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Editorial board and contributors

Roger Barker is co-editor of ACNR, and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular Parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

Alasdair Coles is co-editor of ACNR. He is a University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Mike Zandi is co-editor of ACNR. He 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.

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

David J Burn is the editor of our Conference News Section and 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.

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

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

Peter Whitfield is ACNR's Neuropathology Editor. He is a Consultant Neurologist at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.

Heather Angus-Leppan is ACNR's Neuropathology Editor. She is a Specialist Registrar in Neuropathology at Southampton and has a DPhil in Neuroscience. Her research interests lie in CNS stem cell biology, and the brain's response to injury.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Chairman of the Neuro-Oncology Service, Dept of Neurosciences and Oncology, University and S. Giovanni Battista Hospital, Italy: Chairman of the Neuro-Oncology Service, Dept of Neurosciences and Oncology, University and S. Giovanni Battista Hospital.

Professor Klaus Beek, Austria: Head of the Neurological Department of the KH Kufstein.

Professor Hermann Steffen, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nürnberg.

Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

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- Journal of Neurology
- The Journal of Neuroscience
- The Journal of Head Trauma Rehabilitation
- European Journal of Paediatric Neurology
- Movement Disorders
- Neuro-degenerative Diseases
- Nature Neuroscience
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C horea as a clinical sign is most commonly seen in patients with PD on L-dopa therapy, but out- side of this, it is normally associated with Huntington’s Disease (HD).

However, there are a range of other rare genetic disorders which can cause chorea as part of their clinical features along with the presence of acantho- cytes. 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 mole- cule of great interest to the neurosci- entific community for many years, and in an excellent review article by Joern R Steinert, Tatjana 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 fast succinct account of the possible mechanisms being investigated.**

Andrew Lamer 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 illness visual spread by Manjdi Evans.

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 neuro- logical conditions which will be useful in your daily practice”. In the first in this 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 Gower, we have Chris Butler writing about the attempts that have recently been made to try and reinvigorate this vital area of medicine through the cre- ation of Academic Clinical Fellowships and Lectureships. This excellent account highlights the origins of this scheme and how it has been con- ceived to work. In contrast, Jane Alley in the ABNT section explains the evolution in neurological practice. As with all articles in this series, it is easy to follow and extremely informative.

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.
Inspired by Andrea: diagnosed with epilepsy in 1990

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.
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.

Informa Healthcare have won top honours at this year’s BMA Medical Book Competition. Dr Eduardo 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

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.

John Camm, Professor of Clinical Cardiology at St George’s University of London 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 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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References
4. NEURO-JK2143d Date of Preparation: October 2009 www.neurobloc.com
Nitric Oxide Signalling: Nitric oxide (NO) is the signalling molecule originally identified as endothelium-derived relaxing factor (EDRF) mediating relaxation of blood vessels. It is a small, highly diffusible and reactive molecule with a short half-life, generated from arginine by the cytoplasmic enzyme nitric oxide synthase (NOS). Three NOS genes with distinct tissue localisation and properties are known, namely: endothelial, inducible and neuronal NOS (eNOS, iNOS & nNOS, respectively). Activation of eNOS and nNOS are classically Ca²⁺-dependent, with nNOS being closely coupled to Ca²⁺-permeable NMDA receptor (NMDAR), both of which are linked to postsynaptic densities (PSD-95) of the CNS through their mutual PDZ binding motifs. eNOS and nNOS generate low nanomolar concentrations of NO, whereas iNOS can produce micromolar levels. Such high concentrations affect downstream 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 Ca²⁺-induced nNOS activation. This NO will diffuse and subsequently activate 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 nitric signalling are indicated (AP – action potential, Cav – voltage gated calcium channel, CNG – cyclic nucleotide-gated ion channels, K-V3.1 – potassium channel, L-NMMA - NG-Methyl-L-arginine, LTD – long term depression, LTP – long term potentiation, Nav – sodium channel, CGD – H2[2,4]Oxadiazolo[4,3-a]quinoxalin-1-one, PDE – phosphodiesterase, SNP – Sodium nitroprusside, 7-NI – 7-Nitroindazole).
Nitric oxide (NO) generation by physiological stimuli is difficult. nNOS is widely distributed throughout 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 thalamo-cortical oscillations. There is strong evidence for involvement in learning and memory mechanisms through mediation of specific forms of LTP in the cerebellum,1 hippocampus2 and neocortex3 and LTD in the cerebellum. The cellular and molecular targets of nitricergic 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) results from NO-receptor-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 and trafficking, which mechanisms has a homeostatic-like function in matching postsynaptic excitability to the synaptic traffic. 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, neurons and glial cells, and involvement of microglia and the immune system in nitricergic signalling of the brain. Given the ease of NO diffusion, a key future challenge is to understand the extent to which overproduction of NO in one system (endothelium, immune) can ‘spill-over’ into triggering brain dysfunction and neurodegeneration.

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 O2 to form peroxynitrite (ONOO⁻, Figure 2) decreasing the bioavailability of NO. 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 nitrothiols and nitrotyrosination is the reaction of tyrosine with ONOO⁻ to form 3-nitrotyrosine.

NO can also directly contribute to O2⁻ 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 O2, reducing it to form O2⁻ so further enhancing peroxy nitrite production. It is interesting to note that both Alzheimer’s (AD) and Parkinson’s disease (PD) are associated with a BH4 deficiency.

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 (O2⁻, Figure 2). Normally this is metabolized by superoxide dismutase (SOD) to H2O2, 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 so that susceptibility to neurodegeneration shows complex dependence on local metabolic rates, oxygen availability, antioxidant activity (reduced glutathione and cell stress resistance signalling). Other effects of NO/ONOO⁻ include release of Zn²⁺ from internal stores (such as metallothionein) with concomitant formation of S-nitrosotiol and neurotoxicity. Free Zn²⁺ 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.

