems are mobility devices is being discouraged and usage to improve and maintain biomechanics of sitting posture is explained and encouraged. It is too early to assess the effectiveness of this service.

Future projects

Healthcare is evolving in the UAE, the provision for children with cerebral palsy and other neurological disabilities will evolve and future developments are essential in order to deliver quality service for children with disability in general and children with spastic CP in particular. An integrated team approach and the provision of all spasticity management in one centre is likely to be the way forward for the tertiary care institutes. Furthermore, better access and facilities for children with CP within the school system will be required to ensure better function and participation in the community for children with disability in line with the recently approved World Health Organisation guidelines on this. ◆

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The Association of British Neurologists Meeting

Liverpool: June 22 26th 2009

Message from Professor Alastair Compston, President of The Association of British Neurologists

Alastair Compston, President.

The Association of British Neurologists is moving, at least for this year and next, to a single annual conference in place of the spring and autumn meetings that have been held for many years. However, we are also involved in one further meeting abroad in each of the next few years – The Netherlands (2010), Cuba (2011) and Boston (2012). The first annual UK-based conference will be in Liverpool from Monday 22 June to Friday 26 June. The venue is the spectacular new Arena and Convention Centre situated in the heart of Liverpool (European Capital of Culture in 2008) on the historic world heritage waterfront (www.accliverpool.com).

High attendance is anticipated and the Association has set extremely competitive registration rates on the assumption that there will be a record number of delegates. For those who register early the cost is £350 for the whole week, including the reception and dinner, with 2 day and 1 day rates of £275 and £150, respectively with half those costs for trainees and senior members. Registration will close on 10 June.

The programme is thematic in eight parts each having a scientific symposium and teaching course held in parallel with free communications and including one or more plenary lectures. In the session on stroke, Werner Hacke from Heidelberg will speak on Acute management. That is followed by an historical talk on Sir Charles Sherrington who spent many years in Liverpool given by Colin Blakemore – one of Sherrington's successors as Waynflete professor of physiology in Oxford. Richard Johnson, from John Hopkins University, will give the Gordon Holmes Lecture on Global hazards of infectious disease in the session on acute neurology, prion diseases and viral disorders. Angela Vincent from Oxford is the 2009 ABN Medallist and her lecture on Immunological disorders of ion channels is included in that part of the programme focusing on channelopathies, muscle and mitochondrial disorders which is followed by a clinico-pathological conference presented by Andrew Lees from Queen Square. Eduardo Tolosa from Madrid will speak on Clinical and genetic diversity in Parkinson's disease in the session on neurodegeneration and movement disorders. The half-day devoted to dementia and behavioural neurology ends with a lecture by David Owen – In sickness and in power – in which he will argue that political decision-making in world leaders may be contaminated by an acquired behavioural disorder manifesting as hubris. Finally, Jack Griffin, also from John Hopkins University, will give the Editors of Brain Lecture in memory of PK Thomas (on this occasion) on the Pathophysiology and mechanisms of peripheral neuropathy in the session on peripheral nerve disease. The meeting is interspersed with a symposium on academic neurology for trainees and a session highlighting free communications by younger members of the Association – Tomorrow's world - topped and tailed by an additional teaching course on neuro-ophthalmology and a practical session on how to survive as a neurologist.

The reception will be in the Merseyside Maritime Museum on the Albert Dock. The annual dinner is in the Liverpool Anglican Cathedral at which Baroness Ilora Finlay will be our guest and speaker. The evening will finish with a magnificent blast on the Cathedral Organ and a Son et lumiere performance.

All in all we hope that this much changed structure of the scientific meeting of the Association will appeal to all our members – young and old, NHS and academic appointees, and those wanting both continued professional development and glimpses into the future development of our rich and diverse discipline.

The organisers and Officers of the Association look forward to seeing you in Liverpool.

Werner Hacke

Colin Blakemore

Andrew Lees

Angela Vincent

John Griffin

Richard Johnson

Monday 22 June 2009

09:00	Registration Opens	
NEURO-OPHTHALMOLOGY		
10:00 – 12:00	HALL 1A	
Neuro-ophthalmology: Beyond the bedside **Chair: Gordon Plant, London**		
10:00	A review of perimetric methodology Richard Metcalfe, Glasgow	
10:15	Objective visual field assessment. mfERG/VEP and pupil perimetry Mags Dyan, Newcastle upon Tyne	
10:30	Perimetry in practice: illustrative cases Mike Burdon, Birmingham	
10:45	Beyond visual fields: neglect and disorientation Martin Bracewell, Bangor	
11:00	Optic nerve imaging: practice and pitfalls Simon Hickman, Sheffield	
11:15	Imaging in optic neuritis: all or nothing? Michael Johnson, Leeds	
11:30	Eye movement disorders: the role of the orthoptist and of eye movement recording John Elston, Oxford	
11:45	Eye movement disorders: illustrative cases Gordon Plant, London	
LUNCH : HALL 2C 12:00 – 12:30hrs		
STROKE		
12:30 – 12:45: President's Welcome & Introduction		HALL 1A
12:45 – 13:30: Plenary Guest Lecture: Werner Hacke, Germany – Acute management of stroke		
	Hall 1A: Afternoon Session 1 **SCIENCE: Risk factors & prevention of stroke** **Chair: Ángel Chamorro, Barcelona**	**Hall 1B: Afternoon Session 1** **Papers: Specialty: Papers 1-6** **Chair:**
13:30	Challenges and rewards of clinical research Peter Rothwell, Oxford	
14:00	Acute management of TIA and minor stroke Matthew Giles, Oxford	
14:20	Imaging and treatment of vertebral and basilar stenosis Ursula Schulz, Oxford	
14:40	Vascular dementia Sarah Pendlebury, Oxford	
COFFEE : HALL 2C 15:00 – 15:30hrs		
15:30 – 16:30: Plenary Guest Lecture: Colin Blakemore (Oxford) - Sherrington: The Liverpool Years		HALL 1A
	Hall 1B: Afternoon Session 2 **Papers: Specialty: Papers 7-12** **Chair:**	**Hall 1A: Afternoon Session 2** **TEACHING: Clinical assessment and management of stroke: an interactive whistle stop tour** **Chair: Cathie Sudlow**
		16:30 Introduction: Joined up stroke care Cathie Sudlow, Edinburgh
		16:40 Stroke and TIA: Why neurologists matter John Bamford, Leeds
		17:05 Carotid stenosis: How to intervene, and for whom? Martin Brown, London
		17:30 Why should neurologists be involved with subarachnoid haemorrhage? – Richard Davenport, Glasgow
18:00	**ABN ANNUAL GENERAL MEETING**	HALL 1A
20:00	Welcome Reception, Merseyside Maritime Museum Welcome from Eduardo Martinez Vila (President, SEN) & Alastair Compston (President, ABN)	

Tuesday 23 June 2009

Wednesday 24 June 2009

08:00	Registration Opens	
MUSCLE		
	Hall 1A: Morning Session 1 **SCIENCE: Molecular mechanisms of mitochondrial disease** **Chair: Patrick Chinnery, Newcastle**	**Hall 1B: Morning Session 1** **Papers 37-42** **Chair:**
08:30	Mitochondrial neuro-ophthalmology – why is the eye so vulnerable? – Patrick Yu Wai Man, Newcastle	
08:50	Mitochondrial poisons: iatrogenic mitochondrial diseases of the future? – Brendan Payne, Newcastle	
09:10	New technologies and new genes: how to make a diagnosis fast – Robert Taylor, Newcastle	
09:30	Any new treatments on offer? Patrick Chinnery, Newcastle	
COFFEE, POSTERS & EXHIBITION: HALLS 2G & 2K 10:00 – 10:45hrs		
	Hall 1B: Morning Session 2 **Papers 43-48** **Chair:**	**Hall 1A: Morning Session 2** **TEACHING: Diagnosis & management of muscle disease** **Co-Chairs: Michael Hanna, London & Spanish TBC**
		10:45 Approach to the clinical assessment and diagnosis of the patient with muscle disease – Michael Hanna, London
		11:15 Muscle biopsy evaluation and clinical correlation Janice Holton, London
		11:35 Adult muscular dystrophies – diagnosis and management James Miller, Newcastle
		11:55 Inflammatory and drug induced muscle diseases - diagnosis and management David Hilton-Jones, Oxford
12:15 – 13:00	ABN Medallist Angela Vincent (Oxford) Immunological disorders of ion channels	HALL 1A
13:00 – 14:00	**Lunchtime satellite symposium sponsored by Teva Pharmaceuticals Ltd and Lundbeck Ltd** Title: The timing of treatment in Parkinson's Disease. Chair: TBC	HALL 1B
LUNCH, POSTERS & EXHIBITION: HALLS 2G & 2K 13:00 – 14:00hrs		
EPILEPSY – SPONSORED BY TEVA PHARMACEUTICALS LTD and LUNDBECK LTD		
	Hall 1A: Afternoon Session 1 **SCIENCE: Paroxysmal disorders and channelopathies** **Co-Chairs: Dimitri Kullmann, London & Jose Serratosa, Spain**	**Hall 1B: Afternoon Session 1** **Papers 49-54** **Chair:**
TEA, POSTERS & EXHIBITION: HALLS 2G & 2K 15:30 – 16:00hrs		
	Hall 1B: Afternoon Session 2 **Papers 55-60** **Chair:**	**Hall 1A: Afternoon Session 2** **TEACHING: Management of epilepsy and related disorders** **Co-Chairs: Philip Smith, Cardiff & Antonio Gil-Nagel, Spain**

The Timing of Treatment in Parkinson's Disease - a debate chaired by Professor David Burn

