

ACNR

Advances in Clinical Neuroscience & Rehabilitation



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P E A C E O F M I N D

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march/april 2004

Cover picture is taken from *The Saccadic System: A Neurological Microcosm* (see page 6) and shows a miniature, non-invasive saccadometer in use. In this prototype, stimuli are projected on to a convenient surface by the three miniature lasers at the top; a system of infra-red emitters and detectors monitors the ensuing saccades, the information being analysed and stored in a separate, tiny microprocessor unit which can subsequently communicate with the user's computer through an infra-red link.



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Presentation: Pale yellow tablets containing 25mg, 50mg, 100mg and 200mg lamotrigine, and white dispersible/chewable tablets containing 2mg, 5mg, 25mg and 100mg lamotrigine. **Uses:** *Monotherapy:* Not recommended in children under 12 years. Adults and children over 12 years for partial epilepsy with or without secondarily generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. *Add-on therapy:* Adults and children over 2 years for partial epilepsy with or without secondary generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. Seizures associated with Lennox-Gastaut syndrome. **Dosage and Administration:** Initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash. *Monotherapy:* Initial dose is 25mg daily for two weeks, followed by 50mg daily for two weeks. Dose should be increased by a maximum of 50-100mg every 1-2 weeks until optimal response. 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Add-on to sodium valproate with or without ANY other AED, initial dose is 0.15mg/kg bodyweight/day given once a day for two weeks, followed by 0.3mg/kg/day given once a day for two weeks. Dose should then be increased by a maximum of 0.3mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 1 to 5mg/kg/day given in one dose, or two divided doses. Add-on to enzyme-inducing AEDs with or without other AEDs (but NOT valproate) is 0.6mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2mg/kg/day for two weeks given in two divided doses. Dose should then be increased by a maximum of 1.2mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 5-15mg/kg/day given in two divided doses. Weight of child should be monitored and dose adjusted as appropriate. 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Elevations of liver function tests and rare reports of hepatic dysfunction. Very rarely, increase in seizure frequency has been reported.

Legal category: POM. **Basic NHS costs:** £16.45 for Monotherapy Starter Pack of 42 x 25mg tablets (PL0003/0272); £27.98 for Non-Valproate Starter Pack of 42 x 50mg tablets (PL0003/0273); £8.23 for Valproate Starter Pack of 21 x 25mg tablets (PL0003/0272). £64.37 for pack of 56 x 100mg tablets (PL0003/0274); £109.42 for pack of 56 x 200mg tablets (PL0003/0297). £21.95 for pack of 56 x 25mg tablets (PL0003/0272). £37.31 for pack of 56 x 50mg tablets (PL0003/0273). £8.75 for pack of 28 x 5mg dispersible tablets (PL0003/0346). £21.95 for pack of 56 x 25mg dispersible tablets (PL0003/0347). £64.37 for pack of 56 x 100mg dispersible tablets (PL0003/0348). £9.37 for pack of 30 x 2mg dispersible tablets (PL0003/0375).

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Note: If changes in AED medication are to be made they should be completed before conception.* The UK Pregnancy Register (0800 389 1248) is collecting prospective data on the effects of all AEDs in pregnancy. Please phone for information or to register a patient.

*Crawford P *et al.* Seizure 1999; 8: 201-217

Date of preparation: January 2004

LAM/FPA/04/11193/1



Welcome to another year of ACNR. The journal is now into its fourth year, with a distribution of well over 5000 and the hope of even greater international presence in the next year with input from all our European members of the editorial board. We would also recommend visiting the website, which has all the previous issues of the journal along with case studies and soon a small radiological quiz.

Indeed the website is proving to be very successful, with about 900 individual visitors a month, as well as being in receipt of a commendation at the recent Scottish Magazine awards (many congratulations to Rachael Hansford on this).

We have our usual two review articles, which in this issue cover Huntington's disease and saccadic eye movements. The molecular pathology of Huntington's disease is discussed by Dr Jenny Morton and follows on from a series of other articles on this and related topics - such as the excellent account last year by Gen Sobue and colleagues on SBMA. In her article, Jenny Morton leads us through the emerging complex array of intracellular events that lie downstream of the mutant huntingtin, and makes the important point that intracellular protein inclusions may have different functions at different times in the illness. This is a view that may help reconcile those who believe that inclusions are protective to the cell as opposed to those that view them as toxic.

Roger Carpenter presents a beautiful and thought provoking article on saccadic eye movements - a movement which we make about a quarter of a million times a day. This review sets out the various levels of control that the CNS exerts on this system, and how this may go awry in a range of disorders. In this latter respect, the ease with which saccadic latencies and duration can be recorded nowadays means that we may be able to gain greater insight into disease processes and progression using these measures.

In our series on movement disorders, I have taken on the topic of tremor which is commonly seen in clinic and which is often difficult to treat. I have tried to lay out a pragmatic approach to the clinical problem with a classification that reflects this, and a therapeutic strategy which largely reflects our ignorance and the paucity of proper trials. In this respect there are a number of well known therapies which most of us would use in the clinic in patients with essential tremor, along with a long list of those "worth a go" without much to support their approach. Of course the advent of deep brain stimulation has helped the minority of patients with severe tremor, but how one manages patients with cerebellar/midbrain tremors is still very poor and worthy of much more work, given how disabling this type of movement disorder is to the patient.

This issue also presents a Medtronic sponsored article by Michael Vloeberghs and colleagues, outlining a planned national randomised control study on the use of intrathecal baclofen (ITB) in the treatment of spasticity in children with cerebral palsy. This is clearly an important topic, for which the data on what represents the best therapy is not known. However, there are very encouraging open label studies using ITB. Indeed this article presents data from Vloeberghs *et al* in which 48 out of 52 patients report that they were satisfied with the ITB treatment, although it is not without some significant side-effects in some individuals.

The rehabilitation article discusses "Rehab without walls", and the use of rehabilitation centres abroad, with particular reference to a patient who went to a German neurorehabilitation centre. This use of specialist centres outside the UK is an interesting one, especially in the current climate of greater integration within Europe on so many other issues, and the article discusses the advantages and disadvantages of adopting such an approach.

We also have our usual features and I would particularly draw your attention to the excellent meeting report by Dr Kevin Talbot which explores new developments in motorneuron disease and is a useful adjunct to the excellent article last year by Pam Shaw and colleagues.

So that's about it. Do keep the feedback coming, and we look forward to sharing another exciting year, with ACNR continuing to bridge the clinical-scientific divide of neurology and neuroscience.

Roger Barker, Co-editor

E-Mail: AdvancesinCNR@aol.com

PS: Hope you like the new new picture of me!!

Editorial Board and contributors



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



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



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



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



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

International editorial liaison committee

We are delighted to welcome Professor Soffietti, Italy, to our international editorial liaison committee.



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



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

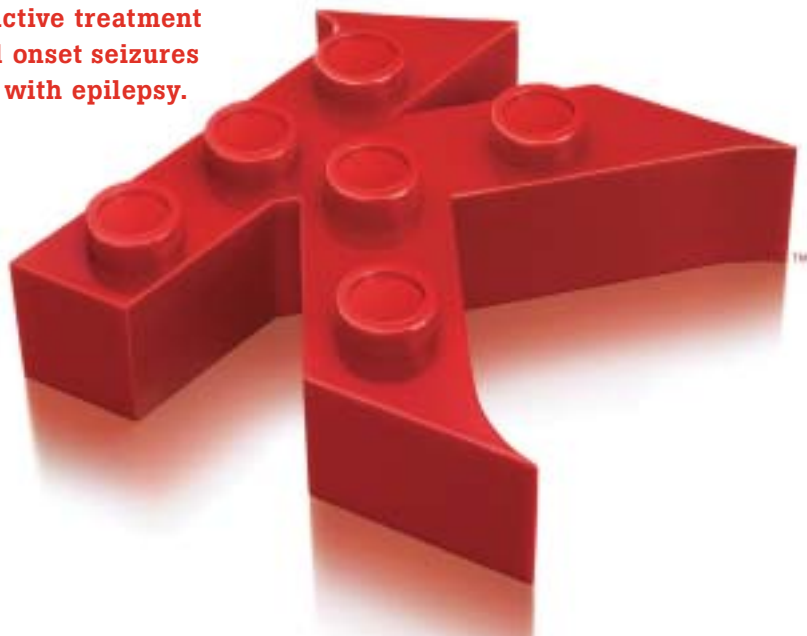


Professor Hermann Stefan, Germany: Professor Stefan trained in neurology, psychiatry, neuropathology, and epileptology at the University Bonn. He is Professor of Neurology/Epileptology in the Department of Neurology, University Erlangen-Nürnberg, and specialises in the treatment of epilepsies, especially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



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

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tasks, e.g. driving vehicles or operating machinery. **Undesirable effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (>10%): asthenia, somnolence. *Common* (between 1%–10%): GI disturbances, anorexia, accidental injury, headache, dizziness, tremor, ataxia, convulsion, amnesia, emotional lability, hostility, depression, insomnia, nervousness, vertigo, rash, diplopia. For information on post-marketing experience see SPC. **Legal category:** POM. **Marketing authorisation numbers:** 250 mg x 60 tablets: EU/1/00/146/004. 500 mg x 60 tablets: EU/1/00/146/010. 1,000 mg x 60 tablets: EU/1/00/146/024. **NHS price:** 250 mg x 60 tablets: £29.70. 500 mg x 60 tablets: £52.30. 1,000 mg x 60 tablets: £101.10. **Further information is available from:** UCB Pharma Ltd., 3 George Street, Watford, Hertfordshire WD18 0UH. Tel: 01923 211811. medicaluk@ucb-group.com **Date of preparation:** February 2004.

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

The Saccadic System: A Neurological Microcosm

Familiarity can breed contempt: perhaps it is precisely because the saccade is the commonest movement we make – about three every second of our waking lives – that we rather take it for granted. Yet, apart from being a movement of extraordinary speed and elegant precision^{1,2} (fig. 1), it not only determines absolutely what we are allowed to see, but precedes and prepares for nearly every directed action that we make. Research over the last couple of decades has demonstrated in detail the involvement in saccadic control of nearly every level of the brain, from the simple neural circuits in the brainstem reticular formation that ensure the saccade's remarkable technical performance, to neurons in frontal eye fields that help decide whether to look at one thing or another^{3,4}. As a result we have a more detailed understanding of the saccadic system, in the sense of being able to relate structure and disorder of structure to quantitative measurements of function, than of any other sub-system of the brain. Because saccades are stereotyped movements, small deviations may carry immense clinical significance. As a result, recent technical advances (in making micro-miniaturised oculometers that store data for subsequent analysis by lap-top) have begun to turn this neurophysiological knowledge into clinical utility, inaugurating what may perhaps turn out to be a new era of genuinely *quantitative* neurology⁵.

The saccadic hierarchy

There is an intrinsic three-fold hierarchy in any motor act, that can be summarised as *what, where, how*: recognition of a target, and decision; localisation and proprioception; and creation of the detailed patterns of forces needed for execution. This general principle of motor organisation is particularly clearly seen in the saccadic system^{2,3} (fig. 2). At the lowest level are the neural circuits in the prepontine and mesencephalic reticular formation, close to the oculomotor nuclei, that generate the highly specific temporal patterns of firing by which the oculomotor neurons move the eye so precisely and rapidly to their new position. Above them, the colliculus primarily has the task of converting information about the visual location of an object into an appropriate command to the brainstem that will move the gaze to the same location; in this it is supplemented by the cerebellum and has assistance from the cortex. But in the real world we are seldom

presented with just a single potential target: we must choose between many, and some will have more significance than others. This choice – deciding what to look at – is a function that culminates specifically in the frontal eye fields. All of these hierarchical levels have immense diagnostic potential; for instance, saccadic slowing characteristic of disorder at the lowest level may be a very early indicator of neurodegeneration⁶. But in this review there is only space to concentrate on the highest level, where recent work has used the stereotyped precision of saccades to discover a great deal about how cortical areas make saccadic decisions^{7,8}.

Latency: the measurement of decision

The two lowest levels of the saccadic hierarchy are in principle all that is needed to generate a saccade that lands accurately and swiftly on a visual target. In a laboratory situation, with single targets presented in the dark, that would be fine. But the real world is full of interesting stimuli competing for our attention. While the collicular level can localise visual targets, what it cannot do is *recognise* them, or evaluate their behavioural significance, for which the cortex appears to be necessary. Consequently, we find that the collicular mechanisms are tonically switched off by descending, ultimately cortical, inhibition, and only permitted to carry out their function when the higher processes of decision are complete. As a result, we have *procrastination*. The time between presenting a stimulus and starting to make a response – the saccadic latency – is far longer than would be expected from the speed of visual transduction, nerve conduction and synaptic action. Reaction time is decision time, and studies of how this latency varies with changing stimuli and circumstances – and in neurological disorder – have yielded much information about how these decision mechanisms work. The result is something called the LATER model: as well as recalling the procrastination the name stands for Linear Approach to Threshold with Ergodic Rate. This succinct but perhaps cryptic expression implies the existence of decision units, whose activity represents the system's degree of belief in different possible targets; at rest, their activity represents prior probability or expectation, and as sensory evidence comes that supports the belief, their activity increases linearly until it reaches a threshold, the point where it is so overwhelm-



Roger Carpenter is Reader in Oculomotor Physiology at Cambridge University, and the author of the popular text-book *Neurophysiology* as well as many papers on higher aspects of saccadic control. For many years he has been Director of Medical Studies at Gonville and Caius College, and in 2000 was one of the inaugural group of twenty winners of £50,000 national teaching awards from the ILTE.

