ISSN 1473-9348 VOLUME 9 ISSUE 5 NOVEMBER/DECEMBER 2009

ACNR

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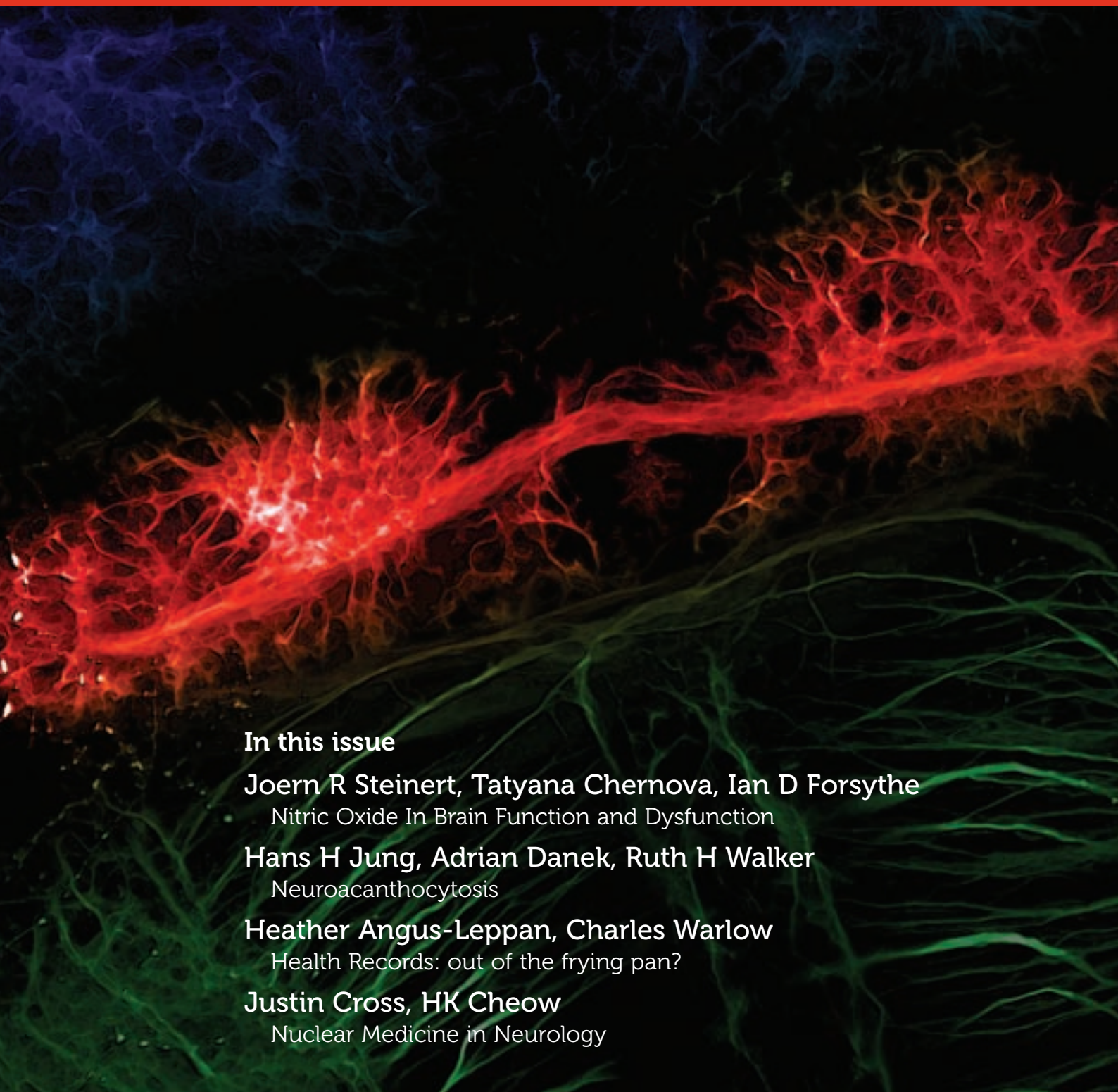
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

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Editorial board and contributors

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David J Burn is the editor of our Conference News Section and is Professor in Movement Disorder Neurology & Honorary Consultant, Newcastle General Hospital. He runs Movement Disorders clinics in Newcastle-upon-Tyne. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

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ACNR

Published by Whitehouse Publishing,
1 The Lynch, Mere, Wiltshire, BA12 6DQ.
Publisher. Rachael Hansford
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ADVERTISING
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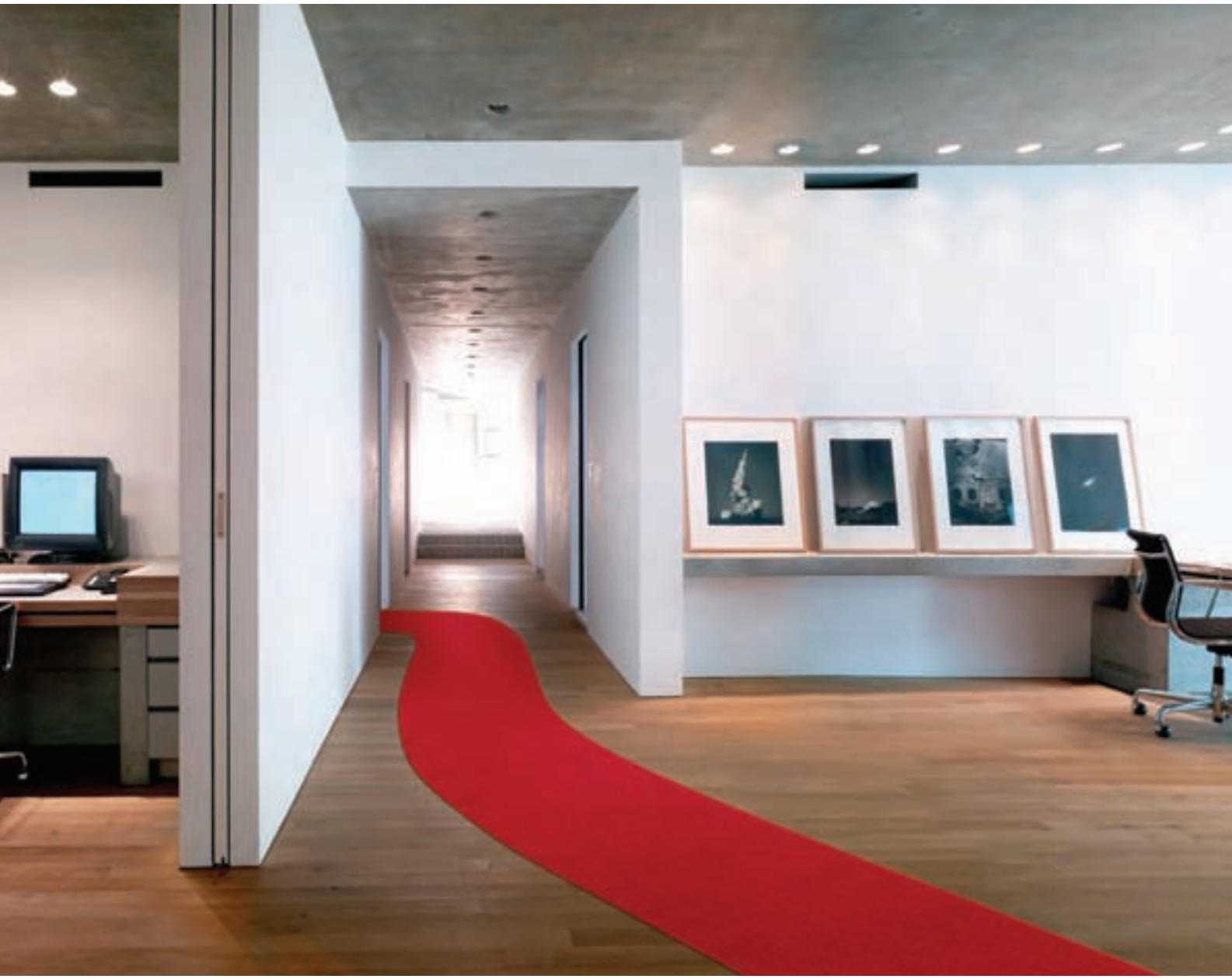
DESIGN & PRODUCTION DEPARTMENT
E. design.dept@sky.com
PRINTED BY
Manson Group Ltd. Tel. 01727 848 440

Cover picture: Neuropil in a zebrafish epithalamus (40x) – Karina Palma, Laboratory of Experimental Ontogeny, Universidad de Chile, Santiago, Chile. Image of Distinction from the Nikon Small World 2009 Competition.



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Chorea as a clinical sign is most commonly seen in patients with PD on L-dopa therapy, but outside of this, it is normally associated with Huntington's Disease (HD). However, there are a range of other rare genetic disorders which can have chorea as part of their clinical features along with the presence of acanthocytes. This is the topic for the excellent review by Hans Jung, Adrian Danek and Ruth Walker as they delineate the key features of these conditions.

Nitric oxide (NO) has been a molecule of great interest to the neuroscientific community for many years, and in an excellent review article by Joern R Steinert, Tatyana Chernova and Ian D Forsythe in this issue of ACNR, we get an up-to-date account of how this molecule may be important to CNS function in health and disease. In particular, the capacity of the NO to diffuse across membranes means that it has great potential to influence a large number of neural elements and as such may serve a unique function in controlling the excitability of a swathe of synaptic connections and networks. How this plays out in disease pathogenesis is not clear, but the expert authors of this review, marshall this complex field to give us a clear, succinct account of the possible mechanisms being investigated.

Andrew Larner once more allows us to explore all aspects of his mind as he gives us two short pieces on the utility of board games as a means of exploring neuropsychological deficits in patients, as well as providing an account of illusory visual spread by Margiad Evans.

Justin Cross and HK Cheow this time take Nuclear Medicine as their topic in the ongoing series on Neuroradiology. In this latest article, Justin and HK explain the basis for the technique and how it has, and will be sued in neurological practice. As with all articles in this series, it is easy to follow and extremely informative.

In this issue of ACNR, we have the first article in our new Neuropaediatric series edited by Dr Anna Maw. This new series aims "to provide practical guidance and information on common paediatric neurological conditions which will be useful in your daily practice". In the first in the series, this is fabulously exemplified as we are taken through the approach to the paediatric patient with neurological problems and the challenges that the younger patient throws up.

The challenge of pursuing a clinical academic career has never been an easy one, but in the last ten years this has become more problematic as the training of doctors changes and academic research is relegated to a level of almost non-existence. In the Training series edited by Boyd Ghosh, we have Chris Butler writing about the attempts that have recently been made to try and resurrect this vital area of medicine through the creation of Academic Clinical Fellowships and Lectureships. This excellent account highlights the origins of this scheme and how it has been conceived to work. In contrast, Jane Alty in the ABNT section explains the (r)evolution in thinking that has led to the Less Than Full Time (LTFT) training scheme that now exists and which is attracting much attention from many neurological trainees. Jane explains how the system works and how you can go about finding out more about it.

Heather Angus-Leppan and Charles Warlow in this issue of ACNR also talk about how we can best develop central sets of notes which allows easy access and yet is secure enough to protect patients – a challenge which if conquered would have major advantages to all in clinical practice.

Trying to stay up to date in neurology is hard and it is useful to be told by Sara Clarke and David Chadwick about a new development called NHS evidence. This new initiative began some 10 years ago but has now evolved to the level of centralised up-to-date accounts of data summarising best clinical practice. Whilst it is increasingly difficult to master all the data that is out there, this is useful second step in that process, after reading ACNR of course!

In our historical series, J Pearce tells us about the origins of adrenaline taking us from observations made in the 18th century to the Nobel prize winning work of Henry Dale. En route, we have a wonderful account of a hugely significant meeting between an enthusiastic physician from Harrogate and a grumpy Professor of Medicine in London.

Finally, we have our usual round up of conference and book reviews, and we would also like to welcome Dr Mike Zandi to the editorial team. . ◆

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

With her fear and denial of epilepsy behind her, Andrea looks forward to the possibilities ahead.

At UCB CNS, our passion for delivering innovative solutions is driven by the desire to make a real difference to the lives of people with epilepsy who inspire us, like Andrea.

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New member of the team for ACNR

We are delighted to welcome Dr Mike Zandi to the team at ACNR, as a co-editor to assist Roger Barker and Alasdair Coles. Mike is an Honorary Specialist Registrar in Neurology at Addenbrooke's Hospital, Cambridge and a Research Fellow at Cambridge University. His research interests are in neuroimmunology, biomarkers and therapeutics in particular.

You can contact him at msz20@cam.ac.uk with your comments and suggestions for ACNR.

Informa wins at BMA book awards

Informa Healthcare have won top honours at this year's BMA Medical Book Competition. Dr Eduardo E Benarroch's *Mayo Clinic Medical Neurosciences: Organized by Neurologic Systems and Levels* won first prize in the Neurology category.

"We are delighted with this award from the highly respected BMA Medical Book Competition," says Lindsey Roberts, CEO at Informa Business Information. "Winning top honours and commendations in four categories is testament to the relevance of our titles as well as to the talent of our authors, editors and publishers."

Mayo Clinic Medical Neurosciences aims to set a new standard for excellence in introductory medical neuroscience education. The authors utilise unique skill-building methods that facilitate learning through problem solving, while keeping students engaged and focused. "This is a refined, very informative, and easily readable text. I liked the clarity of the writing and illustrations. It was a good balance of information and detail," says Dr Morrison, Neurologist from the BMA Awards Programme. "I very much liked this text - it is the highlight of the BMA Medical Books competition for me this year. I will use this as a clinical neurologist, and I will encourage my colleagues to do the same."

"The fact that this book is written by physicians at the Mayo Clinic – one of the most recognised and influential medical institutions in the world – and also that it has been recognised by leaders in its field as a stand-out publication would be enough to ensure pride of place in Informa's catalogue," explains Lindsey. "Winning the BMA Medical Books Award makes it very special, indeed."

For further information T. 020 7017 5000, E. pjb.enquiries@informa.com

Professor Sander receives American Epilepsy Society 2009 Clinical Science Award

Professor Josemir (Ley) W Sander, of the Department of Clinical and Experimental Epilepsy (UCL Institute of Neurology, London) has been named recipient of the 2009 Epilepsy Research Recognition Award for Clinical Science conferred by the American Epilepsy Society (AES). The award recognises Professor Sander for pioneering research into epilepsy, its treatment and consequences in developing countries around the world.

The Epilepsy Research Recognition Award is part of the AES's public recognition programme to encourage and reward clinical and basic science investigators whose research contributes to the effort to understand and conquer epilepsy. This year's award for clinical science will be presented on December 7th during the Society's 63rd Annual Meeting in Boston.

Professor Sander's research is focused on epilepsy outcomes in terms of remission, as well as premature death and its causes; other health complications associated with the disorder; genetic aspects of epilepsy; and the management of epilepsy in resource-poor settings. Professor Sander holds the UCL Established Chair of Epilepsy, funded by the National Society For Epilepsy.

STARS Founder and CEO awarded MBE

Trudie Lobban, Founder and Chief Executive of STARS (Syncope Trust And Reflex anoxic Seizures) was awarded an MBE for her work for STARS and services to Healthcare. The charity was founded in March 1993 after her daughter, Francesca was diagnosed as having RAS.

Trudie and her daughter Francesca.

John Camm, Professor of Clinical Cardiology at St George's University of London Hospital said, "There is no one more deserving of this honour. Trudie has worked hard for children with the symptoms of sudden loss of consciousness. I am very impressed by the energy and dedication that Trudie gives to this and her other charities in the field of heart rhythm disturbances. Her work has improved the quality of life for so many."

Professor Jon Driver awarded a Professorship

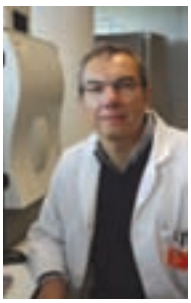
Professor Driver (Wellcome Department of Imaging Neuroscience, UCL Institute of Neurology) is one of a handful of leading scientists to receive the prestigious award, which has been made in celebration of the Royal Society's 350th anniversary.

The award will allow Professor Driver to devote himself to his research on perception, selective attention and multisensory integration – the interplay between different senses – in the normal and damaged human brain.

Professor Driver will hold the award for the next decade, in the Wellcome Trust Centre for Neuroimaging at UCL, and in the UCL Institute of Cognitive Neuroscience, where he was previously Director.

Lord Rees, President of the Royal Society, said, "The individuals selected as Research Professors for the Society's anniversary year are the epitome of world-class scientists. All have already made highly distinguished contributions to their fields. We hope that these professorships will offer them the optimal opportunity to enable them to make further breakthroughs that will enrich science and society."

Professor receives Fulbright award to further Muscular Dystrophy research



University of Portsmouth Professor Darek Gorecki has won a Fulbright Distinguished Scholarship, one of just about two awards conferred annually to outstanding UK professionals or academics by the Fulbright Commission. The awards are highly competitive and previous Fulbright Scholars include 39 Nobel prize-winners.

The award will fund the professor to travel to the US to partner with Harvard, where he will continue his research into the hereditary and lethal muscle weakening disease, muscular dystrophy.

Professor Gorecki is undertaking further research into the role of a specific protein, known as the P2 receptor. The aim is to understand how the absence of dystrophin, the protein which muscular dystrophy sufferers have a deficiency of, affects the production and function of this receptor. He believes that abnormalities in the P2 receptor found in dystrophic muscle cells may be contributing to the progressive muscle damage.

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1. Brin MF *et al Neurology* 1999 **53**(7) 1431-1438.
2. Pappert EJ and Germanson T. *Mov Disorder* 2008 **23**(4) 510-517.
3. Lew MF *et al* Poster presented at the AAP Meeting, Honolulu. January 28-31, 2009.

NEURO-UK2143d
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Nitric Oxide in Brain Function and Dysfunction

Dr Joern R Steinert
is an Investigator Scientist at the MRC Toxicology Unit. He completed his PhD at Kings College London in 2001, exploring vascular dysfunction associated with pre-eclampsia and nitric oxide dysregulation. His neuroscience interests developed with investigations of Drosophila neuromuscular transmission in Heidelberg and he recently returned to studies of nitrergic signalling in the mammalian CNS.

Dr Tatyana Chernova
is an Investigator Scientist at the MRC Toxicology Unit. After receiving her medical degree she continued studying pre-eclampsia and completed a PhD on pre-clinical diagnostics of the condition in 1991. Her current scientific interests lie in explorations of neurodegeneration and heme signalling in the central nervous system.

Prof Ian D Forsythe
received a PhD in Neurophysiology from Southampton University in 1983, a Chair of Neuroscience at the University of Leicester in 2000 and joined the MRC Toxicology Unit as a Group Leader in 2005. His research interests focus on synaptic transmission and the role of voltage-gated ion channels in regulating neuronal excitability in health and disease.

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Neurotoxicity at the Synaptic Interface, MRC Toxicology Unit, Hodgkin Bldg, University of Leicester, LE1 9HN. UK.
Email: IDF – idf@le.ac.uk

Nitric Oxide Signalling: Nitric oxide (NO) is the signalling molecule originally identified as endothelium-derived relaxing factor (EDRF) mediating relaxation of blood vessels.[1] It is a small, highly diffusible and reactive molecule with a short life-time, generated from arginine by the cytoplasmic enzyme nitric oxide synthase (NOS). Three NOS genes with distinct tissue localisation and properties are known, namely: endothel, inducible and neuronal NOS (eNOS, iNOS & nNOS, respectively). Activation of eNOS and nNOS are classically Ca^{2+}-dependent, with nNOS being closely coupled to Ca^{2+}-permeable NMDA receptor (NMDAR), both of which are linked to postsynaptic densities (PSD-95) of the CNS through their mutual PDZ binding motifs.[2] eNOS and nNOS generate low nanomolar concentrations of NO, whereas iNOS can produce micromolar levels. Such high concentrations affect down-stream signalling mechanisms, with low concentrations being neuroprotective and mediating physiological signalling (e.g. neurotransmission or vasodilatation) whereas higher concentrations are neurotoxic. Excessive activation of iNOS has been linked to several neurodegenerative disorders (see below).

The major physiologically relevant receptor for NO is soluble guanylyl cyclase (sGC) which mediates the production of cGMP from GTP. Downstream transduction can be via cyclic nucleotide-gated ion channels, activation of protein kinase G and protein phosphorylation, or direct actions on proteins via S-nitrosylation and nitrotyrosination (Figure 1). Metabolism of cGMP by phosphodiesterases (PDE) suppresses NO/sGC signalling. There are 11 PDE genes with specific differential expression in nervous tissue. Signalling activity will then reflect the equilibrium between cGMP synthesis and degradation; for instance sildenafil/Viagra is an antagonist of PDE5, reducing degradation so that lower activity of sGC can achieve sufficient signalling to relax corpora cavernosa muscle and achieve erection.

There are several well characterised competitive antagonists for nNOS and sGC, and some allosteric modulators allowing pharmacological intervention. But physiological actions of NO are achieved at very low concentrations, so proof of endogenous

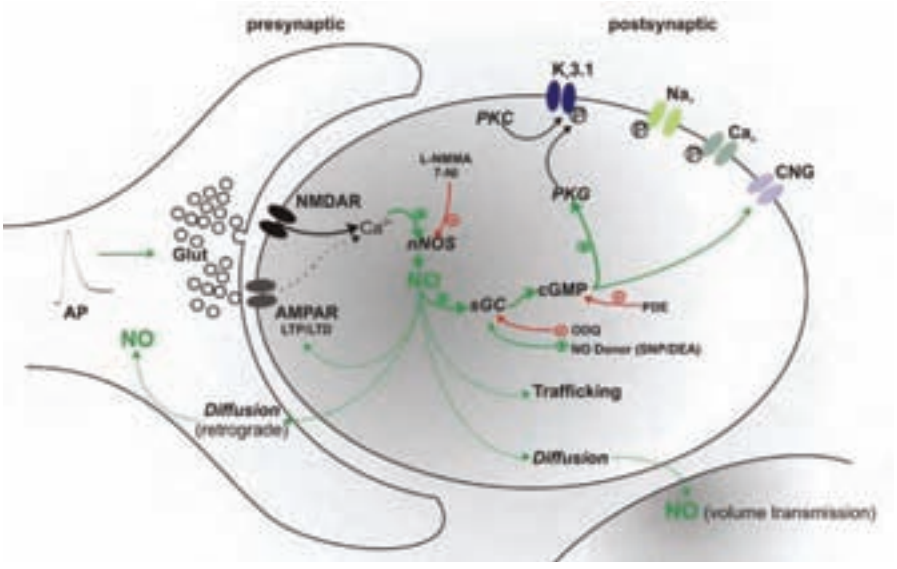

Figure 1: The NO signalling pathways
Nitric oxide, produced from the amino acid arginine by nNOS, has various physiological effects. Synaptic glutamate release activates postsynaptic AMPA and NMDA receptors (AMPAR, NMDAR) leading to Ca^{2+}-induced nNOS activation. This NO will diffuse and subsequently activate sGC to produce cGMP (from GTP) which has several signalling roles, including activation of PKG or cyclic nucleotide-gated ion channels. NO will act locally at the source of production and in neighbouring neurons through a process of volume transmission to affect postsynaptic neuronal excitability or presynaptic neurotransmitter release. Pharmacological studies use 7-NI and L-NMMA as competitive NOS antagonists or ODQ as a sGC inhibitor (red arrows) while there are many different NO donors (e.g. SNP or DEA-NONOate) which generate NO independent to NOS and thereby activate sGC. Other powerful modulation is achieved by PDEs, mediating breakdown of cGMP and reduce NO/sGC signalling. Several ion channel targets for nitrergic signalling are indicated (AP – action potential, Cav - voltage gated calcium channel, CNG - cyclic nucleotide-gated ion channels, Kv3.1 – voltage gated potassium channel, L-NMMA - NG-Methyl-L-arginine, LTD – long term depression, LTP – long term potentiation, Nav – sodium channel, ODQ - 1H-[1,2,4]Oxadiazolo[4,3-a]quinoxalin-1-one, PDE – phosphodiesterase, SNP - Sodium nitroprusside, 7-NI - 7-Nitroindazole).