A lunchtime satellite symposium – Wednesday 24th June, 2009
13:00 – 14:00, Hall 1B, Liverpool Arena & Conference Centre
Sponsored by Teva Pharmaceuticals Ltd and Lundbeck Ltd

Thursday 25 June 2009

MOVEMENT DISORDERS – SPONSORED BY

Hall 1A: Morning Session 1
SCIENCE: Injury & repair in neurodegeneration
Chair: Roger Barker, Cambridge

Hall 1B: Morning Session 1
Neurology in retirement & internationally [papers]
Chair:

COFFEE, POSTERS & EXHIBITION: HALLS 2G & 2K 10:00 – 10:45hrs

Hall 1B: Morning Session 2
Papers 67-72
Chair:

Hall 1A: Morning Session 2
TEACHING: Diagnosis & management of movement disorders
Chair: Carl Clarke, Birmingham

12:00 – 13:00 Plenary Guest Lecture: Eduardo Tolosa, Clinical and genetic diversity in Parkinson's disease HALL 1A

13:00 – 14:00 Are you considering a career in academic neurology? A practical guide for trainees HALL 1A

Opening remarks – aims of the workshop
Patrick Chinnery (Chair, Clinical Research and Academic Committee) & Daniel Blackburn (ABNT CRAC representative)
Why and how I chose an academic career?
Shri Mahad, Wellcome Trust Clinician Scientist, Neurology SpR, Northern Deanery
Academic Neurology - A Detailed Retrospective Cohort Study of N=1
Tom Solomon, Liverpool
Research within the NHS: is it possible?
Nikos Evangelou, Nottingham
What are the options? Various routes into an academic career
Alastair Compston, Cambridge
Open discussion

13:00 – 14:00 Lunchtime satellite sponsored by
Title: The Evolving Role of Continuous Dopaminergic Stimulation (CDS) in Parkinson's disease
Chair: Professor Carl Clarke, Birmingham
HALL 1B

LUNCH, POSTERS & EXHIBITION: HALLS 2G & 2K 13:00 – 14:00hrs

DEMENTIA – SPONSORED BY

Hall 1A: Afternoon Session 1
SCIENCE: Fronto-temporal dementia and Alzheimer's disease
Chair: David Neary, Manchester

Hall 1B: Afternoon Session 1
Tomorrow's World [papers]
Chair:

14:00 Syndromic analysis in dementia
Julie Snowden, Manchester
14:30 Anatomical and functional correlates in imaging of dementia
Alexander Gerhard, Manchester
15:00 Recent advances in neurogenetics of frontotemporal lobar degeneration
Stuart Pickering-Brown, Manchester

TEA, POSTERS & EXHIBITION: HALLS 2G & 2K 15:30 – 16:00hrs

Hall 1B: Afternoon Session 2
Papers 79-84
Chair:

Hall 1A: Afternoon Session 2
TEACHING: Assessment of cognitive function
Chair: Adam Zeman, Plymouth
Joint with British Neuropsychiatry Association

16:00 Mental state assessment: bedside tips and traps
Hugh Richards, Birmingham
16:30 Cognitive assessment in a nutshell
Adam Zeman, Plymouth
17:00 Making the most of the neuropsychologist's assessment
Shelley Channon, University College London

17:30 – 19:30 Plenary Guest Lecture: David Owen – In sickness and in power HALL 1A

19:30 – 19:30 Evening satellite sponsored by
Title: Are motor symptoms or non-motor symptoms the main issue in advanced Parkinson's Disease: A case based discussion
Chair: Dr Malcolm Steiger, Liverpool, UK
HALL 1B

Friday 26 June 2009

PERIPHERAL NERVE

Hall 1A: Morning Session 1
SCIENCE: Immunological disorders of peripheral nerve
Co-Chairs: Hugh Willison, Glasgow & Michael Donaghy, Oxford

Hall 1B: Morning Session 1
Case Presentation Competition
Chair:

08:30 An introduction to ganglionides and autoantibodies
Hugh Willison, Glasgow
08:45 The role of glycolipid antigen density and substrate deprivation therapy as a therapeutic strategy
Kay Greenshields, Glasgow
09:10 The 'anti-GD1b' antibody syndromes
Simon Rinaldi, Glasgow
09:35 Identifying new ganglioside targets using combinatorial glycolipidomics
Katie Brennan, Glasgow

10:00 – 10:45 The Editors of Brain Lecture HALL 1A
Jack Griffin (Baltimore): Pathophysiology and mechanisms of peripheral neuropathy
Sponsored by the Guarantors of Brain

COFFEE, POSTERS & EXHIBITION: HALLS 2C 10:45 – 11:15hrs

Hall 1A: Morning Session 2
TEACHING: Diagnosis & classification of peripheral neuropathy
Co-Chairs: Michael Donaghy, Oxford & José Berciano, Spain

Hall 1B: Morning Session 2
Papers 91-96
Chair:

11:15 An overview of genetically determined peripheral neuropathy
José Berciano/Spain
11:35 Vasculitic neuropathy
Lhanty Mathew, Oxford
11:55 Chronic acquired and conduction block neuropathy
Michael Donaghy, Oxford
12:15 The spectrum of acute inflammatory polyneuropathy
John Winer, Birmingham
12:45 – 13:45 Quiz & Elite Posters (Heather Angus-Leppan, London) HALL 1A

LUNCH: HALL 2C 13:45 – 14:30hrs

PRACTICING NEUROLOGY
Hall 1A
Chair: Chris Allen, Cambridge

SPANISH SESSION
Hall 1B
Chair: Ivan Iranzo

14:30 Clinical excellence awards: Maximising your chances
Alastair Compston, Cambridge
15:00 Local Neurology services: the way forward
Stephen Pollock, Canterbury
15:30 Medicolegal practice: pleasures and pitfalls
Peter Harvey
16:00 Complaints: the sting in the tail
Chris Allen, Cambridge
16:30 CLOSE OF MEETING

Secretariat Details

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Trafalgar House
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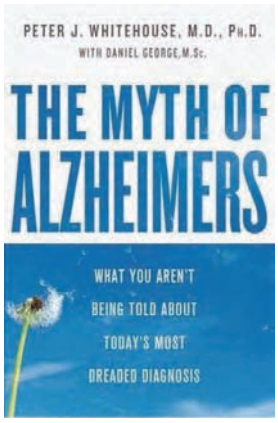
Exhibition Floor Plan

List of Exhibitors

Stand No	Company Name
1	Allergan
3A	CMT United Kingdom
3B	Neurological Conditions Specialist Library
4	Merck Serono
5	Janssen - Cilag Ltd
8	Solvay Healthcare Limited
9A	Teva Pharmaceuticals Ltd and Lundbeck Ltd
11	Bayer Schering Pharma
12 + 13	Biogen Idec
15	Teva Pharmaceuticals Ltd
16	Ipsen Limited
17	Eisai Ltd
19	Cephalon UK Ltd
20	Beacon Pharmaceuticals Ltd
21	GlaxoSmithKline
22	Merz Pharma UK Ltd
23+24	UCB Pharma
25	St George Health Care Group
27	Talecris
28	Britannia Pharmaceuticals
Poster Area	Wisepress Online Bookshop
Table Tops	ACNR
Table Tops	Local Neurology Services for the next decade RCP Working Party
Table Tops	BMJ Group
Table Tops	Grunenthal

The Myth of Alzheimer's. What you aren't being told about today's most dreaded diagosis



Authors: Whitehouse PJ, George D
Published by: St Martin's Press, New York, 2008
Price: $25.95
ISBN: 031236816X

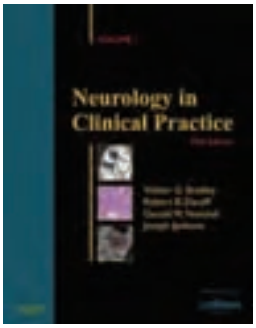
Reviewed by:
AJ Larner,
Cognitive Function Clinic,
WCNN, Liverpool, UK.

In *The making of Mr Gray's anatomy* (Oxford University Press, 2008), Ruth Richardson suggests that the title "Gray's Anatomy", embossed on the spine of the first edition, was a deliberate literary echo of the famous poem "Gray's Elegy", a bid to make the book more memorable, and saleable. Presumably a similar process is occurring with this book, echoing *The myth of mental illness* by Thomas S Szasz (1961). The "myth", as far as I understand it, is that Alzheimer's disease (AD) is a separate disease that can be cured (98), whereas in the formulation of Peter Whitehouse (hereafter PW) "AD" is no more than a diagnostic label for natural brain aging, which we all of us will get if we live long enough (56), and that waiting for a cure is no more than waiting for Godot. This "myth" has been promulgated by an "AD empire", comprising a venal medical profession, rapacious pharmaceutical companies, individual researchers seeking only grants, fame and Nobel Prizes, and the media. (PW, blurbed as "one of the best known Alzheimer's experts in the world", has, of course, had previous links with many of these agencies - how many Alzheimer's experts have appeared on the Oprah Winfrey Show? - now apparently renounced, so could be said to have had at least a hand in the creation of this "myth".) In a possible example of gamekeeper turned poacher, PW demolishes this (straw man?) by proffering a number of solutions: tell a different story about cognitive loss, put more resources into care and prevention, promote healthy brain aging (eat fish, remove lead from your house, etc.), volunteer to work in your community.

I guess your response to this will depend on the perspective you adopt. It may go well with the "baby-boomers" who seem to be the book's intended market, but as a clinician I had reservations. To take just one example: Is late-life cognitive decline always merely physiological "brain aging", or may it be sometimes pathological? Since, empirically, cognitively impaired individuals may become impaired to the point of being unable to care for themselves, I think this cannot be deemed physiological, and hence merits some form of clinical label (though clearly there are problems with operationalising any diagnostic criteria) and intervention. What PW tells patients who have what others might call AD is not entirely clear, but the strategy is recognised to have potential problems (36, 212).