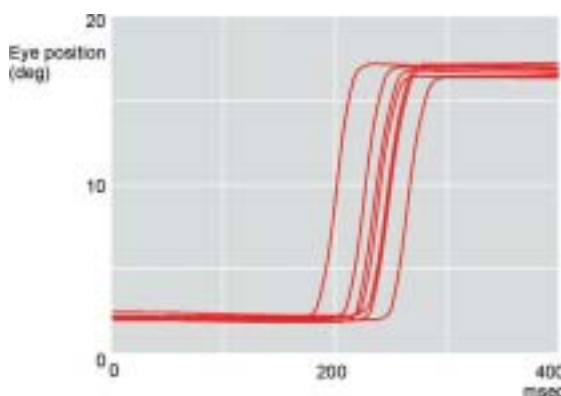


Figure 1. A set of seven human saccades evoked by sudden movement of a target 15 deg to the left, showing that although these very stereotyped movements are rapid in the sense that the velocity of the eye is many hundreds of degrees per second, there is a long latency before the movement starts at all, that varies randomly from trial to trial.

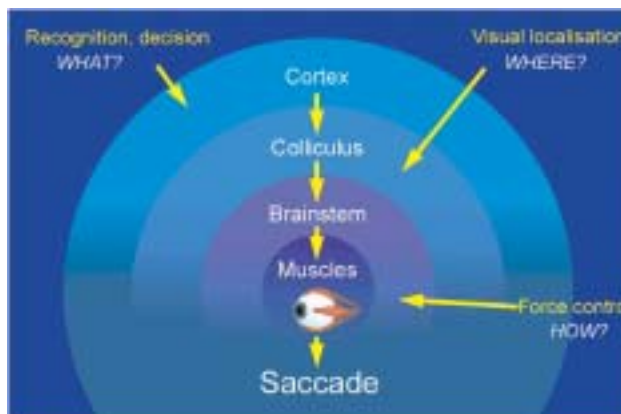


Figure 2. The saccadic hierarchy. At the highest level, a target must be recognised and a decision made as to whether it is worth looking at; this decision gates the intermediate level, at which information about the target's location is translated into selection of an appropriate saccadic metric; and this in turn activates brainstem circuitry that elaborates the complex patterns of neural firing that throw the gaze efficiently and rapidly on to the target, as in figure 1.

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Please refer to UK Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** White to off-white tablets containing modafinil 100 mg or modafinil 200 mg (indicated by '100' or '200' debossed on one side). **Indication:** Excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnoea/hypopnoea syndrome. **Dosage:** Adults: 200–400 mg daily either as two divided doses in the morning and at noon or as a single morning dose according to response. **Elderly:** Treatment should start at 100 mg daily, which may be increased subsequently to the maximum adult daily dose in the absence of renal or hepatic impairment. **Severe renal or hepatic impairment:** Reduce dose by half (100–200 mg daily). **Children:** See contra-indications. **Contra-indications:** Use in pregnancy and lactation, children, uncontrolled moderate to severe hypertension, arrhythmia, hypersensitivity to modafinil or any excipients used in Provigil. **Warnings and precautions:** Patients with major anxiety should only receive Provigil treatment in a specialist unit. Sexually active women of child-bearing potential should be established on a contraceptive programme before taking Provigil. Blood pressure and heart rate should be monitored in hypertensive patients. In patients with obstructive sleep apnoea, the underlying condition (and any associated cardiovascular pathology) should be monitored. Provigil is not recommended in patients with a history of left ventricular hypertrophy nor in patients who have experienced mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia. Studies of modafinil have demonstrated a low potential for dependence, although the possibility of this occurring with long-term use cannot be entirely excluded. **Drug interactions:** Modafinil is known to induce CYP3A4/5 (and to a lesser extent, other) enzymes and so may cause clinically significant effects on other drugs metabolised via the same pathways. The effectiveness of oral contraceptives may be impaired through this mechanism. When these are used for contraception, a product containing at least 50 mcg ethinylestradiol should be taken. Certain tricyclic antidepressants and selective serotonin reuptake inhibitors are largely metabolised by CYP2D6. In patients deficient in CYP2D6 (approximately 10% of the population) a normally ancillary metabolic pathway involving CYP2C19 becomes more important. As modafinil may inhibit CYP2C19 lower doses of antidepressants may be required in such patients. Care should also be observed with co-administration of other drugs with a narrow therapeutic window, such as anti-convulsant or anticoagulant drugs. **Side effects:** Very common (>10%) – headache, nervousness. Common (>1%) – insomnia, anxiety, dizziness, somnolence, depression, abnormal thinking, confusion, paraesthesia, hypertension, nausea, dry mouth, diarrhoea, decreased appetite, dyspepsia, constipation, tachycardia, palpitation, vasodilatation, asthenia, chest pain, abdominal pain and blurred vision. Dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed. (See SmPC for uncommon side effects). **Basic NHS Cost:** Pack of 30 blister packed 100 mg tablets: £60.00. Pack of 30 blister packed 200 mg tablets: £120.00. **Marketing authorisation numbers:** PL 16260/0001 Provigil 100 mg Tablets, PL 16260/0002 Provigil 200 mg Tablets. **Marketing authorisation holder:** Cephalon UK Limited. **Legal category:** POM. **Date of preparation:** September 2003. Provigil and Cephalon are registered trademarks. Full prescribing information, including SmPC, is available from **Cephalon UK Limited**, 11/13 Frederick Sanger Road, Surrey Research Park, Guildford, Surrey GU2 7YD, Medical Information Freephone 0800 783 4869 (ukmedinfo@cephalon.com).

References:

- Young T et al. *N Engl J Med* 1993; **328**: 1230-1235.
- Sforza E and Krieger J. *J Neurol Sci* 1992; **110**: 21-26.
- Guilleminault C and Philip P. *Sleep* 1996; **19**(9): S117-S122.
- Strollo PJ et al. *N Engl J Med* 1996; **334**: 99-104.
- Bedard M-A et al. *J Clin Exp Neuropsychol* 1993; **15**: 330-341.
- Kales A et al. *J Chron Dis* 1985; **38**(5): 427-434.
- US Modafinil in Narcolepsy Multicenter Study Group. *Neurology* 2000; **54**: 1166-1175.
- US Modafinil in Narcolepsy Multicenter Study Group. *Ann Neurol* 1998; **43**: 88-97.
- Broughton RJ et al. *Neurology* 1997; **49**: 441-451.
- Hirshkowitz M et al. *Sleep* 2001; **24** (Ab Suppl): A239.
- Provigil in OSAHS Study Group (5545).



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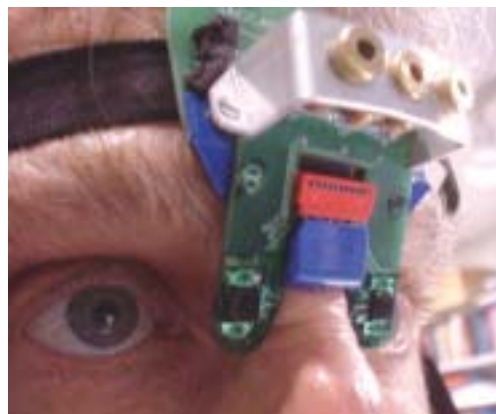


Figure 3.

A miniature, non-invasive saccadometer in use. In this prototype, stimuli are projected on to a convenient surface by the three miniature lasers at the top; a system of infra-red emitters and detectors monitors the ensuing saccades, the information being analysed and stored in a separate, tiny microprocessor unit which can subsequently communicate with the user's computer through an infra-red link.

ingly probable that action is justified, and initiated⁹. Such a system can be regarded as an 'ideal' decision device, in the sense that it makes maximal use of information to alter its estimated probabilities through an essentially Bayesian mechanism.

LATER seems to be applicable to all reaction times, whether saccadic or manual, and inaugurated by visual or auditory or even tactile stimuli, and provides quantitative predictions of what happens when expectations alter, when information is only partially available, or when a subject is under pressure to respond more urgently¹⁰. A well-known feature of latency is that it varies randomly from trial to trial, and this randomness seems to be created 'deliberately' by the brain. Because many such units, corresponding to different possible actions, normally race against one another, the winner determining the response that is finally selected, this randomness in timing results in randomness of choice, perhaps in order to make our behaviour unpredictable, and

References

- Becker, W. (1992). *Saccades*. In *Eye Movements*, ed. Carpenter, R.H.S., pp. 95-137. MacMillan, London.
- Carpenter, R.H.S. (2000). *The neural control of looking*. *Current Biology* 10, 291-293.
- Munoz, D.P. (2002). *Commentary: Saccadic eye movements: overview of neural circuitry*. *Progress in Brain Research* 140, 89-96.
- Carpenter, R.H.S. (1988). *Movements of the Eyes*. Pion, London.
- Leigh, R.J. and Zee, D.S. (1999). *The neurology of eye movements*. Oxford University Press, New York.
- Zarei, M., Nouraei, S.A.R., Caine, D., Hodges, J.R. & Carpenter, R.H.S. (2002). *Neuropsychological and quantitative oculometric study of a case of sporadic Creutzfeldt-Jakob disease at pre-dementia stage*. *Journal of Neurology, Neurosurgery and Psychiatry* 73, 56-58.
- Schall, J.D. (2000). *Decision making: from sensory evidence to a motor command*. *Current Biology* 10, 404-406.
- Schall, J.D., Stuphorn, V. & Brown, J.W. (2002). *Monitoring and control of action by the frontal lobes*. *Neuron* 36, 309-322.
- Carpenter, R. H. S. & Williams, M.L.L. (1995). *Neural computation of log likelihood in the control of saccadic eye movements*. *Nature* 377, 59-62.
- Reddi, B.A.J., Asrress, K.N. & Carpenter, R.H.S. (2003). *Accuracy, information and response time in a saccadic decision task*. *Journal of Neurophysiology* 90, 3538-3546.
- Leach, J.C.D. and Carpenter, R.H.S. (2001). *Saccadic choice with asynchronous targets: evidence for independent randomisation*. *Vision Research* 41, 3437-3445.
- Carpenter, R.H.S. (1999). *A neural mechanism that randomises behaviour*. *Journal of Consciousness Studies* 6, 13-22.
- Hanes, D. P. and Schall, J.D. (1996). *Neural control of voluntary movement initiation*. *Science* 274, 427-430.
- Kobayashi, Y., Saito, Y. & Tadashi, I. (2001). *Facilitation of saccadic initiation by brainstem cholinergic system*. *Brain Development* 23, 524-527.
- Robbins, T.W. (2000). *Chemical neuro-modulation of frontal executive functions in humans and other animals*. *Experimental Brain Research* 133, 130-138.

perhaps also to generate exploration and creativity^{11,12}.

Recordings from the frontal eye fields in monkeys have revealed a population of saccadic movement-related neurons whose activity is very similar to what was predicted by LATER¹³. Before a saccade, firing frequency rises steadily for 100-200 msec before the start of a saccade, the movement being initiated when the activity reaches a fixed threshold level; the rate of rise varies randomly from trial, in correspondence with the variability in the latency itself. LATER-like rise-to-threshold behaviour can be seen in many areas of the cortex in advance of motor responses, and may well represent something quite fundamental about how the cortex works.

Future developments

An attractive aspect of LATER is that the performance of the eye in terms of latency can be summarised essentially by just two numbers, which are in turn directly related to the parameters of the model itself. They represent the fundamental parameters that must be defined for any decision system: for example, whether speed is more important than accuracy, the relative weight to be attached to present rather than past information, and the degree of creativity (randomness). In the brain, these parameters clearly need to be regulated in some way, and an exciting possibility is that they might possibly be related to the several ascending systems – noradrenergic, serotonergic, histaminergic – that innervate cortex relatively diffusely from below^{14,15}. The reason for having so many has always been a puzzle: if all they do is cause 'arousal' one would surely be enough. We hope soon to be able to establish whether defects in these systems do indeed cause the quantitative changes that LATER would predict. If so, the fact that miniature non-invasive devices for measuring eye movements (fig. 3), requiring practically no skill in setting up, will very soon be available at little cost and could revolutionise the diagnosis and monitoring of neurological impairment.