NO generation by physiological stimuli is difficult. nNOS is widely distributed across the brain, but it is normally expressed in a subpopulation of neurons within a given region. Its mobility, unconstrained by cell membranes, allows action across a broad volume (hence the term 'volume transmitter') limited by inactivation (e.g. scavenging or degradation). It has long been postulated that NO could also act as a retrograde messenger, mediating transmission from target neurons back onto the synapse and regulating synaptic plasticity (for example in the hippocampus and cerebellum).

Nitric oxide signalling in the brain can modulate a range of processes such as various forms of plasticity (long term potentiation and depression, LTP and LTD) regulating rhythmic activity, including gut motility, respiratory rhythm, circadian rhythms, locomotor and thalamocortical oscillation. There is strong evidence for involvement in learning and memory mechanisms through mediation of specific forms of LTP in the cerebellum,[3] hippocampus[4] and neocortex[5] and LTD in the cerebellum. The cellular and molecular targets of nitrergic signalling pathways are also diverse and as yet incompletely resolved; there is evidence for modulation of presynaptic transmitter release at excitatory glutamatergic and inhibitory GABAergic synapses, postsynaptic AMPAR phosphorylation and trafficking, calcium channels, potassium channels and interactions with other signalling pathways (such as mGluR, endocannabinoid and catecholamine). Our recent work in the auditory brainstem has highlighted the role of NO in regulating postsynaptic excitability via Kv3 voltage-gated potassium channels in activity-dependent auditory processing. Enhanced synaptic transmission at the calyx of Held synapse onto principal cells of the medial nucleus of the trapezoid body (MNTB) causes NMDAR-mediated and calcium-dependent activation of postsynaptic nNOS. The NO acts in the target neuron and surrounding neurons to suppress voltage-gated potassium channels (particularly Kv3) through a slow time-course (15-30 minutes) phosphorylation mechanism which has a homeostatic-like function in matching postsynaptic excitability to the synaptic traffic.[6] The broad expression of Kv3 channels in fast-spiking interneurons throughout the brain suggests this modulation might be a general mechanism by which NO influences synaptic processing at a postsynaptic rather than a presynaptic site.

An important consideration from the perspective of disease is the extent to which NO mediates signalling between the vasculature, neurones and glial cells, and involvement of microglia and the immune system in nitrergic signalling of the brain. Given the ease of NO diffusion, a key future challenge is to understand the extent to which over-production of NO in one system (endothelium, immune) can 'spill-over' into triggering brain dysfunction and neurodegeneration.

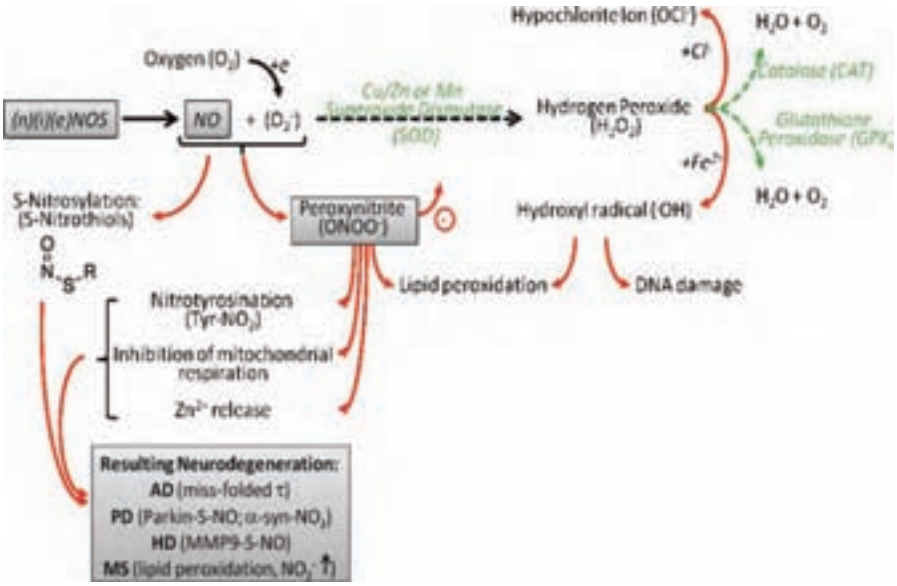

Figure 2: Oxidative and nitrosative stress: pathological consequences of NO generation.
NO will react with superoxide anions (O_2^-) to form the highly reactive peroxynitrite ion ($ONOO^-$). $ONOO^-$ is responsible for protein nitrotyrosination and inhibits mitochondrial respiration. NO itself nitrosylates protein residues leading to the formation of S-nitrothiols. All of the above effects of NO have been implicated in Alzheimer's, Parkinson's and Huntington's disease as well as in multiple sclerosis. There are several cellular antioxidant enzymes (green) which break down reactive oxygen species, namely: Cu/Zn or Mn superoxide dismutase which converts O_2^- into hydrogen peroxide (H_2O_2). H_2O_2 itself can form hypochloride ions or the highly reactive hydroxyl radical ('OH) responsible for lipid peroxidation and DNA damage. Further antioxidant actions (indicated by the dotted arrows) of either Glutathione Peroxidase or Catalase lead to the formation of H_2O from H_2O_2.

So what are the processes whereby NO signalling might contribute to disease?

Production of Reactive Nitrogen Species (RNS): The term nitrosative stress describes this ability of NO and its derivatives (RNS) to damage proteins and DNA. A primary reaction is reaction of NO and O_2- to form peroxynitrite ($ONOO^-$, Figure 2) decreasing the bioavailability of NO.[7] Nitrosylation and nitrotyrosination of proteins are important for the physiological and pathological roles of NO. Nitrosylation is the reaction of NO with cysteine to form nitrosothiols[8] and nitrotyrosination is the reaction of tyrosine with $ONOO^-$ to form 3-nitrotyrosine.

NOS can also directly contribute to O_2^- production since cells with deficient cofactor tetrahydrobiopterin (BH4) or substrate (arginine), cannot catalyze the five-electron oxidation of L-arginine into L-citrulline (thereby generating NO), but can still receive electrons from NADPH and donate them to O_2, reducing it to form O_2^-[9] so further enhancing peroxynitrite production. It is interesting to note that both Alzheimer's (AD) and Parkinson's disease (PD) are associated with a BH4 deficiency.[10,11]

Mitochondria and oxidative stress: Generation of reactive oxygen species (ROS) occurs in every eukaryotic cell; electron 'leakage' from the mitochondrial electron transfer chain reacts with molecular oxygen to make superoxide (O_2^-, Figure 2). Normally this is metabolized by superoxide dismutase (SOD) to H_2O_2, which is further degraded by the antioxidant enzymes, catalase or glutathione peroxidase. Thus mitochondria are also a potential source of RNS. NO and $ONOO^-$ both inhibit the mitochondrial respiratory chain, reducing ATP production[12,13] so that susceptibility to neurodegeneration shows complex dependence on local metabolic rates, oxygen availability, antioxidant activity (reduced glutathione) and cell stress resistance signalling.[14] Other effects of NO/$ONOO^-$ include release of Zn^{2+} from internal stores (such as metallothionein) with concomitant formation of S-nitrosothiol and neurotoxicity.[15,16] Free Zn^{2+} induces respiratory block, opening of the mitochondrial permeability transition pore (mPTP), cytochrome c release, generation of ROS, and p38 MAP kinase activation leading to caspase-independent K^+ efflux with cell volume loss and apoptotic-like death.[17]

Further metabolic compromise may result from mitochondrial fragmentation. This is fast, occurring within minutes after NMDAR activation or NO exposure, and is considered a prelude to neurodegeneration and cell death.[18] Increased mitochondrial fission in response to NO has been reported in AD, PD, amyotrophic lateral sclerosis (ALS) and

NO affects the balance between healthy signalling and neurodegeneration

Huntington's disease (HD).[19] Fragmentation of other organelles, such as the Golgi apparatus is known to occur during apoptosis in several neurodegenerative disorders. NO-mediated Golgi fragmentation is downstream of NMDAR activation and precedes neuronal cell death.[20]

Role in neurodegenerative disease: NO generation in the brain is mediated by NMDAR activation, so excitotoxicity–related neuronal injury could have a nitrergic component. Endogenous levels of oxidizing agents, NO and Zn^{2+} inhibit excessive excitation of NMDAR and limit excessive influx of Ca^{2+} via the NMDAR. Such feedback could ameliorate NMDAR-mediated neurotoxicity. High-affinity Zn^{2+} inhibition, redox modulation or S-nitrosylation of the receptor are mediated with the involvement of at least seven cysteine residues on NMDAR subunits.[21]

NO signalling contributes to several neurodegenerative diseases[22] through production of ROS/RNS and subsequent oxidative/nitrosive stress. Excessive NO production from inflammation is a significant factor in AD, PD, ALS, multiple sclerosis (MS) and HD, and also in the brain damage following ischaemia and reperfusion. Enhanced nitrotyrosine immunoreactivity and oxidative protein damage are evident in brains from AD patients,[23,24] while inhibition of mitochondrial cytochrome c oxidase and enhanced H_2O_2 production in amyloid β (Aβ) mutant mice suggest mitochondrial involvement in ROS generation.[25] The cerebral cortex of patients with AD has high protein nitrotyrosination[26] and nitrated proteins are associated with Aβ deposition[23] along with nitrotyrosination of Tau protein[27] and synaptophysin; consistent with a dysfunction in cholinergic synaptic transmission.[28] Most recently S-nitrosylation of Drp1 has been shown to mediate mitochondrial fission and neuronal damage caused by Aβ.[29]

Exposure of experimental inflammation models to NO cause axonal degeneration, especially when accompanied by propagating electrical activity.[30] Several potential pathogenic mechanisms have been suggested. In PD, S-nitrosylation of Parkin[31,32] initially increases but later decreases Parkin activity. Alpha-synuclein (α-syn) a protein associated with synaptic terminals and synaptic transmission, is heavily nitrated at 4 tyrosine residues and this contributes to aggregation.[33] Nitrated α-syn is more resistant to proteolysis and has reduced lipid binding and solubility.[34] Other contributing mechanisms could include metabolic compromise by RNS (via block of mitochondrial complex I) in substantia nigra[35] since MPTP-induced neuronal loss in this PD model was slowed by competitive nNOS antagonists[36] and nNOS inhibition blocked MPTP-mediated decrease in striatal dopamine levels in mice.[37]

We conclude that nitric oxide has broad physiological actions across many organ systems, in the brain this includes modulation of synaptic transmission as a 'retrograde messenger', but it is also a 'volume transmitter', mediating activity-dependent changes in postsynaptic excitability (Figure 1). Generation of RNS, involvement in oxidative stress and the propensity for 'spill-over' between endothelium and immune signalling into the neuronal environment suggest that we might expect dysfunctional nitrergic signalling to have broad involvement in neurodegenerative disease and these possibilities are under increasing investigation. ◆

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Illusory Visual Spread or Visuospatial Perseveration

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> Another very sudden psychic experience was seeing the aura of a dog… The dog was a black labrador, fat and glossy. I was walking into the village when suddenly he appeared with a bluish-lilac halo all round him in pure daylight. …I was not frightened but …strangely delighted …and coming back from the shop, was disappointed to see the dog a plain black body again without his incandescent background.[1]

This extract might initially prompt concerns in some readers about the author's mental health. Certainly Margiad Evans (1909-1958) did suffer from epilepsy, symptomatic of an underlying brain tumour, which blighted her creative powers in the last years of her life.[2] However, this description from her book describing her experience of epilepsy may well represent an account of a form of visual perseveration known as illusory visual spread or visuospatial perseveration.

Critchley noted a number of unusual subjective visual experiences which might fall under the rubric of "visual perseveration", viz.:[3]

- The hallucinatory and recurring appearance of an object after its removal, in other words palinopsia;
- Visual perseveration *in sensu strictu*, when a disappearing visual stimulus does not fade from view; however, there is no recurrence of the visual image as in palinopsia;
- Illusory visual spread or visuospatial perseveration: the visual stimulus is sensed over an unduly extensive area of environmental space, especially with images of vivid pattern or hue.

The example Critchley gives of illusory visual spread, which is apparently the rarest form of visual perseveration, is of the colour of a bright frock extending to the wearer's face, arms, legs and for a distance beyond. He also reports a case (Case 1) in which this phenomenon occurred at the onset of a migraine. Illusory visual spread has no temporal factor, for when the stimulus is removed the effect disappears.

What mechanism(s) might explain illusory visual spread? My sketchy knowledge of visual neurophysiology is that the brain undertakes parallel processing of various visual attributes (shape, colour, etc), and that some form of "binding" must occur to ensure a coherent, comprehensible visual percept with all these attributes. Perhaps a transient breakdown of this binding process, of colour to shape, might account for the phenomenon of illusory visual spread? ◆

See the next issue of ACNR for a comment on this article by Dominic Ffytche

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Neuroacanthocytosis

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Neuroacanthocytosis (NA) syndromes are a group of genetically defined disorders leading to progressive neurodegeneration of the basal ganglia. The core NA syndromes include autosomal recessive chorea-acanthocytosis and X-linked McLeod syndrome. These disorders have a Huntington disease-like phenotype of a choreatic movement disorder, psychiatric manifestations and cognitive decline, but may have additional multi-system features including myopathy and axonal neuropathy. In addition, patients with McLeod syndrome may develop a cardiomyopathy. Acanthocytes are found in a proportion of patients with Huntington's disease-like 2 and pantothenate kinase-associated neurodegeneration. The association of the erythrocyte membrane abnormality resulting in acanthocytosis and selective neurodegeneration of the basal ganglia suggests a common pathogenic pathway, however, this has not yet been fully elucidated.

NA refers to neurological disorders in which erythrocytes with a thorny appearance are present (Figure 1). The term was previously used for inherited disorders of lipoprotein synthesis, abetalipoproteinaemia and hypobetalipoproteinaemia, in which impaired vitamin E absorption results in posterior column degeneration and cerebellar abnormalities. Currently, it should be reserved for disorders affecting the basal ganglia and resulting in various movement disorders.

Neuroacanthocytosis syndromes are genetically defined neurodegenerative disorders with a Huntington-like phenotype

In chorea-acanthocytosis (ChAc) and McLeod syndrome (MLS), acanthocytes are regularly seen, whereas in Huntington's disease-like2 (HDL2) and pantothenate kinase-associated neurodegeneration (PKAN), they are only occasionally observed. Erythrocyte acanthocytosis can be variable, and the diagnosis of these syndromes does not require their demonstration on peripheral blood smears. All NA syndromes are very rare with cases numbering probably less than five thousand world-wide.

Chorea-acanthocytosis

Autosomal recessive chorea-acanthocytosis (ChAc) is a progressive neurodegenerative disorder with onset of neurological symptoms usually in the twenties.[1] Many patients develop a characteristic phenotype including feeding dystonia with tongue protrusion after contact with the food bolus, orofacial dyskinesias, involuntary vocalisations, dysarthria and involuntary tongue- and lip-biting. The gait may have a "rubber man" appearance with truncal instability and near-falls, and sudden, violent trunk spasms. Most ChAc patients develop generalised chorea which may be indistinguishable from that of Huntington's disease (HD). A minority of ChAc patients have parkinsonism. In addition to orofaciolingual dystonia, limb dystonia is common. In at least one third of patients, seizures, typically generalized, are the first manifestation of disease. Impairment of memory and executive functions are frequently, although not invariably, observed. Psychiatric features are common and may manifest as schizophrenia-like psychosis or obsessive-compulsive disorder.

ChAc progresses slowly over 15-30 years, but sudden death, presumably caused by seizures, or possibly from autonomic involvement, is not uncommon. Neuroradiologically there is progressive striatal atrophy, especially affecting the head of caudate nucleus. Neuropathology demonstrates severe neuronal loss and gliosis primarily of the head of the caudate and to a lesser extent of the putamen, globus pallidus and substantia nigra.

Most ChAc patients have elevated levels of creatine phosphokinase (CK). Clinical neuromuscular manifestations include areflexia, sensory-motor neuropathy, and variable weakness and atrophy. Muscle biopsy and electromyography commonly demonstrate neuropathic changes and, rarely, myopathic alterations.

ChAc is caused by various mutations of a 73 exon gene on chromosome 9, VPS13A, coding for chorein.[2] No obvious genotype-phenotype correlations have been observed. Chorein is implicated in intracellular protein sorting but its physiological functions are not yet known.

McLeod syndrome

The so-called McLeod blood group phenotype is defined by absent Kx red blood cell antigen and weak expression of Kell antigens, and is often incidentally detected on routine screening.[3,4] Most carriers of the McLeod blood group phenotype have erythrocyte acanthocytosis and elevated CK levels, and develop the McLeod syndrome (MLS).[4-6] Onset of neurological symptoms ranges from 25-60 years and disease duration ranges between 10-30 and even more years.[4,5] About 30% of patients present with chorea resembling HD,[4,5]

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Presentation: Neupro® is a thin, matrix-type square transdermal patch. **Active Ingredient:** *Rotigotine. 2 mg/24 h transdermal patch* is 10 cm^2 and contains 4.5 mg rotigotine, releasing 2 mg rotigotine over 24 hours. *4 mg/24 h transdermal patch* is 20 cm^2 and contains 9.0 mg rotigotine, releasing 4 mg rotigotine over 24 hours. *6 mg/24 h transdermal patch* is 30 cm^2 and contains 13.5 mg rotigotine, releasing 6 mg rotigotine over 24 hours. *8 mg/24 h transdermal patch* is 40 cm^2 and contains 18.0 mg rotigotine, releasing 8 mg rotigotine over 24 hours. **Uses:** To treat the signs and symptoms of idiopathic Parkinson's disease, either with or without concomitant levodopa therapy. **Dosage and Administration:** Neupro® is applied to the skin once a day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different application site. *Monotherapy:* treatment is initiated with a single daily dose of 2 mg/24 h. Dose increased by 2 mg/24 h each week (e.g. 2 mg/24 h in Week 1, 4 mg/24 h in Week 2, 6 mg/24 h in Week 3 and 8 mg/24 h in Week 4), until an effective dose is reached. Maximal dose is 8 mg/24 h. *Adjunctive therapy (with levodopa):* treatment initiation is at 4 mg/24 h and increased weekly in 2 mg/24 h increments, up to a maximal dose of 16 mg/24 h. *Hepatic and renal impairment:* Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis. Caution is advised and dose adjustment may be needed when treating patients with severe hepatic impairment. *Children and adolescents:* not recommended. *Treatment discontinuation:* If treatment is to be withdrawn, it should be gradually reduced, in steps of 2 mg/24 h with a dose reduction preferably every other day, to avoid the possibility of developing neuroleptic malignant syndrome. **Contraindications:** Hypersensitivity to rotigotine or to any of the excipients. Neupro® should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns. **Warnings and Precautions:** External heat should not be applied to the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of therapy. Rotate the site of patch application to minimise the risk of skin reactions. In case of generalised skin reaction associated with use of Neupro®, discontinue treatment. Avoid exposure to direct sunlight until the skin is healed. Compulsive behaviours and hallucinations have been reported in patients treated with Neupro®. *Interactions:* Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients taking sedating medicines or other depressants in combination with rotigotine. Co-administration of rotigotine (3 mg/24 h) did not affect the pharmacodynamics and pharmacokinetics of oral contraceptives (0.03 mg ethinylestradiol, 0.15 mg levonorgestrel). Switching to another dopamine agonist may be beneficial for those patients who are insufficiently controlled by rotigotine. *Pregnancy and lactation:* Rotigotine should not be used during pregnancy. Breast-feeding should be discontinued. *Driving etc.:* Rotigotine may have major influence on the ability to drive and use machines. **Adverse Effects:** *Very common (>10%):* nausea, somnolence, dizziness and application site reactions. *Common (between 1%–10%):* hallucinations, confusion state, insomnia, abnormal dreams, headache, dyskinesia, orthostatic hypotension, vomiting, constipation, diarrhoea, dry mouth, dyspepsia, hepatic enzyme increase, rash, hyperhydrosis, erythema, pruritus, asthenic conditions, peripheral oedema, decreased weight, fall. Consult SmPC in relation to other side effects. **Pharmaceutical Precautions:** Store in a refrigerator (2°C–8°C). Store in the original package. **Legal Category:** POM. **Marketing Authorisation Numbers:** EU/1/05/331/001-012. **NHS Cost:** 2 mg Continuation Pack of 28 patches: £77.24. 4 mg Continuation Pack of 28 patches: £117.71. 6 mg Continuation Pack of 28 patches: £142.79. 8 mg Continuation Pack of 28 patches: £142.79. **Marketing Authorisation Holder:** SCHWARZ PHARMA Ltd, Shannon, Industrial Estate, Co. Clare, Ireland. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformation@ucb-group.com. **Date of Revision:** October 2008 (08NE0225). Neupro is a registered trademark.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk
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References: 1. Braun M *et al.* 2005; Poster presented at 9th Congress of the European Federation of Neurological Societies; September 17–20, Athens, Greece. **2.** LeWitt PA *et al. Neurology* 2007; **68**: 1262–7. **3.** Giladi N *et al.* 2006; Poster presented at 10th Congress of the European Federation of Neurological Societies; September 2–5, Glasgow, UK. **4.** Poewe WH *et al. Lancet Neurol* 2007; **6**: 513–20.

Date of literature preparation: January 2009.

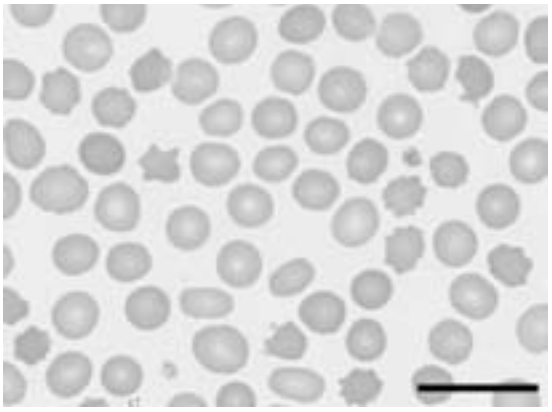

Figure 1: Acanthocytes
Peripheral blood smear showing significant acanthocytosis in a patient with McLeod syndrome manifesting with schizophrenia and later developing generalized chorea, myopathy and cardiomyopathy (May Gruenwald-Giemsa; x100; scale bar = 25 μm).

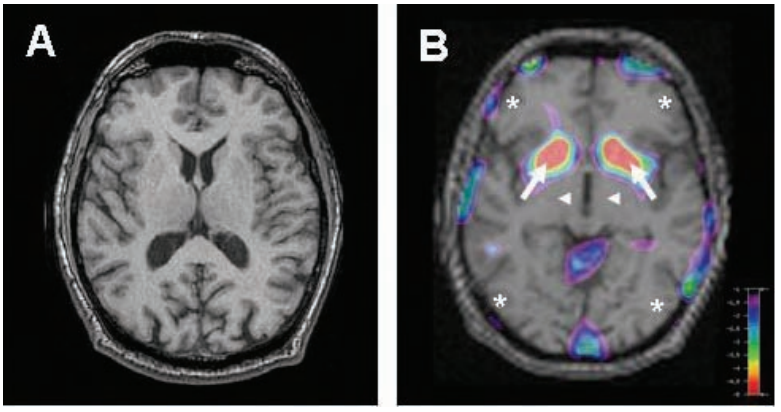

Figure 2: MRI and FDG-PET
(A) T1-weighted cerebral MRI demonstrating only subtle atrophy of the head of the caudate nucleus. (B) Quantative FDG-PET of the same patient demonstrating severe impairment of the FDG-uptake of the striatum (arrow). FDG-uptake in the thalamus (arrowhead) and the cerebral cortex (stars) appears to be normal.

Table 1: Neuroacanthocytosis syndromes

Core neuroacanthocytosis syndromes
Chorea-acanthocytosis (ChAc)
McLeod syndrome (MLS)
Huntington's disease-like 2 (HDL2)
Pantothenate kinase associated neurodegeneration (PKAN; including HARP subtype)
Neuroacanthocytosis with lipoprotein disorders
Abetalipoproteinemia (Bassen–Kornzweig syndrome)
Familial hypobetalipoproteinaemia
Anderson disease
Atypical Wolman disease
Acanthocytosis in systemic diseases where neurological findings may also be present
Severe malnutrition (e.g. anorexia nervosa)
Cancers, sarcoma
Thyroid disorders, myxoedema
Splenectomy
Liver cirrhosis, hepatic encephalopathy
Psoriasis
Eales' disease (angiopathia retinae juvenilis)
MELAS

HARP, hypoprebetalipoproteinaemia, acanthocytosis, retinitis pigmentosa, pallidal degeneration; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.

and most patients will develop this sign during the course of the disease. Involuntary movements may also include facial dyskinesias and vocalisations. In contrast to ChAc, only exceptional McLeod patients have lip- or tongue-biting, dysphagia, dystonia, or parkinsonism.[4] Psychiatric manifestations including depression, schizophrenia-like psychosis and obsessive-compulsive disorder are frequent and may appear prior to the movement disorders.[6] A subset of MLS patients develops cognitive deficits, particularly in later disease stages. Generalised seizures occur in about half of the patients.