Of the many roles that PW has played (he is blurbed as having held professorships in 9 different disciplines!), "key opinion leader" (5), with its possible implication of intolerance of the opinions of others, would seem to me the most significant. Whilst the shortcomings of current approaches to AD are evident, and no one could quibble about replacing "hype with hope", I'm not certain that this "rethinking everything we thought we knew about brain aging" delivers a meaningful agenda for change. I would be delighted to be proved wrong. ◆

Neurology in Clinical Practice (5th edition)



Authors: Bradley WG, Daroff RB, Fenichel GM, J Jankovic (eds)
Published by: Butterworth Heinemann Elsevier 2008
Price: £279.00
ISBN: 9780750675253

Reviewed by:
AJ Larner, Cognitive Function Clinic, WCNN, Liverpool, UK.

Whilst not subscribing to the adage of the Reverend Sydney Smith (1771-1845) – "I never read a book before reviewing it – it prejudices a man so"– it is true that I have not read all the 2000+ pages in these 2 volumes. I did, however, between 1999-2001, read all of the third edition, the last to include David Marsden amongst the editors. The subsequent fourth edition (2004) was similar in format to the third, but for this fifth edition there has been a substantial revision, both of format and authors. The former is described as "multimedia" for there is a website, including the whole text plus videos and suggested reading lists, which will be particularly useful for those who may feel unequal to carrying the book around. The authorship is now almost exclusively North American, in contrast to the situation when Marsden was amongst the editors, and hence some may feel that the transatlantic feel, and appeal, of the book has been lost.

Nevertheless, this is a very high quality production, with an accessible uniformity of style in illustrations and tables. The "Gold Standard in neurology guides" states the blurb, and although Oxford University Press, as publishers of "Brains", might demur, one can certainly have no misgivings in recommending this tome to trainees. The price might seem prohibitive but averaged over a 5-year training period it works out to about £1 a week. It certainly summarises the accepted corpus of neurological knowledge, but regrettably has little to say about the large numbers of patients seen by neurologists who do not have a neurological disorder (?50%), which would seem desirable in a book devoted to practice.

One can always find things to quibble about in a text which aims to be "exhaustive": the definition of specificity is wrong (452), there are incorrect chapter cross references (e.g. in chapter 23), transposition of figures (e.g. 70.4 and 70.10), and some statements are debatable (1897: is conjugal CJD "not reported"? How about Neurology 1998;50:684-8?). Surgery is not mentioned amongst the antecedents of meralgia paraesthetica (2268) but in my practice it is the most common identified cause. Should you wish to learn about exploding head syndrome, you won't find it in the index despite its 80 pages (try 1967, 1988, but no details). These nit-pickings aside, this text will giver a solid grounding to any trainee able and willing to read, mark, and inwardly digest the contents. ◆

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o rachael@acnr.co.uk

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 5 June, 2009

2009

VIREPA, the Virtual Epilepsy Academy Distance learning courses. Genetics of Epilepsy, EEG in the diagnosis and management of epilepsy, Neuroimaging and Clinical Pharmacology and Pharmacotherapy.
www.epilepsy–academy.org

MAY

2nd International Epilepsy Colloquium: Pediatric Epilepsy Surgery
3-6 May, 2009; Lyon, France
W. http://epilepsycolloquium2009ams.fr

Developing Insight/Awareness following brain injury
4-5 May, 2009;Vancouver, BC, Canada
E. info@jrrehab.ca
W. www.jrrehab.ca/

Neuropsychiatric, Psychological and Social Developments in a Globalised World
5-8 May, 2009; Athens, Greece
Mrs Demy Kotta
T. 302-106-842-663
E. appachellas@yahoo.gr

Mending the Brain: Advances in Neurosurgical Techniques
7 May, 2009; London, UK
T. 020 7290 2984/3941
E. cns@rsm.ac.uk

Measuring Mobility: 28th Scientific meeting of the Physiotherapy Research Society
7 May, 2009; Glasgow, UK
E. m.grant@gcal.ac.uk

24th International Training Institute in Neurologic Music Therapy
7-9 May, 2009; London, UK
E. lgriffiths@rhn.org.uk
W. www.rhn.org.uk/institute/doc.asp ?catid=1477&docid=3277

Window on Tomorrow: Advancements in the Science and Medicine in Neuromuscular Conditions
7-9 May, 2009; Auckland, New Zealand
T. +64 9 845 5540
E. events@iconevents.co.nz
W. www.nma2009.org.nz

24th International Training Institute in Neurologic Music Therapy
7-9 May, 2009; London, UK
E. lgriffiths@rhn.org.uk
W. www.rhn.org.uk/institute/ conferencesNMT
T. 020 8780 4500 ext 5140

Molecular Mechanisms Of Neurodegeneration
8-10 May, 2009; Milan, Italy
Angelo Poletti
T. +390250318215
E. triplets@unimi.it

5th ISPRM World Congress
9-13 May, 2009; Istanbul, Turkey
E. traceymole@wfnr.co.uk

UCL May Short Courses
11-15 May, 2009; London, UK
T. 020 7692 2346
E. J.Reynolds@ion.ucl.ac.uk

The Nottingham Systematic Review Course 2009
12-15 May, 2009; Nottingham, UK
Jun Xia T. 0113 3058303
E. jun.xia@nottingham.ac.uk

Health Care Records
12 May, 2009; Derby, UK
T. 01332 254679
W. www.ncore.org.uk

Intensive Neuroradiology Course
13 May, 2009; Coventry, UK
E. rachel.davies2@uhcw.nhs.uk

6th Baltic Congress of Neurology
13-16 May, 2009; Vilnius, Lithuania
Dainora Bandziute
T. 37 0 52 120 003
E. info@balcone2009.com

Joint BSRM/IARM Spring Meeting
14-15 May, 2009; Dublin, Ireland
T. 01992 638865
E. admin@bsrm.co.ukEpilepsy: Psychological and Social Wellbeing

14 May, 2009; Edinburgh, UK

T. 0141 427 4911, www.epilepsyscotland.org.uk

BISWG Training and Education in Brain Injury - Scotland
15 May, 2009; Lanarkshire, UK
Mhairi McKay,
T. 0131 537 6857,
E. fenparry@jspsc.co.uk or mhairi.mckay@lpct.scot.nhs.uk

AAC Technology
15 May, 2009; London UK
E: lgriffiths@rhn.org.uk,
http://www.rhn.org.uk/institute/AAC

12th Multidisciplinary International Conference of Neuroscience and Biological Psychiatry "Stress and Behavior" - 2nd International Stress and Behavior Society (ISBS) Congress
16-20 May, 2009; St Petersburg, Russian Federation
E. isbs-2008@inbox.ru

Exploring Gait as it relates to Posture and Balance for Therapy Assistants
18 May, 2009; Derby, UK
T. 01332 254679
www.ncore.org.uk

Implementing the National Dementia Strategy
18 May, 2009; London, UK
T. 0870 400 1020 Capital Conferences,
E. david.moffat2@capita.co.uk

Exploring Gait as it relates to Posture and Balance for Therapy Assistants
18 May, 2009; Derby, UK
T. 01332 254679
www.ncore.org.uk

Exploring Gait as it relates to Posture and Balance for Qualified Staff
19 May, 2009; Derby, UK
T. 01332 254679
www.ncore.org.uk

Meeting of Regional Acquired Brain Injury Fora and UKABIF
19 May, 2009; Manchester, UK
E. ukabif@btconnect.com
T. 01752 601318

Clinicians at the Helm
20 May, 2009; London, UK
E. Abby Kessler Weiner
kesslera@advisory.com

Clinical update: Neurology for General Physicians and GPs
21 May, 2009; London, UK
www.p-cns.org.uk

BISWG Annual General Meeting
21 May, 2009; Birmingham, UK
E. v.suffolk@btconnect.com

MS Frontiers
21-22 May, 2009; Heathrow, UK
E. Lucy Boyle
lboyle@mssociety.org.uk

The 3rd Migrating Course on Epilepsy
24-31 May, 2009,Pruhonice, Czech Republic
www.epilepsy-academy.org,
E. Petra Novotny petra@epilepsy-academy.org.