Further metabolic compromise may result from mitochondrial fragmentation. This is fast, occurring within minutes after NMDAR activation or NO exposure, and is considered a predisposing event to neurodegeneration and cell death. Increased mitochondrial fission in response to NO has been reported in AD, PD, amyotrophic lateral sclerosis (ALS) and...
Huntington’s disease (HD). 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 presynaptic neuronal injury could have a nitricergic component. Endogenous levels of oxidizing agents, NO and Zn2+ inhibit excessive excitation of NMDAR and limit excessive influx of Ca2+ via the NMDAR. Such feedback could ameliorate NMDAR-mediated neurotoxicity. High-affinity Zn2+ inhibition, redox modulation or S-nitrosylation of the receptor are mediated with the involvement of at least seven cysteine residues on NMDAR subunits. NO signaling contributes to several neurodegenerative diseases through production of ROS/RNS and subsequent oxidative/nitrosative 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 nitrosative immune reactoactivity and oxidative protein damage are evident in brains from AD patients, while inhibition of mitochondrial cytochrome c oxidase and enhanced H2O2 production in neural tissue from APP (β) mutant mice suggest mitochondrial involvement in ROS generation. The cerebral cortex of patients with AD has high protein nitrosylation11 and nitrosated proteins are associated with Aβ deposition12 along with nitrosylation of Tau protein12 and synaptophysin, consistent with a dysfunction in cholinergic synaptic transmission.13 Most recently S-nitrosylation of Drp1 has been shown to mediate mitochondrial fission and neuronal damage caused by Aβ.14 Exposure of experimental inflammation models to NO cause axonal degeneration, especially when accompanied by propagating electrical activity. Several potential pathogenetic mechanisms have been suggested: In PD, S-nitrosylation of Parkin15–17 initially increases but later decreases Parkin activity. Alpha-synuclein (α-syn) is a protein associated with synaptic terminals and synaptic transmission, is heavily nitrosated at 4 tyrosine residues and this contributes to aggregate formation.16 Nitrated α-syn is more resistant to proteolysis and has reduced lipid binding and solubility.17 Other contributing mechanisms could include metabolic compromise by RNS (via block of mitochondrial complex I) in substantia nigra since MPTP-induced neuronal loss in this PD model was slowed by competitive nNOS antagonists18 and nNOS inhibition blocked MPTP-mediated decrease in striatal dopamine levels in mice.19 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 nitrosergic signalling to have broad involvement in neurodegenerative disease and these possibilities are under increasing investigation.20

References

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**Consult Summary of Product Characteristics before prescribing.**

**Uses:** The treatment of disabling motor fluctuations (“on-off” phenomena) in patients with Parkinson’s disease which persist despite individually titrated treatment with levodopa with a peripheral decarboxylase inhibitor and/or other dopamine agonists. **Doseage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 min) and duration of action (about 1 h) may prevent an “off” episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient’s therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with dopaminederivative (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg.

**Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an “on” response to levodopa which is marred by severe dyskinesia or dystonia. Pregnancy and lactation: Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when co-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson’s disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematological tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of erythema, tenderness, induration and panniculitis. Infarction, itching, bruising and pain may also occur. Rarely, injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during “on” periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intrasciatic. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs’ tests and haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported as has peripheral oedema. Prescribers should consult the Summary of Product Characteristics in relation to other side effects. **Presentation and Basic NHS Cost:** APO-go ampules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per cartridge of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per cartridge of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £112.31 per cartridge of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per cartridge of 5 syringes. Marketing Authorisation Numbers: APO-go Ampoules: PL04483/0064. APO-go Pens: PL04483/0065. APO-go Pre-filled syringes: PL05928/0025. Legal Category: POM. Date of last revision: September 2009. For further information please contact: Britannia Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK.

**Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk.** Adverse events should also be reported to Medical Information on 0870 851 0207 or drugsafety@britannia-pharm.com

### Neurological Signs

**Illusory Visual Spread or Visuospatial Perseveration**

**A. J. Larner**

Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery,

Correspondence to: Email: a.larner@the Waltoncentre.nhs.uk

Another very sudden psychic experience was seeing the aura of a dog... The dog was a black labrador. 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.

This extract might initially prompt concerns in some readers about the author’s mental health. Certainly Margiad Edwards (1959-1958) did suffer from epilepsy, symptomatic of an underlying brain tumour which blighted her creative powers in the last years of her life. 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.

- The hallucinatory and recurring appearance of an object after its removal,
- In other words palinopsia;

Visual perseveration in senso stricto, 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 perseverance, 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, comprehensive 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

**References**


Inspired by Terry: diagnosed with Parkinson’s disease at age 46

Parkinson’s disease didn’t stop Terry from staying on track … and running 17 marathons all over the world.

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 Parkinson’s disease who inspire us, like Terry.
Neuroacanthocytosis syndromes are genetically defined neurodegenerative disorders with a Huntington-like phenotype

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 to describe inherited disorders of lipoprotein synthesis, abetalipoproteinemia and hypobetalipoproteinemia, in which impaired vitamin E absorption results in posterior column degeneration, neurological and cataract abnormalities. Currently, it should be reserved for disorders affecting the basal ganglia and resulting in various movement disorders.

In chorea-acanthocytosis (ChAc) and McLeod syndrome (MLS), acanthocytes are regularly seen, whereas in Huntington’s disease-like 2 (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 worldwide.

**Chorea-acanthocytosis**

Autosomal recessive chorea-acanthocytosis (ChAc) is a progressive neurodegenerative disorder with onset of neurological symptoms usually in the twenties. 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 generalised, 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 schizoprenia-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. Neuropathologically there is progressive striatal atrophy especially affecting the head of the 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. 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. Most carriers of the McLeod blood group phenotype have erythrocyte acanthocytosis and elevated CK levels, and develop the McLeod syndrome (MLS). Onset of neurological symptoms ranges from 25-60 years and disease duration ranges between 10-30 and even more years. About 30% of patients present with chorea resembling HD.
What matters to your Parkinson's disease patients?

Sticking to a daily routine? Having a good night's sleep? Whatever is important to them, Neupro® will be there. Its smooth, continuous drug delivery will give them back control through the day, night and into the morning.¹–⁴

Neupro®

Presentation: Neupro® is a thin, matrix-type square transdermal patch.