Neuroimaging reveals selective atrophy of the striatum and impaired striatal glucose metabolism.[4,6] Neuropathological findings consist of non-specific neuronal loss and gliosis predominantly of the caudate nucleus and to a lesser extent of the putamen and the pallidum.[7]

Elevated CK levels are almost always found. Neuromuscular manifestations include myopathy and sensory-motor axonal neuropathy.[8,9] Although about 50% of the MLS patients develop muscle weakness and atrophy during the disease course, severe gait difficulties are rare.[9] Neuromuscular pathology shows sensory-motor axonal neuropathy, neurogenic muscle changes and variable signs of myopathy.[9]

About 60% of MLS patients develop a cardiomyopathy with atrial fibrillation, malignant arrhythmias or dilated cardiomyopathy. Cardiac complications are a frequent cause of death, thus MLS patients and asymptomatic carriers of the McLeod blood group phenotype should have a cardiologic evaluation.[4,9,10]

Some female heterozygotes have been reported to develop CNS manifestations related to MLS with corresponding neuropathological changes. Reduction of striatal glucose uptake was demonstrated in asymptomatic female heterozygotes.[6] In addition, MLS may be part of a "contiguous gene syndrome" on the X chromosome including chronic granulomatous disease, Duchenne muscular dystrophy and/or X-linked retinitis pigmentosa.

MLS is caused by mutations of the XK gene encoding the XK protein, which carries the Kx RBC antigen.[11] Most pathogenic mutations are nonsense mutations or deletions predicting an absent or shortened XK protein lacking the Kell protein binding site. The exact function of the human XK protein is not elucidated but the data from a C. elegans analogue of the XK gene suggest a possible role in apoptosis regulation.[12]

Huntington's disease-like 2

Huntington's disease-like 2 (HDL2) is an autosomal dominant neurodegenerative disorder.[13] All affected families identified to date have been of African ancestry, however, this may be occult and revealed only by haplotype studies. Age at disease onset is variable and disease duration is usually 10-20 years. Initial presentation often includes personality change or other psychiatric symptoms, progressing to a movement disorder, usually chorea, but also parkinsonism and dystonia.[14] Unlike ChAc and MLS, deep tendon reflexes are usually brisk; there are no peripheral nerve or muscle abnormalities, and seizures have not been reported. Acanthocytosis is found in about 10% of patients and CK levels are normal. Neuroimaging reveals bilateral striatal atrophy, in particular of the caudate nucleus. In contrast to ChAc and MLS, generalized cortical atrophy may develop during the disease course. Neuropathologically, ubiquitin-immunoreactive intranuclear neuronal inclusions, similar to those seen in HD, are found.[13]

HDL2 is caused by expanded trinucleotide repeats of the junctophilin 3 gene (JPH3). As in HD, there is anticipation and the age of onset is inversely related to the size of the trinucleotide repeat expansion. Affected individuals have CTG/CAG repeat expansions of 41-59 triplets (normal population: 6-27). JPH3 plays a role in junctional membrane structures, and may be involved in the regulation of calcium.

Panthothenate kinase-associated neurodegeneration

Pantothenate kinase-associated neurodegeneration (PKAN) is an autosomal recessive condition belonging to the group of disorders known as neurodegeneration with brain iron accumulation (NBIA). So far, PKAN is the only NBIA in which acanthocytosis has been reported. PKAN typically presents in childhood with rapid progression over 10 years.[15] Initial manifestations may include orofacial and limb dystonia, choreoathetosis and spas-

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Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk
Adverse events should also be reported to UCB Pharma Ltd.

References: 1. Braun M *et al.* 2005; Poster presented at 9th Congress of the European Federation of Neurological Societies; September 17–20, Athens, Greece.
2. Trenkwalder C *et al. Lancet Neurol.* 2008; **7**: 595–604.

Date of literature preparation: June 2009

Table 2: Predictive Accuracy of MCI from Cache County

Disorder	ChAc	MLS	HDL2	PKAN
Gene	*VPS13A*	*XK*	*JPH3*	*PANK2*
Protein	Chorein	XK	Junctophilin-3	Panthothenate kinase 2
Inheritance	AR	X-linked	AD	AR
Acanthocytes	+++	+++	+ / -	+ / -
Serum CK (U/L)	300 - 3000	300 - 3000	Normal	Normal
Neuroimaging	Striatal atrophy	Striatal atrophy	Striatal and cortical atrophy	"Eye of the tiger" sign
Usual onset	20 - 30	30 - 60	20 - 40	Childhood
Chorea	+++	+++	+++	+++
Other movement disorders	Feeding and gait dystonia, tongue and lip biting, Parkinsonism	Vocalizations	Dystonia, Parkinsonism	Dystonia, Parkinsonism, spasticity
Seizures	Generalized, partial-complex	Generalized	None	None
Neuromuscular manifestations	Areflexia, weakness, atrophy	Areflexia, weakness, atrophy	None	None
Cardiac manifestations	None	Atrial fibrillation, malignant arrhythmias, dilated cardiomyopathy	None	None

ticity. Most patients develop pigmentary retinopathy and one third cognitive impairment. About 8% of PKAN patients have acanthocytosis, possibly due to abnormalities of lipid synthesis.[15] MRI demonstrates the typical "eye-of-the-tiger" pattern of iron deposition in the globus pallidus.

PKAN is caused by mutations of the pantothenate kinase 2 gene (PANK2) (chromosome 20p13). Truncating mutations are responsible for the majority of cases. PKAN catalyses the rate-limiting step in the synthesis of coenzyme A from vitamin B5 (pantothenate). The residual enzymatic activity correlates with the disease phenotype, as typical patients have no active enzyme but atypical patients with adult onset usually harbour PANK2 missense mutations.[15]

Diagnostic considerations

The determination of acanthocytosis in peripheral blood smears is difficult in a standard setting and is not even necessary for the diagnosis of a NA syndrome. Automated blood counts usually show an elevated number of hyperchrome erythrocytes. Although routine blood films may demonstrate acanthocytes, the detection rate is variable and standard values are lacking. A standardised method using a 1:1 dilution with physiological saline and phase contrast microscopy is more sensitive and specific.[16] Serum CK is elevated in most cases with ChAc and MLS. ChAc patients have absent chorein expression in erythrocytes on Western blot. MLS is detected by determination of absent Kx antigen and reduced Kell antigens on the erythrocytes in males and fluorescence absorbent cell sorting with Kell antigens in female heterozygotes. Genetic analysis of the VPS13A and XK genes is confirmatory but may be difficult to accomplish in VPS13 due to the large dimension of the gene. Cerebral MRI is diagnostic only in PKAN, and the diagnosis is confirmed by analysis of the PANK2 gene. Analysis of the JPH3 gene CTG expansion is useful in patients of African ancestry with suspected HDL2.

Therapy

There are no curative or disease-modifying treatments available at present. Recognition of treatable complications such as seizures, aspiration and cardiac problems is essential. Psychiatric problems should be treated according to their clinical presentation. Dopamine antagonists or depleters such as tiapride, clozapine or tetrabenazine may ameliorate the chorea. Non-medical therapies with a multidisciplinary approach are often helpful. Dystonia of the lower face and tongue can result in severe tongue and lip self-mutilation in ChAc and may be ameliorated by a bite plate. Weight loss can be a prominent early feature, and evaluation of swallowing is very important. Placement of a feeding tube may be necessary to avoid nutritional compromise and to reduce the risk of aspiration. Speech therapy and the evaluation of communication devices may be necessary. Gait abnormalities and falls are frequent and physiotherapy may improve gait and balance. Most importantly, extended and continuous multidisciplinary psychosocial support should be provided for the patients and their families.

Conclusions

NA syndromes must be included in the differential diagnosis of HD. Their consideration is mandatory if HD genetic testing is negative. Clinical and paraclinical findings typical for NA include epilepsy, peripheral neuropathy, cardiomyopathy (MLS) and orofacial dyskinesia, and feeding dystonia (ChAc). ◆

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NOTE

The Advocacy for Neuroacanthocytosis Patients - www.naadvocacy.org - supports the collaboration of the authors and makes the diagnostic chorein expression test (http://www.nefo.med.uni-muenchen.de/ adanek/Chorein_Blot.pdf) freely available.
It currently solicits NA research grant proposals: http://tinyurl.com/p3j5so

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Links Between Nerves and Glands: The Story of Adrenaline

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Acknowledgement:
I am grateful to
Prof SW Carmichael who gave
permission to cite his
website (reference 1).

After the discovery of adrenaline, the rudimentary ideas of neurotransmission were developed in the 20-year period 1890-1910. It is entwined with the concept of neural transmission by humoral substances initiated in 1656 by Thomas Wharton and by Glisson, who associated the adrenal glands with nerve plexuses. How this linkage functioned was unknown until Claude Bernard showed that adrenal glands produced 'secretions internes' affecting the milieu intérieur.

John Jacob Abel in 1899, and, independently, Jokichi Takamine in 1901, isolated a suprarenal extract that elevated blood pressure. Three years later Thomas Renton Elliott observed that from the adrenal medulla, a substance could be produced (i.e. adrenaline), whose effects resembled closely those of the sympathetic nervous system, thus echoing Wharton's conclusions. In the 20th century. George Oliver, Edward Schäfer and Henry Dale were to clarify the physiology and show the way for clinical applications of adrenaline.

So well known is adrenaline that the word has passed into common language as an inaccurate metaphor for a burst of anger, energy, or excitement. The discovery of adrenaline[1] was entwined with the new but crucial concept of neural transmission by chemical (humoral) substances (Table 1). This discovery was the essential precursor of the modern neurotransmitter chemistry, necessary for the understanding of neural functions throughout the nervous system. First, the important historical background.

Table 1. Adrenaline: time line

1552	Eustachius published plates showing adrenal glands.
1656	Wharton associated adrenal glands with nerve plexus.
1852	Kölliker described microscopic anatomy: an apparatus appertaining to the nervous system.
1894	Oliver and Schäfer described pressor effect of adrenal medulla.
1896	Cybulski and Szymonowicz also described pressor effect.
1901	Epinephrine discovered independently by Abel and Takamine.
1901	John Newport Langley founded concept of 'receptors'.
1902	Alfred Kohn identified chromaffin cells.
1904	Stolz synthesized adrenaline.
1904	Elliott, showed sympathetic nerves produce their effects by liberating adrenaline.
1906	Henry Hallett Dale insisted on name 'Adrenaline'.
1910	Barger and Dale: sympathetic nerve stimulation more closely mimicked the effects of sympathomimetic pri mary amines than the effects of adrenaline.
1911	Walter B. Cannon and de la Paz showed that anger or fear are associated with adrenaline released in the blood from a cat's suprarenal vein.
1921	The transmission of the effects of nerve impulses, by the release of chemical agents, first became an experimental reality (Dale).

Anatomical links between glands and nerves

Thomas Wharton (1614-73) (Figure 1) was physician to St. Thomas' Hospital, London. In 1656 with remarkable prescience he associated the proximity of the adrenal glands with nerve plexuses: in Chapter 16 of his 1656 text, '*Glandulae renales vel ad nerveum plexum abdominis sitae, earum usus*' (p94), he writes:

"Glandulae ad plexum, certo possumus statuere, non esse materiam plane excrementitam, sed utilem, quia in venas perpetuo recipitur …

Translated: ('We may certainly believe (of the glands beside the plexus) that material is not completely excreted but is used since it is taken up continually by the veins').[2,3]

Wharton and Francis Glisson (1597–1677),[4] reached similar conclusions concerning the glands and their functions: "*De actione et usu Lymphae ductuum sive canalium aquosorum*". His account that postulated the adrenals take a substance from nerves and transfer it to veins preceded the neuroendocrine concept of the adrenal medulla as an anatomical-physiological nexus. Some 300 years later, at the beginning of the 20th century, it was generally thought that nerve impulses acted directly on the muscles or glands. Not until 1921, was it known how the stimulation of a nerve directed the workings of the tissues or organs it supplied.

These were groundbreaking ideas that contributed to the emergence of endocrinology: the control of peripheral organs and tissues by glandular secretions, which contribute to the maintenance of homeostasis. The concept of homeostasis began in 1855 when Claude Bernard postulated that all organs liberate special substances

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STALEVO (levodopa / carbidopa / entacapone)
PRESCRIBING INFORMATION
Indication: Treatment of adult patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment. **Dosage and administration**: Orally with or without food. One tablet contains one treatment dose and may only be administered as whole tablets. Optimum daily dosage must be determined by careful titration of levodopa in each patient preferably using one of the four tablet strengths. Patients receiving less than 70-100mg carbidopa a day are more likely to experience nausea and vomiting. The maximum daily dose of Stalevo 50, 75, 100, 125 and 150mg tablets is 10 per day and of Stalevo 200mg is 7 per day. Usually Stalevo is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone. See SPC for details of how to transfer these patients and those not currently treated with entacapone. *Children and adolescents*: Not recommended. *Elderly*: No dosage adjustment required. *Mild to moderate hepatic impairment, severe renal impairment (including dialysis)*: Caution advised. **Contraindications**: Hypersensitivity to active substances or excipients. Severe hepatic impairment. Narrow-angle glaucoma. Phaeochromocytoma. Concomitant use of non-selective monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine). Concomitant use of a selective MAO-A inhibitor and a selective MAO-B inhibitor. Previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis. **Warnings and precautions**: Not recommended for treatment of drug-induced extrapyramidal reactions. Administer with caution to: patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal or endocrine disease, or history of peptic ulcer disease or of convulsions, or past or current psychosis; patients receiving concomitant antipsychotics with dopamine receptor-blocking properties, particularly D2 receptor antagonists; patients receiving other medicinal products which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias, monitor cardiac function carefully during initial dosage adjustments. Monitor all patients for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully. Caution when driving or operating machines. Doses of other antiparkinsonian treatments may need to be adjusted when Stalevo is substituted for a patient currently not treated with entacapone. Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dosage reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy. Monitor weight in patients experiencing diarrhoea. Contains sucrose therefore should not be taken by patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency. Pathological gambling, increased libido and hypersexuality have been reported in Parkinson's disease patients treated with dopamine agonists and other dopaminergic drugs such as Stalevo. For patients experiencing progressive anorexia, asthenia and weight loss within a short period, consider medical review (including liver function). **Undesirable effects:** *Levodopa / carbidopa* - Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, paranoid ideation and psychotic episodes, depression, cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence. Reports of signs of pathological gambling, increased libido and hypersexuality, especially at high doses and generally reversible upon reduction of the dose or treatment discontinuation. *Entacapone* - Most frequently relate to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and urine discolouration. Common: insomnia, hallucination, confusion and paroniria, Parkinsonism aggravated, dizziness, dystonia, hyperkinesias, diarrhoea, abdominal pain, dry mouth, constipation, vomiting, fatigue, increased sweating and falls. Rare: erythematous or maculopapular rash, hepatic function test abnormal. Very rare: anorexia, urticaria, weight decrease, agitation. Not known: hepatitis, colitis. See SPC for further details. **Legal category**: POM. **Presentations, basic NHS costs and marketing authorisation numbers:** Stalevo 50mg/12.5mg/200mg, 30 tablet bottle £21.11, 100 tablet bottle £70.37, MA numbers: EU/1/03/260/002-003; Stalevo 75mg/18.75mg/200mg, 30 tablet bottle £21.11, 100 tablet bottle £70.37, MA numbers: EU/1/03/260/025-026; Stalevo 100mg/25mg/200mg, 30 tablet bottle £21.11, 100 tablet bottle £70.37, MA numbers: EU/1/03/260/006-007; Stalevo 125mg/31.25mg/200mg, 30 tablet bottle £21.11, 100 tablet bottle £70.37, MA numbers: EU/1/03/260/030-031; Stalevo 150mg/37.5mg/200mg, 30 tablet bottle £21.11, 100 tablet bottle £70.37 MA numbers: EU/1/03/260/010-011; Stalevo 200mg/50mg/200mg, 30 tablet bottle £21.11, 100 tablet bottle £70.37 MA numbers: EU/1/03/260/020-21. **Distributed by**: Orion Pharma (UK) Ltd. Oaklea Court, 22 Park Street, Newbury, Berkshire, RG14 1EA, UK. Full prescribing information is available on request. Stalevo is a registered trademark. **Date of Prescribing Information**: April 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 Orion Pharma (UK) Ltd on 01635 520300.

ORION PHARMA
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Orion Pharma (UK) Ltd., Oaklea Court,
22 Park Street, Newbury, Berkshire RG14 1EA
Item Date: June 2009 STA3284 J19499

Stalevo®
levodopa, carbidopa, entacapone
Efficacy that endures

Figure 1. Thomas Wharton MD, FRCP (above left) and Thomas Renton Elliott, MD,FRS (above right).

into the tissue fluids – later called hormones (a word first suggested by Sir William Bate Hardy, a Cambridge physiologist.) – which maintained the constancy of what Bernard named, the milieu intérieur.[5] Then came proof that endocrine glands secreted humoral substances that determined function or dysfunction in various tissues. Jacob Henle (1809-1885) in 1841 first recognised 'ductless glands', which secrete directly into the blood; this predated Claude Bernard who stated in 1855 that the adrenal glands produced 'secretions internes'.[6,7] In the same year Thomas Addison published his famous monograph: *On the constitutional and local effects of disease of the suprarenal capsules*,[8] although, he did not mention a secretory role, nor any vital humoral factor stemming from the adrenals. It was the neurologist, Charles Édouard Brown-Séquard (1817–1894), who truly founded the vital function of the adrenal glands. On 25 August 1856 he reported to the Académie des Sciences in Paris that removal of both adrenal glands in cats, dogs, rabbits guinea pigs and mice was fatal, usually within 12 hours; but blood from a healthy animal injected into the veins of an animal deprived of its suprarenal bodies prolonged its survival.[9] He had clearly demonstrated the vital humoral factor (cortisol) generated by the adrenals

Adrenal anatomy

The history of adrenaline started with the anatomical discovery of the adrenal glands in 1552 by Eustachius (?-1574). The Danish anatomist Caspar Bartholinus (1655-1738) called them *Glandulae renibus incubentis* and believed they were hollow and filled with black bile – *Capsulae atrabiliarae* – but George Frederic, Baron Cuvier (1769-1832) established in 1805 that they were solid and he distinguished the medulla from the cortex. Nagel in 1836 noticed that the human adrenal gland is composed of a cortical (Rinden) and medullary (Mark) substance;[10] he provided their name – adrenal glands. Rudolph Albert Von Kolliker (1817-1905), Swiss anatomist and physiologist, described their microscopic appearances in 1852.[11] He considered

"the cortical and medullary substances as physiologically distinct.… The former may, provisionally, be placed with the so-called 'blood-vascular glands,' and a relation to secretion assigned to it; whilst the latter, on account of its extremely abundant supply of nerves, *must be regarded as an apparatus appertaining to the nervous system*, …" (my italics).

Thus, Kölliker confirmed and developed Wharton's earlier ideas. In 1831, Philipp Friedrich Arnold (1803-90) thought that the adrenals developed from the embryonic mesonephros (Wolffian bodies), which they resembled. In a remarkable series of articles, Robert Remak (1815-1865) provided a vital link, showing that the adrenal medulla developed in the embryo along with the sympathetic ganglia.[12]

Chromaffin cells

In 1902, Alfred Kohn in Prague had identified the chromaffin cells, derived from the neural crest and intimately associated with the sympathetic nervous system.[13] He found an unidentified substance in the adrenal medulla reacted with chromium salts to produce a brownish colour.[14] He thus created the term chromaffin cells.[15] A common sympathetic-adrenal progenitor cell for chromaffin cells and sympathetic neurons was postulated. Gradually the common embryology was demonstrated between chromaffinomas and the catechol-producing tissues of the adrenal medulla, sympathetic nerves, and ganglia. In 1904 Friedrich Stolz, and in 1905 Dakin synthesized adrenaline. Phaeochromocytomas were identified by Frankel in 1885, but were first named in 1912 by Ludwig Pick, who noted the diagnostic chromaffin reaction of the tumour cells.

But not until 1946 did von Euler showed that purified extract of sympathetic nerves produced the same effects as demythylated adrenaline (Noradrenaline), which he deduced was the sympathetic transmitter.

The idea that chemical substances stimulated nerve transmission was indicated in the late 19th century. Du Bois Reymond's[16] in 1877 observed

"Of known natural processes that might pass on excitation, only two are, in my opinion, worth talking about: either there exists at the boundary of the contractile substance a stimulatory secretion in the form of a thin layer of ammonia, lactic acid, or some other powerful stimulatory substance; or the phenomenon is electrical in nature "

Adrenal extract: clinical significance

In 1895, nine years before Stolz synthesised adrenaline (C9H13NO3) (Figure 2) in 1904,[17] the pharmacological effect of adrenal extract had been shown by George Oliver MD.,FRCP (1841-1915), a Harrogate physician, born in Middleton-in-Teeside. His experiments, remarkably conducted in a small Yorkshire spa town, using suprarenal glands obtained from his local butcher, led him to conclude:

The suprarenal capsules yield to water (cold or hot), to alcohol or to glycerine, a substance, which exerts a most powerful action upon blood vessels, upon the heart, and upon skeletal muscles… The effect upon the blood vessels is to cause extreme contraction of arteries, so that the blood pressure is enormously raised.[18]

He visited Edward Albert Schäfer FRS, (1850–1935), Professor of Physiology at Edinburgh, then at University College London, Carmichael recalls: "The classic story of this breakthrough puts George Oliver and Edward Schäfer at centre stage".[1]

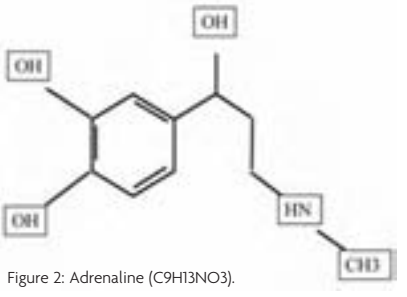

Figure 2: Adrenaline (C9H13NO3).