18th European Stroke Conference
26 –29, May 2009; Stockholm, Sweden
E. esc@akm.ch

Current Trends in Paediatric Neurology
27 May, 2009; London, UK
E. sharon.stone@pat.nhs.uk

1st International Course on Pain Medicine
28-31 May, 2009; Granada, Spain
T. 0208 439 9556/9557,
E. info@wfneurology.org

5th World Congress of Neuroendoscopy
31 May – 6 June, 2009 ; Athens, Greece
Mrs. Penelope Mitroyianni,
E. info@erasmus.gr
T. 302 107 257 693

The Magstim TMS Summer School
29-30 May 2009; London UK
E: BrainTMS@gmail.com
www.magstim.com

JUNE

Update in Neuromuscular Disorders
1-3 June, 2009; London, UK
E. Zoë Scott
z.scott@ion.ucl.ac.uk
E. mhanna@ion.ucl.ac.uk

Exploring Patterns of functional movement in neuro patient, therapy assistants -
2 June, 2009; Derby, UK
T. 01332 254679
www.ncore.org.uk

CNS Clinical Trials
2-3 June, 2009; Brussels, Belgium
E. events@vibevents.com
T. 020 7753 4201,
www.clinicaltrialsevents.com/cns/

Neurology future: Imaging, genomics, proteomics, nanotechnology and AGM
4 June, 2009; London, UK
T. 020 7290 2984/3941
E. cns@rsm.ac.uk

14th Euroacademia Multidisciplinaria Neurotraumatologica Congress (EMN)
4-6 June, 2009; Kaunas, Lithuania
E. info@emn2009.com

Liverpool Neurological Infectious Diseases Course
4-5 June, 2009; Liverpool, UK
E. Doreen Owen,
E. neuroidcourse@liv.ac.uk
T. 0151 529 5461

Clinical Trials in Neuromuscular Diseases
4-6 June, 2009; Freiburg, Germany
E. kathrin.gramsch@uniklinik-freiburg.de

EAT Training Day
5 June, 2009; Liverpool, UK
Tia Jones, EATNW, WCNN,
T. 0151 529 5619,
E.tia.jones@thewaltoncentre.nhs.uk

Cognitive Rehabilitation Workshop
5-6 June, 2009; Gatwick airport, London, UK.
E. enquiries@braintreetraining.co.uk,
www.braintreetraining.co.uk

11th Annual Meeting of the International Behavioural and Neural Genetics Society (IBANGS)
5-8 June, 2009; Dresden, Germany
E. Rupert Overall
ibangs2009@crt-dresden.de

Association for the Scientific Study of Consciousness
5-8 June, 2009; Berlin, Germany
E. mail@assc13.com

13th International Congress of Parkinson's Disease and Movement Disorders
7-11 June, 2009; Paris, France
Sarah Smith, The Movement Disorders Society,
T. 001 414 276 2145,
E. ssmith@movementdisorders.org

12th International Neurotoxicology Association Meeting: INA-12
7-12 June, 2009; Jerusalem, Israel
Helen Goldmunz,
T. 97 226 520 574,
E. meetings@isas.co.il
www.isas.co.il/ina-12/

Thirty Years of Neurobehavioural Rehabilitation
8-9 June, 2009; Northampton, UK
T. 020 8763 2963,
E. Jason@abisolutions.org.uk

Hot Topics in Long Term Ventilation and Neurodisability
9 June, 2009; Tadworth, UK
Gilney Simoes,
T. 01737 365000,
E. gsimoes.@thechildrenstrust.org.uk
www.thechildrenstrust.org.uk

Motivating the Unmotivated: Helping difficult patients
9 June, 2009; Derby, UK
T. 01332 254679
www.ncore.org.uk

Canadian Neurological Sciences Federation 44th Annual Congress
9-12 June, 2009; Halifax, Nova Scotia, Canada
www.cnsfederation.org
E. lisa-bicek@cnsfederation.org
T. 001 403.229.9544

Clinical Trials in Neuroscience and Psychiatry
10 June, 2009; Edinburgh, UK
Register online at
www.edinburghneuroscience.ed.ac.uk/ CTNP2009/index.html

New Developments in Clinical Trials in Neuroscience and Psychiatry
10 June, 2009; Edinburgh, UK
E. Jane.Haley@ed.ac.uk,
www.edinburghneuroscience.ed.ac.uk/ CTNP2009

Reflective Practice
10-11 June, 2009; Derby, UK
T. 01332 254679
www.ncore.org.uk

Arrhythmia Alliance Regional Meeting
11 June, 2009; Edinburgh, UK
Melanie Quinlan
E. events@stars.org.uk
www.heartrhythmcharity.org.uk

The 5th Kuopio Alzheimer Symposium
11-13 June, 2009; Kuopio, Finland
www.uku.fi/alz2009
E. tuija.parsons@uku.fi

Arrhythmia Alliance Regional Meeting
12 June, 2009; Leeds, UK
Melanie Quinlan,
E. events@stars.org.uk
www.heartrhythmcharity.org.uk

MS Life
12-14 June, 2009; Gateshead, UK
E. Lucy Boyle
lboyle@mssociety.org.uk

National Conference and Annual General Meeting - Prioritising epilepsy: who decides?
13 June, 2009; Newcastle, UK
Judith Davies
T. 0113 2108800
E. epilepsy@epilepsy.org.uk

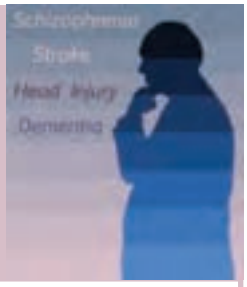
5th Essential Neuro MRI Study Day
13 June, 2009; Liverpool, UK
Kath Tyler,
T. 01515295416/5552,
E.essentialneuromri@hotmail.co.uk

5th World Congress of the International Society of Physical and Rehabilitation Medicine
13-17 June, 2009; Istanbul, Turkey
Ms. Sezen Elagoz,
T. 902 123 438 003,
E. selagoz@teamcon.com.tr

EMBO : ADVANCES IN STEM CELL RESEARCH: Stem cells, systems & synthetic biology
15-17 June, 2009; Cambridge, UK
Claudia Bagni
E. seeck@embl.de

SMART Accredited Assessors Course
15-19 June, 2009; London, UK
E. lgriffiths@rhn.org.uk
www.rhn.org.uk/cat.asp?catid=1336

New Developments in Clinical Trials in Neuroscience and Psychiatry



Wednesday 10th June 2009,
1.30-6pm
University of Edinburgh, Scotland

Stroke, Mental Health problems and Dementia are a huge public health concern, and more effective treatments are needed. The aim of this meeting is to outline some of the new methodological approaches to achieving successful translation of benefits from laboratory research to benefits for patients. This half day workshop is open to all and is organised by the Centre for Clinical Brain Sciences, University of Edinburgh, in collaboration with:

- The MRC Methodology Hub for translational research
- Edinburgh Clinical Trials Collaboration
- Edinburgh Neuroscience
- Scottish Imaging Network: A Platform for Scientific Excellence (SiNAPSE)
- The Scottish Collaboration of Trialists
- The Scottish Research Networks in Stroke, Dementia and Mental Health Research

Registration deadline: Friday 5th June 2009
Location: Small Auditorium, Chancellor's Building, 49 Little France Crescent, Edinburgh, EH16 4SB
Cost: Free, but places limited and registration is required

Register at
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Target audience: Consultants and Specialist Registrars in Neurology and Allied Health Specialists.

Programme
1. Neuro-imaging in CNS Inflammation, David Miller, London
2. CNS Vasculitis, Neil Robertson, Cardiff
3. Neuromyelitis optica, Mike Boggild, Liverpool
4. Neurosarcoid, Desmond Kidd, London.
5. Pitfalls in MS diagnosis, Gavin Giovannoni, London
6. Neuro-Behcet's disease, Adnan Al-Araji, Stoke-on-Trent
7. Is it CNS inflammation or a functional disorder? Jon Stone, Edinburgh
8. Diagnosis and management of viral encephalitis , Peter Kennedy, Glasgow
9. Symposium "Treatment options in active MS" John Isaacs, Newcastle; Martin Duddy, Newcastle; Norman Putzki, Essen, Germany.

Other topics are to include neuroradiology cases and antiphospholipid syndrome amongst others.

Objectives: To present updates, especially on practical diagnostic and management issues in various topics related to CNS inflammation and demyelination.

Format: Includes a special emphasis on practical clinical discussions, case histories and interactive presentation.

Fees: £100.00, to include registration, accommodation for two nights and meals.

Places are limited, please try to register early.
To reserve your place on the course please contact:-
Dr Adnan Al-Araji, Department of Neurology
University Hospital of North Staffordshire, Stoke on Trent, ST4 7LN
Email: kcci2009@uhns.nhs.uk or telephone (01782) 554821

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Neurology Digest from ACNR

Conference details: 17 November, 2009; Royal Society of Medicine, London, UK. ***Reviewed by:*** Dr Roger Barker.

PREVIEW

This new Neurology Digest event, which we hope will become a regular occurrence, is very different from other meetings. It picks up on some of the key features of ACNR - namely topicality, familiarity, and the uniquely eclectic nature of the journal.

In this first meeting we will attempt to present a personal, but relevant, review of three major papers in a given area of work. This will be done by myself and Dr Alasdair Coles and we will be "majoring" in movement disorders and MS.

The idea will be to present and discuss three papers for each condition which touch upon the basic and clinical science, before discussing therapeutics, with a rehabilitation input from Diane Playford.


Roger Barker

These papers will be selected from the published literature over the last 12 or so months and may have been reviewed previously in the Journal review section of ACNR.

We intend that the format will be relaxed, and that it will encourage discussion and debate rather than be a straight "from the front" presentation. We hope that we can convince you as to why we feel these papers are important, but it will also be an opportunity for you to disagree if you feel there have been other more important papers in the past year.

We hope that many of you will come along. The meeting is not just meant for neurologists, but for all those interested in neuroscience and its clinical impact and expression - in fact it is open to every reader of ACNR. ◆

New Developments in Clinical Trials in Neuroscience and Psychiatry

Conference details: 10th June, 2009; Chancellor's Building, Royal Infirmary of Edinburgh, UK. ***Reviewed by:*** Peter Sandercock, Director, Edinburgh Neuroscience.

PREVIEW

The aim of the workshop is to discuss some of the key methodological obstacles to successful translation of benefits in the laboratory to benefits for patients. It is specifically aimed at clinicians and investigators planning or conducting clinical trials in the field. The event is being organised and supported by a number of academic multi-disciplinary and multi-institutional organisations and clinical trial networks based in Scotland, independent of the pharmaceutical industry. The supporting organisations in Edinburgh are: The Centre for Clinical Brain Sciences, Edinburgh Neuroscience, the Edinburgh Clinical Trials Unit Collaboration (ECTU) and the Medical Research Council Methodology Hub for Translational Research. The partnerships involving other Universities in Scotland are: the Scottish Collaboration of Trialists (SCoT), the Scottish Imaging Network: A Platform for Scientific Excellence (SINAPSE) and the three disease-specific research networks in Scotland, in: Stroke, Mental Health and Dementia/Neuro-degeneration. Registration is free, but places will be limited.