Active Ingredient: Rotigotine, 2 mg/24 h transdermal patch is 10 cm² and contains 1.5 mg rotigotine, releasing 2 mg rotigotine over 24 hours. 4 mg/24 h transdermal patch is 20 cm² and contains 3.0 mg rotigotine, releasing 4 mg rotigotine over 24 hours. 6 mg/24 h transdermal patch is 30 cm² and contains 4.5 mg rotigotine, releasing 6 mg rotigotine over 24 hours. 8 mg/24 h transdermal patch is 40 cm² and contains 6.0 mg rotigotine, releasing 8 mg rotigotine over 24 hours. Use: To treat the signs and symptoms of idiopathic Parkinson's disease; either with or without concurrent 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. Mitomycin 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. Maximum 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. Hypothesis 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. Older 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. Compulsive behaviors are known to cause hypereflexia, and monitoring of blood pressure is recommended. Where somnolence or sudden deep sleep occurs, or when 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 minimize the risk of skin reactions. In case of generalised skin reaction with rotigotine. Co-administration of rotigotine (3 mg/24 h) did not affect the pharmacodynamics and pharmacokinetics of oral contraceptives (50 µg 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 minor influence on the ability to drive and use machines. Adverse Effects: Very common (>10%): nausea, somnolence, dizziness and application site reactions. Common (1–10%): hallucinations, insomnia, abnormal dreams, headache, dyskinesia, orthostatic hypotension, constipation, diarrhea, dry mouth, dyspepsia, hyperkinetic movements, rash, hypertension, syncope, pruritus, atrial fibrillation, peripheral edema, decreased weight, MI. Consult SmPC in relation to other side effects. Pharmacist Precautions: Sensitive to ultraviolet (UV) rays in the u.v. spectrum. Legal Category: POM. Marketing Authorisation Numbers: EU/1/05/331/001-012.


Date of literature preparation: January 2009.
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.1

Psychiatric manifestations including depression, schizophrenia-like psychosis and obsessive-compulsive disorder are frequent and may appear prior to the movement disorders.4 A subset of MLS patients develops cognitive deficits, particularly in later disease stages. Generalised seizures occur in about half of the patients.

Neuromuscular manifestations include myopathy and sensory-motor axonal neuropathy.4,8 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.10 Cardiac complications are a frequent cause of death, thus MLS patients and asymptomatic carriers of the McLeod blood group phenotype should have a cardiological evaluation.11,12

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 individuals have CTG/CAG repeat expansions of 41-59 triplets (normal population: 6-27). As in HD, there is anticipation and the age of onset is inversely related to the size of the repeats of the junctophilin 3 gene (JPH3). 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.13

Huntington’s disease-like 2
Huntington’s disease-like 2 (HDL2) is an autosomal dominant neurodegenerative disorder.14 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.15 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. Neuromuscular imaging reveals bilateral striatal atrophy, in particular of the caudate nucleus. In contrast to ChAc and MLS, generalised cortical atrophy may develop during the disease course. Neuropathologically, ubiquitin-immunoreactive intranuclear neuronal inclusions, similar to those seen in HD, are found.16

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.

Pantothenate 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.17 Initial manifestations may include orofacial and limb dystonia, choreoathetosis and spas-
How will restless legs syndrome affect your patients today?

The symptoms of RLS can flare up at any moment, day or night. Neupro® can help no matter when your patients suffer most. Its 24-hour continuous delivery system helps RLS patients to rest, live and sleep.1,2

---

**ABBREVIATED PRESCRIBING INFORMATION**

**Indication:** Neupro® is indicated for the symptomatic treatment of idiopathic Restless Legs Syndrome in adults.

**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. A single daily dose should be initiated at 1 mg/24 h. Depending on the individual patient response, the dose may be increased in weekly increments of 1 mg/24 h to a maximal dose of 3 mg/24 h. The need for treatment continuation should be reconsidered every 6 months.

**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, etc:** 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.

**Adverse Events:**

- Very common (>10%): Nausea, application and instillation site reactions, fatigue, headache.
- Common (between 1%–10%): Vomiting, application and instillation site reactions, fatigue, headache.
- A single daily dose should be initiated at 1 mg/24 h. Depending on the individual patient response, the dose may be increased in weekly increments of 1 mg/24 h to a maximal dose of 3 mg/24 h. The need for treatment continuation should be reconsidered every 6 months. 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 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 1 mg/24 h with a dose reduction preferably every other day to avoid the possibility of developing neuroleptic malignant syndrome. (Please consult the Summary of Product Characteristics (SmPC) before prescribing.) Neupro® 1 mg/24 h transdermal patch, Neupro® 2 mg/24 h transdermal patch, Neupro® 3 mg/24 h transdermal patch. Presentation: Neupro® is a thin matrix-type square transdermal patch. Active Ingredient: Rotigotine. 1 mg/24 h transdermal patch is 5 cm² and contains 2.25 mg rotigotine; releasing 1 mg rotigotine over 24 hours. 2 mg/24 h transdermal patch is 10 cm² and contains 4.5 mg rotigotine, releasing 2 mg rotigotine over 24 hours. 3 mg/24 h transdermal patch is 15 cm² and contains 6.75 mg rotigotine, releasing 3 mg rotigotine over 24 hours. Therapeutic Indications: Neupro® is indicated for the symptomatic treatment of idiopathic Restless Legs Syndrome in adults.

**Date of literature preparation:** June 2009

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**References:**

1. Braun M et al. 2006; Poster presented at 9th Congress of the European Federation of Neurological Societies; September 17–20, Athens, Greece.

**Date of literature preparation:** June 2009

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**Abbreviated Prescribing Information**

(Please consult the Summary of Product Characteristics (SmPC) before prescribing.) Neupro® 1 mg/24 h transdermal patch, Neupro® 2 mg/24 h transdermal patch, Neupro® 3 mg/24 h transdermal patch. Presentation: Neupro® is a thin matrix-type square transdermal patch. Active Ingredient: Rotigotine. 1 mg/24 h transdermal patch is 5 cm² and contains 2.25 mg rotigotine; releasing 1 mg rotigotine over 24 hours. 2 mg/24 h transdermal patch is 10 cm² and contains 4.5 mg rotigotine, releasing 2 mg rotigotine over 24 hours. 3 mg/24 h transdermal patch is 15 cm² and contains 6.75 mg rotigotine, releasing 3 mg rotigotine over 24 hours. Therapeutic Indications: Neupro® is indicated for the symptomatic treatment of idiopathic Restless Legs Syndrome in adults.

**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. A single daily dose should be initiated at 1 mg/24 h. Depending on the individual patient response, the dose may be increased in weekly increments of 1 mg/24 h to a maximal dose of 3 mg/24 h. The need for treatment continuation should be reconsidered every 6 months. 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 1 mg/24 h with a dose reduction preferably every other day to avoid the possibility of developing neuroleptic malignant syndrome. Contraindications, Warnings, etc: 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. Prescriptions: Literature reports indicate that treatment of RLS with dopaminergic medicinal products can result in augmentation. External heat should not be applied to the patch. Dopamine agonists are known to cause hyperthermia, and monitoring of blood pressure is recommended.

**Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk**

**Legal Category:** POM. **Marketing Authorisation Numbers:** 1 mg x 28 patches: EU/1/05/331/040; 2 mg x 28 patches: EU/1/05/331/041; 3 mg x 28 patches: EU/1/05/331/049. **NHS Cost:** 1 mg x 28 patches: £77.24; 2 mg x 28 patches: £77.24; 3 mg x 28 patches: £77.24. **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 534632, Email: medicalinformation@ucb.com. **Date of Revision:** March 2009 (09NE0039). Neupro® is a registered trademark.
ticity. Most patients develop pigmented retinopathy and one third cognitive impairment. About 8% of PKAN patients have acanthocytosis, possibly due to abnormalities of lipid synthesis. 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 nonsense mutations.

### 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. Serum CK is elevated in most cases with ChAc and MLS. ChAc patients have absent choroelin expression in erythrocytes on Western blot. MLS is detected by determination of absent Ks antigen and reduced Kell antigens on the erythrocytes in males and fluorescence absent 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 CAG repeat 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 cyproheptadine, clozapine or tetrabenazine may ameliorate the chorea. Non-medical therapies with a multidisciplinary approach are often helpful. Dysphagia 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 orefacial dyskinesia, and feeding dystonia (ChAc).

### REFERENCES


### Table 2: Predictive Accuracy of MCI from Cache County

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<tr>
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Focus on concordance in epilepsy

A “patient friendly” option

- Designed for concordance
- Once-a-day dose
- Simple evening dose
- Easy to swallow minitablets
- High patient acceptability
- Concordance reduces seizure frequency

Episenta®
Prolonged Release Sodium Valproate

Designed for concordance
Once-a-day dose
Simple evening dose
Easy to swallow minitablets
High patient acceptability
Concordance reduces seizure frequency

### Episenta® (Prolonged-Release Sodium Valproate)

**ABBREVIATED PRESCRIBING INFORMATION**

See Full SmPC for Details. Episenta 150mg & 300mg capsules and Episenta 500mg & 1000mg sachets contain prolonged release sodium valproate minitablets.

**Indication:** The treatment of all forms of epilepsy.

**Dose:** Give in 1 - 2 single doses. **Monotherapy:** Adults: Start at 600mg daily increasing by 150-300mg at three day intervals to a max of 2500mg/day until control is achieved. **Children over 20kg:** Initial dosage - 300mg/day increasing to max. of 35 mg/kg bw/day until control is achieved. **Children under 20kg:** 20mg/kg bw/day; max 40mg/kg/day. **Patients with renal insufficiency:** May require decreased dose.

**Combined Therapy:** Dosage adjustments may be required. **Administration:** Swallow without chewing the prolonged-release minitablets.

**Contraindications:** Liver disease. Personal or family history of hepatic problems. Porphyria. Hypersensitivity to valproate.

**Precautions:** Suicidal ideation reported. The onset of an acute illness is an indication of the early stages of hepatic failure and requires immediate withdrawal of the drug. Routinely measure liver function in those at risk before and during the first six months of therapy. Discontinue if signs of liver damage occur or if serum amylase levels are elevated or if spontaneous bruising or bleeding occurs. Review patients who have issues with pancreatitis, renal insufficiency, SLE, hyperammonaemia, weight gain, diabetes or blood tests.

Withdrawal of sodium valproate should be gradual. **Interactions, Pregnancy and Lactation:** See full SPC. **Undesirable Effects:** See full SPC. Further information & MA Holder: Beacon Pharmaceuticals Ltd. 85 High St., TN1 1YG UK. **Presentations & Prices:** POM. Episenta 150mg capsule x 100 PL 18157/0021, Episenta 300mg capsule x 100 PL 18157/0022, Episenta 500mg sachet x 100 PL 18157/0023, Episenta 1000mg sachet x 100 PL 18157/0024 have the following NHS prices: £5.70, £10.90, £18.00 & £35.00 respectively. **Date of text:** Oct 2008. Advert prepared June 2009.

Further information from Beacon
85 High St, Tunbridge Wells, TN1 1YG.
Tel: 01892 600930
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 adrenaline1 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.

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 nervosum plexum abdominis sitae, eorum usus’ (p94), he writes:

‘Glandulae ad plexum, certo possimus 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 usa 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

### Table 1. Adrenaline: time line

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1552</td>
<td>Eustachius published plates showing adrenal glands.</td>
</tr>
<tr>
<td>1656</td>
<td>Wharton associated adrenal glands with nerve plexus.</td>
</tr>
<tr>
<td>1852</td>
<td>Kölliker described microscopic anatomy: an apparatus appertaining to the nervous system.</td>
</tr>
<tr>
<td>1894</td>
<td>Oliver and Schäfer described pressor effect of adrenal medulla.</td>
</tr>
<tr>
<td>1896</td>
<td>Cybulski and Szymonowicz also described pressor effect.</td>
</tr>
<tr>
<td>1901</td>
<td>Epinephrine discovered independently by Abel and Takamine.</td>
</tr>
<tr>
<td>1906</td>
<td>Henry Hallett Dale insisted on name ‘Adrenaline’.</td>
</tr>
<tr>
<td>1910</td>
<td>Barger and Dale: sympathetic nerve stimulation more closely mimicked the effects of sympathomimetic primary amines than the effects of adrenaline.</td>
</tr>
<tr>
<td>1911</td>
<td>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.</td>
</tr>
<tr>
<td>1921</td>
<td>The transmission of the effects of nerve impulses, by the release of chemical agents, first became an experimental reality (Dale).</td>
</tr>
</tbody>
</table>
For the treatment of patients with Parkinson’s disease and end-of-dose motor fluctuations not stabilised on their current levodopa/DDC inhibitor treatment.