Sir Henry Dale engagingly described the discovery of Oliver (1841-1915) and Schäfer:[19]

"Dr. George Oliver, a physician of Harrogate, employed his winter leisure in experiments on his family, using apparatus of his own devising for clinical measurements. In one such experiment he was applying an instrument for measuring the thickness of the radial artery; and, having given his young son, who deserves a special memorial, an injection of an extract of the suprarenal gland, prepared from material supplied by the local butcher, Oliver thought that he detected a contraction or, according to some who have transmitted the story, an expansion of the radial artery. Whichever it

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Prescribing Information UK

Mirapexin® prolonged-release (pramipexole)
Mirapexin 0.26mg, Mirapexin 0.52mg, Mirapexin 1.05mg, Mirapexin 2.1mg and Mirapexin 3.15mg prolonged-release tablets containing **0.375mg, 0.75mg, 1.5mg, 3mg** and **4.5mg** respectively of pramipexole dihydrochloride monohydrate. **Indications:** The treatment of the signs and symptoms of idiopathic Parkinson's disease (PD), alone (without levodopa) or in combination with levodopa. **Dose and Administration:** Adults only. Take each day at about the same time with or without food. 0.375mg salt (0.26mg base) per day for first 5-7 days. Increase to 0.75mg salt (0.52mg base) in second week and 1.5mg salt (1.05mg base) in third week. If necessary increase daily dose by 0.75mg salt (0.52mg base) at weekly intervals up to a maximum of 4.5mg salt (3.15mg base). See SPC for more information on dose schedule. Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Renal impairment: See SPC for revised dosage. Hepatic impairment: Dose adjustment in hepatic failure is not required. **Contra-indications:** Hypersensitivity to any constituent. **Warnings and Precautions:** Inform patients that hallucinations (mostly visual) can occur. Somnolence and uncommonly, sudden sleep onset have been reported; patients who have experienced these must refrain from driving or operating machines. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including pramipexole. Impulse control disorders such as binge eating and compulsive shopping can occur. Patients with psychotic disorders. Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension. If dyskinesias occur in combination with levodopa during initial titration of pramipexole in advanced Parkinson's disease, the dose of levodopa should be reduced. **Interactions:** Inhibitors of the cationic secretory transport system of the renal tubules such as cimetidine, amantadine and mexiletine may interact with pramipexole resulting in reduced clearance of either or both drugs. Consider reducing pramipexole dose when these drugs are administered concomitantly. The dosage of levodopa should be reduced, and other Parkinsonian medicinal products kept constant, while increasing the dosage of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. Coadministration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** Effects of pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used during breast-feeding. **Undesirable Effects:** Frequency of adverse reactions from placebo controlled clinical trials in Parkinson's disease includes; Very Common (≥1/10) – nausea, dizziness, dyskinesia, hypotension and somnolence. Common (≥1/100 to <1/10) - insomnia, hallucinations, amnesia, behavioural symptoms of impulse control disorders and compulsions, restlessness, visual disturbance including vision blurred and visual acuity reduced, headache, fatigue, constipation, vomiting, weight decrease, abnormal dreams, confusion and peripheral oedema. Hypotension may occur at the beginning of treatment, especially if Mirapexin is titrated too fast. Especially at high doses seen in Parkinson's disease, signs of pathological gambling, increased libido and hypersexuality have been reported, generally reversible upon reduction of dose or treatment discontinuation. See SPCs for other undesirable effects. **Pack sizes and NHS price:** 30 tablets: 0.26mg (**0.375mg**) £28.65; 0.52mg (**0.75mg**) £57.30; 1.05mg (**1.5mg**) £114.60; 2.1mg (**3mg**) £229.20; 3.15mg (**4.5mg**) £343.80. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. **MA Numbers:** EU/1/97/051/014 (0.26mg (**0.375mg**)); EU/1/97/051/017 (0.52mg (**0.75mg**)); EU/1/97/051/020 (1.05mg (**1.5mg**)); EU/1/97/051/023 (2.1mg (**3mg**)); EU/1/97/051/026 (3.15mg (**4.5mg**)). Prescribers should consult the Summary of Product Characteristics for full prescribing information. Prepared in October 2009. Further information is available from Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, Berkshire RG12 8YS.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk
Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

Boehringer Ingelheim

Date of preparation: October 2009 PPX1262

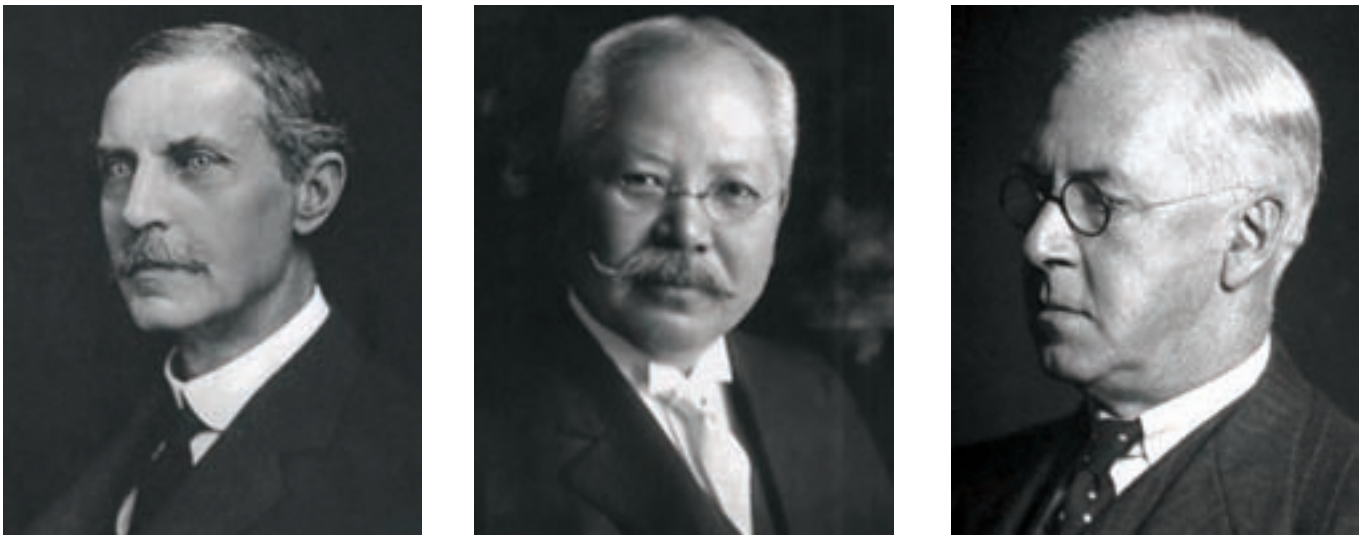

Figure 3: left to right: JN Langley, FRS, Jokichi Takamine, Sir Henry Hallett Dale, MD, FRS.

was, he went up to London to tell Professor Schäfer what he thought he had observed, and found him engaged in an experiment in which the blood pressure of a dog was being recorded; found him, not unnaturally, incredulous about Oliver's story and very impatient at the interruption. But Oliver was in no hurry, and urged only that a dose of his supra- renal extract, which he produced from his pocket, should be injected into a vein when Schäfer's own experiment was finished. And so, just to convince Oliver that it was all nonsense, Schäfer gave the injection, and then stood amazed to see the mercury mounting in the arterial manometer till the recording float was lifted almost out of the distal limb.

Thus the extremely active substance formed in one part of the suprarenal gland, and known as adrenaline, was discovered. And in due course there came to light the curious correspondence between the effects produced by this potent substance and those produced by nerves of the so- called sympathetic system; and Professor TR Elliott, then a postgraduate research student in Cambridge, was led to make the brilliant suggestion that these sympathetic nerves produce their effects by liberating small quantities of adrenaline at the points where they end in contact with muscle fibres and gland cells."

Carmichael states that: "Their publication in 1894 resulting from their subsequent experiments is heralded as the first demonstration of a hormonal effect. Many historians regard this study of the adrenal medulla as a milestone in endocrinology."

Oliver and Schäfer collaborated, to show that when the suprarenal extract was injected into anaesthetised animals there was a marked vasoconstrictor effect which caused a rise in blood pressure. They presented their results to the Physiological Society[20] and raised the possibility of using adrenaline to achieve haemostasis, and in Addison's disease.[21] However, the extract had no name until John Jacob Abel (1857-1938) at Johns Hopkins' prepared adrenal extracts in 1897 and called them 'epinephrin',[22,23] whilst others used the term 'suprarenin'.

An important parallel discovery was made by Napoleon Cybulski (1854-1919)[24] at Krakow, who in 1896 published the effects of extirpation of the adrenal glands in anesthetised dogs. His assistant, Wladyslaw Szymonowicz (1869-1939) removed the left adrenal of a dog on 17 December 1894, and 12 days later removed the other adrenal. The dog's "blood pressure fell from a control value of 145/98 to 12/3 in the next 10 hours." When Szymonowicz injected an aqueous extract of adrenal glands, the blood pressure rose to 130/104 and the heart rate fell.[25] This complemented the clinical experiments of Oliver and Schäfer. Davenport[22] perhaps surprisingly, attributed this massive fall in BP to acute hypoglycaemia resulting from acute adrenalectomy.

The discovery of Suprarenal extract

In parallel with these physiological discoveries, John Jacob Abel (1857-1938) in 1899, and independently, Jokichi Takamine (1854-1922) (Figure 3) in 1901 isolated a suprarenal extract that elevated blood pressure. In 1900 the Japanese chemist Takamine, after visiting Abel's laboratory, with Keizo Uenaka purified the extract,[26] since he realized Abels' preparation was contaminated by a benzoyl derivative whose physiological actions were not those of pure adrenaline. Takamine patented his techniques with Parke, Davis & Co. who marketed the pure crystalline substance as Adrenalin. His patent application on November 5, 1900, was entitled "Glandular extractive product on a blood pressure raising principle". He named the crystalline substance "Adrenalin" But commercial controversy was to erupt. Walter Dowson, Director of Wellcome Physiological Research Laboratories, founded in 1895, suggested instead that the word Epinephrine should be used. The recently appointed Henry Hallett Dale (1875-1968) became inextricably involved. Dale had been at University College as Sharpey Scholar for only six months before he was appointed as pharmacologist to the Wellcome Laboratories in 1904, where he became Director in 1906. But Dale insisted that British physiologists used the name adrenaline to describe the active principle of the adrenal glands, and did not imply a specific commercial preparation. He considered epinephrine inappropriate and inaccurate, and refused to use it instead of Adrenaline.[27] After protracted debate in which Wellcome's commercial interest was questioned, Dale prevailed: adrenaline was the name to be established in Britain.

Meanwhile, in 1904, Thomas Renton Elliott (1877-1961), MD, FRCP, FRS (Figure 1) later, Professor of Medicine at University College, London, advanced understanding of the mechanism. In a series of animal experiments on contraction of the ileocolic sphincter and bladder, he observed that from the adrenal medulla, a substance could be produced (i.e. adrenaline), whose effects resembled closely those of the sympathetic system. Elliott, in keeping with Wharton, deduced that the impulses in the sympathetic nerves released adrenaline in the nerve endings, which would then be the real vehicles of the stimulation effect.[28] For a detailed biography and account of Elliott's experiments see Henry Dale's Obituary notice in Biographical memoirs of Fellows of the Royal Society, Volume 7 - 1 Nov 1961; Pages 52-74.

Physiology and pharmacology

These salient physiological and pharmacological observations were made before the clinical significance of adrenaline was fully elucidated. (*vide infra*).

The Cambridge physiologist, John Newport Langley, FRS (1852-1925) (Figure 3) between 1905-12, gave the first scientifically founded concept of receptors. He cut the preganglionic sympathetic fibres in a cat and allowed them

Zebinix is indicated as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

PRESCRIBING INFORMATION
Zebinix®
(eslicarbazepine acetate)
Please refer to the SmPC before prescribing. ***Presentation:*** Tablets containing 800 mg eslicarbazepine acetate. ***Indication:*** Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. ***Dose and administration:*** May be taken with or without food. Starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. The dose may be increased to 1200 mg once daily. Withdraw gradually to minimise the potential of increased seizure frequency. ***Elderly patients:*** Caution (See SmPC). ***Children and adolescents <18 years of age:*** Not recommended. ***Patients with renal impairment:*** The dose should be adjusted according to creatinine clearance (CL_{CR}) (see SmPC). Not recommended in severe impairment. ***Patients with hepatic impairment:*** No dose adjustment in mild to moderate impairment. Not recommended in severe impairment. ***Contra-Indications:*** Hypersensitivity to the active substance, other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or any excipients. Known second or third degree AV block. ***Pregnancy:*** No data on the use of Zebinix in pregnant women. If women receiving Zebinix become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given. Zebinix interacts with oral contraceptives. An alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped. ***Lactation:*** Excretion in human breast milk is unknown. Breastfeeding should be discontinued during treatment. ***Warnings and precautions:*** Zebinix has been associated with some CNS reactions such as dizziness and somnolence. Concomitant use with oxcarbazepine is not recommended. Rash has been reported. If signs or symptoms of hypersensitivity develop, Zebinix must be discontinued. Presence of HLA-B*1502 allele in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Screening for this allele should be undertaken in such individuals. Serum sodium levels should be examined before and during treatment in patients with pre-existing renal disease or in patients concomitantly treated with medicinal products which may lead to hyponatraemia. Serum sodium levels should be determined if clinical signs of hyponatraemia occur. If clinically relevant hyponatraemia develops, discontinue Zebinix. Use in primary generalised seizures is not recommended. Prolongations in PR interval have been observed. Caution in patients with medical conditions or when taking concomitant medicinal products associated with PR prolongation. Monitor for signs of suicidal ideation and behaviours. Appropriate treatment should be considered. ***Drug interactions:*** In vitro eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. In vivo eslicarbazepine may have an inducing effect on the metabolism of medicinal products which are mainly eliminated by metabolism through CYP3A4 or conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Zebinix or changing the dose, it may take 2 to 3 weeks to reach the new level of enzyme activity. Time delays must be taken into account when Zebinix is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19. Phenytoin: concomitant use may require an increase of Zebinix dose and a decrease of phenytoin dose. Lamotrigine and topiramate: no dose adjustments are required. However, clinical review should be considered. Valproate and levetiracetam: Concomitant administration with valproate or levetiracetam appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Carbamazepine: Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded. Carbamazepine increases eslicarbazepine clearance. Zebinix slightly increases the clearance of carbamazepine. Oral contraceptives: Interacts with the oral contraceptive. Women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued. Warfarin: Zebinix has been shown to decrease exposure to S-warfarin. There are no effects on R-warfarin or coagulation. Monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment. Digoxin: no effect. MAOIs: an interaction between eslicarbazepine acetate and MAOIs is theoretically possible. ***Side effects:*** Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with Zebinix. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): Headache, abnormal coordination, disturbance in attention, tremor, diplopia, vision blurred, vertigo, nausea, vomiting, diarrhoea, rash, fatigue, gait disturbance. Uncommon (≥1/1,000 to <1/100): anaemia, hypersensitivity, hypothyroidism, increased appetite, decreased appetite, hyponatraemia, electrolyte imbalance, cachexia, dehydration, obesity, insomnia, apathy, depression, nervousness, agitation, attention deficit/hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, stress, psychotic disorder, memory impairment, balance disorder, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, autonomic nervous system imbalance, cerebellar ataxia, cerebellar syndrome, grand mal convulsion, neuropathy peripheral, sleep phase rhythm disturbance, nystagmus, speech disorder, dysarthria, hypoaesthesia, ageusia, burning sensation, vision disturbance, oscillopsia, binocular eye movement disorder, ocular hyperaemia, saccadic eye movement, eye pain, ear pain, hypoacusis, tinnitus, palpitations, bradycardia, sinus bradycardia, hypertension, hypotension, orthostatic hypotension, dysphonia, epistaxis, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, duodenitis, epigastric discomfort, gingival hyperplasia, gingivitis, irritable bowel syndrome, melaena, odynophagia, stomach discomfort, stomatitis, toothache, liver disorder, alopecia, dry skin, hyperhidrosis, erythema, nail disorder, skin disorder, myalgia, back pain, neck pain, nocturia, menstruation irregular, asthenia, malaise, chills, oedema peripheral, adverse drug reaction, peripheral coldness, blood pressure decreased, weight decreased, blood pressure diastolic decreased, blood pressure increased, blood pressure systolic decreased, blood sodium decreased, haematocrit decreased, haemoglobin decreased, heart rate increased, transaminases increased, triglycerides increased, triiodothyronine (T3) free decreased, thyroxine (T4) free decreased, drug toxicity, fall, joint injury, poisoning, skin injury. For rare side effects see SmPC. When treated concomitantly with carbamazepine, diplopia, abnormal coordination and dizziness are reported more frequently. Use of Zebinix is associated with an increase in the PR interval. Adverse reactions associated with PR interval prolongation may occur. No second or higher degree AV block was seen in Zebinix treated patients. Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. ***Legal Category:*** POM. ***Basic UK NHS cost:*** Zebinix 800 mg: pack of 30 £154.20. ***Marketing authorisation numbers:*** EU/1/09/514/012-020. ***Marketing authorisation holder:*** Bial-Portela & Cª., S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado – Portugal. ***Further Information from:*** Eisai Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, UK. ***Date of preparation:*** July 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 Eisai Ltd on 0208 600 1400/0845 676 1400 or Lmedinfo@eisai.net

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Date of preparation: October 2009
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Eisai

to degenerate. He saw that

"application of warm 1 p.c. nicotine to the deafferented ganglion produces effects like those produced by brief stimulation of its preganglionic fibres,…it follows, I think, that nicotine does not stimulate nerve-endings of preganglionic pilomotor fibres, and it is probable that it does not stimulate the nerve-endings of any pre-ganglionic fibres.

"In other words, nicotine, and by extension other drugs, act directly upon the cells of the ganglion."

He then cut the nerves to leg muscles of chickens. After axon endings on the muscles had degenerated, injection of nicotine still caused the muscles to contract and injection of curare blocked the action of nicotine. He concluded:

"all cells contain two constituents: (1) substances concerned with carrying out the chief functions of the cells, such as contraction, secretion, the formation of special metabolic products, and (2) receptive substances especially liable to change and capable of setting the chief substance in action. Further, that nicotine, curare… as well as the effective material of internal secretions produce their effects by combining with the receptive substance, and not by an action on axon-endings if these are present, nor by a direct action on the chief substance."[29]

Adrenergic and cholinergic transmission

Ten years after Elliott's researches, Sir Henry Dale (1875-1968) (Figure 3) played a crucial role in developing adrenaline.[30] With his friend Otto Loewi (1873–1961), Dale also investigated acetylcholine, which they found related closely to the effects of the parasympathetic stimulation – succinctly summarised in Loewi's Nobel lecture – *The Chemical Transmission of Nerve Action.* Until that time, acetylcholine had not been isolated and could not be considered as a transmitter of nerve impulses. Dale and Loewi later demonstrated its crucial neurotransmitter role, for which they shared the Nobel Prize of 1936. Dale proposed the terms "cholinergic" and "adrenergic" to describe fibres by the kind of chemical (rather than the chemical itself) they might use…"to assist clear thinking".[31]

Further clarification came when in 1948, Raymond Ahlquist (1914-83), an American pharmacologist, writing about adrenergic nervous transmission,[32] proposed that different receptors, not different molecular modifiers, caused different tissue responses. These specific receptors for epinephrine and norepinephrine, he localised to different tissues; they were named alpha and beta-receptors.

Transmission of nerve impulses

In his Nobel Lecture, December 12, 1936, entitled: *Some Recent Extensions of the Chemical Transmission of the Effects of Nerve Impulses*, Sir Henry Dale elucidated its physiology:

"The transmission of the effects of nerve impulses, by the release of chemical agents, first became an experimental reality in 1921. In that year Otto Loewi published the first of the series of papers from his laboratory, which,… established all the principal characteristics of this newly revealed mechanism, so far as it applied to the peripheral transmission of effects from autonomic nerves to the effector units innervated by them."[33]

Dale's own work had been principally concerned with ergot alkaloids but his move to Wellcome laboratories prompted his immediate involvement with adrenaline. But by 1910, Barger and Dale showed that sympathetic nerve stimulation more closely mimicked the effects of sympathomimetic primary amines than the effects of adrenaline;[34,35,37] they just missed identifying noradrenaline as the sympathomimetic transmitter. Dale went on to become a world-renowned clinical pharmacologist, rewarded by the FRS in 1914 and with Loewi, by the Nobel Prize in 1936.

Walter B Cannon (1871-1945) and de la Paz[34] developed the physiological studies of adrenaline, highlighting its role in the "subjugation of the viscera to sympathetic control" and "the emotion of anger or fear associated with the appearance of adrenaline in the blood from a cat's suprarenal vein."

In summary, the story of adrenaline highlights the fundamental principles of neural transmission by humoral substances. The isolation and physiology of adrenaline by Abel, Takamine Stolz, and Elliott in the brief period: 1890-1910 followed the concept of neural transmission initiated in 1656 by Thomas Wharton. The clinical physiology, elegantly revealed by George Oliver and Edward Schäfer was further investigated and developed by Sir Henry Dale and others, who showed the way to its widespread clinical utility. ◆

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Nuclear Medicine in Neurology

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Principles of Nuclear Medicine

Nuclear Medicine (NM) imaging is a modality which utilises radioactivity emitted by a radiopharmaceutical to generate an image. Most of the radiopharmaceuticals are made up of a radioactive element (isotope) bound to a biologically active molecule (ligand). They are typically injected intravenously. The advantage of NM over many other methods of imaging is that physiological processes can be investigated (eg blood flow, glucose uptake, binding of neurotransmitters). The main disadvantage is that the images obtained are of lower spatial resolution than computed tomography (CT) or magnetic resonance imaging (MRI).

Physical and physiological considerations of a nuclear medicine study

Gamma- camera (Figure 1)

Traditional nuclear medicine uses a crystal detector NaI(Tl) which scintillates (gives out a short burst of light) on exposure to radiation. Photomultiplier tubes or photodiodes positioned adjacent to the crystal will amplify and convert the weak light signal emitted by the scintillator crystal to electrons. These electrons are then fed into a computer to generate an image. The collimator is a device to channel the radiation (gamma rays or photons) produced by the radiopharmaceutical in an appropriate direction to the crystal detector.

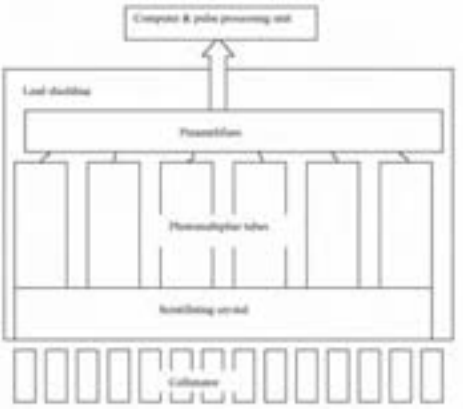

Figure 1: Cross-section through the detector head of a gamma camera.

Photon energy

The optimum energy for detection of photons is around 150 keV using the conventional gamma camera. In practice, the useful energy is between 50 keV and 300 keV. Below this energy, much of the emitted radiation is absorbed within the patient. Photons which are too high in energy will penetrate a standard scintillator crystal without producing a useful image. A thicker and denser crystal will be needed.

Half life

The radioactive half life can be defined as the time in which radiation emission decreases by a half and is an important feature in NM. It governs the ideal time to image and the dose of radiopharmaceutical given to the patients. By understanding the half life of a radiopharmaceutical, one can utilise its property to study various physiological process. Materials with a very short half life can be imaged instantaneously but require a high initial dose given to the patients. The disadvantage of such reagents with a short half life is that their production must be close to the patient. This makes them costly and inconvenient to use. Materials with a very long half life are useful in imaging over a period of time. However, patients remain radioactive for a considerable time and the initial dose of the radiopharmaceutical has to be kept low which could compromise the quality of the images.

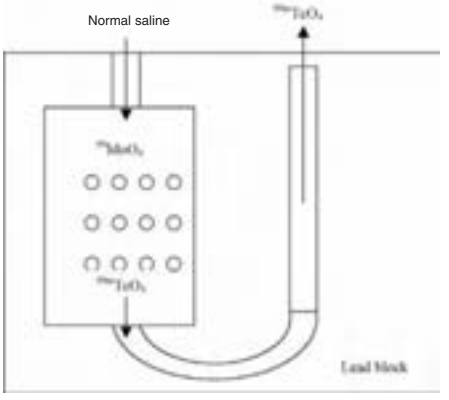

Figure 2a: Technetium-99m is produced from a generator which contains ^{99}MolybdenumO$_4$ adsorbed onto beads in column. The generator produces sufficient activity for about one week's supply of Tc-99m. The Tc-99m is eluted from the column by the addition of a solution of normal saline. The more soluble ^{99m}TcO$_4$ is preferentially released from the beads. The generator can be eluted once every six hours.

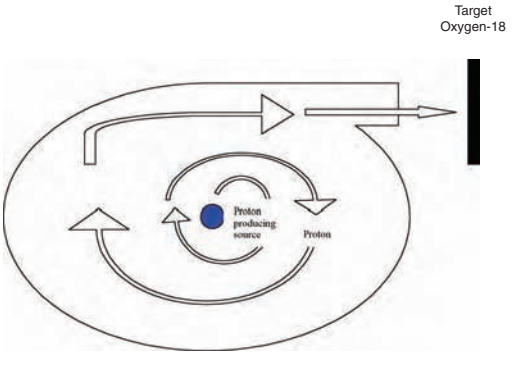

Figure 2b: Fluoride-18 and a neutron are produced by a cyclotron by the collision of Oxygen-18 with a proton.

Production of radiopharmaceutical (Figure 2)

The isotope most commonly used in conventional NM is Technetium-99m (^{99m}Tc) because it emits gamma radiation of an easily detectable energy (140keV) and has a biologically useful half life (six hrs). It is produced from a molybdenum-99/ technetium-99m generator. The generator is portable; it can be purchased and stored in a secured unit in the hospital.

Production of PET isotopes requires an expensive, large machine called a cyclotron which accelerates subatomic particles to nearly the speed of light. The particles or protons then collide against a target to produce an unstable positron emitter isotope.