Topics:

- What are the methodological challenges for clinical trials in neuroscience and psychiatry?
- Pitfalls and potential benefits of imaging as a surrogate outcome in treatment trials in
  - o Stroke
  - o Schizophrenia
  - o Dementia
- Increasing the power of clinical outcome measures in trials in Parkinson's Disease, Dementia and other neurodegenerative diseases.

It is a half day meeting, and it will close with a distinguished guest lecture by Dr Walter Koroshetz, Deputy Director, National Institutes for Neurological Disorders and Stroke, National Institutes of Health, Bethesda, USA. on 'Tackling the challenges of translational research in Neuroscience: an NIH perspective.' ◆

Register at www.edinburghneuroscience.ed.ac.uk/CTNP2009/index.html

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Positive Steps in Parkinson's Disease

Conference details: 27-28 February 2009, Manchester UK. ***Reviewed by:*** David Burn and Doug MacMahon.

The second Positive Steps in Parkinson's Disease meeting, sponsored by Teva Pharmaceuticals Ltd and Lundbeck Ltd, was held on February 27th-28th in Manchester. The presentations and discussions spanned the full PD spectrum from pre-symptomatic through to palliative care stages, although several themes recurred throughout the meeting: the general move to earlier treatment; phenotypic heterogeneity within PD, and the importance of understanding which subtype of patients are most suited to different treatments.

Professor Ray Chaudhuri proposed a reappraisal of the PD clinical state. He highlighted that we now know that non-motor symptoms of PD (e.g. constipation, sleep problems, pain, and anxiety) can often be recognised in a patient before the classic motor symptoms of PD emerge and, moreover, these non-motor symptoms often predominate at the end-stages of the disease. A new staging scheme based on non-motor symptoms that progress at variable rates compared with motor symptoms will be proposed at international congresses later this year. This scheme highlights at least five different PD subtypes; somnolence predominant PD, PD with REM behaviour disorder, painful PD, dysphagic PD and PD with non-motor fluctuations. Early identification of these patient subtypes can have direct relevance to treatment decisions. For example, patients with somnolence predominant PD have a higher risk for developing problems with sudden onset of sleep which should be taken into account when up-titrating dopamine agonists. Recognition of these non-motor symptoms of PD means timely treatment of the predominant symptom.

The theme of recognising patient subtypes was taken up by Dr Paul Worth who discussed the practical relevance of genetics in PD. Although monogenetic forms of PD are relatively uncommon, the likelihood of genetic mutations being pathogenic is higher in certain populations. For example, if the patient presents aged 20 or younger, there is an 82% probability that the autosomal recessive PARKIN gene is the underlying cause; if the age of onset is less than 45 years old, the chance of PARKIN is between 5–10%. Since patients with the PARKIN mutation usually have an excellent response to levodopa but a high potential to develop levodopa-induced dyskinesia, recognising the presence of this gene has very practical implications for levodopa dosing.

Professor Carl Clarke explored the issues in treatment of early PD. A major debate is not necessarily what to treat with (NICE recommend levodopa, dopamine agonists and/or MAO-B inhibitors as monotherapy), but when to initiate treatment. Data from the PD-LIFE trial show that roughly half of patients in the UK are initiated on therapy straight away but that, for the rest, treatment appears to be initiated later when the patients experience significant functional disability. This practice of reserving treatment was originally brought into question by an editorial which used the DATATOP (selegiline), ELLDOPA (levodopa) and TEMPO (rasagiline) trials as support for earlier treatment. All of these studies conducted in early PD (now further supported by the recent rasagiline ADAGIO trial) showed a significant functional benefit to the patient of initiating dopaminergic treatment earlier versus placebo or delayed initiation. Although there are questions on interpretation of these studies, Professor Clarke suggested that there is a general groundswell of evidence towards the earlier treatment of PD. However, it is unknown when this will be enough to change practice. Moreover, recent trial failures, such as the failure of Stalevo to delay dyskinesias, highlight the need to continually evaluate the pros and cons of each treatment for each patient.

The topic of avoiding dyskinesias was explored by Dr Monty Silverdale who argued that dyskinesia is an overactive form of synaptic plasticity, which (at its most basic level) is caused by the pulsatile activation of striatal dopamine receptors through non-continuous drug therapy (e.g. levodopa t.i.d.). Providing a more continuous stimulation (e.g. levodopa and apomorphine infusions) has proven beneficial in reducing dyskinesia in advanced disease and there is much interest in this approach in avoiding the "priming" of the basal ganglia in early PD.

Dr Malcolm Steiger discussed treatment of advanced disease by highlighting apomorphine as a useful and reliable rescue therapy for unpredictable OFF periods. Apomorphine is underused in the UK mainly due to misconceptions of adverse events and the reluctance to use injectable therapies. However, Dr Steiger argued that these problems can usually be easily overcome with appropriate education and that in his view there is currently no better pharmacotherapy for managing the later stages of the disease. Apomorphine is not associated with significant neurocognitive effects. Though DBS can be a life-changing therapy, the risk of increased suicide and depression with DBS led Dr Steiger to emphasise strongly the need to perform a full neurocognitive and neuropsychiatric assessment on every DBS candidate.

Dr Peter Fletcher tied together many of the earlier themes when discussing the management of elderly patients with PD. The typical elderly patient with PD will suffer from a multitude of non-motor symptoms, particularly autonomic dysfunction, which are a significant source of morbidity. The incidence of both dementia and depression in PD increase with age and have considerable impact on caregivers and family. In general, he suggested that elderly patients should be started on antiparkinsonian therapy sooner, and drug choice limited to those with a simple regime and tolerable profile. The benefits of dopamine agonists need to be carefully weighed against the potential for causing

cognitive and neuropsychiatric problems. Since elderly patients will have shorter disease duration, it is important to plan for palliative, end-of-life care relatively early on. He reminded us that improved cancer and cardiac care means that more patients will survive and develop PD; however changing UK demographics mean that by 2050 there will be around a third of the current levels of carers available to care for them.

Looking to the future, Dr Roger Barker discussed the role of stem cells as a neurorestorative treatment. Recent advances in developing Induced Pluripotent Stem (IPS) cells now allow the generation of stem cells from the patient's own skin, thus avoiding many of the ethical problems of embryonic stem cells. However, numerous technical problems and uncertainty around the maturity of cells within implants have meant that this technology is currently best used as a way to model and study the disease rather than as a treatment. Furthermore, experience with foetal grafts into the striatum tells us that we should again pay close attention to patient selection. In the famous Swedish foetal graft studies, younger patients with localised nigral pathology fared extremely well, whereas those older patients who suffered from postural instability and gait dysfunction tended to have a more widespread Lewy Body pathology and experienced minimal benefit and "runaway" dyskinesias.

Professor Peter Jenner closed the meeting by looking at PD pharmacotherapy advances for the next 5–10 years. A number of potential non-dopaminergic drugs have recently failed in Phase III studies. Similarly, research into neuroprotective and neurorestorative therapies has not produced any real candidates for treatment. However, our improved understanding of the ongoing compensatory mechanisms within the parkinsonian basal ganglia has shown that more strategic use of the mainly dopaminergic drugs already available can have a significant impact on improving patient care. For example, it is thought that initiating dopaminergic treatment as early as possible may help prevent structural changes occurring in the medium spiny striatal neurons, keeping the dopaminergic input as constant as possible may prevent priming of the basal ganglia for dyskinesia, and earlier use of adjunct therapy (e.g. lower dose levodopa with adjunct MAO-B and/or COMT inhibitors) may be the best approach to manage the problems of more advanced disease.

The robust discussions and debate flowed into the workshops and interactive sessions and participants left already looking forward to the next meeting planned for 5-6 March 2010. ◆

Publication of this meeting report was made possible by an educational grant from Teva Pharmaceuticals Ltd and Lundbeck Ltd.

A Time to Reappraise the Timing of Treatment in PD?

Conference details: 1 April, 2009; Bournemouth, UK. ***Reviewed by:*** Dr Peter Fletcher.

The current hot topic in Parkinson's disease (PD) management is not so much what to treat with, but when to treat. This issue was debated at the Teva Pharmaceuticals and Lundbeck Sponsored Symposium "Timing of treatment in Parkinson's disease" during the Bi-annual Meeting of the British Geriatric Society at Bournemouth.

It is estimated that in the UK, roughly half of all patients diagnosed with PD are not immediately started on medication. This is often due to patient choice, but mostly due to the assumption that all treatments are purely symptomatic and that most antiparkinsonian medications carry significant risks of side effects including the development of motor complications such as wearing-off and dyskinesia. Hence traditional teaching has been that it is better to wait until the patient suffers significant disability before initiating treatment.

However, proponents for the early treatment of PD argue that a number of studies (e.g. DATATOP, ELLDOPA, TEMPO and the recent ADAGIO delayed-start study) demonstrate that earlier initiation of treatment offers significant benefits to patients in terms of both clinical progression of the disease and in quality of life. Moreover, we now have a better understanding of how to use therapies such as MAO-B inhibitors and dopamine agonists to delay the use of levodopa and keep the levodopa dose low when it is initiated.

It was also noted that there is a need to reappraise when changes are made to the patient's medication, for example to manage wearing-off. There is a wealth of data to demonstrate the efficacy of MAO-B inhibitors, COMT inhibitors and dopamine agonists as adjunct therapy and there is now also a move to introduce adjunct therapy much earlier than before. The choice of which class of medication to use should be individualised, effects on cognition (especially with dopamine agonists) and other side effects need to be taken into account.