For a case report on vertical supranuclear gaze palsy, see <http://acnr.co.uk/case%20report.htm>

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Molecular Pathogenesis of Huntington's Disease

Huntington's disease (HD) is a genetic neurodegenerative disease with a complex set of symptoms and an insidious progression that continues until death. The cause of HD is the pathological expansion of an unstable (CAG_n) trinucleotide repeat within the coding region of the HD gene (for references, see 1). The CAG repeat codes for a polyglutamine repeat in the huntingtin (htt) protein. To date, 9 other 'polyglutamine repeat' diseases have been identified, including spinobulbar muscular atrophy (SBMA), several of the spinocerebellar ataxias (SCA1,2,3,6,7 and 17) and dentatorubralpallidolysian atrophy (DRPLA). In each of these diseases, the protein carrying the mutation and also the distribution of neuronal loss is different. (The different protein context in each disease is likely to be responsible for the difference in the patterns of neurodegeneration). However, the fact that all of these diseases are caused by a similar mutation, coupled with the fact that they are all are dominant, (except SBMA that is X-linked), adult-onset, progressive neurodegenerative diseases, suggests that they may have a common underlying pathological mechanism.

Htt, a protein with elusive function

The precise function of htt remains unknown. It is a large cytoplasmic protein found loosely associated with synaptic vesicles in nerve terminals, and with microtubules in dendrites. It has no homology with any other protein and no distinguishing features that predict its biological function: There are no membrane spanning domains, it does not appear to have enzymatic activity and is not a structural protein. Htt is essential for mammalian development, since deletion of both copies of the HD gene retards the development of the embryo and kills it in mid-gestation. However, when only one copy of HD is knocked out, growth and development appears to be normal. Further, although deleting one copy of the gene causes subtle

deficits in adult mice, these are very mild compared with those seen in mice carrying the HD mutation⁽²⁾. Since patients who are homozygous for the HD gene are neurologically normal until the onset of their disease, it seems that the expanded polyglutamine repeat does not interfere with the normal function of htt. Rather, HD is caused by a novel *gain* of function of the mutant protein.

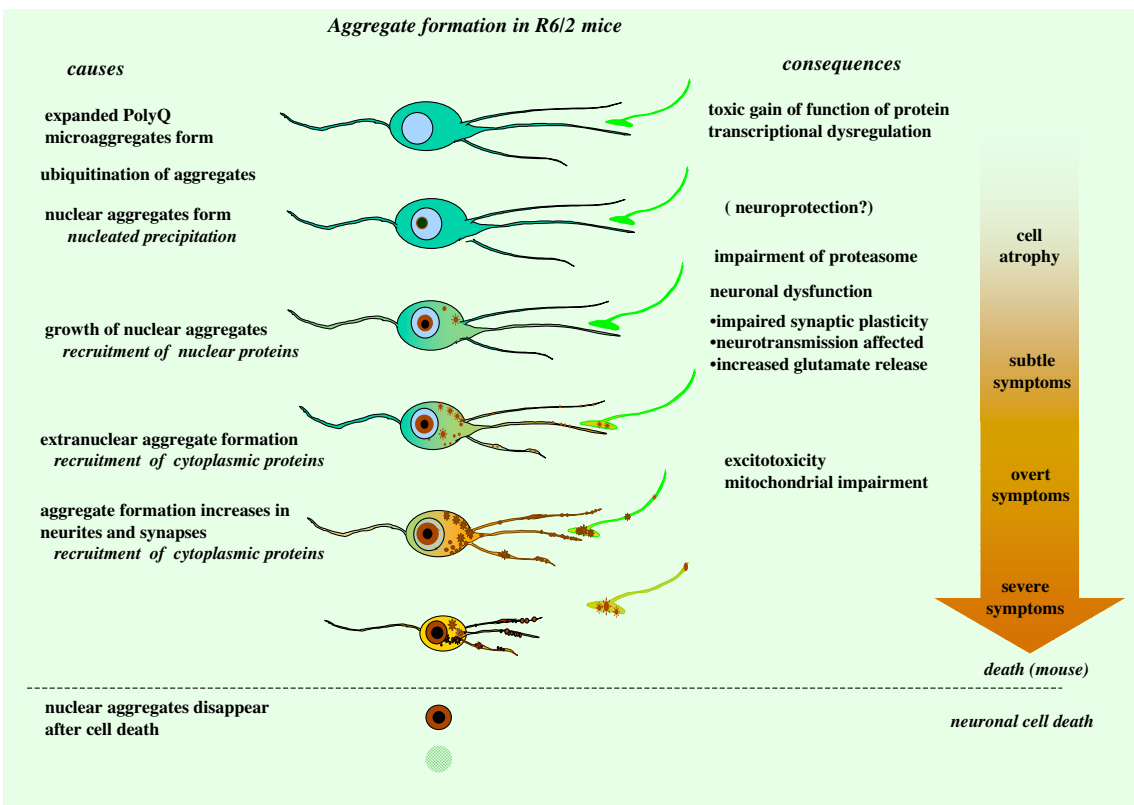
Abnormal protein-protein interactions with mutant htt

A number of proteins are known to interact with htt⁽³⁾ (Table 1). Some of these interactions change when the protein carries a polyglutamine repeat in the pathological range. For instance, interactions of htt with htt-associated protein 1 (HAP1) are increased, and interactions with htt-interacting protein 1 (HIP1) are decreased with increased polyglutamine length⁽⁴⁾. This suggests that a change in the interaction between htt and the interacting protein(s) may also contribute to the pathology underlying HD. For example, HIP1, when over-expressed in neurons, is neurotoxic⁽⁴⁾. If mutant htt has a reduced binding capacity for HIP1, this may result in an endogenous toxicity mediated by increased intracellular HIP1. The precise roles of some of the proteins with which htt interacts are themselves unknown. However, their putative roles give strength to the possibility that changes in their interactions with htt may contribute to the pathogenesis in HD (Table 1).

Why do striatal neurons degenerate in HD?

The medium-sized spiny GABAergic neurons of the striatum (caudate nucleus and putamen) degenerate in HD, and atrophy of the caudate and putamen is the pathological hallmark of HD. Striatal degeneration is the first and most obvious neuropathology in the early-grade HD brain. However, later, profound loss of neurons in other regions (particularly the neocortex) is also seen.

Dr Jenny Morton is a Senior University Lecturer. She has been working on HD since 1990, first with neurochemical models, and more recently with transgenic mouse models of HD. Her recent work has been aimed at characterising the neurological phenotype of HD mouse models, paying particular attention to the progression of cognitive deficits and to identifying potential biomarkers for HD.



Interestingly, the pattern of degeneration in HD does not directly reflect the expression pattern of htt. Although htt is relatively abundant in striatal neurons, it is widely expressed throughout the brain, for example in cortex (pyramidal neurons), cerebellum (Purkinje cells) and thalamus. While a number of proteins are preferentially distributed in the striatum; however, as yet there is no evidence to suggest that any of them is directly responsible for the selective degeneration of striatal neurons in the early stages of HD.

Increased striatal vulnerability in HD

The striatum is the main target for glutamatergic output neurons from both the cortex and the thalamus. Striatal neurons are sensitive to glutamate, and excitotoxic neurodegeneration can be induced by injecting the glutamate agonist quinolinic acid, directly into the striatum. However, excitotoxicity in the striatum can also be induced indirectly, by using metabolic poisons such as 3-nitropropionic acid (3-NP)⁽⁵⁾. 3-NP depletes energy levels in neurons and makes them more vulnerable to excitotoxicity mediated by endogenous levels of glutamate. The striatal neurons are also the main target for dopaminergic input from the substantia nigra. Dopamine modulates the toxicity of endogenous glutamate, since removing the dopamine input to the striatum markedly reduces the size of 3-NP lesions⁽⁶⁾. There is compelling evidence from both animals and human studies to suggest that energy levels are compromised in HD⁽¹⁾. There is also evidence from animal studies that glutamatergic activity of the corticostriatal pathway is abnormal in HD mice⁽⁷⁾. Thus, either a change in energy levels and/or an change in the activity of glutamate input could increase the vulnerability of striatal neurons in HD.

Abnormal protein aggregation in HD

A number of transgenic mouse models have been made for HD. These have been particularly valuable for studies

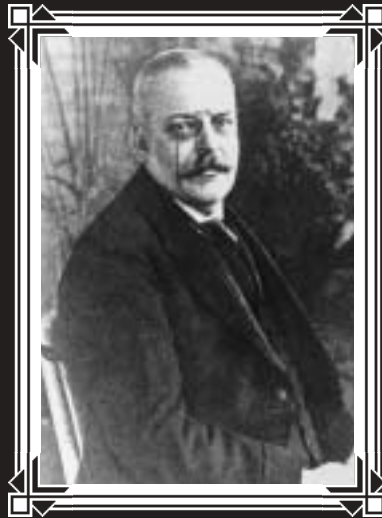
of pathology and behavior (for references, see 1). Ubiquitinated protein aggregates containing htt fragments and other key proteins were first observed in the R6/2 mouse model of HD⁽¹⁾. However, they have now been seen in post mortem brains from HD patients, as well as in patients and mouse models of other polyglutamine repeat diseases. These aggregates, also known as inclusions, are found in the nuclei as well as the neuropil of affected neurons. There is much debate about the role of these aggregates - in particular whether or not they are neurotoxic or protective - there is no doubt that they are a hallmark of HD. In fact, when all of the evidence is reviewed, it seems highly likely that the aggregates play a role in polyglutamine toxicity⁽⁸⁾.

In the R6/2 line of HD mice, aggregates appear first in the nuclei, and then in axons, dendrites and synapses of neurons (Fig.1). Their appearance correlates with the onset of symptoms. However, the progressive and changing nature of the neurological phenotype in the R6/2 mouse suggests that the aggregates may also have changing roles^(1,9). Aggregation of abnormal and potentially toxic htt protein may initially be beneficial or benign, simply because the toxic protein is removed from the cell milieu. However, it seems likely that if mature inclusions recruit essential cell proteins (e.g. heat shock proteins, proteasome components, /-synuclein), then the presence of the aggregate itself would be deleterious to cellular function. Further, the presence of aggregates of protein in axons, dendrites or synapses could directly impair essential functions of these structures.

In symptomatic R6/2 mice, ubiquitinated aggregates are found in virtually all neurons. However, in post mortem HD brain, nuclear aggregates are relatively sparse in striatal neurons, but are predominant in the cortical neurons (for references, see 1). The cause of this unexpected distribution of aggregates is not known. It may be that when striatal neurons degenerate, the aggregates disappear. Thus, the lack of striatal aggregates in post

Table 1 Some examples of proteins that interact with huntingtin (for others, see 1, 3)

Interacting protein		PolyQ-length dependent interaction?	Functional role
AKT/PKB	serine theronine kinase	no	cell signaling
CA150	co-activator 150	no	transcriptional activator
CBP	cAMP response element binding protein	yes (increased binding)	transcriptional co-activator
CIP4	Cdc42-interacting protein 4	yes (increased binding)	signal transduction
CtBP	co-repressor C-terminal binding protein	yes (decreased binding)	transcription factor
Grb2	growth factor receptor-binding protein 2	not known	growth factor receptor-binding protein
HAP1	huntingtin-associated protein 1	yes (increased binding)	membrane trafficking
HAP40	huntingtin-associated protein 40	not known	??
HIP1	huntingtin-interacting protein 1	yes (decreased binding)	endocytosis (proapoptotic)
HIP14/HYP-H	huntingtin-interacting protein 14	yes (decreased binding)	receptor trafficking, endocytosis
HYP J (/-adaptn C)		yes (decreased binding)	endocytosis
HYPA/FBP11		not known	pre-mRNA splicing factor
N-CoR	nuclear receptor co-repressor	yes (increased binding)	transcriptional regulator
NFkB		not known	transcriptional factor
P53		no	transcriptional factor
PACSIN1	protein kinase C and casein kinase substrate in neurons 1	yes (increased binding)	endocytosis
PSD-95	post-synaptic density protein 95kDa	yes (decreased binding)	synaptic scaffolding protein
RasGAP		Not known	Ras GTPase-activating protein
SH3GL3		yes (increased binding)	endocytosis
Sin3a		yes (increased binding)	transcriptional repressor
Sp1		yes (increased binding)	transcriptional factor
TAFII-130	TBP-associated factor II 30	no	transcriptional factor



DR. ALOIS ALZHEIMER

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IT DIDN'T HAVE A REALISTIC TREATMENT



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Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** *Adults/elderly;* 5 mg daily which may be increased to 10 mg once daily after at least one month. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. *Children;* Not recommended. **Contra-Indications:** *Pregnancy.* Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Lactation:** Excretion into breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may

be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinus pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive

behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £68.32. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £95.76. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** January 2002.



mortem striatum may merely reflect striatal neuronal cell loss. Alternatively it could mean that in HD, cortical dysfunction occurs first, and drives striatal neurodegeneration by the excitotoxic mechanisms outlined above.