Imaging (Figure 3)

Planar – This is a useful method to give an overview to large parts of the body, e.g. bone, lung and renal scintigram, but brain imaging requires more precise definition. Therefore planar view is rarely used in routine brain studies.

Single photon emission tomography, SPET – (also known as single photon emission computed tomography, SPECT) is a method using data from gamma radiation obtained in 360 degrees for multiplanar reconstructions similar to MR images.

Positron emission tomography, PET – is a technique which uses isotopes which undergo an annihilation reaction. Certain nuclei of the radioactive material emit positrons (anti-electrons). On collision with electrons, both the positron and electron are annihilated and two gamma rays are emitted, each with energy of 511 keV. Conveniently for imaging, the gamma rays are emitted at exactly 180 degrees which allows back projection for precise localisation of the source of emission.

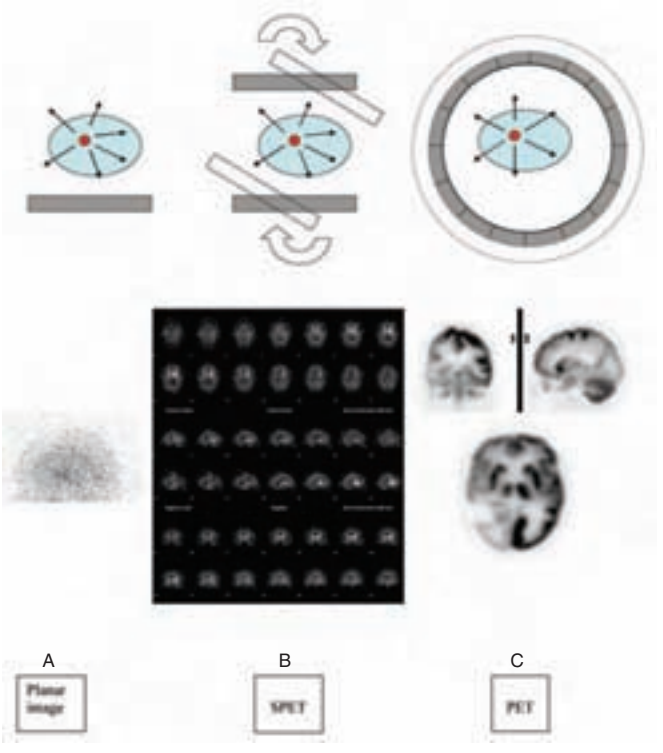

Figure 3: Nuclear Medicine imaging
A. Planar image. The scintillating crystal detects radiation (gamma rays or photons) emitted from the patient in one direction. Radiation that is not directed in the direction of the crystal is lost.
B. Single photon emission tomography. Two detectors are rotated around the patient. This method results in a more efficient radiation capture and allows reconstruction of multiplanar images.
C. Positron emission tomography. A ring of detectors around the patient detects radiation from all directions. Each annihilation event results in two photons being emitted along the same line at approximately same time, a coincidence circuit will be able to pick the correct signals within a fixed coincidence time window. Signals outside this time frame are rejected. The location of the annihilation event can then be traced back along the line of response.

Radiopharmaceuticals available

Planar/SPET

^{99m}Tc- Hexa-Methyl-Propylene-Amine-Oxime (HMPAO)

This is a non specific radiopharmaceutical which is able to cross the blood-brain barrier because of its lipophilic property. It is extracted from the bloodstream into the cerebral parenchyma and is dependent on the cerebral blood flow. This has a role in the imaging of neurodegenerative conditions with characteristic findings in Alzheimer's disease and frontotemporal dementia as well as other neurological conditions (Figure 4). It has also been used in epilepsy and shows increased uptake in focal seizures when injected during the seizure (ictal imaging). Hypoperfusion may be demonstrated on interictal imaging.

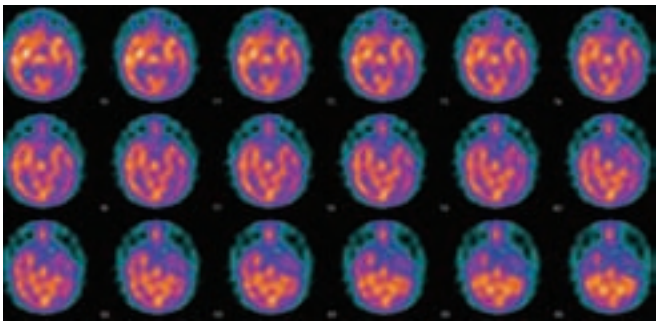

Figure 4: ^{99m}Tc-HMPAO SPET brain images of a patient with Alzheimer's dementia. There is reduced perfusion seen in the left temporoparietal region.

^{123}I-ioflupane (Dopamine transporter, DaTSCAN)

This is a specific radiopharmaceutical which is taken up by dopamine specific transporters found in the presynaptic nerve terminal. These transporters are found most abundance in the basal ganglia. In Parkinson's disease, parkinsonian syndromes (multiple system atrophy, progressive supranuclear palsy & corticobasal degeneration) and Lewy body dementia, the uptake is reduced significantly in the basal ganglion (Figure 5). In drug-induced Parkinson's disease or essential tremor, uptake is not affected (Figure 6).

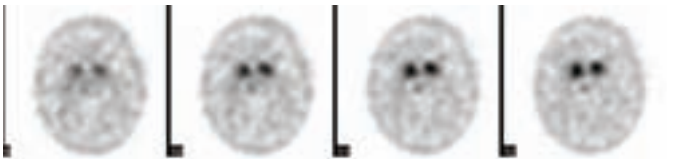

Figure 5: ^{123}I-ioflupane (DaTSCAN) SPET brain images of a patient with parkinsonian syndrome. There is bilateral reduction in the tracer uptake seen in the basal ganglion.

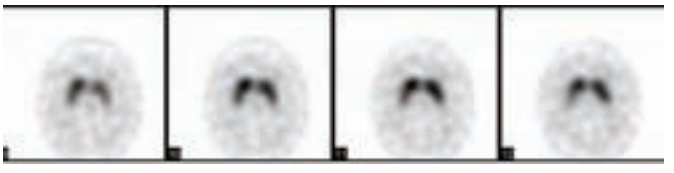

Figure 6: ^{123}I-ioflupane (DaTSCAN) SPET brain images of a normal patient.

PET

^{18}F Deoxy Glucose (18FDG)

^{18}FDG is a non specific positron emitting radiopharmaceutical. Its uptake in tissue is directly related to cellular glycolytic activity. Because of this property, infection, inflammation or tumour can be difficult to differentiate one from the other. Glucose is the only source of fuel for the brain; therefore ^{18}FDG is taken up avidly by the brain. Grey matter shows relatively higher ^{18}FDG tracer uptake as compared to the white matter. A focal reduction in tracer uptake can be seen in several neurodegenerative conditions (Figure 7). This method has better spatial resolution than

HMPAO SPET. Primary brain tumour or metastasis can sometimes be identified by this method (Figure 8). However, low grade malignancy can be missed and benign lesion such as meningioma, pituitary adenoma can show avid tracer uptake.

Figure 7: ^{18}FDG PET brain images in a patient with frontal lobe dementia. There is reduction in tracer uptake seen in the frontal lobe (arrow) (courtesy of M O'Doherty, Clinical PET Centre, London).

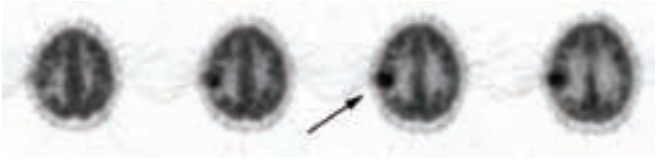

Figure 8: ^{18}FDG PET brain images in a patient with a brain tumour (arrow) (courtesy of M O'Doherty, Clinical PET Centre, London).

^{18}FluoroThymidine (^{18}FLT) and 11CarbonMethionine (^{11}C-Met)

This nucleotide analogue (FLT) and amino acid (^{11}C-Met) shows promise in diagnosis of cerebral tumours and uptake correlates with cellular proliferation. Tumour recurrence can be identified in the region of the brain where previous surgery or radiotherapy has been taken place (Figure 9).

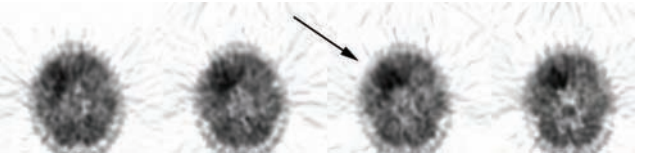

Figure 9: 11C- methionine PET brain images in a patient who had undergone surgery for oligoastrocytoma. PET images show region of increased tracer uptake consistent with recurrent disease (arrow) (courtesy of M O'Doherty, Clinical PET Centre, London).

^{18}F-Misonidazole (^{18}F-MISO)

This compound accumulates in hypoxic tissues and may be of use in predicting tumour recurrence following radiotherapy and other oncological treatments in conditions such as carcinoma of lung and glioblastoma.

Pittsburgh Compound B (PiB)

This tracer is taken up in cells containing beta amyloid and may be useful in detecting pathology such as Alzheimer's disease at an early stage.

Conclusion

Nuclear medicine is an important part of the medical imaging specialty in both clinical and research settings. With better understanding of human physiology, new tracers and techniques will no doubt continue to evolve and flourish.

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NHS Evidence – Neurological Conditions

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NHS Evidence – neurological conditions is a freely accessible website which provides access for NHS healthcare professionals to the best available evidence on neurological conditions. There is a vast and growing number of sources of evidence-based information available on the internet and it can sometimes be confusing and time-consuming going through them all. The collection brings them together into one place for you to access.

The service first arose in 1999, with a programme for the National electronic Library for Health (NeLH) being described by Sir Muir Gray and Simon de Lusignan in the BMJ.[1] By 2002, this had developed into a collection of 'Virtual Branch Libraries' available on the internet. The NeLH programme morphed into the National Library for Health in 2006; and the then Neurological Conditions Specialist Library was launched in November 2007 at the ABN conference in London. It now comes under the umbrella of NHS Evidence as one of 34 specialist collections in key clinical areas, such as diabetes, cancer, cardiovascular and commissioning. The collections filter the vast quantity of published research and provide regular updates on relevant sources of information as well as reviewing new publications.

NHS Evidence emerged from Lord Darzi's strategy for the future of the NHS, High Quality Care for All (June 2008).[2] Launched in April 2009, it ensures that everyone working in health and social care has worldwide access to the best available information via a single portal by allowing users to search a wide range of databases simultaneously, including internationally respected evidence-based sources such as, the Cochrane Library, British National Formulary and National Institute for Health and Clinical Excellence.

NHS Evidence – Neurological Conditions is led by Professor David Chadwick, emeritus consultant at the Walton Centre in Liverpool. He is supported by a project team based at the Royal Free Hospital Medical Library. An editorial board, made up of clinicians and stakeholders from across the country, is regularly consulted about the development of the collection, and a group of topic advisers provide advice and support. A full list of contributors to the collection can be seen at www.library.nhs.uk/neurological/AboutUs.aspx.

What does the collection include?

NHS Evidence – Neurological Conditions includes: Guidelines (NICE, SIGN, ABN and other relevant national and international guidelines); Systematic Reviews (especially Cochrane reviews and those published in a selection of the leading neurology journals); Health Technology Assessments and Economic Evaluations; policy and other relevant documents (e.g. documentation on the NSF for Long Term Conditions); online learning materials and links to high quality patient information. The records include an abstract, describing what's included in the resource. The majority of resources listed are freely available online. Resources are arranged by condition so it's easy to see quickly what new evidence has been published in your area of special interest. There is information on investigation and diagnostics, including a section on clinical neurophysiology. Sections on neurosurgery and neurorehabilitation are currently being developed.

Annual Evidence Updates

In addition to the regular content that is added to the website, the collection publishes Annual Evidence Updates on key topic areas within neurological conditions. Annual Evidence Updates (AEUs) highlight the best evidence published in the last year in the diagnosis, treatment and management of specific conditions. A comprehensive search is carried out to find relevant papers, which are then reviewed by topic advisers and assessed for inclusion. Only the best quality papers are included in the AEU. Commentaries are written by the topic advisers, who are specialists in the field, and attention is drawn to papers which point to a potential change in practice. Carrying out an AEU in this way provides the busy clinician with an easy overview of the best evidence from the past year. The AEU is available online and can be downloaded.

AEUs are currently carried out on epilepsy, headache, Parkinson's disease and multiple sclerosis. The recent AEU in headache highlighted four new guidelines and 22 new systematic reviews.

DUETs

The UK Database of Uncertainties about the Effects of Treatments (UK DUETs) publishes uncertainties about the effects of treatment which cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.[3] NHS Evidence – neurological conditions contributes to UK DUETs by identifying and compiling uncertainties that have been identified in systematic reviews.

Keeping up to date with the latest news in your area

In addition to the Annual Evidence Updates, NHS Evidence – neurological conditions provides a number of services to help clinicians stay up to date with the latest evidence. It publishes a monthly email bulletin summarising the latest additions to the collection, together with an overview of upcoming events of interest.[4] It also provides a number of subject specific RSS feeds,[5] as well as regular updates via Twitter (@nhs_ev_neuro). Feedback on the resource is welcomed from clinicians, for example, at events such as the Association for British Neurologists annual meeting. You can also leave comments via the website.

www.library.nhs.uk/neurological

1. http://www.bmj.com/cgi/content/full/319/7223/1476
2. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085825
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Manual of Botulinum Toxin Therapy

Authors: Truong D, Dressler D, Hallett M (eds.).
Published by: Cambridge University Press, 2009
Price: £42.75
ISBN: 9780521694421

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Around twelve years ago the late (and great) Professor Marsden was warming up the audience at a sponsored meeting on botulinum toxin treatment. I'd graduated from seeing one and doing one to teaching one and attending conferences and in those days in the UK that was about as expert as you needed to be. He asked "How many of the audience inject at multiple sites in each muscle for spasmodic torticollis?" – the hands went up. "How many of you have any evidence for that?" The hands went down. "How many of you use EMG guided injections?" The hands went up again. "How many of you have any evidence for that?" The hands went down. Since then I've been injecting botulinum toxin in my own way waiting for the definitive evidence and the definitive guide, whilst the uses and the experts have multiplied. So does the average UK neurologist need a manual? We know botulinum works, usually. We know almost anyone can be taught to do it safely and effectively, usually. After reading and sharing this book with colleagues I am persuaded that the answer is yes. It doesn't give all the answers and it almost certainly doesn't describe all the applications out there (some very much out there) but it is a pretty good manual. It covers, as comprehensively as current evidence permits, the treatment of at least 45 different conditions, and that's counting headache and spasticity as one each.

There is some general information on the history, development, production and testing of each available toxin (though not, thankfully, on its military efficacy), and then chapters considering groups of applications. There are some paragraphs on the conditions, the differential diagnoses and appropriate tests. The emphasis is on lots of tests, with seemingly little concern for cost or false positives (do spasmodic torticollis patients really need an MRI of the cervical spine?). Maybe the credit crunch will see to that. The text describes, with the help of easy to follow illustrations, where to inject and doses are given in all the different currencies. Where evidence is available it is cited. Not surprisingly the evidence is good for the earliest applications, and "it works because we say it does" for the recent ones. The evidence of efficacy is so good for the early uses that one meta-analysis even suggests we start looking closely at the technical aspects instead; Marsden was obviously ahead of his time.

The book does not have a UK perspective and I found myself wondering whether the authors, with their multiple tests and EMGs, would survive in a ten minute each, thirty-five patient solo UK botulinum toxin clinic, and whether their patients are any better off than mine. There is an occasional nod to cost-effectiveness but nothing about the costs of setting up a service or how to negotiate with commissioners. But maybe that is to expect too much from a world-wide (well, first world) manual. Certainly the chapters speak from a position of great expertise and no other manual is needed to gain the appropriate knowledge. It was a little alarming to find that I've obviously been doing it rather badly for some time, albeit without too many complaints. But it's OK; when the GMC does call me in, this book (at a bargain and cost-effective price of £42.75) will also give me the essential guide to treating "crows' feet" and "bunny lines". ◆

Restless Legs Syndrome

Restless Legs Syndrome
Authors: Hening WA, Allen RP, Chokroverty S, Earley CJ (eds.).
Published by: Saunders Elsevier, 2009
Price: £64.99
ISBN: 9780750675185

Restless Legs Syndrome
Authors: Chaudhuri KR, Ferini-Strambi L, Rye D (eds.).
Published by: Oxford University Press, 2009
Price: £5.99
ISBN: 9780199234882

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

One of the first books I ever reviewed was on the subject of restless legs syndrome (RLS), but this was subordinate to discussions of akathisia induced by neuroleptic medications (JNNP 1996;60:595). It perhaps says much for the advances in the field of RLS that two books devoted in their entirety to the condition have recently been published, notwithstanding the fact that the first clinical description dates to Thomas Willis in the late 1600s (curiously, both books reviewed here ascribe a knighthood to Willis, which was news to me). Since the prevalence of RLS may be somewhere between 5-10%, it is the business of every neurologist, albeit that only a small proportion of these individuals reach medical attention. The largely subjective nature of the symptoms (although periodic leg movement disorder may be a motor sign of RLS, with high sensitivity but low specificity) and the difficulty in producing an animal model may have contributed to the delay in RLS achieving widespread medical attention.

Hening et al. aspires to be the definitive textbook on RLS, and has the multi-author credentials and high production values to be so. There is some repetition, but this is an inevitable consequence of the in-depth coverage of both scientific and clinical aspects. The delineation of dopaminergic diencephalospinal pathways and the physiology of brain iron metabolism may not be easy reading for some clinicians, but the relevance becomes clear in the management sections of the book which are particularly thorough, likewise the comorbidities section. I would have liked to read more about the link, if any, with migraine, and also the nature of the cognitive deficits which may accompany RLS (it may present de novo to memory clinics) probably related to sleep disturbance. Aficianados will certainly want this book, price notwithstanding.

Chaudhuri et al is a more modest affair, handily portable in a jacket pocket, but with relatively broad coverage of the topic: symptoms, epidemiology, differential diagnosis, treatment. Copy editing and/or proof reading seems to have been kept to a minimum: how else to explain (p4) the statement to the effect that a 1923 publication consolidated another document published in 1945? The "secondary RLS" chapter overlaps with the (same author's) chapter on RLS in neurological disorders in the Hening book. Nonetheless, this book represents good value for money (as previously noted for books in the various Oxford Library series; ACNR 2007;7(4):28). ◆

Paediatric Neurology Series

All adult neurologists come across "paediatric" problems in their clinical practice – giving an opinion on an adolescent with MS, assessing a family with a mitochondrial disorder, or caring for the increasing number of young adult survivors of severe neurological disease in childhood. Often teenagers are just booked straight into an adult clinic, and although the pathology may be familiar, the clinical approach may not.

This is the first article in a new series on paediatric neurology. We make no apology for beginning with the basics – history, examination and child development and will move on to consider specific conditions such as epilepsy, headache, stroke and regression later on.

Our aim is to provide practical guidance and information on common paediatric neurological conditions which will be useful in your daily practice. – *Anna Maw, series editor.*

Anna Maw,
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Paediatric Neurology – History and Examination

For those not on familiar territory, paediatric neurology presents a double challenge – not only are children very different from adults, but their neurology is different too. The applicability of the classical neurological approach is limited as children tend to be affected by diffuse rather than focal pathology. Aetiology is also different with a high proportion of inherited and congenital conditions. Working with young children requires a significant shift of mindset with the clinical emphasis on observation rather than structured examination. Making sense of clinical findings in the under 5's is all but impossible without a working knowledge of child development and patterns of delay.

In this article we will look at the consultation, history and examination of children and young people and highlight points of particular importance in paediatric practice that differ from those in adults.

The Paediatric consultation

Children are, almost invariably, presented to the doctor by another person. As such, they often join the consultation in a passive role and are at an immediate disadvantage. They may not even know why they are there. Even adolescents and teenagers can be excluded and talked over and it requires a conscious effort on the part of the doctor throughout the consultation to establish a rapport and keep the child involved.

Getting children to talk can be difficult. The child needs to feel safe and secure in the consultation environment and to know that you are genuinely interested in him, his condition and what he has to say.

Setting the scene

Organise the physical environment so that the child is sitting next to you. You can then put questions and comments directly to him and observe him easily. Smaller children may well remain totally silent but this does not mean that your words are lost on them.

Start by introducing yourself directly to the child and the rest of the family. Work out who everyone is at the start to save embarrassment – mother, aunt, grandmother, father, stepfather (sometimes both), social worker and the community nurse will often attend. Remember to acknowledge siblings and ask their names and ages.

Clinic Letters are routinely copied to families. Check surnames and ask about other recipients (father may live at another address and parents may not be on speaking terms).

Take a moment to acknowledge the strain and worry which carers bring to a paediatric consultation. Anxiety can make people morose, aggressive, tearful and confused. Reassure everyone that they will get the opportunity to air concerns and ask questions.

Get the child involved

- Sit the child next to you
- Introduce yourself directly to the child
- Show concern and interest
- Address questions gently but directly
- Actively facilitate the child's involvement
- Check back with the child "is what your mum is saying right?"
- Acknowledge explicitly that some questions will be addressed directly to the parent

Choose your words carefully

- Avoid stigmatising terms
- Consider "**other** children of this age" rather than "**normal** children of this age"
- Use "young people" rather than "children" in the over 12s
- Use "you" rather than "he"
- Small children listen carefully even when they seem to be playing.
- Remember - Doctors' words are powerful and may resonate for years

Taking the history

The difference between taking a history in paediatrics and adult practice is largely one of emphasis. Information from the antenatal, neonatal and developmental history can be especially important in putting the presenting complaint into context. A new onset of seizure disorder, for example, may have quite different diagnostic implications if it comes on a background of previously normal development compared to a child with global developmental delay or recent onset of school failure.

The degree to which a child can provide the history himself will depend on age, developmental stage and social confidence. Children as young as 3 can often describe symptoms quite clearly but are unlikely to volunteer information unless they are asked.

Older children

The majority of adolescents and teenagers are willing and able to give most of the history themselves. Young people will often give a very candid account of the nature of their illness, its impact on functioning and the situation at school and home. However, if you do not make a conscious effort to include them, many will remain silent throughout. This is bad for everyone – he will grow to resent being ignored, and you may miss vital clues to the diagnosis.

Younger children

Younger children of primary school age should also be included from the beginning "why don't you tell me something about your headaches? Where do they hurt?" Many children will defer immediately to their parents, but they will appreciate that you asked them and may well be more likely to volunteer information at a later date.

In reality, the majority of the history in this age group is likely to be provided by the carer with occasional contributions from the child. While the parent is talking, take time to check back with child - "is what your mum is telling me right? Do you think there is anything she has missed out? What else do you think I need to know?"

Bear in mind that young children are very suggestible and will be desperate to get the answer "right". It is even more important than usual to avoid leading questions.

Toddlers and babies

While you are taking the history from the adult, watch and listen to the child. This could be the best chance you have to assess development. This is also the child's chance to weigh you up and decide whether or not to co-operate with the examination later.

Social, family and school history

Aim to get a good all round grasp of the child's social, family and academic functioning. Specific points are listed in the boxes to the right. Most children should have a few friends they can name and something they like to do outside school. School failure is a common presentation in paediatrics and should be taken as a significant problem.

Developmental history

A brief review of major developmental milestones is important – smiling, sitting, crawling, walking, talking, feeding and self-care.

The next two articles in this series are devoted to child development and its assessment and will give guidance on what information to seek and how to use it.

Antenatal history

- Maternal health during pregnancy
- Complications
- Intercurrent illnesses
- Scan results
- Previous pregnancies and outcomes
- Same biological father as siblings?

Birth history

- Gestation
- Mode of delivery (why?)
- Birth weight (centile)
- Duration of labour and complications

Neonatal history

- Any special care
- Feeding problems
- Mode of feeding
- Initial growth
- Vitamin K

Social history

- Age and occupation of parents
- Who else lives in the home?
- Recent family events – divorce, redundancy, moving house
- Friends in and out of school
- Leisure activities
- Benefits, disability living allowance
- Support network

School history

- Mainstream or special school?
- Year of school
- School progress
- School happiness
- Special needs or statement of SN
- Bullying
- Recent school move

Family history

- Siblings, parents and cousins
- Exclude consanguinity
- Ask about developmental problems, seizures, early death, recurrent miscarriage, learning problems and motor delay.