This debate was the first in a series, which will be held throughout the UK during 2009. ◆

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Abstract Submission Deadline: 3 February 2010
Early Registration Deadline: 21 April 2010

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EDITOR'S CHOICE

PARKINSON'S DISEASE: A stimulating new approach

Electrical stimulation of the brain has been explored in PD for some time, most notably in the form of deep brain stimulation of the subthalamic nuclei. However other targets and approaches have been sought including cortical stimulation and now, in a recent paper in Science, the spinal cord! Fuentes et al have used dorsal column stimulation (DCS) in the treatment of experimental PD. They have done this using a number of different animal models but in all cases they have implanted electrodes in the upper thoracic cord, which are stimulated at a frequency of around 300Hz. In their first experiment, they show that knocking out dopamine synthesis using inhibitors of the pathway (i.p. alpha-methyl-tyrosine) causes deficits in locomotion and abnormalities in corticostriatal neuronal activity both in terms of local field potentials and single unit recordings. They then show that high frequency stimulation of the upper thoracic cord increases locomotor activity both in the dopamine depleted and non-depleted animals, but that the effect is much greater in the depleted state. This improvement in locomotion was accompanied by a move towards normalisation of neuronal activity, as assessed immediately after the period of stimulation, a series of benefits that were also seen in the DAT-KO mice with acute dopamine depletions. The next experiments involved chronic lesions using 6-OHDA striatal terminal lesions in rats and stimulating the thoracic cord for 30 seconds every 10 minutes with the animals in an open field test chamber (as a way of looking at locomotion). The stimulation improved locomotion for the duration it was on and for about 100 seconds afterwards. Thus the authors conclude "that stimulation of the dorsal column pathways using epidural implanted bipolar electrodes can restore locomotive capability". The method by which this is achieved is unknown, but the authors propose that it works through ascending effects via the thalamus and from there to the corticostriatal system, rather than by non-specific brainstem arousal effects or effects on spinal cord locomotor circuits. In other words dorsal column stimulation works by activating large cortical areas which then activate the striatum in such a way as to overcome the block to the motor system that the striatum mediates in response to its lost nigral dopaminergic input. This is all very interesting and will stimulate much debate especially with respect to how it works. Indeed until this is better understood, it may well remain as a curious experimental observation. ***– RAB***

Fuentes R, Petersson P, Siesser WB, Caron MG, Nicolelis MA.
Spinal cord stimulation restores locomotion in animal models of Parkinson's disease.
SCIENCE
2009:323:1578-82.

PARANEOPLASIA: Yet another limbic antibody

There was a time when the only antibody that mattered in neurology was the acetylcholine receptor antibody. Those days are long gone. First we had a range of antibodies against channels in the peripheral neuromuscular junction... which we could just about get our head around. But in recent times, more and more antibodies have been identified against targets with incomprehensible names.... and it is getting pretty bewildering.... Does it really matter if you have an antibody against "collapsin response-mediator protein-5"? None of this is helped by some pretty shoddy research in the lower-tier journals. Nor is the situation clarified when different centres use different assays and get different results, so that – for instance – a positive "anti-basal ganglia antibody" in the US is one thing, and in the UK is quite another.... And why do anti-GluR3 antibodies do different things in Israel than other countries....?

Josep Dalmau is the Pennsylvania King of Paraneoplastic Neurology, and has characterised many weird and wonderful antibody-associated paraneoplastic syndromes. And his team has come up with yet another one: against AMPAR, a glutamate receptor. I think we can quite reasonably ask: "so what"? Well, first of all, he is looking at an important-not-to-miss disease: the potentially treatable limbic encephalitis, which may be mistaken for untreatable conditions like the degenerative dementias. Roughly speaking, three-quarters of such patients will have antibodies which recognise the surface of neurones in the laboratory; and, of these, less than half will be directed to the potassium channel. The rest will be a rag bag of antibodies against NMDA, GAD, Hu, Ma, amphiphysin, CV2 and CRMP5..... and a lot will remain uncharacterised. So the Dalmau lab went through its freezers and identified 10 patients with limbic encephalitis, without defined autoantibodies, whose sera bound the brain and cerebellum of rats in a similar way. Clinically, they were kosher cases of limbic encephalitis: with encephalopathy, seizures and medial temporal MRI abnormalities. 9/10 were women and 7/10 had had tumours of the lung, breast, or thymus. 9/10 improved dramatically after the presenting episode, with immunotherapy, but there was a tendency to relapse. The Dalmau team soaked some hippocampal neurones in the patients' sera and then immunoprecipitated the antigens, and ran them through a mass spec. The resulting signature suggested the antigens came from the GluR1 and GLuR2 subunits of the AMPAR. Some juggling with transfectants led to the conclusion that some patients had antibodies to GluR1, some to GLuR2 and some to both. And, when they took the sera back to the neuronal cultures, they found that it specifically reduced the number of GLuR2-AMPAR clusters at the synapse, with a much lower effect on the overall AMPAR cluster density. In answer to the "so what?" question: Dalmau has potentially identified a new test for "anti-VGKC negative" limbic encephalitis patients; and a positive result should lead to a hunt for cancer. His team has also shown how this antibody might be working: by effectively shunting AMPARs away from the synapse... now that is both useful and interesting! ***– AJC***

Meizan Lai, Ethan G. Hughes, Xiaoyu Peng, Lei Zhou, Amy J. Gleichman, Huidy Shu, Sabrina Matà, Daniel Kremens, Roberta Vitaliani, Michael D. Geschwind, Luis Bataller, Robert G. Kalb, Rebecca Davis, Francesc Graus, David R. Lynch, Rita Balice-Gordon, Josep Dalmau.
AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location (p NA).
ANNALS of NEUROLOGY
Published Online: Mar 18 2009 6:27PM.

EPILEPSY: and head-nodding

I am always impressed to hear of clinicians who are able to identify a new disease, especially in a context where clinical services are stretched beyond the comprehension of most Western physicians. I usually assume that when something is new to me, that is just my ignorance, a fairly safe assumption as a rule. In fact, head-nodding disease was originally identified in about 1960, in Tanzania but has become more widely known in Africa in the last decade. It is not the involuntary response of a beleaguered populace to an oppressive military regime, but a clinical condition characterised by head nodding, mental retardation, clinical signs and other seizures as well. In this study of 62 patients, only about ten underwent MRI or EEG as this would have involved travelling 300km to Dar es Salaam but clinical data were available in all, skin biopsies in many and CSF in about three quarters. The onset was usually between the ages of six and ten years and 45% of patients had only head nodding but the same number also had other seizures, especially tonic clonic seizures. In some patients seizures were triggered by food. Some patients had focal signs and others "brain damage", although this is not clearly defined. There was evidence of onchocerciasis in 84% on blood tests or skin biopsy, the authors do not comment on the background rate in the community. Hippocampal sclerosis was present in 42% of those who underwent MRI. This is not an epilepsy syndrome I recognise in patients with hippocampal sclerosis and the geography points to a local predisposition; genetic or environmental, as yet to be determined with certainty. I await further studies with interest. ***– MRAM***

Winkler AS, Friedrich K, König R, Meindl M, Helbok R, Unterberger I, Gotwald T, Dharsee J, Velicheti S, Kidunda A, Jilek-Aall L, Matuja W, Schmutzhard E.

Head nodding syndrome – Clinical classification and possible causes.

EPILEPSIA

2008;2008-2015.

PARKINSON'S DISEASE: Oh Glia! Where is the problem?

The loss of the dopaminergic nigrostriatal pathway is the core event in Parkinson's disease (PD), but what causes the death of these cells is unclear. There is though an emerging consensus that part of the problem is intrinsic to the cells, but that this may not be the whole story and the glia may contribute to the disease process. This evidence includes:

- Histological data on microglia activation in pathological specimens of PD brains;
- Microglia activation in vivo using PK11195 PET;
- Pathology in grafted dopaminergic cells in patients who have had fetal ventral mesencephalic grafts for their advanced PD; and
- The proven role of glia in other neurodegenerative disorders such as MSA and motor neuron disease.

Adding to this is the recent data from Chen et al in which they show that astrocytes are important in the loss of dopaminergic cells in MPTP treated animals. The experiments begin by showing that mice treated with MPTP using their dosing regime have reduced nigrostriatal dopamine and increased GFAP astrocytosis in these same areas – namely the striatum and nigra. They then sought to follow the transcription of genes containing the antioxidant response element (ARE). ARE regulates many cytoprotective genes via the transcription factor Nfe2 related factor (Nfe2) and using a reporter system they showed that MPTP increased Nfe2-ARE signalling in the nigra and decreased it in the striatum.

In order to study what this meant, MPTP was then given to Nfe2 knockout mice (Nfe2-/-) as well as normal wild type mice (Nfe2+/+). It was found that in the Nfe2-/- mice there was an increased toxic effect of MPTP and that this was NOT related either to major baseline changes in the integrity of the dopaminergic nigrostriatal system nor the capacity to generate more MPP+ (the toxic metabolite of MPTP). However there was an increase in the astroglial response in the Nfe2-/- mice in response to MPTP. Furthermore, when they overexpressed Nrf2 in GFAP positive cells (astrocytes), they dramatically protected the animals from the toxic effects of MPTP and attenuated the astroglial response and this included in Nfe2-/- mice. Thus it appears that MPTP induced dopaminergic loss involves a major astroglial component and oxidative stress. Of course whether this is relevant to patients with PD remains unproven. ***– RAB***

Chen PC, Vargas MR, Pani AK, Smeyne RJ, Johnson DA, Kan YW, Johnson JA.

Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: critical role for the astrocytes.

PNAS

2009; 106: 2933-2938.

SLEEP DISORDERS: what next after RBD?