Proteolysis and proteasome dysfunction

In normal cells, abnormally folded proteins are conjugated with multiple ubiquitin molecules and targeted for degradation by the proteasome, a multicatalytic protease complex. The protein aggregates seen in HD are ubiquitinated, suggesting that the proteins have been marked for degradation by the proteasome. The fact that the proteins are not degraded, but aggregate instead, implies an impairment of the cell chaperone and proteasome machinery. Htt is cleaved by a number of different proteases, including some caspases (proteases that are key mediators of programmed cell death pathways) and calcium-dependent proteases such as calpain⁽¹⁰⁾. The N-terminal fragments released by such cleavage appear to be more toxic than the full-length protein⁽¹¹⁾. Further, although they do not appear to impair proteasome function greatly in cellular models, these fragments impair the cells' normal response to stress and toxicity⁽¹²⁾. However, proteasome components have been found within aggregates in HD cell models, suggesting a direct involvement in the aggregate pathology⁽¹³⁾. Proteasomal dysfunction would have both direct and indirect effects on a cell, firstly because the mutant htt is not being degraded and secondly because the proteasome would also not be able to degrade other misfolded proteins that might have deleterious effects on cell function. Proteasome dysfunction would have a further 'knock-on' effect in the cell, because the proteasome plays a central role in the turnover of normally-folded but short-lived proteins in the cell. Thus proteasome dysfunction could mediate multiple pathways of dysregulation of normal cell function.

Transcriptional dysregulation in HD

A large number of genes are abnormally expressed in HD mouse models (for references, see 1). The protein products of these genes are found in key molecular systems, including neurotransmitter pathways (particularly dopamine), intracellular signaling pathways and calcium homeostasis. However, at present it is not possible to tell which of the many genes that are dysregulated in HD are involved in the primary pathology and which are secondary. While some of the dysregulated genes have been shown to result in altered protein expression (e.g. those coding for DARPP-32 and complexin II (CPLXII)), most have not been studied in depth.

Abnormalities in synaptic transmission

As well as changes in neurotransmitters and receptors, modulators of transmission have also been implicated in HD. For example, CPLXII is decreased in both HD post mortem brain and HD mouse brains⁽¹⁴⁾. CPLXII is a modulator of neurotransmitter release, and CPLXII knockout mice exhibit progressive motor and cognitive deficits⁽¹⁵⁾. This suggests that the decrease in CPLXII seen in HD may underlie some of the cognitive and motor deficits. Other evidence suggesting that synaptic dysfunction is one of the earliest changes in HD includes the observation that, as with human patients, symptoms in all of the mouse models appear before there is frank neurodegeneration (for references, see 1). In mice, abnormalities in synaptic plasticity and transmitter release are measurable before overt symptoms appear. Thus it appears that neuronal

dysfunction rather than neurodegeneration might give rise to the earliest symptoms in HD.

Summary

Although the mutation causing HD appears to be relatively simple, the downstream consequences of the mutation are extremely complex. First, it seems likely that neuronal dysfunction precedes neurodegeneration in both animals and humans. Second, the HD mutation appears to perturb multiple intracellular pathways. Only some of these will be primary responses to the toxic gain of function of the HD mutation. Knowing which of the changes is 'cause' and which is 'effect' will be fundamental to advancing our understanding of HD to a level where treatment becomes a realistic possibility.

References

- Bates GP, Harper PS and Jones AL. (2002) Huntington's disease, 3rd edition. Oxford University Press, Oxford
- Catteneo E, Rigamonti D, Goffredo D, Zuccato C, Squitieri F and Sipione S. (2001) Loss of normal huntingtin function: new developments in Huntington's disease research. *Trends in Neurosci* 24:182-8
- Harjes, P. and Wanker, E. (2003) The hunt for huntingtin function: interaction partners tell many different stories. *Trends in Biochem. Sci.* 28: 425-4433
- Hackam AS, Yassa AS, Singaraja R, Metzler M, Gutekunst CA, Gan L, Warby S, Wellington CL, Vaillancourt J, Chen N, Gervais FG, Raymond L, Nicholson DW, Hayden MR. (2000) *Huntingtin interacting protein 1 induces apoptosis via a novel caspase-dependent death effector domain.* *J Biol Chem.* 275: 41299-308.
- Albin RL. (2000) *Basal ganglia neurotoxins.* *Neurol Clin.* 18: 665-80.
- Reynolds DS, Carter RJ, Morton AJ. (1998) *Dopamine modulates the susceptibility of striatal neurons to 3-nitropropionic acid in the rat model of Huntington's disease.* *J Neurosci.* 18: 10116-27
- Klapstein GJ, Fisher RS, Zanjani H, Cepeda C, Jokel ES, Chesselet MF and Levine MS. (2001) *Electrophysiological and morphological changes in striatal spiny neurons in R6/2 Huntington's disease transgenic mice.* *J Neurophysiol* 86:2667-77
- Michaelik, A. and Van Broeckhoven, C. (2003) *Pathogenesis of polyglutamine disorders: aggregation revisited.* *Hum. Mol. Genet.* 12: R173-186
- Morton AJ, Lagan MA, Skepper JN, Dunnett SB. (2000) *Progressive formation of inclusions in the striatum and hippocampus of mice transgenic for the human Huntington's disease mutation.* *J Neurocytol.* 29: 679-702.
- Tarlac V, Storey E. (2003) *Role of proteolysis in polyglutamine disorders.* *J Neurosci Res.* 74: 406-16
- Zhou H, Cao F, Wang Z, Yu ZX, Nguyen HP, Evans J, Li SH, Li XJ. (2003) *Huntingtin forms toxic NH2-terminal fragment complexes that are promoted by the age-dependent decrease in proteasome activity.* *J Cell Biol.* 163: 109-18
- Ding Q, Lewis JJ, Strum KM, Dimayuga E, Bruce-Keller AJ, Dunn JC, Keller JN. (2002) *Polyglutamine expansion, protein aggregation, proteasome activity, and neural survival.* *J Biol Chem.* 277(16): 13935-42
- Waelter S, Boeddrich A, Lurz R, Scherzinger E, Lueder G, Lehrach H, Wanker EE. *Accumulation of mutant huntingtin fragments in aggresome-like inclusion bodies as a result of insufficient protein degradation.* *Mol Biol Cell.* 2001 May; 12(5): 1393-407.
- Morton AJ, Faull RL, Edwardson JM. *Abnormalities in the synaptic vesicle fusion machinery in Huntington's disease.* *Brain Res. Bull.* 2001 Sep 15; 56(2): 111-7.
- Glynn D, Bortnick RA, Morton AJ. (2003) *Complexin II is essential for normal neurological function in mice.* *Hum Mol Genet.* Oct 1; 12(19): 2431-48.

Tremor

Tremor is a common condition that can occur in isolation or be part of an evolving neurological condition. It is amenable to treatment in most cases, but if first line therapies fail then often the management is complex and consideration for deep brain stimulation is considered. In this short review we outline a pragmatic approach to the patient with tremor.

Definition and Classification

Tremor is defined as a rhythmic sinusoidal movement of a body part, due to regular rhythmic muscle contractions. The most useful classification of tremors is clinical and based on the circumstances in which they are seen (see Table 1). Static tremor occurs when a relaxed limb is fully supported at rest. Postural tremor appears when a part of the body is maintained in a fixed position and may also persist during movement. Kinetic or action tremor occurs specifically during active voluntary movement of a body part. If the amplitude of such an action tremor increases as goal-directed move-

ment approaches its target, it is termed an intention tremor. This latter tremor suggests damage in the cerebellum and its efferent connections to the brainstem and is of a frequency of 2-3Hz. Psychogenic tremors are generally rare and typically are of sudden onset with a variable but rarely remitting clinical course and typically affect the trunk or limb with standing and/or using the limb respectively.

Physiologic tremor has a frequency in the 7-11 Hz band and is typically symptomatic in states of increased sympathetic nervous activity whilst symptomatic postural tremors occur in association with a wide range of neurologic



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Table 1: Classification of tremor

Type	Definition	Causes
STATIC or REST	Present with hands or head held relaxed at rest	<ul style="list-style-type: none"> • Parkinson's disease • Parkinsonism (inc. drug-induced, postencephalitic) • Other extrapyramidal diseases • Multiple sclerosis
POSTURAL	When limb or body is held in certain position	<ul style="list-style-type: none"> • Physiological tremor • Exaggerated physiological tremor, as in: Thyrotoxicosis anxiety states and stress alcohol drugs (e.g. sympathomimetics, anti depressants, sodium valproate, lithium) heavy metal poisoning (i.e. mercury—the 'hatter's shakes') • Structural neurological disease, as in: severe cerebellar lesions ('red nucleus or midbrain tremor')¹ Wilson's disease Neurosyphilis peripheral neuropathies • Essential (familial) tremor • Task specific tremors (e.g. primary writing tremor)²
KINETIC or ACTION (inc intention)	When performing an action of some sort, such as picking up cup of tea	<ul style="list-style-type: none"> • Brain-stem or cerebellar disease, as in: Multiple sclerosis Spinocerebellar degenerations Vascular disease Tumour
PSYCHOGENIC		

¹ Midbrain tremors results from damage in the region of the red nucleus, typically in the context of either MS, head trauma or a vascular insult. It is characterised by a combination of rest, postural and action tremor which is often severely disabling and very hard to treat, and this includes using stereotactic surgical thalamic lesions.

² Dystonic tremors can be kinetic, postural or task specific and are irregular asynchronous and usually affect the arm and neck. Primary writing tremor is such an example.

disorders. These tremors can be distinguished neurophysiologically as they have a different frequency, although there is significant overlap in tremor frequency in several common conditions associated with tremor (for example, essential tremor and Parkinson's disease).

Clinical approach to the patient with tremor

The most useful approach to a patient with tremor is a clinical one.

History and examination:

• When did it first appear?

Long standing implies essential tremor (ET)

• Where is the exaggerated physiological tremor?

Hands: Unilateral versus bilateral with bilateral tremor implying exaggerated physiological or ET. Unilateral tremor is more suggestive of either Parkinson's disease or dystonic tremor

Voice involvement implies dystonic or ET

Head involvement with head titubation suggests either cerebellar/brainstem pathology, dystonic head tremor or ET

Legs/body involvement especially when at rest with a feeling that standing still produces an intense sense of imbalance that passes off with walking is highly suggestive of orthostatic tremor

• What, if anything, makes it better?

Alcohol helping the tremor suggests ET

• What brings out the tremor?

Certain actions or movements implying it is either an action tremor, postural tremor, intention tremor or dystonic (e.g. with writing) (see Table 1).

All tremors worsen with stress and anxiety, so this is non-discriminatory

• Is there any family history of a tremor?

Helpful for ET and other inherited conditions where tremor is a feature (beware of the patient diagnosed as "tremor dominant Parkinson's disease" where ET was actually more likely). Are there any other neurological symptoms – bradykinesia, myoclonus and so on suggestive of Parkinson's disease or other neurodegenerative condition

• Are there any medical problems and what drugs is the patient taking?

Especially important to look for thyrotoxicosis or paraproteinaemic neuropathies. For example, consider cimetidine, valproate, amiodarone, β -agonist inhalers.

Investigation (see Table 2)

Treatment (see Table 3)

Certain specific tremor conditions

ESSENTIAL (FAMILIAL) TREMOR

An illness characterised by a 5-8Hz postural tremor of the arms and head. ET can present at any age, is slowly progressive and generally causes mild disability although severe cases may be functionally incapacitating (hence the potentially inappropriate use of the term "benign", sometimes used to prefix this disorder). It can cause handwriting to be

tremulous or "corrugated". The cause of ET is unknown but a positive family history is obtained in over half of such patients and the pattern of inheritance in such families indicates an autosomal dominant trait. No pathological or biochemical abnormality has been identified in essential tremor, but recent functional imaging studies have pointed towards abnormal activation of the cerebellum, red nucleus and thalamus, and in some patients alcohol relieves the tremor. In a small number of families, genetic loci, but not the causative gene(s), have been isolated.

The typical clinical presentation is tremor in one or both hands on maintaining a posture, as when holding a cup or glass, but is not present at rest. On movement, as in finger-nose testing, the tremor continues but does not get strikingly worse, as is the case with cerebellar intention tremor. Tremor of the head (titubation) and jaw is present in about 50 per cent of cases, and tremor of the legs occurs in about a third. Despite the tremor, tests of co-ordination usually are performed normally, walking is unaffected, and there are no other neurological abnormalities.

Some other variants of the syndrome are encountered occasionally. Thus isolated, inherited, head tremor may occur, with either 'yes-yes' or 'no-no' movements, and tremulous 'writer's cramp' (primary writing tremor) is recognised. This is classified by some as a dystonic tremor. Tremor of the legs on standing, at around 5 to 8 Hz may occur in some patients with essential tremor and is thought to be different from primary orthostatic tremor (see below).

The treatment of this condition involves beta-blockers which work in about 30-40% of cases (up to a dose of 240mg/day). Primidone, in standard anticonvulsant dosages, also helps some patients but is very sedating. These two classes of drug have a reasonably solid evidence base for efficacy in ET. Other therapies, with little or no evidence to support their use, include clonazepam, gabapentin and topiramate, (see Table 3). Stereotaxic thalamotomy may be required in the very small number of patients whose tremor is so severe although more recently this has been superseded by the use of deep brain stimulation in the ventral intermediate nucleus of the thalamus.