STALEVO, OFFERING YOUR PD PATIENTS A LONG-TERM COMMITMENT OF CARE

STALEVO is now available in a new range of six doses

PATIENTS

Indication: Treatment of adult patients with Parkinson’s disease and end-of-dose motor fluctuations not stabilised on levodopa/ dopamine 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, 150 and 200mg tablets is 18 per-day and if 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, CHF and/or advices: Not recommended. Elderly: No dosage adjustment required. MD to: moderate hepatic impairment, severe renal impairment (including dialysis): Caution advised. Contraindications: Haemoperfusion to, active substances or excipients. Severe hepatic impairment, Narrow-angle glaucoma. Phenacetin/amintylyn. Concomitant use of non-selective monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine). Concomitant use of non-selective monoamine oxidase inhibitors and end-of-dose motor fluctuations not stabilised on 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. Common success therefore should not be taken by patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or a severe-metabolic disturbance. Pathological gambling, increased libido and hypersalivation 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 medullary movements, nausea, Albuminuria changes, paranoid ideation and psychotic episodes, depression; cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradycardic episodes (the “off” phenomenon), anorexia, vomiting, diarrhoea, and somnolence. Reports of signs of pathological gambling, increased libido and hypersalivation, especially at high doses and generally reversible upon reduction of the dose of treatment discontinuation. Entacapone: Most frequently leads to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and/or nausea. Common: insomnia, hallucination, confusion and paranoia. Parkinsonian aggravated dyskinesia, extrapyramidal side-effects, akinesia, abdominal pain, dry mouth, constipation, vomiting, fatigue, increased sweating and falls. Rare: syncope or psychiatric disorder, hepatic function test abnormal. Very rare: anorexia, urticaria, weight decrease, agitation. Not known: hallucinosis, coma. See SPC for further details. Legality category: POM. Presentations: basic NHS costs and marketing authorisation numbers: Stalevo 50mg/7.5mg/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 £31.11, 100 tablet bottle £170.37, MA numbers: EU/1/03/260/010-011; Stalevo 150mg/37.5mg/200mg, 30 tablet bottle £31.11, 100 tablet bottle £170.37, MA numbers: EU/1/03/260/012-013; Stalevo 200mg/50mg/200mg, 30 tablet bottle £31.11, 100 tablet bottle £170.37, MA numbers: EU/1/03/260/020-021. Distributed by: Orion Pharma (UK) Ltd, 316, 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.
into the tissue fluids – later called hormones (a word first suggested by Sir William Bate Hardy, a Cambridge physiologist) – which maintained the internal milieu. But George Oliver, named the milieu intérieur. 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’. In the same year Thomas Addison published his famous monograph: The constitutional and local effects of disease of the suprarenal capsules, 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. 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 incabantis and believed they were hollow and filled with black bile – Capsulae atrohalinae – but George Frederic Baron Cuvier (1769-1832) established in 1805 that they were solid and he distinguished the medulla from the cortex. 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.

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. He found an unidentified substance in the adrenal medulla reacted with chromium salts to produce a brownish colour. He thus created the term chromaffin cells. 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 synthesised 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 Reymond16 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, 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.”

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.”

Sir Henry Dale engagingly described the discovery of Oliver (1841-1915) and Schäfer: “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 0.75mg, 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 pramipexole.

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, generally reversible upon reduction of dose or treatment discontinuation. See SPCs for other undesirable effects. Pack sizes and WHO price: 10 tablets: 0.26mg (0.375mg) £28.45; 0.52mg (0.75mg) £57.30; 1.05mg (1.5mg) £114.40; 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.

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, anemia, behavioral 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 edema. 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. 

A whole day in one dose
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 measured. As Schäfer had already suspected that he might be able to produce a hormonal effect, he readily agreed to try the extract. The results were remarkable: when the suprarenal extract was injected into anaesthetised animals, there was a marked rise in blood pressure. They presented their findings to the Physiological Society in 1894 resulting from their subsequent experiment which led to make the brilliant suggestion that these sympathetic fibres liberate small quantities of adrenaline at the points where they end in contact with muscle fibres and gland cells. 

Oliver and Schäfer collaborated, to show that 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 and raised the possibility of using adrenaline to achieve haemostasis, and in Addison’s disease. However, the extract had no name until John Jacob Abel (1857-1938) at Johns Hopkins’ prepared adrenal extracts in 1897 and called them ‘epinephrin’, whilst others used the term ‘supraarenin’. 

An important discovery was made by Napoleon Cybulski (1854-1919) at Krakow, who in 1896 published the effects of extirpation of the adrenal glands in anaesthetised 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. This complemented the clinical experiments of Oliver and Schäfer Davenport 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, since he realized Abel’s 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 Sharpay 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. 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. 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.

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

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

**Dosage and Administration:**
- The dose should be adjusted according to creatinine clearance.
- The dose should be gradually adjusted to minimize the potential of increased seizure frequency.

**Contraindications:**
- Hypersensitivity to the active substance, other carbamazepine derivatives, or any excipients.
- Patients with severe hepatic impairment.

**Warnings:**
- Patients with hepatic impairment:
- The dose should be adjusted according to creatinine clearance.
- The dose should be gradually increased to minimize the potential of increased seizure frequency.

**Precautions:**
- Patients with hepatic impairment:
- The dose should be adjusted according to creatinine clearance.
- The dose should be gradually increased to minimize the potential of increased seizure frequency.

**Drug Interaction:**
- Carbamazepine increases eslicarbazepine clearance.
- Oral contraceptives: Interacts with the oral contraceptive.

**Adverse Reactions:**
- Common effects:
  - Headache, abnormal coordination, dizziness, anxiety, tremor, diplopia, vision blurred, vertigo, difficulty in concentration, insomnia, drowsiness, dry mouth, abdominal discomfort, abdominal distension, cholestasis, epigastric discomfort, gingivitis, gingival hyperplasia, gingival bleeding, allergic reactions.

**Further Information:**
- Further Information from:

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**Drug Information:**
- Basic UK NHS cost:
  - Zebinix 800 mg: pack of 30 £154.20.

**Further Information:**
- Further Information from:

**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 1400/066 676 1450 or lemefr@eisai.net.

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**Table:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine</td>
<td></td>
</tr>
<tr>
<td>Zebinix</td>
<td></td>
</tr>
</tbody>
</table>

**Note:**
- Zebinix is under license from Bial.

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**Pharmacology:**
- **Pharmacodynamic:** Zebinix is a carbamazepine derivative.
- **Pharmacokinetic:**
  - Absorption: Oral administration.
  - Distribution: Widely distributed.
  - Metabolism: Metabolized by CYP2C19 and UDP-glucuronyl transferases.
  - Elimination: Excreted in urine and bile.