REM sleep behaviour disorder (RBD) is mainly characterised by a loss of the normal muscle atonia that accompanies REM sleep. Patients with RBD present with excessive motor activity while sleeping, and this includes kicking or crying during dreaming. Recent studies have shown that RBD appears to be a feature of α-synucleinopathies, presumably mediated by degeneration of sleep regulating nuclei in the brain stem such as the pontine tegmentum. As such there is great interest that RBD can occur long before the development of Parkinson's disease (PD), dementia with Lewy bodies (DLB) or multiple system atrophy (MSA) (all α-synucleiopathies). If this is the case then there is the possibility of studying patients with RBD to see the extent to which they go onto develop one of these disorders, especially PD.

Postuma et al therefore studied patients with RBD and quantified the risk of subsequently developing a neurodegenerative disorder. They used 93 patients who had attended a sleep disorders clinic and met inclusion criteria for RBD as well as a life table analysis to define disease risk over 5, 10 and 12 years. Some of the inclusion criteria included a polysomnogram confirming RBD, complex motor behaviours during REM sleep, absence of any neurodegenerative disorder confirmed on a baseline neurologic examination. Interestingly, 26 out of the 93 patients developed a neurodegenerative disease; 15 developed parkinsonism and 11 dementia. Out of the 15 who developed Parkinsonism, 14 were diagnosed with idiopathic PD and one with multiple system atrophy (MSA). For the 11 patients with dementia, seven met clinical criteria for LBD and four met clinical criteria for AD. There was no difference in RBD duration between those who did or did not develop disease.

The current study has clearly demonstrated that the risk of developing a neurodegenerative disorder such as PD is lower than previously reported in other studies – this may relate to issues of sample size, follow up periods, diagnostic criteria and so on. Thus it will be essential to continue follow up in all cases of RBD using bigger sample sizes to see if a clearer picture may emerge on why some patients with synucleinopathies have RBD and how this differs from idiopathic RBD. ***– CA***

Postuma, R, Gagnon, J, Vendette, M, Fantini, M, Massicotte-Marquez, J, Montplaisir, J.

Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behaviour disorder.

NEUROLOGY

January 7 2009 [EPUB].

EPILEPSY: the risk from head injury

In this study the authors used the Danish National Registry to identify all patients born from 1977-2002 who developed epilepsy or who had a head injury. This association does not prove causation in every case, there may have been a few whose head injury was the consequence of a seizure and some who had a head injury and were going to develop epilepsy anyway, but in the great majority it is likely that the association was causative. They defined a mild head injury as one with loss of con-

sciousness for less than 30 minutes, post-traumatic amnesia for less than 24 hours and GCS no less than 14. Severe head injury included evidence of intracerebral contusion or haemorrhage. They analysed patients with skull fracture separately. They were then able to measure the relative risk of developing epilepsy against the remainder of that birth cohort. It is not clear how they categorised patients who may have had more severe clinical markers of head injury than the mild group but did not have evidence of intracranial haematoma, and these may not have been analysed. This differs from the previous standard study of Annegers, in which they were considered moderately severe.

The authors followed about 1.6 million individuals for nearly 20 million person years and found that the risk of epilepsy was approximately doubled by a mild brain injury or a skull fracture and increased sevenfold by a severe head injury. The risk was highest in those over the age of 15 and persisted for more than ten years after injury. The risk was maximal in the first year for those with brain injury but did not seem to be related to time, for those with a skull fracture. For those with a mild brain injury, a family history of epilepsy substantially increased the risk of seizures, with an effect that was between additive and multiplicative. For severe head injuries it appeared to be closer to additive.

This study confirms findings in previous studies and adds to them by clarifying the issues in relation to mild head injuries in the era of neuroimaging. It also, for the first time, describes in a large cohort, the contribution of genetic factors to the risk of epilepsy. It will be of great use to those advising patients with head injury and great profit to the medicolegal fraternity. It will also provide a valuable baseline for any studies which may be undertaken in the future with anti-epileptogenic drugs, if they become available. It must be remembered however, that it is restricted to patients under the age of 25 at the time of their trauma. ***– MRAM***

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A population based study of seizures after traumatic brain injury.
N Engl J Med
1998;338:20-24.

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Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study.
LANCET
2009 Mar 28;373(9669):1105-10.

EPILEPSY: anti-epileptic drugs in pregnancy affect the baby's IQ

This multicentre UK and USA study recruited over 300 pregnant women taking monotherapy with common antiepileptic drugs; phenytoin, carbamazepine, lamotrigine and valproate. They evaluated these women at baseline and found them to be similar for maternal IQ, epilepsy severity, folate use and gestational age at birth. For children exposed in utero to phenytoin, carbamazepine or lamotrigine, the main determinant of IQ at 3 years of age was maternal IQ. However, the children exposed to valproate in utero had a dose-related reduction in IQ. On average, children exposed to valproate had an IQ score 9 points lower than those exposed to lamotrigine, 7 points lower than those exposed to phenytoin and 6 points lower than those exposed to carbamazepine. These results were statistically significant but there was no significant difference between the other drugs. A further analysis will be made when the children are six. This study provides convincing evidence of the dangers of valproate to the foetus over and above obvious major malformations. They will cause increasing headaches to those of us who find ourselves with a limited choice of medication in patients with generalised epilepsy, especially juvenile myoclonic epilepsy. When do these problems arise? Is it safe to start valproate in the 2nd-3rd trimester for patients where no other drug will do? I guess we shall never know. Do you under-treat the mother to save harm to the foetus? It must be remembered that in one confidential enquiry into maternal mortality, the risk of maternal death in women with epilepsy was ten times expected. Treating mothers remains the first priority and sometimes the risks may be unavoidable. What about other drugs? Can one justify giving levetiracetam? The balance of the hope of the future against the devil you know. A balanced decision needs to made with each mother prior to conception. This new knowledge is crucial but the decisions just get harder. ***– MRAM***

Meador KJ, Baker G, Browning, N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW for the NEAD Study Group.
Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs.
NEJM
2009; 360:1597-1605.

MULTIPLE SCLEROSIS: A convenient pill?

Time was when people with multiple sclerosis would have been content with anything that was effective as a treatment for their disease, no matter how unpalatable. Over the years, people ingested snake venom, stung themselves with bees, drunk bottles of coke laced with venlafaxine, immersed themselves in hyperbaric chambers.....But now the concept of convenience has crept into the lexicon of multiple sclerosis therapeutics. And what could be more convenient than a pill? No more needles in the bathroom, or monthly visits to the hospital to spend all day waiting for the Tysabri infusion. And there is no shortage of contenders to be the first pill to be licensed for multiple sclerosis: fingolimid, cladribine, and now fumarate.

What is fumarate? Nothing to do with smoking. It activates the nuclear-factor-E2-related factor-2 (Nrf2) transcriptional pathway, -as you can tell from another review in this journal ("Oh Glia!") – may mean that the drug could be both anti-inflammatory and neuro-protective, which would be handy. 257 patients with relapsing-remitting multiple sclerosis were given fumarate in three different doses, and compared to a placebo, for 24 weeks then there was a "safety extension study" where everyone got active drug. The principal outcome measure was the total number of gadolinium-enhancing lesions added up from four scans done throughout the first 24 weeks. On the highest dose of fumarate (240mg tds) there was a statistical difference from placebo: a reduction in new lesion total by 70%. Before getting too excited, let me remind you that this is about the same as interferon-beta's effect on MRI scans. The lower doses did not make the statistical cut. There was no effect on any clinical outcome, although to be fair the group taking the highest fumarate dose trended towards the lowest relapse rate. Taking the drug did not seem to cause much bother; some flushing and GI upset only. My bottom line is that fumarate, for all its Nrf2-thingummy, shows no sign of being any more efficacious than the interferons, so far at least. So, a lot of time and money is being put into phase 3 trials, plans to get the drug licensed and all the rest.... for convenience. But it is not exactly convenient to have inadequately treated multiple sclerosis. ***– AJC***

Kappos L, Gold R, Miller DH, Macmanus DG, Havrdova E, Limmroth V, Polman CH, Schmierer K, Yousry TA, Yang M, Eraksoy M, Meluzinova E, Rektor I, Dawson KT,Sandrock AW, O'Neill GN; BG-12 Phase IIb Study Investigators
Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study.
LANCET
2008 Oct 25;372(9648):1463-72.

SonoSite's MicroMaxx® system is the right choice for regional nerve blocks

Russells Hall Hospital in Dudley has recently acquired a MicroMaxx® system, and will soon add a new M-Turbo® system, to its portfolio of SonoSite point-of-care ultrasound units, specifically for the administration of regional nerve blocks in theatre.

Dr Wilson Thomas is a consultant anaesthetist at Russells Hall, and explained the benefits of the MicroMaxx system. "I have been working with SonoSite for over four years, since I first trained in using ultrasound needle guidance for nerve blocks. I also regularly use the MicroMaxx system in theatre for orthopaedic patients undergoing limb surgery, to administer cervical plexus blocks for carotid

endarterectomy and in guiding the needle during tranverse abdominal plane (TAP) blocks. Using ultrasound guidance is a safer technique, as you can visualise exactly where the needle is with respect to the nerve, and avoid vital tissue structures. We chose the MicroMaxx system because of the excellent resolution, which makes it very good for nerve blocks. We use a 13 MHz probe, and the image quality is very clear. It is a very robust system, and easy to manoeuvre, even mounted on a trolley; it has a quick start up and is easy to use - all important features in theatre."

For more information T. 01892-600930.