Neurological examination of children

Mobile children over 5

Children with a developmental age over 5 should be able to co-operate with a structured neurological examination, as you would use in adult practice. Instructions should be clear and short and accompanied by lots of praise and encouragement. Most children will be keen to co-operate but their ability to do so may well be reduced by anxiety and a fear of failure. Often children like to have the task demonstrated for them ("try to walk like me, as if you're on a tightrope").

Mobile children under 5

Clinical examination of this group is done largely by observation and stealth. Make the most of every opportunity to observe the child – particularly on the walk from the waiting room and while you are taking the history from the parent.

- **Listen** for language and conversation skills (many small children are electively mute around doctors), interaction with adults and evidence of imaginative play
- **Watch** for normal visual behaviour, fine motor skills – pincer grip, midline transfer, manipulation of small toys, Gross motor skills – gait, strength, symmetry of movements, running, bending, crouching, coordination
- **Play** with the child and encourage him to walk on a tightrope and turn round quickly, perform Gower's manoeuvre, walk on his heels, run, hop and jump up from the ground.

Cranial nerves

Observe visual behaviour, watch for fixing and following and eye movements. Test visual fields with a toy. Get a carer to stand behind you and distract the child while you have a quick look in the fundi.

- Watch facial movements
- Speak quietly with your hand covering your mouth to see if the child responds appropriately
- Ask about excessive dribbling or observe the child drinking
- Ask the child to stick his tongue out and shrug his shoulders

Neuromuscular examination

If you suspect a peripheral disorder, then proceed to a modified neuromuscular examination.

- Remove the child's clothing as far as he is willing
- Observe gait, muscle bulk, symmetry, posture and joint positions
- Look specifically for lordosis, scoliosis, hip flexion, ankle inversion or eversion
- Examine tone, joint ranges and power using lots of encouragement.
- Put your thumb over the tendon when testing reflexes.

Immobile children with a developmental age under 5

Be particularly careful with such children who may be easily distressed. Once a nine-month-old baby is crying and is frightened of you, it is

extremely hard to retrieve the situation!

Do not move the child unnecessarily – if he is happy in the pushchair, leave him there as long as possible.

Observe and note

- Developmental level
- Vision and hearing
- Any vocalisation
- Orthoses
- Obvious dysmorphism

Cranial nerves

Fixing and following – on a large toy, small toy and bright light.

- Look for symmetry of eye movement and pupillary reaction to light
- Response to sound
- Response to voice and smile
- Ask about swallow and feeding

Neuromuscular examination

- Watch for best motor function – antigravity movements of all 4 limbs, rolling, sitting and pulling to stand
- Pull to sitting and watch for head lag – low tone, reduced power
- If head control is good can he sit with or without support?
- Pick him up under the armpits – does he slip through your hands (hypotonia)?
- Gently manipulate joints to assess tone

Essentials for all children

- Lots of cajoling
- Look at the spine
- Neurocutaneous stigmata
- Head circumference and weight – are they on the same centile?
- Mood and engagement
- fundi

Conclusion

Every medical consultation has its own challenges. Consulting with children and families can present specific difficulties depending on the age of the child, the family context and the condition concerned. Older children and teenagers require a sustained effort on the part of the doctor throughout the consultation to enable them to give the most useful history and co-operate well with the examination. Younger children need a more flexible approach to examination which is based in close observation, opportunism and a good grasp of child development. As you watch a 4 year old patient running down the corridor away from your room yelling at the top of his voice, try not to think "where did I go wrong?" but rather "Hmm…symmetrical gait, bilateral heel strike, good visual acuity, age appropriate language, not evidently dysarthric…." ◆

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Not studied in severe renal or hepatic impairment – administration not recommended. *Elderly:* Clearance of ropinirole is decreased in patients over 65 years of age - titrate dose in normal manner. *Children:* Studies have not been carried out in patients under 18 years of age – do not give to children. **Contra-indications** Hypersensitivity to ropinirole or to any excipients, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Special warnings and precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with a history or presence of major psychotic disorders should only be treated with dopamine agonists if potential benefits outweigh the risks. Pathological gambling, increased libido and hypersexuality reported in patients treated with dopamine agonists for Parkinson's disease, including ropinirole. Ropinirole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. 4 mg only – contains sunset yellow (E110) which may cause allergic reactions. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's disease but, as is common practice, care should be taken when adding a new drug to a treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma concentrations of ropinirole have been observed with high doses of oestrogens. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. Smoking induces CYP1A2 metabolism therefore if a patient stops or starts smoking during treatment with ropinirole, dose adjustment may be required. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Effects on ability to drive and use machines** Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Adverse reactions** *Psychiatric disorders; common:* confusion, hallucinations, *uncommon:* Psychotic reactions including delusion, paranoia, delirium. Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. *Nervous System Disorders; very common:* somnolence, dyskinesia, syncope *common:* dizziness (including vertigo), *uncommon:* extreme somnolence, sudden onset of sleep. *Vascular disorders; common/uncommon:* hypotension, postural hypotension. *Gastrointestinal disorders; very common:* nausea, *common:* abdominal pain, vomiting, dyspepsia, constipation. *General disorders and administrative site conditions; common:* peripheral oedema. *Hepatobiliary disorders; very rare:* hepatic enzymes increased. **Overdosage** Symptoms of overdose likely to be related to dopaminergic activity. **Legal category** POM **Marketing Authorisation Holder** SmithKline Beecham plc t/a GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. **Further information is available from:** Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; customercontactuk@gsk.com; Freephone 0800 221 441. **Prescribing information last revised:** January 2009. **REQUIP®** is a trademark of the GlaxoSmithKline group of companies.

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REQ/FPA/09/44192/1
November 2009

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Less Than Full Time Training in Neurology

Jane Alty
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There was a time when being a doctor could only mean working full time and 'full time' could mean over 100 hours a week. This left many doctors facing tough decisions regarding work-life balance. Many female doctors wondered whether they should have children at all. If they did so, some changed specialty or left medicine altogether while others saw little of their growing children.

Thankfully times have moved on and from 1995 more doctors were able to train part time in supernumerary positions. This system worked well for trainees, but was unpopular with trusts who felt they did not get value for money. Few posts became available and word spread fast that part time work may not be so feasible after all. A new contract for Less Than Full Time (LTFT) training was therefore introduced in 2005 with new funding arrangements and a revised pay scale.

Who can apply to work less than full time?
All doctors can apply to train less that full time but there is no obligation for employers to grant this request. Each case is assessed individually and those in category one are given priority (see Table 1). A 2008 BMA survey revealed that 78% of flexible trainees were caring for young children and 22% reported personal ill health or disability.[1] Smaller deaneries may find it harder to resource and support LTFT training.

How popular is LTFT training?
PMETB estimates that 4.1% of doctors are training LTFT. 9.2% of all respondents to a 2007 PMETB survey said that they would like to train flexibly. In the 2008 BMA survey, 8% of all respondents were flexible trainees (13% of female trainees) and a further 22% of all trainees (32% female, 11% male) had considered part time training.[1]

Table 1: Reasons for applying for LTFT

Category one
Doctors with disabilities or suffering from ill health.
Doctors caring for young children.
Doctors caring for ill or disabled partners, relatives or other dependents.
Category two
Doctors training for national or international sporting events.
Doctors who take on short term extraordinary responsibility e.g. membership of national committees.
Doctors training for religious roles.
Doctors undertaking non-medical professional development.

How to apply
Each deanery has a named member of staff responsible for LTFT training. If you are interested in applying you should contact this person as soon as possible as the process may take several months. Typically you will be expected to send in an application form explaining your reasons for requesting LTFT. Some deaneries may then invite you for a face-to-face discussion about the various options. Your application will be discussed between the associate dean and the programme director. If the trainee is turned down for LTFT an appeal may be held. Once the deanery has agreed to fund your application there is some more paperwork to deal with (see ABNT website for details).

Slot share vs supernumerary posts
There are two main ways that you can work LTFT. Most deaneries would prefer you to be part of a slot share i.e. two doctors share one full time position. Some deaneries provide funding to allow each trainee to work 60-80% of full time so that they may both attend training days etc. However many deaneries are now stipulating that each trainee may work a maximum of 50% each. Supernumerary posts may still be funded if there is nobody available for the trainee to slot share with.

LTFT training in neurology
Female neurologists seem to make life choices influenced by their careers.[2] They are more often childless, have fewer children and have children later when compared to their male colleagues.[2] Relatively few neurologists work LTFT at present, but many more (including significant numbers of men) say they would like to work part time at some point in their careers. The changing expectations of both sexes, as well as the increasing proportion of female trainees, have important implications for workforce planning in neurology. Increased part time working will require additional training posts to ensure that service requirements are met.

The availability of LTFT training is crucially important to promote equal opportunities and allow doctors to make choices about their work-life balance.

Despite the bureaucracy involved, LTFT work is a realistic option for neurology trainees. Three of the eight members of the current ABNT committee (including the author) are training flexibly and highly recommend it! ◆

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The Research Series

In this issue we have continued our journey along the path of an academic career. In the last issue, Geraint Fuller described the various routes taken by trainees to complete a PhD and in this issue Chris Butler has continued this to the next stage. Chris is a lecturer in Oxford and has used his own experience to explain the intricacies of the lecturer position and its limitations.

Also in this issue Beth Mallam, the ABNT research rep, has written about the work of the "Clinical Research and Academic Committee" (CRAC). This subcommittee of the ABN works to represent the interests of the academic community and it is heartening to realise that they are so active. I hope trainees and consultants alike will find these articles useful and interesting. ◆

Boyd Ghosh, Series Editor.

Boyd Ghosh
is currently carrying out research for a PhD in Cambridge, investigating biomarkers and social cognition in Progressive Supranuclear Palsy. He is the current secretary for the ABNT.

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STOP PRESS
The ABNT is collating information to create an interactive research networking database on the ABN website. This will include cross-referenced lists of Academic Neurologists, research groups and research posts available in the UK. If you would like to find out more, or ensure that your group is represented, please contact the ABNT Research Rep, Beth Mallam: bethmallam@doctors.org.uk.

Chris Butler
is an Academic Clinical Lecturer at the University of Oxford. He is in his third year of specialist training in neurology. His research interests are in cognitive neurology and, in particular, the impairment of memory in epilepsy.

In the olden days, a period of research was a rite of passage to the leather armchairs and cigar smoke air of British neurology. A minority of initiates remained active in academia thereafter, but all had learned the life skills of critical thinking, tenacity and rarely seeing your family. However, for a variety of reasons that all had to change. The 2005 'Walport report'[1] lamented that academic medicine in the UK was in a "perilous state". The new-look, target-driven NHS apparently had no time for test tubes – there were waiting lists to deal with. Academic medicine needed rescuing. The report identified three principle deterrents to those considering a clinical academic career: i) the lack of a clear route of entry and transparent career structure, ii) the lack of flexibility in training posts and iii) a shortage of well structured posts upon completion of training.

The proposed remedy was a new "integrated clinical academic career path", designed to dovetail with the new Modernising Medical Careers specialist training structure. The core recommendation of the report was the development of the Academic Clinical Fellowship (ACF) and the Academic Clinical Lectureship (ACL). In this article, I will discuss the format of these new posts, how they are supposed to address the three problems identified above, and what other issues the budding clinical academic should be aware of when considering whether to apply.

i) Entry and structure

The ACF and ACL are run-through posts that fit into the overall training structure as illustrated in Figure 1. They are designed to see the aspiring clinical academic through his or her specialist training whilst, at the same time, providing the flexibility to conduct research towards a higher degree (during the ACF) and develop postdoctoral independence (during the ACL). Training centres are awarded funding for these posts by national competition, and appoint to them by a locally constituted committee. You, the successful candidate, are awarded a National Training Number (Academic) (NTN(A)). Your first year as an ACF is identical to the standard ST1 year, and may be predominantly based in district general hospitals to ensure early exposure to coalface medicine. The second year is again mainly clinical, but includes dedicated sessions for academic training and for preparation of an application to independent funding bodies, such as the Medical Research Council or Wellcome Trust, for a competitive training fellowship. With such a fellowship, you then spend two or three years working towards a higher degree – MD or PhD. Upon completion of this, you apply for an ACL post, splitting your time equally between academic and clinical work. The ACL post is designed to give you time to develop your skills as an academic, providing you with the post doctoral research skills needed to successfully apply for a clinician scientist or senior lecturer award through, for example, MRC or Wellcome Trust. Parallel opportunities exist for those wishing to specialise in medical education rather than research. For an interim period, whilst the first batch of ACFs ripens, ACL posts are being appointed separately to applicants who already hold a higher degree. In addition, there are some University lecturer posts available. These are not funded in the same way and often involve a significant amount of teaching.

ii) Flexibility

The flexible structure of the ACF and ACL posts is intended to stop you feeling as if you are moonlighting every time you go off to the lab, and ease the tension that can develop between academic and clinical commitments. The posts are appointed ad personam, with the salary associated with the individual rather than the institution. This confers geographical flexibility: if you move to a different centre, to learn a new experimental technique or to develop collaborations, the money moves with you. There is temporal flexibility too, so that the ratio of clinical to research activities can be altered according to your needs. Of course, fulfilling curricular requirements as well as the pragmatics of fitting in with the registrar rota will place important constraints on this flexibility. Issues such as how to arrange on-call commitments, teaching responsibilities, time

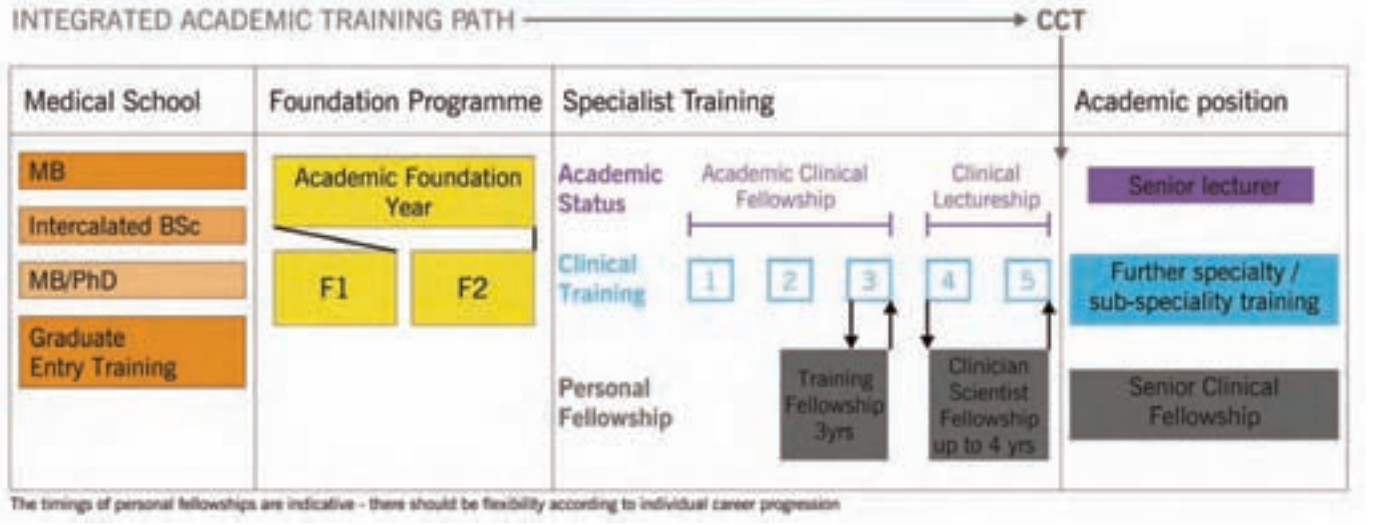

Figure 1: A schematic of the integrated academic training path, taken from the 2005 Walport Report.

spent in district hospitals and participation in specialist clinics will all need to be decided locally, on a case-by-case basis, and will require some creativity. You must also take into account that diluting your clinical training with research means that it takes longer to come out the other end and that, as yet, no one seems to know quite how much longer. With a three-year PhD plus, say, a further four years as an ACL, you are looking at being perhaps five years older than some of your contemporaries when you finally become a consultant. For a small number of trainees who wish to pursue an academic career in the context of a narrow clinical specialism, an attractive alternative may be to gain direct entry to the Specialist Register, on the recommendation of the Postgraduate Medical Education and Training Board (PMETB), without completion of the requirements for CCT.

It remains to be seen how tolerant this new, integrated academic career path will be of those who wish to get on late or get off early, or of those wanting to take time out for child rearing. The Walport report certainly recognised the importance of flexibility in these aspects as well, and recommended the introduction of 'catch-up' programmes for people returning to research after a career break. Part-time clinical lectureships for up to six years are also available.

iii) Exit

Having encouraged people through the early stages, it is, of course, also vital to ensure that clinical academics don't have a nasty surprise when they get to the end of their training and find that there aren't enough senior posts to go round. Some provision has been made for this in the form of a cohort of 'new-blood' senior clinical lectureships, owned in partnership by NHS Trusts and educational establishments.

Other issues

Money: The ACL posts do not include any funding for bench costs, consumables, equipment or travel. It is likely, therefore, that your first six months in the job will be dominated by grant applications. A good place to start is the Academy of Medical Sciences/Wellcome Trust Starter grant (http://www.acmedsci.ac.uk). The intention behind these smallish grants (up to £30,000 over two years) is to allow you to develop work that will eventually form the basis of a Clinician Scientist application.

Mentoring: Good mentorship from other clinical academics, both within and without your educational establishment, is critical. The Academy of Medical Sciences has a national mentoring programme for Clinical Lecturers.

This new programme has now been running for just over two years. It is important to note that it was never intended to be the only route to a career in academic medicine. The old-fashioned way of separating research and clinical training before combining them at consultant/senior lecturer stage remains viable and, for some, preferable. For more information, visit the Academy of Medical Sciences (http://www.acmedsci.ac.uk) or the National Institute for Health Research (http://www.nccrcd.nhs.uk). ◆

1. *Medically- and dentally-qualified academic staff: recommendations for training the researchers and educators of the future* (the 'Walport report'). The Academy of Medical Sciences. 2005.

CRAC

Beth Mallam

is the ABNT Research Representative. She is currently working towards a PhD with Professor Scolding's team at Frenchay Hospital, Bristol. Her research is looking at the potential of mesenchymal stem cells as a therapy for Multiple Sclerosis.

The Historical Perspective

CRAC is the "Clinical Research and Academic Committee" set up by the Association of British Neurologists (ABN) to facilitate research and academic activities amongst UK Neurologists. As such it seeks to support not only those in full time academic posts but also NHS appointed consultants and trainees wishing to engage in research. In order to carry out this function there is wide representation on the committee (see box 1), designed to represent stroke and DeNDRoN research networks as well as regional areas in the UK.

Current Issues

There are currently many issues which CRAC is seeking to influence. Generally CRAC aims to promote UK research by supporting a strong research presence at the ABN meetings and facilitating the establishment of research networks amongst collaborators. CRAC also has a strong partnership with the British Neurological Surveillance Unit (BNSU) and its chair Rustam Al-Shahi Salman. Using the BNSU we aim to obtain a detailed assessment and the location of rare neurological cases.

Consultants

CRAC has assisted with the development of Academic Clinical Fellowships and lectureship

and senior lectureship programs, as outlined by Christopher Butler in this issue of ACNR. CRAC is also very keen to support academic activity amongst NHS colleagues. To that effect CRAC is committed to protecting the 'supporting clinical activities' (SPAs) as an essential component of the consultant job plan, enabling practising clinicians to contribute to the knowledge-base underpinning their discipline. Members can apply for funded sessions through their local clinical research networks.

Trainees

CRAC has been instrumental in organising the ABN Fellowship Scheme. This will be an annual application process operating on behalf of several small charity based fellowships. A single committee will be convened by CRAC to allow peer review and assessment of candidates so that recommendations can be made to the charities for funding. It is expected that the first round of this scheme will take place in 2010. Further details will be advertised at the 2010 ABN meeting in Bournemouth, as well as on the ABN website. CRAC also organised the Research Forum which took place at the ABN meeting in Liverpool in 2009 and will be organising the Research Forum in 2010 in Bournemouth, as discussed in the previous issue of ACNR. CRAC has also published papers detailing funding opportunities, guidelines on starting out in research, and a list of the main academic neurology departments in the UK (see below for a list of publications). These publications were prompted by a survey carried out by the ABNT in 2005 and there are plans for CRAC, in partnership with the ABNT research representative, to update these and develop them into a more accessible cross referenced web based resource.

Medical Students

CRAC also supports medical students by supplying intercalated degree bursaries (previously known as BMedSci Bursaries). These awards provide at least four months of support if full time research is involved. The primary supervisor need not necessarily be a neurologist but a consultant neurologist who is a member of the ABN must be a co-applicant. Two bursaries are usually awarded each year.

Useful further reading:

- *Academic Neurology in the United Kingdom: Threats, Opportunities and Recommendations*
  Printed shorter version WITHOUT appendices
  Full version with ALL appendices
  A report prepared for the Association of British Neurologists by the Clinical Research & Academic Committee, June 2003.
- *Neurology Funding Opportunities*
  A report prepared for the Association of British Neurologists by the Clinical Research & Academic Committee, October 2004.
- *Research in Training*
  Guidelines re supervision and career advice for trainees without a Neurology NTN who would like to undertake research, a report prepared for the Association of British Neurologists by the Clinical Research & Academic Committee, Jan 05.
- *Academic Neurology Departments in the UK: main research areas, staffing & prospects for new posts*
  Information prepared and updated annually by the Clinical Research & Academic Committee, April 2005.

Current members of CRAC are:

Professor Patrick Chinnery (Chairman, North East),
Dr Rustam Al-Shahi Salman (BNSU Chair, Scotland),
Dr Heather Angus-Leppan (ABN Honorary Associate Secretary),
Professor Martin Brown (Stroke Networks Representative),
Professor Clive Hawkins (Chair, UKCRN/NIHR Specialty Group for Epilepsy & Neurology),
Professor Nigel Leigh (London),
Professor David Miller (London),
Dr Beth Mallam (ABNT Research Representative),
Dr Huw Morris (Wales),
Professor Martin Rosser (DeNDRoN Director),
Professor Neil Scolding (South West)
Dr Stephen Wroe (ABN Honorary Secretary)

The Neuropsychology of Board Games, Puzzles and Quizzes

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Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery,

Correspondence to:
Email: a.larner@thewaltoncentre.nhs.uk

A potentially bewildering array of neuropsychological tests exists, examining the various domains of cognitive function, such as intelligence, memory, language, perceptual (especially visuoperceptual) skills, praxis, and executive function. Board games, puzzles, quizzes and other parlour diversions have a number of common features, including being rule bound and subject to the play of chance, and require various degrees of strategy, planning, and flexibility for their execution. Hence, they may be regarded as tapping some of the same functions explored by neuropsychological tests, as examined in the following tentative suggestions. Readers may be able to conjure further examples. Like neuropsychological tests, the diversions are seldom tests of a single function.

Memory
Quizzes are usually tests of semantic (facts) memory. Examples include the board game Trivial Pursuit, the long-running radio programme Brain of Britain, and TV shows such as University Challenge, Mastermind and The Weakest Link. These are essentially testing recall, although the wording of questions may move questions more toward the recognition paradigm (NB the board game Mastermind taps very different cognitive skills). Tests more inclined towards working memory are seldom encountered, although occasional questions in University Challenge, of the "Buzz as soon as you know the answer" type, based on mathematical calculations, do occur. A semantic memory test with a forced choice paradigm is presented in Who wants to be a millionaire, usually 1 of 4, but occasionally 1 of 2 ("50:50"), and recourse to external memory aids is also possible ("Ask the audience" and "Phone a friend").

Visual memory games often revolve around recalling the locations of matching cards or symbols which are only briefly uncovered, or objects shown and then removed (the "tray game"); all may fall under the rubric of Pelmanism. (My personal experience suggests that children are better than this adult at these games.)

Language
Many board games are essentially linguistic in the skills they tap, such as Scrabble and Boggle, where lettered tiles must be used to make words. The latter has a visuospatial element in that letters in the array must be adjacent (vertical, horizontal, or diagonal) to be used to make words, and also there is a fixed time element. The "against the clock" factor for word generation also looms large in the TV show Countdown, where word length earns the points rather than number of words generated. Clearly there is an executive function, as well as linguistic, component to these games, tapping particularly phonemic verbal fluency. Crosswords, depending on their degree of cryptic-ness, probably tax executive function more than simply linguistic skills. The game Articulate taps semantic modules, requiring words to be conveyed by giving their meanings.