ORTHOSTATIC TREMOR

This is a very rare condition in which there is tremor of the legs and body especially when the patient stands still, which gives the patient the feeling of being very unsteady when standing still. As soon as they start moving the condition improves.

The tremor can be seen in some patients although in others it is best diagnosed by listening over the thighs where the tremor can be heard as the sound of distant helicopters. It responds well to clonazepam.

Table 2: Investigation of tremor

Routine haematology and biochemistry to exclude major metabolic problem including renal failure, liver disease +/- alcoholism
Thyroid function tests
Immunoglobulins and electrophoretic strip
Copper/Caeruloplasmin in young patients
Consider genetic tests such as SCA screening

Consider imaging, EMG-NCS, and CSF but only if tremor is late onset or evolving with other neurological signs and symptoms

Table 3: Treatment of tremor*

Stop any drug that may be causing tremor
Inc. Lithium, SSRIs, neuroleptics, sodium valproate, beta agonists, thyroxine, aminophylline etc

Drugs which are worth trying:

Beta blockers
Primidone
Benzodiazepines
Gabapentin
Topiramate

Botulinum toxin injections for some dystonic tremors

Deep brain stimulation/Thalamotomy of VIM thalamic nucleus

Other drugs and manipulations which have been tried in the treatment of tremor (ET unless otherwise indicated) with possible benefit in some cases:

Phenobarbitone
Carbonic anhydrase inhibitor (Methazolamide)
Clonidine
Amantadine
Clonidine (probably not effective in ET)
Isoniazid (probably not effective for intention tremor)
Clozapine/Olazepine/Quetiapine
Mirtazapine
Vagal nerve stimulation

* the treatment of the tremor in PD lies outside the scope of this article but clearly revolves around the use of L-dopa and dopamine agonists. It is controversial whether anti-cholinergic agents and the newer dopaminergic agonists have more anti-PD tremor effects than L-dopa based therapies.

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Stalevo (levodopa / carbidopa / entacapone) Brief Prescribing Information

Indication: Treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment. **Dosage and administration:** Orally with or without food. One tablet contains one treatment dose and may only be administered as whole tablets. Optimum daily dosage must be determined by careful titration of levodopa in each patient preferably using one of the three tablet strengths. Patients receiving less than 70-100mg carbidopa a day are more likely to experience nausea and vomiting. The maximum Stalevo dose is 10 tablets per day. Usually Stalevo is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone. See SPC for details of how to transfer these patients and those not currently treated with entacapone. **Children and adolescents:** Not recommended. **Elderly:** No dosage adjustment required. **Mild to moderate hepatic impairment, severe renal impairment (including dialysis):** Caution advised. **Contraindications:** Hypersensitivity to active substances or excipients. Severe hepatic impairment. Narrow-angle glaucoma. Pheochromocytoma. Concomitant use of non-selective monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine). Concomitant use of a selective MAO-A inhibitor and a selective MAO-B inhibitor. Previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis. **Warnings and precautions:** Not recommended for treatment of drug-induced extrapyramidal reactions. Administer with caution to: patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions, or past or current psychosis; patients receiving concomitant antipsychotics with dopamine receptor-blocking properties, particularly D2 receptor antagonists; patients receiving other medicinal

products which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias, monitor cardiac function carefully during initial dosage adjustments. Monitor all patients for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully. Caution when driving or operating machines. Doses of other antiparkinsonian treatments may need to be adjusted when Stalevo is substituted for a patient currently not treated with entacapone. Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dosage reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy. **Undesirable effects:** Levodopa / carbidopa – Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, depression, cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence. Entacapone – Most frequently relate to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and urine discolouration. Common: insomnia, hallucination, confusion and paroniria, Parkinsonism aggravated, dizziness, dystonia, hyperkinesias, diarrhoea, abdominal pain, dry mouth constipation, vomiting, fatigue, increased sweating and falls. See SPC for details of laboratory abnormalities, uncommon and rare events. **Legal category:** POM. **Presentations, basic NHS costs and**

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References

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

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Management of Spasticity in Children with Cerebral Palsy, A National Randomised Controlled Study on Intrathecal Baclofen

Introduction:

Several approaches to the treatment of spasticity in children are available, aiming to improve ease of motion in the short term and reducing limb and spine deformity in the longer term. These approaches are based on a background regime of physiotherapy to improve joint ranges, muscle power and motor patterns. Single or combined oral medication, such as Baclofen, Tizanidine and Dantrolene can be considered, but the appropriate dose to reduce spasticity is often associated with unacceptable side effects.

Recently there has been an increase in the use of Botulinum toxin A injections to treat spasticity in individual muscles. This is usually given under mild sedation and produces significant improvement in muscle tone for approximately four months, after which the treatment needs to be repeated. There is extensive literature documenting the benefits in specific muscles of the lower limb in both ambulant and non-ambulant children with cerebral palsy. Injections to the upper limb can also be used for specific goals, including improved reach, ease of motion during dressing and other aspects of care as well as for the pure cosmetic appearance of the limb. The treatment is limited to approximately six large muscles in one session to avoid mild botulism as a side effect.

When a child has severe and global spasticity, which interferes with function, dorsal rhizotomy or intrathecal baclofen can be considered. Dorsal rhizotomy is carried out extensively in the USA and Europe and involves surgery to selectively cut afferent spinal roots, which inhibits the reflex arc in the spinal cord and so reduces muscle tone. This succeeds, but often with accompanying muscle weakness. Detrimental effects on bladder function and spinal integrity have been reported. A recent meta-analysis of three randomised controlled trials of dorsal rhizotomy concluded there was significant functional improvement, but that the improvement was limited and should be balanced against the time, effort and risks involved.

Continuous Intrathecal Baclofen [ITB] is the treatment of choice to reduce severe spasticity in a non-mobile child with severe quadriplegia [GMFM stage 5], especially when there is pain and spasms. Baclofen spreads throughout the CSF, reducing tone in all limbs, and sometimes improves dysphagia when oral-motor hypertonia is present. This approach can also be used in diplegics with severe hypertonia, GMFM stages 3-4, in order to reduce lower and upper limb spasticity. ITB is beneficial in dystonic cerebral palsy, an effect that is not reported with dorsal rhizotomy. ITB has the disadvantage compared to rhizotomy of being more expensive, and there is the relative inconvenience of regular 2-3 monthly refills of the pump reservoir. Conversely, ITB has the advantage of being a reversible, non-destructive technique.

While there have been excellent open studies describing the benefits of ITB in children, there are none with objective measures and we aim to address the need to show the effect of ITB in two randomised controlled trials.

Current results of the Nottingham ITB activity:

The programme began with the first tests in October 1998. Severe deformity was present in 52 Children. 17 could manage to walk short distances with a frame and some help, a further 7 could weight bear but not walk, while 28 were unable even to weight bear. All were wheelchair dependent for distances of more than a few tens of

metres. One third have mainstream cognition, the remainder having various degrees of learning disability.

All patients in programme	
Awaiting test	5
Unsuccessful test	3
Successful test, parents declined implant	1
Successful test, awaiting implantation	11
Implanted	52
Total	72
Implanted patients	
Satisfied with treatment	48
Treatment stopped on request	3
Death (unrelated)	1
Total	52

Table I. Patients in the CIBI programme

Aetiology:

Of the 52 implanted patients, 48 (92%) had cerebral palsy in association with premature birth. 1 patient was dystonic, and the remaining 3 had suffered cerebral insults through drowning, trauma, and non-accidental injury (figure 1). Their ages ranged from 2.5 to 17 years. 34 (65%) were male, 18 female.

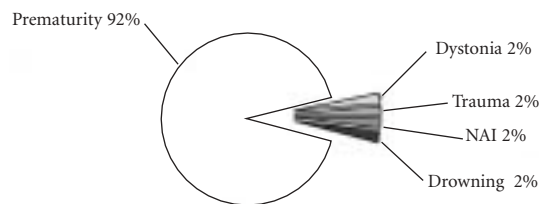


Figure 1. Aetiology of spasticity

Adverse events:

Adverse Event	Number of cases	Resolution
Pump infection	3	Pump removed
Catheter migration	4	Catheter revision
Catheter fracture	3	Catheter revision
Pressure sore	1	Pump replaced
Battery expiry	1	Treatment stopped
Baclofen side effects	1	Dose reduction

Table II. Adverse events

There were a variety of adverse events related to pump implantation and use (Table II). Most seriously, there were 3 infected pumps that had to be removed. In one case there was leakage of CSF from the lumbar wound, and there were 2 cases each of subcutaneous CSF collections in the lumbar and anterior abdominal regions. All of these settled with conservative management. The commonest problem was catheter migration (4 cases), or fracture (3 cases), all of which were treated uneventfully by catheter replacement. One of the patients with catheter migration later went on to have a repeat of the same complication. One pump has been replaced because of a low battery and another because of the development of a



Rachel Keetly is presently working at Queen's Medical Centre, Nottingham as a Research Physiotherapist for Medtronic, on a multi-centre randomised controlled study of the effects on function and quality of life of continuous intrathecal baclofen in children with cerebral palsy. Her role is to co-ordinate the trial, collect the results and complete the physiotherapy assessments for the trial subjects at Queen's Medical Centre.



Richard Morton is Consultant Paediatrician at Derby Children's Hospital. He has particular research interests in feeding, gait and motor control in disabled children. Dr Morton runs a multidisciplinary clinic for hypertonia, and is keen to explore the relative advantages of oral anti-spasticity therapy, Botulinum, Intrathecal Baclofen, and dorsal rhizotomy in children.



Michael Vloeberghs trained in general medicine surgery at the Vrije Universiteit Brussels, Belgium. He then took on Neurosurgical training, partly training in the UK, specifically in Paediatric Neurosurgery. Becoming a consultant in Brussels in 1993 and was offered a position at the University of Nottingham in 1995. He is currently a Senior Lecturer in Paediatric Neurosurgery and consultant Paediatric Neurosurgeon. His clinical practice involves only children and covers all children's Neurosurgical disorders.

pressure sore overlying it. One patient developed baclofen-related side effects (headaches and GI upset), which responded to dose reduction. One patient in the series died of unrelated causes 1.5 years following implantation.

In 3 of 52 implanted cases treatment was terminated on request. In one of these cases the pump battery expired and the parents decided to see how things went without treatment before committing their child to revision surgery. The parents refused further intervention in another case, after two catheter migrations. In the third case the baclofen appeared to work well but the consequent disruption of the dependent patient-carer relationship caused such psychological difficulties that both the patient and carer were dissatisfied and requested removal of the pump.

In all 49 other cases carers reported improvements in nursing care. All of these saw a reduction in spasticity and an improved range of motion in unfixed joints.

Optimum dosage was arrived at by iteration as described above and ranged from 50 – 900 ug/24h.

In addition to the reduction in spasticity and consequent effects on nursing care, additional benefits were noted. In most cases there were improvements in bulbar function (better speech and swallowing, less drooling) and upper limb function. In two cases pre-existing divergent squints disappeared. Many children appeared to become more socially interactive. Reduction in spasticity tended to cause the child to put on weight. This is to be expected, because a large fraction of the patient's energy intake is expended by their spasticity. Weight gain is to an extent desirable for a number of reasons, not least the improved soft tissue-cover for the bulky pump housing, but it is a mixed blessing as extra weight can make nursing more difficult.

Seizures have been observed to occur with increased frequency in epileptic patients on CIBI. This can be explained by the weight gain when CIBI is started when the anticonvulsants haven't been increased.

Description of the Randomised Controlled Trial for Ambulant and Non-Ambulant Children:

1) Patient Selection:

Non-ambulant and ambulant children between the ages 5 – 16 with severe spasticity, which is thought to interfere significantly with their function, mobility and quality of life, will be selected for participation in the trials. The non-ambulant children should be unable to walk 1 step, the ambulant children at least 1 step, with or without aids. They will have tried an oral anti-spasticity treatment beforehand. They may still be taking oral medication for spasticity but should not have received botulinum toxin or orthopaedic surgery in the previous six months. They should not have been previously planned to receive orthopaedic surgery over the course of the 18 months study. The worst affected muscle groups in the lower limbs should be Ashworth grade 3 or above.

A test dose of intrathecal baclofen is given (50 mcgs). Sufficient improvement to justify surgical insertion of a pump and admission to the study is considered if the two most severely affected lower limb muscle groups with spasticity improve on the Ashworth scale by at least one point. 40 children will be recruited for the non-ambulant trial and 60 to the ambulant trial.

2) Method

Both groups are assessed in the same way at 0, 9 and 18 months by the physician and by the physiotherapist (Table. III). In both trials the children will firstly be divided into age bands (5-10 or 11-16) and then randomly allocated to Group A or Group B. Group A are immediately implanted with a pump, Group B are implanted with a pump at 9 months. This allows for a 9 month comparison period between Group A and B.

Once the pump is implanted, baclofen dosage is increased according to clinical requirement at each refill (approximately every 2 months).