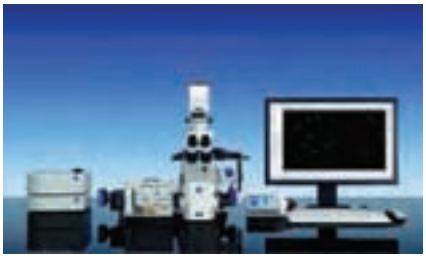
Carl Zeiss launches Cell Observer SD to Capture Life's Transient Events

In the last few years live cell imaging applications have increased dramatically, led by an array of new fluorochrome molecules with outstanding quantum efficiency and stability. However, capturing fast cellular processes without damaging the cells under observation and whilst maintaining the optimum conditions for survival over a long period is still a challenge.

Carl Zeiss has responded with the launch of the Cell Observer SD, which fully integrates the CSU-X1 confocal scanning unit manufactured by Yokogawa Electric Corporation (Japan) and, for the first time, optimises the unit's features for the exacting requirements of live cell imaging. With Cell Observer SD, confocal observation and documentation of experiments on living cells over a long period of time and with high frame rates is possible.

"The combination of high resolution, sensitivity and speed is essential to track the communication and interaction of cells, organisms and structures," says Aubrey Lambert, Carl Zeiss UK. "Cell Observer SD makes that possible to deliver outstanding image quality and exceptional sensitivity and open up a new time window for confocal microscopy." Cell Observer SD is ideal for research in molecular cell biology, developmental biology, neurobiology and live cell imaging in general. Together with the entire line of incubation accessories from Carl Zeiss, Cell Observer SD enables users to observe living specimens for hours without damaging them. All major incubation parameters such as temperature and CO2 content are saved automatically together with the image data and all settings are also made via the AxioVision software.

For more info E. micro@zeiss.co.uk



Zeiss introduces Laser TIRF 3 Imaging System for targeted brain lesion treatments

With the introduction of the Laser TIRF 3 microscope system, Carl Zeiss significantly enhances the capability of scientists to visualise near-cell membrane dynamic processes while maintaining optimum specimen incubation conditions. Single molecule dynamic processes in cell-free systems may also be observed and, in combination with other techniques such as Atomic Force Microscopy (AFM), the new microscope provides a complete solution for users in the life sciences, biochemistry, molecular biology and biophysics arenas.

The Laser TIRF 3 maintains Carl Zeiss' long-standing commitment to system flexibility. A range of incubation options maintain viable conditions for live cell experiments. Together with the Definite Focus module, users can be assured of accurate quantitative data over long time periods. The new laser module may be equipped with up to four solid-state lasers, is AOTF-controlled (Acousto-Optical Tuneable Filter) and may be operated entirely from the AxioVision software interface.

The TIRF slider is available in two versions; either manual or fully-motorised and software controllable. The motorised version permits a

given illumination angle to be set with significantly greater accuracy and speed than other current systems and the reproducible angle setting results in reproducible penetration depths for the light beam. Together with the corrected beam-path and special filter sets, the apochromatically-corrected optics of the TIRF slider guarantee maximum image quality.

AOTF control and angle setting are integrated into the 'Fast Image Acquisition' module of the AxioVision software, enabling significantly more high resolution images to be acquired within any given timeframe.

For more information E. micro@zeiss.co.uk

RANSOM study shows non-adherent patients can pay with their lives!

The recently published RANSOM study looked at the effect of non-adherence in over 33,000 patients and they concluded that it is vital for physicians to promote treatment strategies for epilepsy that offer an increased likelihood of adherence.

After reviewing data on more than 150,000 patient years they found that 26% of patients had at least 20% deficit in the quantity of AED's dispensed versus that prescribed. These non-adherent patients had a 222% increase in mortality compared to the compliant group.

The non-adherent group also showed a 21% increase in fractures, a 50% increase in emergency department visits, an 86% increase in hospitalisations and a 108% increase in motor

vehicle accidents. (Ref: Faught E et al (2008) Neurology 71(20) 1572-8). It is clear that non-compliance is widespread and that this can lead to serious consequences.

Previous studies have shown that compliance can be improved by making the AED easier to take including moving to a simple once a day dose regimen. Formulations have been developed for some AED's to make this possible.

For more information on how compliance may be improved with sodium valproate contact Beacon Pharmaceuticals on T. 01892-600930.

Benefits of Subtilis® shown in new DVD from The Electrode Company

The Electrode Company Ltd (TEC) specialises in non-invasive monitoring, optical sensors and high performance pulse oximetry. TEC has now developed Subtilis, a truly diagnostic pulse oximetry system, that calibrates itself both to the sensor and to the patient's variables. As a result, a new, brief DVD is now available on this unique non invasive blood spectrometry device.

The DVD is all about receiving something which is measurably different and better than conventional pulse oximetry, namely blood spectrometry. This is the next generation of blood oxygenation monitoring technology. The DVD covers a number of areas, including:

- How pulse oximetry has become well established, resulting in clinicians reliance on it for vital medical decisions.

- How 36 UK hospitals have been surveyed, and reveal that up to one third of pulse oximeters could impact adversely on clinical decisions.
- How in a patient undertaking breathe down exercises to deoxygenise his blood, a 'high' reading pulse oximeter can become even less reliable as SpO_2 falls.
- How blood levels of melanin interfere with the absorption of light, thereby causing pulse oximetres to read 'high'. Subtilis adjusts to varying levels of melanin, thus providing precise and personalised blood oxygen monitoring.

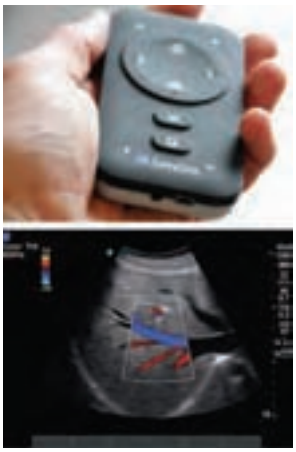
For your copy of the DVD or for more information, visit www.electro.co.uk or T. 01291 650279.

Powerful new technology for M-Turbo™ system

SonoSite, specialist in hand-carried ultrasound for point-of-care medicine, has developed SonoGT™ Global Targeted technology, which capitalises on the power of the M-Turbo platform to provide point-of-care ultrasound with targeted solutions. SonoGT offers a new level of colour flow imaging, wireless connectivity and workflow integration for acute point-of-care ultrasound, such as anaesthesia, emergency medicine and critical care.

The SonoGT platform offers ColorHD™ technology, a proprietary, colour Doppler algorithm, to increase colour performance, sensitivity and frame rates, for increased diagnostic information and better visualisation of colour flow. Wireless solutions include SonoRemote™ control, which untethers the clinician from the ultrasound system during procedures to increase ergonomic comfort, and is expected to be very useful in sterile field procedures. SonoRoam™ technology allows wireless image transfer from the M-Turbo system to a PACS system or to a personal computer so that clinicians can quickly retrieve the information from any location. For improved workflow integration, new features facilitate seamless clinical integration of ordering, scheduling, image acquisition, storage, viewing and billing of patient procedures. Patient demographics can be entered before, during or after the examination, allowing flexibility in time-critical situations.

For more information contact T. 01462 444 800, E. europe@sonosite.com, www.sonosite.com



MD Anderson Cancer Center acquires Leksell Gamma Knife Perfexion for targeted brain lesion treatments

The University of Texas MD Anderson Cancer Center (Houston, Texas) will add Elekta's Leksell Gamma Knife® Perfexion™, an advanced radiosurgery device specifically designed to treat one or more lesions in the head in a single session, to their radiation oncology department.

"Leksell Gamma Knife Perfexion suits our clinical needs," says Eric Chang, MD, Director of MD Anderson's Central Nervous System Stereotactic Radiation Program. "The device will be used initially to treat primary brain and skull base tumours as well as single and multiple brain metastases in a single session."

Designed to extend the system's reach down to the level of the skull base and cervical spine, Perfexion was scheduled to be delivered to MD Anderson by March 2009 and should be operational by mid-2009, he adds.

"Elekta is committed to supporting radiosurgery and neuro-oncology by providing highly refined tools that support specific clinical objectives, yet share a common foundation in terms of image and information management," says Joseph K Jachinowski, President and CEO of Elekta North America. "The result is a complete line of stereotactic treatment solutions designed to meet the goals of any type of radiosurgery programme."

For further information, E. michelle.lee@elekta.com

If you would your news to feature in ACNR, please contact Rachael Hansford, T. 01747 860168, E. rachael@acnr.co.uk

MS patients treated with Tysabri® remain free of disease activity for two years

Biogen Idec and Elan Corporation, plc recently announced that five-times as many multiple sclerosis (MS) patients taking TYSABRI® (natalizumab) were free from disease activity versus placebo in the overall patient population. Results from this retrospective analysis showed that two years after beginning treatment with TYSABRI, 37% of patients remained free of disease activity, compared to 7% of placebo-treated patients. 64% of patients showed no sign of relapse or sustained disability progression and 58% were free of radiological disease activity. Both of these measures were used to define freedom from disease activity in this analysis of the AFFIRM clinical trial. These data were published in the March 2009 issue of The Lancet Neurology.

The analysis also suggests that the efficacy of TYSABRI may increase over time. The data show the proportion of MS patients who were free of disease activity in the TYSABRI group were greater in the second year than in the first year, while the number of MS patients in a placebo group free of disease activity stayed about the same in the second year.

For more information visit www.tysabri.com www.biogenidec.com or www.elan.com

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Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. Children (12 - 18 years) No specific studies. Data suggests safety profile similar to that seen in adults. Children (<12 years) Not recommended. Elderly No specific data. Impaired renal function No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). Pregnancy. **Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. >1%: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Do not freeze. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £524.31. **Product Licence Number** – 10921/0023. **Further Information** – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. **Date of Preparation** – March 2009.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.

Date of Preparation: March 2009 C0309/566a

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