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**Prescribing Information:**
- **Zebinix**
- **(eslicarbazepine acetate)**
- Please refer to the SmPC before prescribing.
- Tablets containing 800 mg eslicarbazepine acetate.
- **Indication:**
  - Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation.
- **Dosage 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 in 300 mg increments.
- **Contraindications:**
  - Hypersensitivity to the active substance, other carbamazepine derivatives, or any excipients.
  - Patients with severe hepatic impairment.
- **Warnings:**
  - Patients with hepatic impairment:
    - The dose should be adjusted according to creatinine clearance.
    - The dose should be gradually increased to minimize the potential of increased seizure frequency.
- **Precautions:**
  - Patients with hepatic impairment:
    - The dose should be adjusted according to creatinine clearance.
    - The dose should be gradually increased to minimize the potential of increased seizure frequency.

**Drug Interaction:**
- **Carbamazepine:**
  - Concomitant treatment with carbamazepine increased the risk of diplopia, abnormal coordination and dizziness.
  - An increase in other adverse reactions caused by concomitant use of carbamazepine and eslicarbazepine acetate cannot be excluded.
- **Cimetidine:**
  - Eslicarbazepine increases eslicarbazepine clearance.
  - Zebinix slightly increases the clearance of carbamazepine.
- **Oral contraceptives:**
  - Interacts with the oral contraceptive.
- **Common effects:**
  - Headache, abnormal coordination, dizziness, anxiety, tremor, diplopia, vision blurred, vertigo, difficulty in concentration, insomnia, drowsiness, dry mouth, abdominal discomfort, abdominal distension, cholestasis, epigastric discomfort, gingivitis, gingival hyperplasia, gingival bleeding, allergic reactions.

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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 Eisai Ltd on 0208 600 1400/066 676 1450 or lemefr@eisai.net.

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**Date of preparation:** October 2009

**Zebinix UK2019**
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 pre-
ganglionic fibres. ... it follows, I think, that nicotine does not stimulate nerve-endings of pre-
ganglionic plasmotor products, 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.”

Adrenergic and cholinergic transmission

Ten years after Elliott’s researches, Sir Henry Dale (1875-1968) played a crucial role in developing adrenaline.

With his friend Otto Loewi (1873-1961), Dale also investigated acetylcholine, which they found related closely to the effects of the parasympathetic stimu-
lization – succinctly summarised in Loewi’s Nobel lecture – “The Chemical Transmission of Nerve Actions. Until that time, acetylcholine had not been isolated and could not be con-
sidered 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 neurotransmitter (rather than the chemical itself) they might use “to assist clear thinking.”

Further clarification came when in 1948, Raymond Ahlquist (1914-83), an American pharmacologist, writing about adrenergic nervous transmission, proposed that different receptors, not different molecular modifiers, caused different tissue responses. These specific receptors for epinephrine and norepineph-
rine, 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 in which he showed that nerve stimulation more closely mimicked the effects from autonomic nerves to the effector system. The discovery of the visceral 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 hormonal substances. The isolation and physiology of adrenaline by Abel, Takamine Stoltz, and Elliott in the brief period: 1890-1910 followed the concept of neural transmission initiated in 1856 by Thomas Wharton. The clinical physiology, elegantly revealed by George Oliver and Edward Schäfer, was further investigated and developed by Sir Henry Dale, who showed the way to its widespread clinical utility.

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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 (e.g., 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.

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 processes. 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.

Dr Justin Cross, Dr HK Cheow

Dr Justin Cross, Consultant in Nuclear Medicine at Addenbrooke’s Hospital, has a special interest in paediatric neuroradiology and has published articles on the measurement of cerebral tumour volume, carotid imaging and the use of spectroscopy in clinical practice.

Dr HK Cheow, Consultant in Nuclear Medicine at Addenbrooke’s Hospital. HK is trained in both radiology and nuclear medicine and has published widely on the applications of radioisotope imaging to clinical medicine.

Correspondence to:
Dr Justin Cross, Department of Radiology, Box 218, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 0QQ, UK.
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.

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.

- **$^{123}$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 abundantly in the basal ganglia. In Parkinson’s disease, parkinsonian syndromes (multiple system atrophy, progressive supranuclear palsy and 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).

**PET**

- **$^{18}$F Deoxy Glucose (18FDG)**
  This 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 18FDG is taken up avidly by the brain. Grey matter shows relatively higher 18FDG 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.

18FDG PET brain images in a patient with a brain tumour (arrow) (courtesy of M O’Doherty, Clinical PET Centre, London).

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.

18FluoroThymidine (18FLT) and 11CarbonMethionine (11C-Met)
This nucleotide analogue (FLT) and amino acid (11C-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).

18F-Misonidazole (18F-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.

REFERENCES
NHS Evidence – Neurological Conditions

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.² 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.

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](http://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 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.¹ 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.¹ It also provides a number of subject specific RSS feeds,² as well as regular updates via Twitter (fnhs_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](http://www.library.nhs.uk/neurological)
Manual of Botulinum Toxin Therapy

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

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 entirely 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. Aficionados 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, diagnostic, 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;3(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.

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 5s 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 cooperate 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

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 – pointer 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

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**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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**References**

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**Addenbrooke’s Hospital**
**CONSULTANT**
**PAEDIATRIC NEUROLOGY**

Reference: 180CON0257

Applications are invited for this new post at Addenbrooke’s Hospital. The successful applicant will join the 3 existing Neurologists providing a tertiary service across the Eastern region (population 4.4 million). There is an existing network of 15 outreach clinics, with very good links, caring for children within District Hospitals and liaising with other specialist services at Addenbrooke’s. The duties will be within Acute, General and subspecialty Neurology. There is good office and clinical space on the Addenbrooke’s site, within the Child Development Centre, where the service is based.

The successful applicant will be welcome to develop further subspecialist services and research interests. There are excellent links with the University of Cambridge and allied academic/research teams. Teaching at all levels will be an integral part of the post. The post attracts 10 Programmed Activities. The Paediatric Neurologists provide out of hours telephone advice. Applicants are required to be on the GMC’s Specialist Register or within 6 months of their expected date of receipt of a CCT at the time of interview. Applications are welcomed from those unable to work full time for personal reasons or those wishing to job-share.

Addenbrooke’s Hospital is an equal opportunities employer.

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**Informal enquiries about this post should be addressed to Dr Alasdair Parker, SDU Lead, telephone 01223 216662, email: alasdair.parker@addenbrookes.nhs.uk**

The full application pack for this post is available electronically and can be downloaded from our website: [wwwaddenbrookesorguk](http://wwwaddenbrookesorguk)

Alternatively this can be forwarded to you by email by sending a request to medical.staffing@addenbrookes.nhs.uk

Please include the words Consultant in Paediatric Neurology 180CON0257 in the subject title of your email.