Games involving numerical calculation might be included here, since numbers are a form of language. Certain card games are based on addition (Pontoon, Cribbage). In one form of dominoes, matching of the two end tiles to be multiples of 3 and 5 is the basis of scoring in the game (cf. below). Sudoku obviously tests numerical as well as spatial functions.

Perceptual (especially visuoperceptual) skills
Snap is a classic game of simple visual matching, amenable to even very young children. In one form of dominoes, matching of spots and getting rid of your tiles are the sole objects of the game (cf. above), as in variants such as Triominoes. Card games such as Rummy and Patience and even Poker require visual matching, to collect cards with like characterisitics, combined with executive function, with rather more complex rules than snap. Any game involving trumps may also share these cognitive demands.

Visual recognition lies at the heart of Wordsearch puzzles, with visual scanning of an array of letters in search of salience (word recognition). Likewise games such as charades probe visual recognition skills (older readers may recall that this was televised as Star Turn on BBC children's TV, before the format was ripped off by ITV as Give Us A Clue). Pictionary also taxes visual recognition skills. Jigsaw puzzles require matching of visual patterns and colours, but also sometimes shape (e.g. edges, large areas of monochrome sky or grass). Playstation and DS are alleged by some to promote visual/manual coordination.

Praxis
Testing of acquired skilled motor movements seems less profitable as a theme for parlour games, as compared to other domains. One might argue that Jenga and Buckaroo are all about fine motor control.

Executive function
As mentioned, executive function plays a part in many of the games already alluded to. Whereas the throw of the dice determines everything in Snakes & Ladders (truly, alea jacta est!) and largely so in Frustration or Sorry, greater cognitive demands are imposed in dice games such as Monopoly and Careers (in what proportions do you choose to pursue fame, happiness or fortune?), in which strategy (as well as luck) is important. Cluedo requires information to be pursued and inferences to be made.

Conclusions
In light of these considerations, it may be worth asking patients and carers about facility, or loss thereof, in playing board games and doing puzzles as one element of history taking in the cognitive clinic. However, it must be borne in mind that some games seem largely bereft of all intellectual function: it is hard to see what cognitive functions are tapped in deciding in which order to open a set of boxes (Deal No Deal).

Examination of the ability to play games effectively lies at the heart of some existing cognitive tests, such as Wisconsin Card Sorting and tests of gambling such as the Iowa Gambling Task and the Cambridge Gamble Task. Might Monopoly, cards, charades, etc be introduced to the cognitive clinic? Patients might find them less daunting than unfamiliar neuropsychological tests, and it might add some fun to consultations. A loss of enjoyment in such innocent diversions might also be indicative of cognitive disorders with frontal lobe involvement. ◆

Health Records: out of the frying pan?

Heather Angus-Leppan MSc (Ep), MD, FRACP, FRCP

was born in South Africa, trained in Australia and won a Scholarship as Visiting Australasian Registrar to the Radcliffe Infirmary, Oxford, in 1993. 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, past Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and Chair of the Map of Medicine Epilepsy Group, UK.

Charles Warlow, BA MB BChir MD FRCP FMedSci, FRSE

s Emeritus Professor of Medical Neurology, Western General Hospital, Edinburgh. Stroke has been his research interest for 30 years, particularly the epidemiology of stroke, randomised trials of treatment to prevent stroke, and meta analysis of such trials. He now concentrates on broader issues such as research design and bias, the ethics of research and publication, editing 'Practical Neurology' while continuing research into functional neurological problems. He is Non-Executive Advisor to the Association of British Neurologists.

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ABN.
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We have all experienced it. The nightmare is a busy clinic, we are running late, and groan at the site of twelve inches of chaos – our next patient's notes – spewing across the floor in our haste to get to their heart. We hope that our frantic thumbing through them will guide us to our dream – that crisply written summary that will light our way through the tricky consultation.

Like motherhood and evidence-based medicine, we all believe in secure, accessible, standardised patient records. The Association of British Neurologists (ABN) agrees that medical records are a crucial component of patient care and need to be as full, accurate and up to date as possible. Balancing accessibility and security is essential. They must be accessible to health care professionals and patients, yet secure and protected from abuse, tampering or inappropriate access.

The early NHS hospital records were easy to navigate, at least the 'medical bits' were accessible. For each 'episode' the order of in-patient sections was pretty standard throughout the UK – history of presenting complaint, general health, past medical history, family history, social history, physical examination and then follow-up notes. For the doctor, this standard form allowed rapid navigation, even when starting a job in a new hospital. What was chaotic was the order in which the various sections relating to different encounters with the hospital were arranged (outpatient notes, outpatient letters, tests) and the lack of care in keeping the notes in order. The chaos and the bulk have worsened, with the addition of nursing and other notes (the single patient record), along with long protocols that have little written on them (for example the Waterlow score sheets).

Electronic notes provide a wonderful opportunity to sort out the chaos and to have a standard format across the UK allowing the professionals involved with patient care quickly to locate the sections they need. As clinical care becomes fragmented, with multiple hand-overs between teams, and with doctors and other professionals moving up and down the spokes from work in the community to activity at the hub, and with movement of patients and doctors around different areas of the UK, it would be wonderful to have a standard system with a familiar format e-record for each individual patient, available in primary, secondary and tertiary care, and also accessible to the patient.

Implementation of this should not be hasty, as complex issues are involved. The suggested goal of making this operational within five years is probably over-ambitious. We must avoid the mistakes that occurred with other systems– for example, in the electronic forms used in MTAS; problems with PACS (with reporting of delays, mistakes and clinical incidents to the National Patient Safety Agency and the Joint Neuroscience Council attesting to the problems) and Cerner implementation in some hospitals with high-profile adverse clinical incidents. Extensive trials will be needed by the many professional groups involved. Issues of patient consent, decisions about information access to those outside the immediate care team, data security (without being cumbersome) need careful consideration. The format has to be correct. "Consumer" confidence in the Government track record to get IT right (loss of government-held personal data and MTAS for example) is at a low ebb. Resources for this task must be adequate – ongoing close working partnerships between IT and medicine are essential if past mistakes are to be avoided.

Getting the electronic-records right will be extremely time-consuming, and must be funded and tested to destruction. The momentum must be kept up, and liaison between active clinicians and IT specialists is paramount, as well as frequent feedback to organizations with an interest in the system for dissemination to their members, in order to maintain enthusiasm for the vast task.

Although it may seem obvious to clinicians, the evidence that standardisation of patient records improves patient care and outcome is limited. We suggest that the evidence-base should not be overstated. If it is, this will attract criticism and deflect attention from implementation. It will be crucial to cull the established (electronic) record systems in use which are not standardised across all locations. Duplication of records is cumbersome and potentially risky, as pieces of information can be overlooked or erroneously transcribed. Although a computer looks neater than a dozen sets of disorganized notes, the potential for chaos and mistakes is just as great.

Each 'stakeholder' – in our case UK neurologists – must ensure their special needs are addressed or, as in the past, they will splinter off and set up their own departmental records. Some of the needs specific to neurology are:

- plenty of space for a free-hand history (but then e-records should have unlimited space)
- a neurological examination proforma (may be one comprehensive system for neurologists and another, abbreviated version, for medical SHOs)

- electronic, ideally clickable, links to radiology and pathology images and neurophysiology results.
- a fail-safe system for clinicians to reliably receive results of ordered tests electronically. With results arriving erratically and at unpredictable intervals, it is impossible for the clinician to chase results on all tests ordered. There are many examples of serious clinical incidents due to failure of results being fed back to clinicians. Previously, results were sent back to the clinician on paper. This is now haphazard, and a reliable system of returning results electronically to the clinician for action is essential for patient safety.
- Decent record keeping and updating of records is vital. This has been a major problem with paper notes. So often the paper notes fall into disarray in the hands of under-funded records departments. There is no inherent magic in an electronic system, and processes and resources will be required in order to keep these tidy. Clinicians should not be expected to take on this process without IT and administrative back-up.
- There must be an audit trail – records will no doubt be updated – and the responsible clinician must review who writes what and when, and be able to edit the information if necessary
- There is a need for sections to be printable and downloadable.
- Incorporation of down-loadable information sheets, or web-links to patient information – and clinical information such as the BNF or current version of MIMS
- A system allowing the records to follow the patient from hospital to hospital linked to GP records.
- Clinical records should be person-based – independent of (that is, not determined by) location or clinician
- Records and the related structure and content standards should follow a patient through stages of care.
- There must be scope for 'pages' to be added and deleted. For example, do all users want a page on 'information given to patients' in the summary to the General Practitioner?
- The whole thing needs to be cleverly designed, like the very best websites, so it is easily navigated and amended.
- Patients should be involved at an early stage – but there is a danger of slowing down the process if too many parties are involved in formulating details of the records. We suggest that early patient involvement should focus on consent, access and the considerable ethical issues.
- We support the use of names, as well as numbers for identification, as this provides additional security and is less open to transcription errors.

The ABN will continue active involvement in the project and can offer a representative to champion this. We support the model of involving active clinicians, not just web designers who may need guidance in the aims and needs of the system that evolves. The ABN is well organised to seek consensus with consultants, to liaise with colleagues in Neurosurgery and Neurophysiology and (importantly) with trainees who write most in the electronic notes, as well as other health care professionals, such as neuroscience nurse practitioners. Some of our members already work in centres with electronic records and so have first-hand experience.

The Association of British Neurologists (ABN) looks forward to working with the Royal College of Physicians and others on standards for the structure and contents of health care records. We applaud the efforts to date, but emphasise the need for enough time and resources to implement these safely and correctly. ◆

2009

November

Functional Fascial Taping
9 November, 2009; Leicester, UK
www.physiouk.co.uk

MS Trust Conference
8-10 November, 2009; Kenilworth, Warwickshire
E. conference@mstrust.org.uk

Parkinson's Plus study day
9 November, 2009; Derby, UK
www.ncore.org.uk

Cervical Auscultation
10 November, 2009; Derby UK
T. 01332 254679,
www.ncore.org.uk

UKABIF Annual Conference: Developments in Acquired Brain Injury
11 November, 2009; London, UK
T. 01752 601318,
E. ukabif@btconnect.com
www.ukabif.org.uk

University Classes in Multiple Sclerosis VI
11 November, 2009; Lisbon, Portugal
E. m.friedrichs@charcot-ms.eu
www.charcot-ms.eu

Functional Fascial Taping
12 November, 2009; London, UK
www.physiouk.co.uk

European Charcot Foundation Symposium "A new Treatment Era in Multiple Sclerosis"
12-14 November, 2009; Lisbon, Portugal
E. m.friedrichs@charcot-ms.eu
www.charcot-ms.eu

Functional Fascial Taping
13 November, 2009; Winchester, UK
www.physiouk.co.uk

Functional Fascial Taping: Make an instant difference to Pain & ROM in nearly any patient
14 November, 2009; Bristol, UK
www.physiouk.co.uk

Motivating the Unmotivated: helping 'difficult' patients
17 November-2009, Derby, UK
T. 01332 254679,
www.ncore.org.uk

Bringing down the Barriers - Translational Medicine in Inherited Neuromuscular Diseases
17-19 November, 2009; Brussels, Belgium
E. stephen.lynn@ncl.ac.uk

Brain Injury Rehabilitation Trust Seminar
18 November 2009; Liverpool, UK
E. redford.court@thedtgroup.org

5th National Autism Today Conference
17-18 November, 2009; Edinburgh, UK
MA Healthcare Ltd,
T. 0207 501 6762,
www.mahealthcareevents.co.uk

6th International Congress on Vascular Dementia
19-22 November, 2009; Barcelona, Spain
E. vascular@kenes.com

West of England Seminars in Advanced Neurology (WESAN)
19-20 November, 2009; Exeter, UK
www.aquavenuesolutions.com/wesan2009

Neurological Cancers Study Day
20 November, 2009; Middlesex, UK
Anni Hall, T. 01923 844177,
E. anni.hall@mvh-tr.nhs.uk

Brain Injury Rehabilitation Trust Seminar
20 November 2009; Milton Keynes, UK
E. tem@birt.co.uk

Be Activated Courses: A unique NMS treatment technique
21-22 November, 2009; London, UK
www.physiouk.co.uk

Multidisciplinary Brain Tumour Study Day 2009
23 November, 2009; London, UK
E. malcolm.galloway@royalfree.nhs.uk

Complaints Management and Investigation
24 November-2009, Derby, UK
T. 01332 254679,
www.ncore.org.uk

Be Activated Courses:A unique NMS treatment technique
24-25 November, 2009; Manchester, UK
www.physiouk.co.uk

Brain Injury Rehabilitation Trust Seminar: "Measuring Outcomes of Rehabilitation at Fen House"
26 November 2009; Ely, UK
E. fh@birt.co.uk

Royal College of Physicians Of Edinburgh Symposium: Neurology
27 November, 2009; Edinburgh, UK
www.rcpe.ac.uk/education/events/neurology-nov-09.php,
E. Christina Gray, C.Gray@rcpe.ac.uk

9th Annual King's Neuromuscular Symposium
27 November, 2009; London, UK
T. 020 7848 5541/2,
E. Sophie.Morris@iop.kcl.ac.uk
www.iop.kcl.ac.uk/events/?id=809

BSRM Conference: The Work Agenda: from novice to expert
27 November 2009; Bristol, UK
T. 01249 814910,
E. philippa@thecataloguer.co.uk

Be Activated Courses: A unique NMS treatment technique
28-29 November, 2009; Scotland, UK
www.physiouk.co.uk

RAatE 2009
30 November-1 December, 2009; Coventry, UK
http://www.hdti.org.uk/raate

December

Posture & Balance in Neurological Conditions, lower limb, Qualified staff
1-2 December-2009, Derby, UK
T. 01332 254679,
www.ncore.org.uk

4th UK Stroke Forum Conference
1-3 December, 2009; Glasgow, UK
E. Helen.Chapman@stroke.org.uk

4th International Congress on Brain and Behaviour & 17th Thessaloniki Conference
3-6 December, 2009; Thessaloniki, Greece
T. 30 210 749 9353,
E. lianae@triaenatours.gr

Edinburgh Neuroscience Christmas Lecture Stem Cells for Neurological Disorders - where now?
4 December, 2009; Edinburgh, UK
E. edinburgh.neuroscience@ed.ac.uk

Epilepsy Study day
4-December-2009; Derby, UK
T. 01332 254679,
www.ncore.org.uk

Attention & Information Processing: Advanced Cognitive Rehabilitation Workshop
4-5 December, 2009; Gatwick airport, London, UK.
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

10th Annual UK Movement Disorders Meeting
4-5 December, 2009; London, UK
E. neurolgy@boehringer-ingelheim.com

63rd Annual Meeting of the American Epilepsy Society
4-8 December, 2009; Boston, USA
T. 860 586 7505,
E. csluboski@aesnet.org

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 8 December, 2009

Anatomy and Mobilisation of Hands & Feet for Assistants
8 December, 2009; Derby, UK
T. 01332 254679
www.ncore.org.uk

2nd National Sleep Disorders Conference
10 December, 2009; London, UK
MA Healthcare Ltd,
T. 0207 501 6762,
www.mahealthcareevents.co.uk,

Brain Injury Rehabilitation Trust Seminar: "Specialist Brain Injury Rehabilitation – Is It Worth It?"
10 December 2009; Collumpton, UK
E. woodmill.admin@disabilities-trust.org.uk

Cambridge Dementia Course
10-11 December, 2009; Cambridge, UK
E. penny.pearl@btinternet.com

18th WFN World Congress on Parkinsons Disease & Related Disorders - WFN 2009
13-16 December, 2009; Miami, USA
Peter Sewell, T. 41-229-080-488,
E. parkinson@kenes.com

Cellular & Integrative Neuroscience Themed Meeting
14-16 December, 2009; Cardiff, UK
T. 020 7269 5715,
E. meetings@physoc.org
www.physoc.org/meetings

2010

January

Development of the human neocortex
5-7 January 2010, Oxford, UK
E. g.j.clowry@ncl.ac.uk,
www.anatsoc.org.uk/events/event_details.php?id=115

Advances in Chronic Pain Management
21-22 January, 2010; London, UK
T. 020 7501 6768,
E. lisa.freeman@markallengroup.com

3rd European Neurological Conference on Clinical Practices: Neurovascular and Neurodegenerative Diseases
22-24 January, 2010; Bucharest, Romania
T. 33 0 153 644 489,
E. alexandra.quetard@discovery-cascade.com

International Symposium on Protein Phosphorylation in Neurodegenerative Diseases
28-30 January 2010; Valencia, Spain
E. catedrasg@cac.es
www.fundacioncac.es/catedrasg

February

Neurological Futures: Speculation, Value and Promissory Hope in the Bioeconomy
5-6 February, 2010; Oxford, England
E. ENSN@lse.ac.uk

12th National Dementias Conference
18-19 February, 2010; London, UK
E. conferences@markallengroup.co.uk

EDDP 2010 International Conference on Early Disease Detection and Prevention
25-28 February, 2010; Munich, Germany
www.paragon-conventions.com/eddp2010

1st European Traumatic Brain Injury Conference
24-27 February, 2010; Vienna, Austria
E. Dr Nikolaus Steinhoff,
nikolaus.steinhoff@hochegg.lknoe.at
tbi2010@medacad.org

Long-term (Neurological) End of Life Care Conference
25 February, 2010; London, UK
Mr Mark Baker,
T: 0208 780 4500 ext 5010,
E: mbaker@rhn.org.uk
www.rhn.org.uk/institute

3rd International Congress on Gait & Mental Function
26-28 February, 2010; Washington, USA
E. gait@kenes.com
www.kenes.com/gait

March

The International Brain Injury Association's 8th World Congress on Brain Injury
March 10-14, 2010; Washington, DC, USA
E. congress@internationalbrain.org
www.internationalbrain.org

1st International Congress on Epilepsy, Brain & Mind
17-20 March, 2009; Prague, Czech Republic
Marcela Rajtorova,
T. 42 0 284 001 444,
E. epilepsy2010@guarant.cz

6th World Congress for NeuroRehabilitation
21-25 March, 2010; Vienna, Austria
E. christian.linzbauer@medacad.org
www.wcnr2010.org

20th Annual Rotman Research Institute Conference – The Frontal Lobes
22-26 March, 2010; Toronto, ON, Canada
Paula Ferreira,
T. 416 785 2500 ext. 2363,
E. pferreira@baycrest.org

International Symposium on Disturbances of Cerebral Function Induced by Food and Water Contaminants
23-25 March, 2010; Valencia, Spain
E. catedrasg@cac.es,
www.fundacioncac.es/catedrasg

11th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy
24-27 March, 2010; Geneva, Switzerland
E. jharbison@siumed.edu /
ahamilton@siumed.edu

European Association of Neurosurgical Societies Annual Meeting (EANS 2010)
25-27 March, 2010; Groningen, Netherlands
T. 41 229 080 488,
E. eans2010@kenes.com

British Neuropsychological Society Spring Meeting
30-31 March, 2010; London, UK
E. dana.samson@nottingham.ac.uk

April

62nd Annual Meeting of the American Academy of Neurology
10-17 April, 2010; Toronto, Canada
E. memberservices@aan.com
www.aan.com

6th European Conference on Comparative Neurobiology (ECCN6)
22-24 April, 2010; Valencia, Spain
E. catedrasg@cac.es
www.eccn6valencia.es

May

The 15th Euroacademia Multidisciplinaria Neurotraumatologica Congress
7-9 May, 2010; Antalya, Turkey
E. aguven@symcon.com.tr

International Child Neurology Congress 2010 - ICNC 2010
7-10 May, 2010; Cairo, Egypt
E. mohamed@icnc2010.com
www.icnc2010.com

Association of British Neurologists Annual Meeting
11-14 May, 2010; Bournemouth, UK
E. karen.reeves@theabn.org

14th International Neuroscience and Biopsychiatry Conference "Stress and Behavior"
16-20 May, 2010; St. Petersburg,
Russian Federation

3rd International Epilepsy Colloquium: Surgery of Extratemporal Lobe Epilepsy
19-22 May, 2010; Cleveland, OH, USA
T. 216 983 1239 / 800 274 8263,
E. medcme@case.edu

International Symposium on Usher Syndrome and Related Diseases
27-29 May, 2010; Valencia, Spain
E. catedrasg@cac.es
www.fundacioncac.es/catedrasg

3rd International Congress on Neuropathic Pain (NeuPSIG 2010)
27-30 May, 2010; Athens, Greece
T. 41 229 080 488,
E. neuropathic@kenes.com

June

20th Meeting of the European Neurological Society
19-23 June, 2010; Berlin, Germany
www.ensinfo.org

July

7th International Congress on Neuroendocrinology
10-15 July, 2010; Rouen, France
T. +33 149 284 676,
E. william.rostene@st-antoine.inserm.fr

August

15th World Congress of Psychophysiology - the Olympics of the Brain - IOP2010
30 August-4 October, 2010; Budapest, Hungary
Mark Molnar,
T. 61 350 1854,
E. worldcongress2010@world-psychophysiology.org

September

XVIIth International Congress of Neuropathology
11-15 September, 2010; Salzburg, Austria
Brigitte Millán-Ruiz,
T. 43 1 404 005 573,
E. brigitte.millan-ruiz@meduniwien.ac.at

Congress of Neurological Surgeons Annual Meeting
16-21 September, 2010; San Francisco, USA
Congress of Neurological Surgeons
T. +847 240 2500,
F. +847 240 0804,
E. info@1CNS.org
www.neurosurgeon.org

14th Congress of the European Federation of Neurological Societies (EFNS 2010)
25-28 September, 2010; Geneva, Switzerland
T. 41 229 080 488,
E. efns2010@kenes.com

2nd World Parkinson Congress
28 September-1 October, 2010; Glasgow, UK
Elizabeth Pollard,
T. (001) 212 923 4700,
E. info@worldpdcongress.org

October

AANEM Annual Scientific Meetings
6-9 October, 2010; Quebec City, Quebec, Canada
T. + (507) 288-0100,
F. + (507) 288-1225,
E. aanem@aanem.org

World Stroke Congress
13-16 October, 2010; Seoul, Korea
E. stroke2010@kenes.com

2010 Congress of the European Committee for Treatment and Research in Multiple Sclerosis
13-16 October, 2010; Gothenburg, Sweden
T. +41 61 265 4464,
E. secretariat@ectrims.eu

10th International Congress of Neuroimmunology
26-30 October, 2010; Barcelona, Spain
Francesca Mariani,
T. 39 0 65 193 499,
F. 39 0 65 194 009,
E. mariani@eemservices.com

EHMTIC 2010 - Migraine
October 28-31, 2010; Nice, France
www.ehmticongress2010.com

December

The 7th International Congress on Mental Dysfunctions & Other Non-Motor features in Parkinson's Disease (MDPD 2010)
9-12 December, 2010; Barcelona, Spain
T. 41 229 080 488,
F. 41 229 069 140,
E. mdpd@kenes.com

2011

March

10th International Conference on Alzheimer's & Parkinson's Disease
9-13 March, 2011; Barcelona, Spain
E. adpd@kenes.com

April

63rd Annual Meeting of the American Academy of Neurology
9-16 April, 2010; Honolulu, HI
www.aan.com

September

AANEM Annual Scientific Meetings
14-17 September, 2011; San Francisco, California, USA
T. + (507) 288-0100, F. + (507) 288-1225,
E. aanem@aanem.org

October

Congress of Neurological Surgeons Annual Meeting
1-6 October, 2011; Washington D C, USA.
Congress of Neurological Surgeons
T. +847 240 2500,
F. +847 240 0804,
E. info@1CNS.org
www.neurosurgeon.org

2012

September

Congress of Neurological Surgeons Annual Meeting
29 September-4 October, 2012; San Francisco, USA. Congress of Neurological Surgeons
T. +847 240 2500,
F. +847 240 0804,
E. info@1CNS.org
www.neurosurgeon.or

2013

October

Congress of Neurological Surgeons Annual Meeting
19-24 October, 2013; San Francisco, USA.
Congress of Neurological Surgeons
T. +847 240 2500,
F. +847 240 0804,
E. info@1CNS.org
www.neurosurgeon.org

European Federation of Neurological Societies (13th Congress)

Conference details: 12-15 September, 2009; Florence, Italy. ***Reviewed by:*** AJ Larner, Walton Centre for Neurology and Neurosurgery, Liverpool, UK

Florence's most famous son was Dante Alighieri, author of what came to be known as the *Divine Comedy.* Whether by chance or not (and he was, to my knowledge, not once mentioned at the meeting), this year's EFNS coincided with the anniversary of his death, on the night of 13/14 September, from malaria, in exile in Ravenna in 1321.[1] Did this conference lead delegates to Paradise, Purgatory, or the Inferno?