During this period there should be no additional intervention for spasticity (e.g. medications, botulinum). The same aids and appliances should be maintained, although can be changed for growth if necessary.

Table III:

<p>The assessments at 0, 9 and 18 months will consist of:</p> <ul style="list-style-type: none"> • Physician-led clinical examination; including weight, Ashworth Scale, assessment of range of movement. • Hip x-ray • Gillette Functional Assessment Questionnaire (9) • Lifestyle Assessment Questionnaire (Marchie <i>et al</i> 1998) • Care-givers Questionnaire (Schneider <i>et al</i>). • Physiotherapist-led Paediatric Evaluation of Disability Inventory (Feldman <i>et al</i> 1990); Gross Motor Function Measure (GMFM); Tabulation of aids and appliances • Orthopaedic Assessment – prediction of possible orthopaedic intervention

Conclusion:

The initiation of these studies was driven by the lack of formal controlled evidence on the effectiveness of ITB in Children with CP. Although the treatment is currently undertaken in Nottingham in the form of a clinical outcome study, hard objective evidence is necessary. The spectacular benefit seen in spastic quadriplegic patients answers the demand for improved quality of life and ease of care. The role of ITB in ambulant e.g. functional patient with severe spasticity remains unproven and is to be addressed by this trial. The pluridisciplinary team involved in this study aims to establish improved patient selection in both groups and to balance risk and morbidity to the benefit of ITB.

At the end of the study the results will be compared using repeated measures analysis to assess changes in tone, mobility, self-help skills and quality of life.

References for this article can be found on our web site at www.acnr.co.uk/contents4-1.htm

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

Neurological Therapeutics. Principles and Practice

Everything about this book is massive: 345 authors, 271 chapters in 14 sections, over 3000 pages. If you stand atop the two volumes you will be 5 inches taller; if you try to pick them up you risk a hernia. Surely this is the ultimate riposte to those benighted souls who persist in the erroneous belief that the only condition neurologists can successfully treat is vitamin B12 deficiency?

In the interests of producing a timely review (i.e. before a second edition emerges), I have read only about one fifth of the chapters, selecting common conditions, disorders in which I have a particular interest, recently encountered clinical problems, and some just for the sake of curiosity. Chapters are of variable length, but most are fairly short (< 10 pages), and cover particular conditions, detailing epidemiology, aetiology, pathogenesis, genetics, clinical features, investigation findings and natural history, as well as therapeutics. Hence this is a textbook of neurology on a par with other major textbooks, but with a rather more systematic approach to the evidence base for treatment. At least, this is true in some chapters, since in some the treatment

component may be very brief, e.g. prion disease, which nonetheless merits two chapters, and also crops up in the "non-Alzheimer dementias" chapter. There is also repetition elsewhere, perhaps unavoidable in such a huge tome.

There are a few oddities: I am still puzzling over syringomyelia turning up in the movement disorders section. Certain omissions occurred to me: no mention of cannabis in the treatment of MS. I could find only a single sentence mentioning pituitary apoplexy.

Although a strong case may be made for every department of neurology possessing a copy of this handsomely produced book, I am uncertain whether it will appeal to individual neurologists, and not only on grounds of cost and size. With the trend to specialisation, much of the information may be redundant for many practitioners, or too simple for cognoscenti of particular subspecialties. A companion volume, a mere 656 pages containing 600 graphics from the book, is also available.

AJ Larner, WCNN, Liverpool



Edited by: John H Noseworthy
Publisher: Taylor and Francis
ISBN: 1-85317-623-0
Price: £275.00

Interactive Head and Neck CD

In all but one respect, this CD-Rom is the ideal resource to learn head and neck anatomy. As with the Primal Pictures' *Interactive Spine*, the software allows for layers of muscles, nerve and vessels to be slowly peeled off their bony structures. Each image can be rotated and tilted. There is no better way to appreciate the complex 3D anatomy of, say, the larynx or the orbit. This reviewer was pleased finally to understand splenius capitis, long the hoped-for target of the Botox needle. It turns out that neck muscle anatomy is incredibly complicated; can you honestly say you know what rectus capitis superior minor does? All is revealed here. There are accompanying MRI scans, co-registered with the computer images, quizzes and multiple-choice questionnaires. Videos demonstrate features of surface anatomy and there are a few slides of pathological specimens. My favourite feature was the animations of muscles acting at the tempero-mandibular joint (just like Tyrannosaurus rex, thought my three-year old son).

The beauty and elegance of the computer images of the neck raised great expectations for the depictions of the brain. And here was the disappointment. There were a few pictures of the surface anatomy of the brain and some frankly childish cartoons of the internal structures, poorly registered with MRI images, which went no higher than the level of the midbrain.

So, this CD-ROM is highly recommended for head and neck surgeons, less so for neurologists, except those who struggle to know just where that Botox is supposed to go.....

Alasdair Coles, Cambridge



The neck from the back. The orbit from above.

Edited by: Bernard J. Moxham, Claudia Kirsh, Dr Barry Berkovitz, Gus Alusi, Tony Cheeseman
Publisher: Primal Pictures
ISBN: 1902470834
Price: £99 for readers of ACNR (see page 31), normally £150

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Clinical Pathways in Neuro-Ophthalmology: An Evidence-Based Approach

The Foreword by Dr Neil Miller sums up this book very well. "By providing basic, clinically relevant information regarding various disorders, their diagnosis, and treatment, this book teaches the reader how to approach a patient with a known or presumed neuro-ophthalmologic problem in a logical, straightforward, and cost-effective manner."

The 20 chapters address either clinical presentations, such as transient visual loss, diplopia, papilloedema and ptosis or diagnostic entities, such as optic neuritis, nonarteritic ischaemic optic neuropathy, ocular myasthenia gravis and thyroid eye disease. Section headings are commonly in the form of a question, e.g. What clinical features suggest giant cell arteritis? A great deal of detail is packed into the 125 tables, for example an exhaustive list of aetiologies of third nerve palsy by topographical location with relevant references. There are several algorithms, such as "Evaluation of sixth nerve palsy". There are no illustrations, which gives the text a rather "intense" appearance. It also means that a significant amount of background knowledge is assumed. The neurologist unfamiliar with the entity of optic disc oedema with a macular star will need to consult another text for guidance.

This book is crammed full of information, with a wealth of minutiae for such a relatively small volume and extensive lists of references. Although there is much emphasis on the provision of "evidence-based guidance" with reference to Class I-IV evidence and Level A-C or U strength recommendations, the most striking

feature is the constant impression that the book is written by people who "have been there". The authors' combined immense clinical experience is very apparent. Some readers will find the text too dense and pedantic, but that reflects the day-to-day practice of neuro-ophthalmology. If the finer points of clinical assessment are ignored, patients are at risk of being managed inappropriately. Similarly most patients will have run of the mill diagnoses but occasionally the esoteric needs to be considered. The tables in this book provide an easy reference for the busy clinician keen not to miss the unusual.

There are a few criticisms. In the section entitled "What is hypertropia or hyperglobus", the only clue given is that "hypertropia or hyperglobus may result in an abnormal position of the eye under a normal eyelid"! There is irritating repetition, for those reading through the whole chapter on Diplopia, between the sections on horizontal diplopia and those on vertical diplopia.

Overall the authors, an ophthalmologist and a neurologist, have managed to write a comprehensive, detailed and accessible guide to clinical neuro-ophthalmology. The book would be a useful addition to the personal library of anyone regularly seeing patients with neuro-ophthalmological problems. All trainee neurologists will benefit from it being available on the neurology ward.

Paul O'Riordan-Eva, London



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Rehabilitation Abroad - Why?

BACKGROUND

Rehab Without Walls started in 1994. We manage severely brain injured patients, mostly in the community, using case managers who set up and implement individual treatment programmes. Our case managers come from different backgrounds including social work, therapy, and nursing. Our referrals come largely from lawyers or insurers, as most of our 85 patients are involved in compensation claims.

We recently referred one patient (KL) to a rehabilitation unit in Germany for post acute rehabilitation, after acute early rehabilitation in an English rehabilitation unit. KL's English rehabilitation consultant was a great support. KL is the second patient we have sent to a foreign unit. KL had achieved his early rehabilitation goals, and we agreed with his rehabilitation consultant that further rehabilitation was needed. We carried out an options appraisal looking at British units in the statutory and independent sector. We could not identify any that both met KL's needs, and he was happy to attend. We proposed a German unit that we knew well, and matters developed from there.

I have been heavily involved in rehabilitation in Europe, through my involvement in the European Brain Injury Society (EBIS), which allowed me to interact with rehabilitation staff from a large number of European countries, and to visit their units. I rapidly identified some units to which I would very much like to send my patients, because of the presence of very well trained, highly motivated and enthusiastic staff, who worked as part of a team in a unit that was bright, friendly and clean.

ADVANTAGES OF REFERRING ABROAD

We find three advantages: rehabilitation quality; "look and feel"; and rehabilitation philosophy.

Rehabilitation Quality

High quality neurorehabilitation is available in Britain. However, the quality and quantity may be driven by the exigencies of local policies and budgets. Key staff come and go, and a unit that last month was excellent, next month may be rather mediocre (this point applies to any unit). As we work in the independent sector, we use whatever resources are necessary, including statutory sector, the independent and charitable sector and unusual quirky individual resources. From time to time, we find difficulty in interacting with staff in the statutory services, who see us as "private", and motivated only by financial matters, particularly personal greed.

In British rehabilitation units there is usually a rehabilitation team, but this may exist in name only, comprising individuals with their own professional agendas, who meet briefly (perhaps once a week), and then disappear to work independently with the patient. Instead of a dynamic team in which everyone pulls together, we see a "parallel tube" model of service. There is an occupational therapy "tube", a medical "tube" and so on. They each are concerned about their individual specialist matters, and while individual clinicians may be skilled, they do not share skills with each other, or to any major degree support each other. We also worry about the extent to which a rehabilitation team constructs individual goals which are specific to our patient, or simply slots the patient into a generic rehabilitation system which may, or may not, meet the patient's needs.

When I consider the specifics of the service in Germany which we used (Kliniken Schmieder), the issue of quality

becomes starkly apparent. Kliniken Schmieder was set up over 50 years ago by Dr Schmieder, and has been owned by the same family ever since. The current director is the daughter of the founder, and she jealously guards the quality and reputation of the service. The service has 827 rehabilitation beds spread over 5 units, 3 of which specialise in neurorehabilitation at varying stages after injury, and two of these have full neurodiagnostic facilities including an MRI with consultant neuroradiologist, and neurophysiology laboratory. There are very strong links with local medical schools and related higher education facilities. For our patient we had the opportunity of a single room, double room, or apartment – we chose the latter. Our patient's timetable was full and detailed, and contained no "time fillers" such as 2 hours of morning "personal hygiene". Our patient had timetabled therapy and treatment between 9.00am and 5.00pm, which included formal sessions of rest/sleep. The nature and intensity of treatment components changed as our patient's clinical status changed.

As a general matter, a comparison of British rehabilitation units with German units is very revealing. A unit of hundreds of beds, with full neurodiagnostic facilities is by no means unusual in Germany, where the patient essentially has a "one stop shop", so that all needed services are available on site. This is in marked contrast to the British scene of small (often very small) units, which may have very limited specialist medical, technical, and nursing support immediately available.

The Fabric of the Unit

It is a cliché to talk about the rundown state of many NHS facilities, and this paper is not an exercise in NHS bashing. Our patient and his family were staggered at the difference in presentation between a (good clinically) English rehabilitation unit, and the German unit to which we made the referral. The German unit was bright, light, airy and above all, clean. The cleaners were evident, they appeared to be everywhere, and were highly diligent, committed to doing a good job.

Rehabilitation Philosophy

This aspect is important, and usually ignored in British rehabilitation. This is the existential issue of recovering from any trauma, particularly a brain trauma. The idea that a patient might have spiritual needs, and facing existential problems (who am I now?, what can I do? what will I be able to do?), is alien to many neurorehabilitation services in Great Britain. In the German unit, this aspect was taken for granted and built into the rehabilitation programme.

DISADVANTAGES

There are three areas of potential disadvantage: practical issues; cost; and English language and related matters.

Practical Issues

The most difficult practical issues were more peripheral issues such as, for example, liaising with local taxi firms. We drew on all our resources here, including two staff members who were German speaking, other colleagues in Germany as and when necessary, and of course, staff in the German rehabilitation unit.

Other practical matters, such as access to airports, wheelchair access (our patient at that time was in a wheelchair), and liaison with the low cost airline that we chose, concerned us. With sufficient notice given to airport



Dr Neil Brooks trained as a Clinical Psychologist, and with Cathy Johnson, set up Rehab Without Walls in 1994. They use case managers to manage people with severe brain injury in their community, using a "whatever it takes" model, mixing and matching statutory and independent resources as needed.

authorities and the airline, and two reminder phone calls to each, there were no problems at either end.