A hard copy of the application pack can be requested by post or fax from: Medical Staffing Department (Box 154), Level 3, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 0QQ.

Fax 01223 586968.

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(please refer to the full summary of Product Characteristics before prescribing.)

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Patients may be switched overnight from ropinirole immediate release tablets to ropinirole prolonged-release tablets, and the dose is based on the total daily dose of immediate release formulation that the patient was receiving. Switch doses as follows: 3-4 mg immediate release – 4 mg prolonged-release, 4 mg immediate release – 5 mg prolonged-release, 7.5-9 mg immediate release – 12 mg prolonged-release, 15-18 mg immediate release – 21 mg prolonged-release, 24 mg immediate release – 28 mg prolonged-release, 24 mg immediate release – 30 mg prolonged-release. If patients are taking a different total daily dose of ropinirole immediate release to those typically prescribed as described above, then they should be switched to the nearest available dose of ropinirole prolonged-release tablets. After switching to REQUIP® XL prolonged-release tablets, patients will initially require more frequent and careful monitoring in order to adjust the dose of necessary. If sufficient symptomatic control is not maintained after switching to a dose of less than 4 mg once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg at weekly or longer intervals up to a dose of 8 mg once daily of ropinirole prolonged-release tablets. If sufficient symptomatic control is not achieved or maintained at a dose of 8 mg or greater once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg at 2 or 3 weekly intervals. Individual dose titration against efficacy and tolerability is recommended. Patients should be maintained on the lowest dose of ropinirole prolonged-release tablets that achieves symptomatic control. Do not exceed 24 mg/day. Concomitant l-dopa dose may be reduced gradually depending on clinical response. When switching from another dopamine agonist follow manufacturer’s guidance on dose reduction before initiating the patient on ropinirole immediate release tablets. Only once sufficient symptomatic control is achieved can patients be switched to ropinirole prolonged-release tablets. If treatment is interrupted for one day or more, re-initiation by dose titration on ropinirole immediate release tablets should be considered. Discontinue ropinirole gradually by reducing the daily dose over one week. Renal or hepatic impairment: No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. Elderly: 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 psychiatric 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 episodes 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 sorbitol (E972) which may cause allergy reactions. Drug interactions: Thioridazine and other centrally active dopamine antagonists may diminish the effectiveness of ropinirole – avoid concurrent use. No dosage adjustment needed when co-administering with L-dopa or dopamine agonist. 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 regime. 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 CYP2D6 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 titrated in normal manner, however, if HRT is stopped or reintroduced 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. Dermatitic reactions 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, uncoordinated. Psychiatric 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, dizziness, syncope. Common: dizziness (including vertigo), uncoordinated. extreme somnolence, sudden onset of sleep. Vascular disorders; common/uncommon hypertension, postural hypotension. Gastrointestinal disorders; very common: nausea, common; abdominal pain, vomiting, dyspepsia, constipation. Gynaecological disorders; very common: breast enlargement, changes in breast size, breast pain, uterine disorders and uterine bleeding. Drug withdrawal syndrome, sudden onset withdrawal symptoms following sudden withdrawal of drug, may include; restlessness, tremor, rebound motor fluctuations, hallucinations, paranoia, confusion, dyskinesia, syncope. peak-dose symptoms (e.g. anxiety, sweating, tachycardia, nausea) may occur with excessive peak-dose symptoms requiring a reduction in dose or withdrawal from treatment. Seizures have been reported in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Common: dizziness, drowsiness, headache, dyskinesia, syncope. Uncommon: vertigo, nausea, vomiting, abdominal pain, dry mouth, constipation. Very rare: liver/renal disorders and administrative site conditions; common: peripheral oedema. Hepatobiliary disorders: very rare: hepatitis, increased AST, ALT. Overdosage: Symptoms of overdosage 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; customersupport@uk.gsk.com Freephone 0800 221 441. Prescribing information last revised: January 2009. REQUIP® is a trademark of the GlaxoSmithKline group of companies. All rights reserved. Adverse events should be reported. Reporting forms and information can be found at: www.yellowcard.gov.uk. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.
Jane Alty

qualifed from Cambridge University Medical School and has trained at Addenbrookes Hospital, Manchester Royal Infirmary and The National Hospital for Neurology and Neurosurgery. She has a specialist interest in movement disorders, neuroimaging and dementia and has undertaken a Movement Disorders Fellowship in Melbourne, Australia and published two books on ultrasound imaging. She now works as a Neurology Specialist Registrar at Leeds General Infirmary and has trained less than full time for a year since the birth of her daughter.

Correspondence to:
Jane Alty
E Floor, Martin Wing, Leeds General Infirmary, Leeds, West Yorkshire, LS1 3EX
Email: altyjane@doctors.org.uk

ASSOCIATION OF BRITISH NEUROLOGIST TRAINEES

REFERENCES
1. BMA survey of junior doctors 2008: flexible training opportunities.

Less Than Full Time Training in Neurology

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.

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.3 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!

Table 1: Reasons for applying for LTFT

<table>
<thead>
<tr>
<th>Category one</th>
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<tbody>
<tr>
<td>Doctors with disabilities or suffering from ill health.</td>
</tr>
<tr>
<td>Doctors caring for young children.</td>
</tr>
<tr>
<td>Doctors caring for ill or disabled partners, relatives or other dependents.</td>
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</tbody>
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<table>
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<tr>
<th>Category two</th>
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<tr>
<td>Doctors training for national or international sporting events.</td>
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<tr>
<td>Doctors who work on long term extraordinary responsibility e.g. membership of national committees.</td>
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<tr>
<td>Doctors training for religious roles.</td>
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<tr>
<td>Doctors undertaking non-medical professional development.</td>
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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.

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 initiatives 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’ 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 determinants 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...
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).

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 lecturership 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
- Neurology Funding Opportunities
- Research in Training
- Guidelines in 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.

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Research Fellow in Movement Disorder Neurology

Full-time, fixed-term for 2 years

You will have an MRCP in medicine and be wishing to pursue a career in clinical neurology. You will have preferably have done research at BSc level or above and may have clinical/scientific publications. You will also have a good understanding of research methodology. A capacity for critical analysis is essential as is evidence of scientific writing skills. The research will be a continuation of ongoing work in the use of Single positron emission computed tomography (SPECT) and ultra high resolution Magnetic Resonance Imaging in the diagnosis of Parkinson’s disease and Parkinsonian disorders. You will attend weekly movement disorder clinics and have an opportunity for exposure to acute neurology during your tenure. This post would be an excellent preparation for further neurological training. Candidates will be encouraged to apply for an MD/PhD through the Nottingham University Programme.