Picking my way with care, as one must in the busy Florentine streets, through the schedule (having no Virgil or Beatrice to guide me) I found, for good or ill, the apparently most intellectually profitable sessions to be drug company sponsored satellite symposia and focused workshops. In the former category, results of a trial (RE-LY; www.rely-trial.com) of dabigatran etexilate versus warfarin for the prevention of stroke and systemic embolism in atrial fibrillation (P Gorelick, USA) showed non-inferiority of the trial medication, and indeed superiority to warfarin at a dose of 150 mg bd, in a trial of >18000 patients with 99.9% follow up. Adverse events showed less intracranial haemorrhage but more dyspepsia than warfarin, but with the benefit of no necessity of INR monitoring. The same symposium also presented trial (ECASS3) and registry (SITS-MOST) data regarding the safety and utility of rt-PA up to 4.5 hours, as opposed to the previous limit of 3 hours, after acute stroke, which may have major implications for clinical practice.

Another satellite symposium included data from a trial of Souvenaid, a multi-nutrient drink, in Alzheimer's disease (AD). Preclinical studies have suggested that precursors to phosphatides can enhance numbers of neuronal dendritic spines. Although brief (12 weeks), the trial found benefit in delayed verbal memory in the treatment group, and was taken to show proof of concept (P Scheltens, Netherlands), prompting further trials of this "medical food". Also on the subject of AD, a survey (IMPACT) of physicians, caregivers, the general public and payers (including those who commission services) in five European countries was the topic of one symposium. Amongst the findings, it suggested that time from symptom onset to diagnosis of AD has improved in the UK (32 months in a previous survey,[2] to 10 months). A salient finding for me was that only 16% of payers thought the diagnosis of AD was difficult, much lower than the other groups, a finding perhaps not surprising for anyone who has read the UK National Dementia Strategy.

The absence of treatment for vascular dementia (cholinesterase inhibitors [ChEIs] have no licence, despite a modest evidence base) may have prompted the re-emergence of cerebrolysin, a peptide mixture said to have neurotrophic properties. A 24-week trial from Russia suggested improvement in ADAS-Cog and CIBIC+ in mild to moderate vascular dementia, and another trial from Spain suggested equivalence to donepezil in AD with combined donepezil/cerebrolysin treatment tending to superiority. However, cerebrolysin requires iv administration, so it may be less acceptable than oral medication.

No EFNS is complete without a lecture from Hans-Christoph Diener. His review of new acute and prophylactic treatment for migraine suggested that the ones to watch as potentially beneficial were, in the former category CGRP antagonists such as telcagepant (MK0974), which unlike triptans lacks any vasoconstrictive properties, and 5HT-1F agonists (COL144). Amongst new prophylactic agents, he did not rule out the controversial possibility of botulinum toxin noting the big placebo response in trials (50% respond to saline injections!), the lack of a defined mechanism of action (modulation of peripheral nociceptive inputs?) and the tendency for an "all-or-nothing" response. Neurostimulation (DBS, occipital nerve stimulation) also seems to hold promise for the future. In the treatment of chronic migraine, Jean Schoenen noted that the most efficacious preventive treatments also have the most side effects. The importance of treating comorbidity (e.g. depression) was emphasized. The exclusion of medication overuse headache is also crucial, a fact underscored by a poster (one of 6) from the Norwegian Akershus study of chronic headache showing that this is akin to dependency, using the Severity of Dependence Scale.[3]

What can one observer make of 1700+ posters (minus no shows, which must amount to several hundred)? Few messages of possible clinical relevance emerged for me. The possible change in normative performance in the Mini-Mental State Examination over 20 years, reported from Portugal, will, if true (as for general intelligence), require changes in cutoffs, and so further undermine use of this instrument as a measure for ChEIs efficacy. In movement disorders, new cognitive tests are being piloted for use specifically in Parkinson's disease, such as SCOPA-Cog and PANDA, as well as ACE-R. Camptocormia may be relieved by sensory tricks such as placing the hand on the thigh or a table or bar in front of the patient. Awareness of NMDA-R antibody encephalitis in association with ovarian teratoma seems to be increasing, with reports in three posters, from Ireland, Japan, and Singapore. An illustrative case from Austria showed that a provisional diagnosis of "Hashimoto encephalopathy", based on the finding of anti-thyroid antibodies, required revision to paraneoplastic limbic encephalitis when an underlying malignancy (bronchial carcinoma) was found by PET scanning. ChEIs have been used (off licence) for sleep-related disorders (OSAHS, narcolepsy) with apparent benefit in terms of the Epworth Sleepiness Scale; this was a surprising inclusion since a poster submission on ChEI treatment (off licence) for MS-related cognitive impairment from this centre was not accepted.

Most focused workshops were on predictable topics but one on Wernicke's encephalopathy (WE) caught the eye. The prevalence is higher in alcoholics, often undernourished, but increased interest in WE has been kindled by cases (2 per 1000) in the context of bariatric surgery, indicating that the obese are not immune to this condition, an unbalanced diet perhaps being key to its occurrence (e.g. hyperemesis gravidarum, hunger strikers despite oral thiamine supplements). The evidence base for thiamine treatment is thin (e.g. dose? route? duration?) but good practice points have been formulated by an EFNS Task Force such as using parenteral thiamine (iv), to be given before glucose in suspected WE, and return to a balanced diet as soon as possible. These guidelines will appear in the European Journal of Neurology in due course. ◆

REFERENCES

1. Lewis RWB. *Dante. A life.* London: Phoenix, 2001.
2. Bond J et al. *Inequalities in dementia care across Europe: key findings of the Facing Dementia Survey.* Int J Clin Pract 2005;59(suppl146):8-14.
3. Grande RB et al. *The Severity of Dependence Scale detects people with medication overuse: the Akershus study of chronic headache.* J Neurol Neurosurg Psychiatry 2009;80:784-9.

Brain Injury Rehabilitation Trust Biannual Conference

Conference details: 23-24 September, 2009; Birmingham, UK. ***Reviewed by:*** Professor Michael Oddy, Director of Clinical Services for BIRT.

The Brain Injury Rehabilitation Trust held the latest in its series of biannual conferences on brain injury rehabilitation on the 23rd and 24th September in Birmingham.

As with previous conferences the goal was to provide a good balance between advances in the basic science underlying brain injury rehabilitation and talks concerning current best practice.

The first day comprised of keynote speakers from around the world. Professor Robyn Tate from the Rehabilitation Studies Unit at the University of Sydney reviewed the somewhat neglected topic of motivational changes following brain injury. She gave a useful evaluation of measures of motivation that can be employed and then reviewed current treatment approaches, both pharmacological and behavioural. She concluded that there is weak evidence that stimulants may be helpful in treating low motivation following brain injury but that the amount of progress made in developing pharmacological and behavioural interventions over the past 20 years was disappointing.

Professor James Fawcett from the Cambridge University Brain Repair Centre described the state of play in terms of the development of treatments to stimulate both axon regeneration and plasticity. As far as the former is concerned Phase 2 trials are currently underway. Plasticity is a double edged sword and Prof Fawcett emphasised the need for a combination of appropriate training with simultaneous pharmacological intervention to promote plasticity if functional recovery is to be achieved.

Dr Tamara Ownsworth from Griffiths University in Queensland emphasised the huge significance that return to work has for the individual following brain injury before reviewing the evidence for predictors of return to work following acquired brain injury. The factors with the strongest predictive value were pre-injury occupational status, functional status at discharge, certain aspects of cognition (notably executive function and global intellectual ability), emotional status and amount of rehabilitation and vocational support. Dr Ownsworth also examined the role of awareness of deficit in terms of return to work and concluded that impaired self-awareness does not preclude a return to work and indeed such a return may be necessary to enable self-awareness to improve. She advocated approaches which combined self-awareness and self-regulation training with modification or enhancement of the vocational environment (ie educating employers, providing on-the-job support etc).

Dr Tedd Judd from Washington State gave what proved to be a popular and entertaining talk on neuropsychotherapy. His presentation was riddled with common sense advice and clinical wisdom and he gave many examples of how one can circumvent the memory and the other cognitive deficits associated with brain injury to provide good psychotherapeutic assistance in the process of adjustment to brain injury.

The second day of the Conference consisted of three parallel sessions, each of which was either in the form of a workshop or a short symposium. Topics for workshops ranged from smart technology to sexual consent and from challenging behaviour to cross-cultural considerations. There were symposia on training staff (both in how to promote basic functional skills and in how to communicate with someone with a severe brain injury) in the measurement and management of challenging behaviour and in the controversial topic of 'effort testing'. This concept arose in a medicolegal context and suggests that performance on cognitive tests is not always optimal for reasons of differing motivation and that so-called effort tests should always be employed to gauge the extent to which the person is performing to the best of their ability. The message was that effort testing should be incorporated into all cognitive assessments and that the best effort tests were those embedded in existing neuropsychological tests. Care has to be taken, however in the interpretation of failure on effort tests as it is not, as has sometimes been assumed, synonymous with malingering.

In a talk entitled 'From the farmer's field to the airfield' Dr Sarah Mackenzie-Ross from UCL described the evidence for the neuropsychological effects of toxins in these two areas. In the farmer's field she described a study suggesting that exposure to organophosphates was associated with deficits in response speed, mental flexibility, memory functioning and fine motor control with significant correlations between neuropsychological performance and duration and intensity of exposure. Exposed farmers also scored higher on tests of depression and anxiety and were more likely to complain of other symptoms such as fatigue, joint stiffness and sleep disturbance.

The toxicity relating to the airfield concerned the air circulating in aircraft. During flights the air in the cockpit and the cabin is a mixture of recirculated air and 'bleed' air. The latter is taken from the engine and can be contaminated by engine oils and lubricants and may contain carbon monoxide. The number of air contamination events is difficult to quantify as aircraft do not have air monitoring equipment. The study related to 27 self-selected pilots. Nine were eliminated as they had other health problems which could influence their performance. The remaining 18 pilots were assessed neuropsychologically and found to have intact language, perceptual and general intellectual ability but were poorer than expected on tests of psychomotor speed, attention and executive skills.

Dr MacKenzie-Ross emphasised that both these studies were preliminary and that causality was not conclusively proven in either case but her findings would certainly appear to justify further investigation.

One workshop considered the issue of capacity to consent to sexual relationships following severe brain injury which often leads to anxiety amongst staff in residential brain injury units. Professor Glynis Murphy, University of Kent and Dr Camilla Herbert, BIRT explored the relevant law with the Sexual Offences Act 2003 being the most significant act in this respect but both speakers agreed that difficult dilemmas still arise.

Children who suffer brain injuries were not forgotten. Fiona Adcock from the Children's Trust, Tadworth Court, described the work of a Community Support Services Team and Drs Phil Yates and James Tonks from Exeter University described a series of studies they have conducted into the developmental consequences of brain injury in childhood. Their message was that such children face increasing problems as they struggle to keep up with their rapidly developing peers in adolescence and may continue to face problems in adulthood. ◆

RAatE

Recent Advances in Assistive Technology and Engineering

Conference

Hilton Hotel, Coventry

30th November and 1st December

This conference will be of interest to everyone who uses, works with, develops or conducts research on assistive technologies (AT). The conference program has, over the past years, regularly included new technological developments, service innovations, results of formal research projects, service based research and development and a wide range of other stimulating topics. Known as a friendly and productive conference, RAatE offers you a chance to meet and share knowledge and experience with other people working in AT.

hdti

For further information visit www.raate.org.uk or email hdti.info@coventry.ac.uk

Royal College of Physicians

Setting higher medical standards

THE NEUROLOGY OF OLD AGE

Thursday 18 February 2010

Joint conference with the British Geriatrics Society

Medical clerking often omits the Central Nervous System or describes it in a cursory way. Many non-specialists feel rather vulnerable when assessing a complex elderly person with poor mobility, falls, incontinence or cognitive impairment.

The aims of this conference are to improve diagnostic acumen when assessing old people with neurological disorders, to know whom to refer and when and to be aware which investigations have therapeutic payoff and which are inappropriate or unnecessary.

Target audience: Hospital doctors especially neurologists, geriatricians, acute physicians, rehabilitation specialists, physiotherapists and speech and language therapists.

Programme and booking forms are available on-line at **www.rcplondon.ac.uk/conferences** or from:

Conference Department, Royal College of Physicians
Tel: 020 7935 1174 Ext. 300/252/436
Fax: 020 7224 0719
Email: conferences@rcplondon.ac.uk

BNPA

The British Neuropsychiatry Association

23rd Annual General Meeting

10/11/12 February 2010

The British Neuropsychiatry Association
23rd Annual General Meeting
11/12 February 2010
With a joint meeting, 10 February, with the
Section of Neuropsychiatry, RCPsych
Venue: The Institute of Child Health, Guilford St, London

Topics to include:

- Memory (SoN/BNPA)
- Encephalopathy and delirium
- Head Injury
- Neuropsychiatry and the Self

For outline programme and registration form visit:

www.bnpa.org.uk

For details of exhibition/sponsorship opportunities, contact: Jackie Ashmenall on
Phone/Fax: 020 8878 0573/Phone: 0560 1141307
Email: admin@bnpa.org.uk
or jashmenall@yahoo.com

Ideas which make every load portable

Hygiene, safety and stability make high demands on mounting systems for medical equipment and monitors. Patient monitors, flat screens and/or keyboards need to be easily adjustable, but be stable in every desired position. CIM med GmbH specialises in developing appropriate solutions for any requirement in the healthcare sector.

The Bavarian enterprise provides a functional instrument mounting system in which cables only run inside the system. The uniqueness lies in the fact that users can integrate the cables by themselves thus offering the opportunity of changing cables at any time - this CIM Cable Integrated Mounting Systems is patent-pending. The advantages of hidden cable management are obvious: Power and data cables are protected against external influences. At the same time the ever-annoying cable clutter in hospital environments is regulated. Up to now cables were led outside the support arm or fastened externally with additional cable clips. The danger of cutting the connecting leads to the digital circulation system is considerably lower with the CIM system.

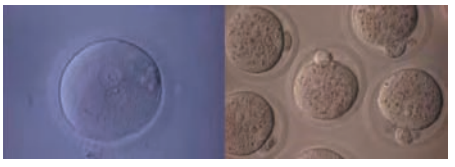
All mounting solutions hold a 6-fold safety factor of the indicated maximum weight. Only a 4-fold safety factor is required by law. A slow-flowing gas pressure spring is used which prevents the arm from shooting up quickly when the device or monitor is removed. This not only ensures safe operation of all variable height arms, but also allows the joints to be moved smoothly. CIM med GmbH offers a three year warranty.

For more information contact Manuela Loibl, T. +49 89 978 94 0800, E. manuela.loibl@cim-med.com

Enhanced specimen image contrast

Nikon has announced the availability of a new light microscopy contrast method – NAMC (Nikon Advanced Modulation Contrast). Offering enhanced image sharpness and definition, NAMC can be used in all applications that traditionally use Hoffman Modulation Contrast and is particularly important in live cell applications, such as IVF, for the observation of specimens in plastic dishes. NAMC is currently available for Nikon's Ti series inverted microscopes.

In the same way as Hoffman Modulation Contrast, NAMC is used to enhance contrast in both stained and unstained specimens. The NAMC system uses new Plan Fluor objectives and a full 360-degree rotating modulator with a convenient 'stop' mechanism. NAMC accessories include



condensers, turrets and modules and five specifically designed NAMC objectives, including Super Plan Fluor ELWD 20x and 40x, and Achromat 10x, LWD 20x and 40x.

For more information please contact Nikon Instruments Europe, T. 0208 247 1718, E. info@nikoninstruments.eu, www.nikoninstruments.eu/ti

Siemens and the Stroke Association launch Stroke for Stroke 2010

Siemens plc and The Stroke Association have launched the third annual Stroke for Stroke campaign, in a bid to raise awareness of stroke and to highlight the benefits of a healthy diet and regular exercise in its prevention. The campaign will run between 25th and 31st January 2010 and will challenge members of the public to row 10km (or more), helping to raise funds.

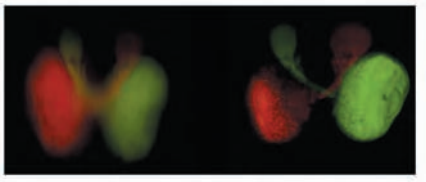
Siemens plc and The Stroke Association have launched the third annual Stroke for Stroke campaign. (Left to right): Ric Egington, GB Rower; Alex Partridge, GB Rower; and Rachel Christie, Miss England.

The campaign is now in its third year and has raised over £70,000 to date by encouraging members of the public to complete a sponsored 10km row. In addition to raising funds, the campaign aims to highlight that anybody, irrespective of age, can suffer from a stroke and that a healthy lifestyle, including a healthy diet and regular exercise, can help to significantly reduce the risks.

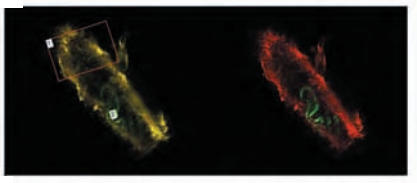
The timing of the event at the end of January means that anyone looking to get back in shape after the festive season will still have time to warm up and shift those Christmas pounds before taking on the 10km rowing challenge.

The Stroke for Stroke campaign has teamed up with Nuffield Health to offer free access to their nationwide network of Fitness & Wellbeing Centres for everyone taking part. The campaign is open to everyone across the UK by visiting www.strokeforstroke.co.uk or calling 020 7566 1503.

Live cell confocal imaging on a large scale



Zebra fish eyes in vivo, double labelled with GFP and mCherry, Courtesy of Marine Biology Laboratory, USA



Drosophilia Pupa before and after spectral un-mixing of auto-fluorescence. Courtesy of Ms Aude Porcher, Research Unit UMR218, Curie Institute, Paris

Combining the groundbreaking AZ100 Multizoom and advanced C1 confocal microscope, Nikon has created the ultimate imaging platform for developmental biology, cell biology, stem cell and tissue research. For the first time, researchers can view large specimens in confocal mode enabling the capture of more information than ever before. Designed for macro imaging, the AZ-C1 can not only capture fields of view of larger than 1cm, but also permits deeper confocal imaging than conventional microscopes thanks to its large working distance objectives. Whole organisms can be monitored and documented over time (for example, embryos) offering a wealth of continuous information on development or the organism's response to experimental variables.

Observations ranging from macro imaging of a whole organism to micro imaging of a single cell can be achieved with just one lens. Up to three separate objective lenses can be attached, offering a large optical zoom range to easily achieve high magnifications using stepwise or continuous zoom mode. The addition of a motorised stage further expands imaging possibilities by allowing image capture in multiple fields of view.

Offering exceptional flexibility, the C1 confocal system is expandable from easy-to-use personal point scanning systems to spectral point scanning systems which will separate closely associated fluorophores and auto fluorescence. The innovative AZ-C1 also offers many other features such as: an ergonomic tilting eyepiece tube, up to seven laser lines, fibre-coupled optics, modular system, telecentric zoom system, epi-illumination light path separated from the imaging path and is future-proofed to offer CLEM and other techniques.

For further information contact Nikon Instruments Europe, T. 0208 247 1718, E. info@nikoninstruments.eu, www.nikoninstruments.eu

SteREO Discovery stereomicroscopes acquire single-channel capability

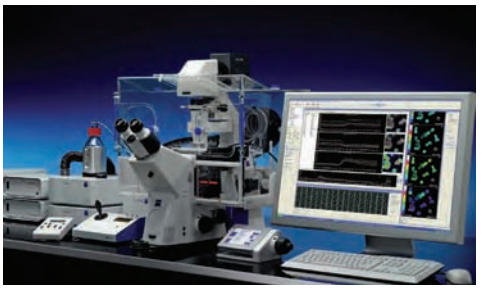
The Carl Zeiss SteREO Discovery range of stereomicroscopes can now be transformed into a single-channel zoom microscope at the touch of a button with a coded, three-position nosepiece and motorised Y intermediate tube.

On the SteREO Discovery.V20, a continuously variable magnification range of up to 233:1 provides users with high quality, 3D images, convenient binocular observation at maximum resolution, and parallax-free documentation over the entire magnification range. Fast and reliable zooming into object details with a structure width of up to 0.5 micrometers is possible from low-power magnifications with a field diameter of up to 11 millimeters.

The new Parfocality Manager ensures the microscope image always remains exactly in focus even after a change of objective. Furthermore, beam delivery of the overall system is automatically adjusted on the nosepiece after the change between stereo observation and parallax-free, single-channel vertical observation. This guarantees permanent binocular observation in both 3D and 2D.

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

More flexible and faster FRET experiments



Cell and development biologists can now use the sophisticated functions of the Zeiss AxioVision software, such as the enhancement of fluorescence signals and the suppression of image noise, to support their FRET investigations. The new features are found in the physiology module of the AxioVision 4.7 microscopy software and make FRET experiments easier and simpler.

The FRET software is used to determine the energy transfer portion between two adjacent protein molecules through fluorescence energy transfer (FRET), measure the distance between adjacent protein molecules below the microscope resolution and obtain quantitative temporal and spatial information about the bonding and interaction between proteins, lipids, enzymes, DNA and RNA in vivo. It is ideally matched to the motorised Axio Imager or Cell Observer microscope systems, although it can be used with manual fluorescence microscopes.

The software offers numerous additions to existing and new methods of FRET measurement by using different corrective techniques or acceptor bleaching. Users can define their own formulas for the tasks to be performed or use pre-programmed FRET formulas.Furthermore, it is possible to modify existing FRET formulas and easily create new evaluation techniques via the formula field.

AxioVision enables the wide range of microscope accessories and software functions to be used for processing. For instance, up to 140 frames per second are available with the AxioCam HS and the dual camera module more than doubles the speed of capture. In addition, all required time series images (donor, acceptor and FRET) can be captured using the physiology module.

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

SonoSite ultrasound systems chosen for cutting edge anaesthesia

Anaesthetists from Hull and East Yorkshire Hospitals NHS Trust are using SonoSite's S-Nerve™ and MicroMaxx® point-of-care ultrasound systems to perform pioneering regional nerve blocks that are transforming the way orthopaedic surgery is managed. Continuous nerve block infusions can provide up to 80 hours of pain relief, eliminating the need for opioids and allowing patients to go home the same day as their surgery. Reg Edward, consultant anaesthetist at the Trust, explained: "We can move a substantial number of cases from inpatients to day surgery by using continuous nerve block infusions. The ongoing pain relief provided by this technique makes patients extremely comfortable, without the side effects of many pain-relieving drugs, and so they don't need to stay in hospital. This is obviously preferable for patients, as well as offering large cost benefits to the Trust."

"We are one of the first Trusts in the UK to adopt this strategy extensively, using SonoSite systems to guide all our nerve blocks. The good image resolution and portability of the systems make them easy to move between wards and theatres. We also run courses in ultrasound guided nerve blocks, and the system is an excellent tool for teaching purposes."

For information on SonoSite courses contact education@sonosite.com

Study shows Azilect® can slow the clinical progression of people with PD

The ADAGIO study recently showed that earlier treatment with Azilect® (rasagiline 1mg once daily) can slow the clinical progression of people with Parkinson's disease (PD). Patients newly diagnosed with PD who were given rasagiline 1mg had sustained clinical benefits at 18 months compared with patients in whom treatment was delayed for 9 months.

ADAGIO is the first major study to assess the effects of earlier treatment on the progression of PD using a rigorous "delayed start" design. This study design allows researchers to differentiate between the normal symptomatic effects of a treatment and any underlying effects on the rate of clinical progression.

Professor David Burn, Professor in Movement Disorder Neurology & Honorary Consultant, Newcastle University, and ADAGIO principal investigator in the UK, said, "The results of ADAGIO are promising. The data show that earlier treatment of PD may slow patients' clinical progression. These data also suggest there may be some benefit for patients if rasagiline treatment is started soon after diagnosis. Longer term follow up will be useful to assess whether this benefit can be maintained"

For further information E. Brenda.mccleary@ashleycomms.com

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COPAXONE® (glatiramer acetate)
PRE-FILLED SYRINGE PRESCRIBING INFORMATION
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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