Cost

The main costs involved are the treatment and hotel costs at the rehabilitation unit, transportation, and the case manager's time. Rehabilitation costs are difficult to compare with those in England, because of the problem of comparing like with like, and because Kliniken Schmieder has a sliding scale depending upon severity of brain injury, and nature of accommodation. The costs for Kliniken Schmieder are between around £2200 and £3400 per week, with all services and treatment included. In England, costs are between around £1100 and £3400 per week, depending upon the nature of the service. The cheaper services are typically offering care/support rather than active rehabilitation. The costs must be considered in the context of the "one stop shop" approach to service delivery discussed above, and we considered that the costs were extremely low for the high quality of input which our client received. Transportation costs were minimised by using a low cost airline, and a taxi firm which had a relationship with the rehabilitation unit, and which therefore gave us a discount. Case management time was no more than would have been the case had a UK unit been used.

English

All of the rehabilitation staff in the German unit spoke English to some degree, so day to day communication was not an issue. Ancillary staff such as cleaners mostly did not speak English, but they were so cheerful and friendly that our client rapidly learned basic meet and greet German phrases from them. The real issues about English came in documentation, and in leisure time. We had agreed before rehabilitation began that the initial assessment and treatment plan would be translated into English. This did not immediately happen, and this was a source of (minor) frustration that was solved readily, by giving the documentation to one of our German speaking staff, and ask-

ing for a rapid translation! English may have become a problem had we wanted therapy for subtle language problems, or had we needed more psychologically driven therapy, such as psychotherapy. The major issue about English, and access to English, came in the evenings and weekends. We had arranged with the clinic that at least one English language satellite television station would be available, but this arrangement never materialised. In the event, our client was not particularly concerned about this lack, as he rapidly discovered a bar in the local village which was the haunt of the local "bikers". Our client had been a biker and rapidly became something of a local celebrity, looked after, indeed protected, by the community in the local bar. He learned more German that way, but I am not sure that the German he learned was grammatical or socially appropriate. The situation in Germany about evening and weekend times was no different from the situation in any British unit.

In conclusion, we had a very positive experience in organising and achieving rehabilitation in a German neurorehabilitation unit. The unit was carefully chosen, based on our experience of appropriate units. There were practical issues, such as arranging taxis and ensuring that airport transportation went without hitch, but those were readily dealt with by our case manager and other staff. We have already sent one other patient to the same unit (this time for assessment and treatment planning rather than rehabilitation). We would not hesitate to make similar arrangements again.

How do you refer abroad?

Each patient is different, and needs his/her own options appraisal. If rehabilitation abroad seems appropriate, then I can certainly recommend Kliniken Schmieder (see contact details right). A further alternative is to approach the secretary of EBIS (European Brain Injury Association) and ask for advice, and for a list of EBIS members (this includes skilled rehabilitation physicians in various countries in Europe).

Neil Brooks has no financial or other interest in Kliniken Schmieder

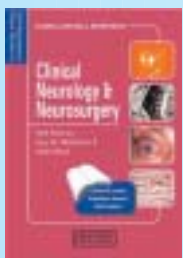
Information

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Internet http://www.kliniken-schmieder.de
2. European Brain Injury Society (EBIS)
Secretary (English speaking):
Mrs B Logan;
Tel. +33 (0) 55 322 5668

Correspondence address:
Dr Neil Brooks, Consultant
Neuropsychologist
Director Rehab Without Walls
E-Mail: neil@rww.org.uk

Self Assessment Colour Review of Clinical Neurology & Neurosurgery

Eds: Neil Kitchen, Guy McKhann II, Hadi Manji
(Soft cover)

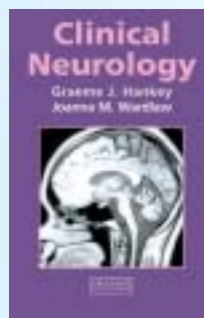


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References:

1. Sharma KR. Myasthenia Gravis: a critical review. *IM Intern Med* 1996;August:47-69
 2. Drachman DB. Myasthenia Gravis. *N Eng J Med* 1994;330:1797-1810
 3. Buckley C. Diagnosis and treatment of Myasthenia Gravis. *Prescriber* 2000;11(Issue 22):107-113
 4. Genkins G et al. Treatment strategies in Myasthenia Gravis. *Ann NY Acad Sci* 1993;681:603-608
- Date of Preparation:** February 2002

The 57th American Epilepsy Society Annual Meeting

5-9 December, 2003; Boston, US

Most delegates arrived just 24 hours before the airport was closed by the heaviest December snowstorm for over 20 years. This forced them with various degrees of enthusiasm to attend the conference as it was the only event that could be reached without walking outside in blizzard conditions. We got away as the snow started thawing to watch the Ottawa Senators, a Canadian Ice Hockey Team play the Boston Bruins, in which the electronic advertising and blaring commentary were as entertaining as the match itself, not to mention skimpily clad ice maidens who cleared the ice of debris every few minutes – of more appeal to MM than EC!

There was a mixture of educational programmes and scientific presentations. Taxonomy continues to tax many clinicians. A new patient-orientated epilepsy classification has been developed at the Cleveland Clinic Foundation according to epileptogenic zone, seizure type(s), etiology, severity, and related medical conditions. Unlike the International League classification, all patients can be categorised in this 5-dimensional classification which they have found more useful in clinical practice. However, cases continue to be identified that defeat existing classifications. Twelve affected individuals from four families showed that clinical features of juvenile myoclonic epilepsy and idiopathic photosensitive epilepsy overlap; 50% of individuals with visual aura had myoclonic jerks, although visual aura is characteristic of IPOE and myoclonus of JME.

A retrospective study of 857 patients with status epilepticus from Richmond, Virginia found that 60% of cases were African Americans (over-represented). Their mortality was lower (22%) than in Caucasians (33%) and this may partly be due to different causes; more drug withdrawal and head injury. The authors speculated there may also be some biological factors that are worthy of exploration.

The Mayo clinic has been applying the ketogenic diet to a wide variety of adults with epilepsy and achieved a 50% seizure reduction in 73%. Metabolic changes did occur with a rise in cholesterol levels and reductions in

magnesium and selenium. Changes in phosphorus and potassium were also seen. Most patients lost weight. Given the similarities, it was only a matter of time before someone tried the Atkins diet and indeed ketosis was achieved in 3 of 5 patients from Baltimore who tried it. Two became seizure free for 2-4mths at the time of writing.

The difficulties of the diagnosis of epilepsy and complexities of multiple pathology in the elderly combine to delay diagnosis in this patient group. The Florida group found that for 159 people aged between 59-96, clinicians were able to identify GTCS reasonably quickly, but focal epilepsy took a long time to diagnose and associated cardiovascular disease delayed diagnosis, with a mean time to diagnosis for the whole group of 1.7yrs. The word needs to be spread: not all paroxysmal events in the elderly are TIAs, and an open mind and a good history are the best investigative tools.

Hyperventilation during the EEG is well established for childhood absence epilepsy. In a Brazilian study of 102

patients with intractable focal epilepsy 23.5% had their typical seizures during hyperventilation; 18 of 63 with TLE, 4 of 6 with multilobar epilepsy but only 1 of 20 with FLE. The induced seizures peaked at 4 minutes of hyperventilation and decreased thereafter – we need to push our patients

harder. This proved a cost effective and safe means of evaluating focal epilepsy as the time spent on video-EEG monitoring can be significantly reduced.

It is widely believed that prolonged GTCS are associated with foetal hypoxia and occasional fetal death but that partial seizures probably do not significantly affect the foetus. A 46 year old woman was described with a cavernous haemangioma manifesting maternal tachycardia and fetal bradycardia during a focal seizure. There were limited motor manifestations and no increase in uterine contractions to explain the foetal bradycardia, suggesting that the seizure may have triggered maternal dysautonomia and brought about fetal cardiac deceleration. This is worthy of further study.

The medical community is taking on Tony Blair's mantra of "education, education, education"! The National Sentinel Clinical Audit of epilepsy related death (UK) highlighted poor support and education for patients during complex treatment regimen and access to specialist advice for patients and general practitioners. A telephone advice service run by the Epilepsy Specialist Nurse (ESN) at Queen Square is aimed to address some of these longstanding inadequacies. It has improved continuity of care and reduced morbidity and has proved cost effective for both patients and the health service.

The American Epilepsy society sponsors a programme known as TELE Consults in epilepsy for Allied Health Care Professionals. The programme is free to those interested and further details can be obtained on line at www.aesnet.org.

Clinical trials can be a little bit like elections; everybody has a reason for saying that they won no matter how awful their result seems to be, but not in this veterans administration study. They compared carbamazepine 600mg with lamotrigine 150mg and gabapentin 1200mg in the

“Clinical trials can be a little bit like elections; everybody has a reason for saying that they won no matter how awful their result seems to be”



Boston in the snow

treatment of 593 patients with a first seizure over the age of 60 (570 men). Clinicians were allowed to titrate up the dose if necessary. The average number of co-medications was 7! The primary outcome variable was retention which is generally considered the best composite measure of adverse effects and efficacy. Lamotrigine (about 50% retention) and gabapentin (about 40%) were both significantly better than carbamazepine (<30%). The study is sufficiently large and the results sufficiently convincing that I think this one paper is enough to change practice.

"Why are all my seizures at night?" is a common question. Diurnal variation of seizures in rats appears to be the same as in humans, even though they are nocturnal creatures, so the simple explanation of a relationship to brain activity and the sleep-wake cycle seems incorrect. My reply to patients will have to be changed to a more honest "I don't know"!

One snowed-in morning of the conference was devoted to temporal lobe epilepsy. The neuroimaging was beautiful, stunningly detailed anatomical pictures with 4.5 Tesla magnets. But two talks devoted to basic mechanisms probably carried the most important message of the conference. Interest has grown in recent years in fast rhythms: Gamma are 30-80Hz and are probably physiological or pathological depending on circumstances; ripples are 80-200Hz and fast ripples are >200Hz. Ripples and fast ripples seem to depend on axo-axonal interactions, gap junctions, ephaptic transmission and inhibito-

ry circuits. Fast ripples may be detected in the EEG hours before a seizure and are probably responsible for the electrodecremental response before some seizures. This in itself may prove clinically useful. March Dichter described how in models of TLE and in human slice preparations, these ripples appear in small hyperexcitable islands of cells in the entorhinal cortex and subiculum before any changes are seen in the hippocampus. Robert Sloviter discussed networks in TLE and presented data that hippocampal granule cell hyperexcitability correlates with hilar cell loss and restoration of inhibition correlates with mossy fibre sprouting. Seizures precede mossy fibre sprouting suggesting this is not an epileptogenic mechanism after all. Taking these lines of evidence, these researchers argued that the entorhinal cortex may be crucial in epileptogenicity and that changes in the hippocampus may be important in seizure expression but are secondary. They cite the frequency of dysplasia in the temporal lobes in patients with TLE as supportive evidence. If true, this will lead to a major re-think of mechanisms in TLE, which is likely to have far-reaching consequences.

*Erica B Chisanga BSc (Hon),
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14th International ALS/MND Symposium

17-19 November, 2003; Milan, Italy

Each year for the past 14 years the Motor Neurone Disease clinical and research 'community' (and an increasing number of people with MND) have assembled to share the latest research into this most devastating of neurological diseases. In keeping with the difficult nature of the condition, most of the presentations given demonstrate the necessity of international collaboration. In this respect one has to acknowledge the role of the Motor Neurone Disease Association in being a catalyst for change in bringing together basic and clinical researchers on one hand and patients and carers on the other.

MND/ALS remains a clinical diagnosis. The identification of a biomarker for ALS would have the effect of improving the accuracy and speed of early diagnosis, help to dissect out the relationship between different forms of motor neurone disease and provide an objective measure of progression for clinical trials. New technology in the form of protein chips provides the potential to produce a molecular signature of the disease to act as a biomarker. A combined study from Boston and Pittsburgh used CSF from patients with ALS on CIPHERGEN® protein chips which use a novel physical method to profile the protein content of biological material. Using complex statistical algorithms they reported that their method could reliably identify about 80% of patients with ALS, with a few false positives. Sounds marginally less accurate than a clinical neurologist but it is a promising approach in principle.

The search for therapies for MND has recently taken on a high throughput screening approach. Lucy Bruijn, the research director of ALSA (the US ALS Association), described how, under the umbrella of the National Institutes for Neurological Diseases and Stroke (NINDS), 1040 compounds (750 FDA approved) have been screened for efficacy in motor neurone diseases. This has involved approximately 20 centres in the USA and Europe which have some sort of in vitro assay of motor neurone survival (e.g. glutamate toxicity). This work has produced the surprising result that 3 types of cephalosporin seem to have a motor neurone protective effect and that ceftriaxone in particular may be useful. However, it was a little depressing to note this produced a modest survival in G93A SOD1 mutant mice (the archetypal animal model of ALS). Overall, this very expensive and labour intensive enterprise has not been a conspicuous success.