Location: National Parkinson Foundation Centre of Excellence for Parkinson’s Disease, Derby Hospitals NHS Foundation Trust and University of Nottingham.

Contact: For an informal discussion please contact Dr Nin Bajaj on 01332 254 890/0115 924 9924 ex 66815 or via nin.bajaj@nuh.nhs.uk

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)
A potentially bewildering array of neuropsychological tests exists, examining the various domains of cognitive function, such as intelligence, memory, language, perceptual (especially visuospatial) 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, or 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.

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Perceptual (especially visuospatial) 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 characteristics, combined with executive function, with rather more complex rules than snap. Any game involving trumps may also share these cognitive components.

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.

The Neuropsychology of Board Games, Puzzles and Quizzes

Aj Larner
Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery.

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

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Health Records: out of the frying pan?

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 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 nurses and other professionals involved with patient care quickly to locate the sections they need. As clinical care becomes fragmented and 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 that works 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) 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 disorganised 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 handwritten history (but then e-notes should have unlimited space)
- a neurological examination proforma (may be one comprehensive system for neurologists and another, abbreviated version, for medical SHOs)
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 Ascutlation
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. 07512 601358,
E. ukabif@ukabifconnect.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

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. reford.court@pfrontgroup.org

5th National Autism Today Conference
17-18 November, 2009; Edinburgh, UK
www.mahhealthcarevents.co.uk

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

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

Neurological Cancers Study Day
20 November, 2009; Middlesex, UK
Annis Hall, T. 01923 844177,
E.annis.hall@mshaclf.org

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

Be Activated Courses: A unique MMS 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@royalwesph.nhs.uk

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

Be Activated Courses: A unique MMS 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; Elly, UK
E. F Caldwell@tiscali.co.uk

Royal College of Physicians Of Edinburgh Symposium: Neurology
27 November, 2009; Edinburgh, UK
www.rcpe.ed.ac.uk/education/events/ neurologyconference09.php
E. Christina Gray, C. Gray@rcpe.ed.ac.uk

9th Annual King’s Neuromuscular Symposium
27 November, 2009; London, UK
T. 020 7948 1547,  020 7849 8490,
E. philippa@fth.ac.uk

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

RAeT 2009
30 November-1 December, 2009; Coventry, UK
http://www.rdf3.org.uk/ratea

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. 03 210 749 9335,
E. laissue@priavetravours.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@braintraining.co.uk
www.braintraining.co.uk

10th Annual UK Movement Disorders Meeting
4-6 December, 2009; London, UK
E. neurology@boehmingeelheim.com

3rd Annual Meeting of the American Epilepsy Society
4-8 December, 2009; Boston, USA
T. 860 586 7355,
E. csluboski@aesnet.org
To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.org.uk by 8 December, 2009.
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. 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 (RELY; www.relytrial.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 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.

orders, new cognitive tests are being piloted for use specifically in Parkinson’s disease, such as SCOPA-Cog and PANDA, as well as ACER. 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 unpredictable 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
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 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. He gave a useful evaluation of measures of motivation that can be employed and then reviewed current treatment approaches, both pharmacological and behavioural. He 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 Ted Judd from Washington State gave what proved to be a popular and entertaining talk on neuropsychopharmacology. His presentation was evidence-based 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 ‘bled’ air. The latter is taken from the engine and can be contaminated by engine emissions 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.  

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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.

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

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

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
111th Meeting of the British Neuropathological Society

January 6-8th 2010
Institute of Child Health,
Guilford Street, London WC1N 1EH

Symposium: ‘Reversing Neurodegeneration’
Organiser: Professor Seth Love, Bristol, UK
Speakers: Professor Gillian Bates, London, UK
Professor Giovanna Mallucci, Leicester, UK
Professor Steven Gill, Bristol, UK
Professor James Nicoll, Southampton, UK
Professor Berislav Zlokovic, Rochester, USA

Dorothy Russell Memorial Lecture:
Professor Eliezer Masliah, University of California, San Diego, USA
- Full programme of talks and posters
- The Society Dinner to be held at The Honourable Society of Gray’s Inn

We welcome Neuropathologists, Neurologists and Neuroscientists to a meeting attracting a wide range of speakers from the UK and abroad. Trainees in Neuropathology and Neurology are particularly encouraged to attend.

Join us for a full academic programme with an excellent opportunity to meet and discuss professional and academic matters.

Full details: http://www.bns.org.uk/

The 12th national conference
Dementias 2010
A review and update on current developments in the dementias; in the fields of research, investigations, clinical care and service and policy issues

The Institute of Engineering & Technology (IET), Savoy Place, London
18th & 19th February 2010

PROGRAMME ADVISORS: Professor Tom Arie, CBE, Professor Emeritus of Health Care of the Elderly, Nottingham University and Professor Alistair Burns, Professor of Old Age Psychiatry, University of Manchester

To book your place at this event please visit our website www.mahealthcareevents.co.uk
Alternatively call our booking hotline on 020 7501 6762
MA Healthcare Ltd, St. Jude’s Church, Dulwich Road, London SE24 0PB

40 YEARS OF MEDICAL EDUCATION
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

Live cell confocal imaging on a large scale

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

Live cell confocal imaging on a large scale

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 runs between 25th and 31st January 2010 and will challenge members of the public to row 10km (or more), helping to raise funds.

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 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.

For more information contact Manuela Loibl, E. manuela.loibl@cim-med.com

Ikea 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
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 23:1 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 micrometres is possible from low-power magnifications with a field diameter of up to 11 millimetres.

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.

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
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 and efficacy in real life – studies. Children (<12 years) Not recommended. Elderly No specific data. Elderly – 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 urticarial reactions. 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, puritus, oedema, inflammation, hyperpigmentation, injection site atrophy). An immediate post-injection reaction (one or more of vasodilatation, 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, facial oedema, vomiting, skin discoloration, dyspepsia, headaches, eye disorders, 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 (2ºC to 8ºC). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15ºC to 25ºC) once for up to one month. Do not freeze. Legal Category – POM. Package Quantity – 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.

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