In much of the experimental work on ALS/MND in the past there has been undue focus on the cell body as the seat of the pathophysiology of the disease. Axonal and dendritic processes account for at least 95% of the volume of a motor neurone and it was therefore encouraging to see that increasing attention is now being given to role of axonal degeneration. Chris Miller from Kings College in London reviewed the evidence that axonal protein transport is dysfunctional in transgenic mouse models of ALS.



Dr Letitia Mazzini, who presented the session on stem cell transplants

Glass and colleagues from Emory University in Atlanta presented some elegant longitudinal traditional neuropathological studies in transgenic mice harbouring human SOD1 mutations. Mice were examined at 28, 47, 80 and 120 days post-natally. The first signs of pathological change were evident by day 47 in the motor end plate. This is before the disease is clinically evident in the mice. By day 80 when mice have overt muscle weakness as evidenced by poor performance on a rotarod test, 60% of ventral roots have degenerated. Remarkably motor neurons in the spinal cord are not reduced in number, suggesting that the disease process begins in the periphery. A patient with early MND who died unexpectedly was examined at autopsy and showed similar degenerative changes in the NMJ and ventral roots. On a similar theme Michael Sendtner, working on autosomal recessive Spinal Muscular Atrophy due to mutations in the SMN gene, demonstrated that the specific transport of subclasses of mRNA in the axon may be critical for motor neurone integrity.

Away from the sober world of hard science, two more sensational presentations caused quite a stir. A group of Italian Neurologists from Turin have performed a 'feasibility' study of direct intraspinal implantation of mesenchymal (bone marrow) stem cells (MSCs) in ALS. Seven patients had autologous MSCs which had been expanded in culture for 32 days, implanted by directly surgically exposing the thoracic spinal cord. The best that could be said was that this extraordinary procedure did not seem to hasten the disease. Just because it is feasible does not mean it is justified. Explaining this to patients in the MND clinic, who are understandably desperate, is not easy. Perhaps the most lively session of the whole meeting was from Deborah Annetts who is the chief executive of the Voluntary Euthanasia Society (who incidentally have removed the word Euthanasia from their website and are now known as VES!). She is a lawyer by training and an impressive and professional proponent for the cause of 'choice' in when to end life. This is a profoundly serious and controversial issue and was a brave choice for a platform presentation to an audience including carers and patients. Whatever the legal or moral position surrounding assisted suicide no one can doubt that an open and honest discussion is to be welcomed.



Delegates at the conference

*Dr Kevin Talbot
Honorary Consultant Neurologist,
Radcliffe Infirmary, Oxford*

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

2004

3rd International Syncope Symposium
5 March, 2003; Stratford-upon-Avon, UK
E. trudie@stars.org.uk

EPTA Spring Scientific Meeting and AGM
6 March, 2004; Stafford, UK
E. nigel.hudson@phnt.swest.nhs.uk

Neurology Study Days
8-12 March, 2004; Institute of Child Health, London, UK
E. courses@ich.ucl.ac.uk,
Tel. 020 78298692

Neuro-Oncology Conference
9 March, 2004; VA, US
Fax. 757-446-6146,
E. cme@evmsmail.evms.edu

2nd NNI-NUS Neuroscience Symposium
12-14 March, Singapore, Singapore
E. claire_lee@tsh.com.sg

Brain Awareness Week
15-21 March, 2004, UK
E. enquiries@edab.net, Tel. 020 7019 4914

Life Sustaining Treatments & Vegetative State: Scientific Advances & Ethical Dilemmas
17-20 March, 2004; Rome, Italy
E. gigli.gianluigi@aoud.sanita.fvg.it,
Fax. 0039 0 432 552 719

Austrian Society of Neurology Meeting
18-20 March, 2003; Austria
E. klaus.berek@bkh-kufstein.at
A Practical Approach to Epilepsy
19 March, 2004; Institute of Child Health, London, UK
E. courses@ich.ucl.ac.uk,
Tel. 020 78298692

BSCN Scientific Meeting
19 March, 2004; Newcastle, UK
E. bscn@secretariat.freesserve.co.uk

3rd European Eiscsa Congress, 'Current Concepts In Training And Therapy'
19-20 March, 2004; Freiburg, Germany
E. EIsinfo2004@msn1.ukl.uni-freiburg.de

Parkinson's Disease: An Essential Update for Healthcare Professionals
22 March, 2004; London, UK
Tel. 020 7834 3181

2nd Cambridge Workshop on Universal Access and Assistive Technology
22-24 March, 2-4; Cambridge, UK
E. Aejaz.Zahid@bdgh-tr.trent.nhs.uk

Electrophysiology in the Young and Adults: A New Frontier
23-25 March, 2004; Saudi Arabia
E. web_symposia@kfsbhc.edu.sa

3rd Unterinntal-Neurological Congress
24 April, 2004; Kufstein, Austria
E. klaus.berek@bkh-kufstein.at

Update in Spinal Imaging
24 March, 2004; London, UK
E. tamara.anderson@bir.org.uk

Growth And Death In The Nervous System
24-28 March, St Moritz, Switzerland
Fax. +41 1 255 44 02,
E. adriano@pathol.unizh.ch

36th International Diagnostic Course: diseases of the Brain, Heart & Neck
27 March - 2 April, 2004; Davos, Switzerland
Fax. 00-41 13 849 339,
E. idkd@congressorg.ch

6th Neurochemistry Winter Conference
March 27 - April 4, Soelden, Austria
Fax. 00 43 5 125 043 716,
E. alouis.saria@uibk.ac.at

Annual Scientific meeting of the Pain Society
30 March - 2 April, 2004; Manchester, UK.
Tel. 020 7631 8870,
E. meetings@painsociety.org

Osteoporosis and other Metabolic Bone Diseases
31 March - 2 April, 2004; Oxford, UK
E. conferences@endocrinology.org

April

2nd Neuroimmunology Update Course
1-4 April, 2004; Turkey
E. rk01-l@tr.net,
www.noroimmunoloji2004.org

2nd Mediterranean Congress of Neurology
2-4 April, 2004, Nicosia, Cyprus
Fax. 35 - 725 721 644,
E. congress@congresswise.com

Birmingham Movement Disorders Course
2-4 April, 2004; Birmingham, UK
E. susan.pope@swb.nhs.uk

British Neuropsychological Society Spring Meeting
6-7 April, 2004; London, UK
www.hop.man.ac.uk/bns

ABN Spring Scientific Meeting
14-16 April, 2004; London, UK
Tel. 020 7405 4060,
E. abn@abnoffice.demon.co.uk

7th Annual Meeting of the Infantile Seizure Society: International Symposium on Neuronal Migration Disorders and Childhood Epilepsies
16-17 April, 2004, Tokyo, Japan
E. yfukuyam@sc4.so-net.ne.jp,
www.field.gr.jp/ISS

Advanced Techniques in Spinal Decompression & Fixation
16-18 April, 2004; MO, US
Fax. 001 314-535-8214,
E. pawslab@slu.edu

American Association of Neuroscience Nurses 36th Annual Meeting
17-20 April, 2004; San Antonio, US
Fax. 001 847 375 6333,
E. info@aann.org

First Congress of the European Neuropsychological Societies
18-20 April, 2004; Modena, Italy
Fax. 051 309477,
E. i.bortolotti@planning.it

British Society for Rheumatology 22nd AGM
19-22 April, 2004; Brighton, UK
E. caroline@rheumatology.org.uk,
Fax. 020 7242 3277

Is There Such a Thing as a Life not Worth Living? End of Life Issues Conference and Debate
22 April, 2004; Liverpool, UK
E. mnt@gnc.u-net.com,
Tel. 0151 298 2999

VI International Congress on Headache in Children & Adolescents
21-25 April, 2004; Vienna, Austria
E. icha2004@akh-wien.ac.at

British Geriatric Society Spring Meeting
22-24 April, 2004; Derry, Northern Ireland
E. editor@bgsnet.org.uk

Annual Symposium: Advances in Strabismus and Neuro-Ophthalmology
23-24 April, 2004; Cleveland, US
Fax. 001 216 445-3676,
E. sardelj@ccf.org

American Academy of Neurology 56th Annual Meeting
24 April-1 May, 2004; San Francisco, US
Tel. 1 651 695 1940, Fax. 1 651 695 2791,
E. Istrachota@aan.com

May

Occupational Therapy for the Physical Rehabilitation of Neurological Disorders
May, 2004; London, UK
Tel. 020 7834 3181

American Association of Neurological Surgeons 2004 Annual Meeting
1-6 May, 2004; Orlando, US
Fax. 00 847-378-0600, E. info@aans.org

Ireland MS Week
1-8 May, 2004; Ireland
www.ms-society.ie

Nerve Damage & Neuropathic Trigeminal Pain
4-5 May, 2004; Vancouver, Canada
Fax. 00 514 343 2233,
E. francine.belanger@umontreal.ca

Joint Annual Meeting of the American Pain Society and the Canadian Pain Society
6-9 May, 2004; Vancouver, Canada
Fax. 001 877 734 8758,
E. info@ampainsoc.org

Eastern Rehab Group Study Day
7 May, 2004; Addenbrookes Hospital, Cambridge, UK
E. maya.desouza@addenbrookes.nhs.uk

Seventh Eilat Conference on New Antiepileptic Drugs
9-13 May, 2004; Sardinia, Italy
Fax. 00 972 2 5175155,
E. eilatvii@targetconf.com

14th European Congress of Physical & Rehabilitation Medicine
12-15 May, 2004; Vienna, Austria
Tel. +43 1 405 13 83 22,
E. ecprm2004@medacad.org,
www.ecprm2004.org

13th European Stroke Conference
12-15 May, 2004; Mannheim, Germany
E. henneric@eurostroke.org

Alzheimer's Disease: Update on Research, Treatment, and Care (CME conference)
13-14 May, 2004; San Diego, US
E. sjohnson@ucsd.edu

3rd Regional International Society of Psychoneuroendocrinology (ISPNE) Congress for Central & Eastern Europe
13-15 May, 2004; Cappadocia, Turkey
Fax. 00 903 124 677 062,
E. ccosanoz@serenas.com.tr

Neuropathic Pain: Changing Paradigms and Treatment
13-16 May, 2004; Madrid, Spain
Fax. 00 41 22 732 2850,
E. ncohen@kenes.com

Inaugural Meeting of the AEP Section on Neuroimaging
27-28 May, 2004; London, UK
Tel. 0115 969 2016

June

46th Annual Scientific Meeting of the American Headache Society
1-4 June, Philadelphia, US
Fax. 001 856 423 0082,
E. ahshq@talley.com

American Association on Mental Retardation 128th Annual Meeting
1-5 June, Philadelphia, US
Fax. 001 202 387 2193

11th Asian & Oceanian Congress of Neurology
3-6 June, 2004; Singapore
E. claire_lee@tsh.cm.sg

3rd Research Forum of the European Association for Palliative Care - Methodology for Palliative Care Research
3-6 June, 2004; Stresa, Italy
Fax. 00 39 02 380 06761,
E. mariagrazia.taconi@effetti.it

American Society of Neuroradiology - 42nd Annual Meeting
5-11 June, 2004; Washington, US
Fax. 001 630 574 0661,
E. meetings@asnr.org

College of Occupational Therapists 28th Annual Conference & Exhibition 'Occupation Matters'
8-11 June, 2004; Harrogate, UK
Tel. 020 8977 0011

Meeting of the Canadian Congress of Neurological Sciences
8-12 June, 2004; Calgary, Canada
Fax. 00 403 229 1661,
E. brains@ccns.org

SRR Summer Meeting
8-9 June, 2004; Glasgow, UK
Ann Hughes, Tel: 0115 9249924

EPTA Continuing Professional Development Conference
9-11 June, 2004; Lincoln, UK
E. nigel.hudson@phnt.swest.nhs.uk

EULAR 2004: European Congress of Rheumatology
9-12 June, 2004; Berlin, Germany
E. eular@bluewin.ch

Conference on MND for Health and Social Care Professionals
10 June, 2004; Birmingham, UK
Tel. 01604 611845 or
E. pam.aston@mndassociation.org

46th Annual Scientific Meeting of the American Headache Society
10-14 June, 2004; Vancouver, Canada
Fax. 001 856 423 0082,
E. ahshq@talley.com

3rd Brain Stem Society Meeting
11-12 June, 2004; 2004
Fax. 39-0 55 570 227,
E. m.daliana@oic.it

The Movement Disorder Society's 8th International Congress of Parkinson's Disease & Movement Disorders
13-17 June, 2004; Rome
Fax. 414 276 3349,
E. congress@movementdisorders.org

8th European Congress of Research in Rehabilitation
13-17 June, 2004; Ljubljana, Slovenia
Tel. ++386 1 437 66 00,
E. crt.marincek@mail.ir-rs.si

12th World Congress of the International Association for the Scientific Study of Intellectual Disabilities
14-19 June, 2004; Montpellier, France
Fax. 020 610 812, E. felce@cardiff.ac.uk

7th Headache Congress - European Headache Federation
16-20 June, 2004; Rotterdam, The Netherlands
Fax. 00 41 227 322 850,
E. headache@kenes.com

Advances in Neuroblastoma Research
16-19 June, 2004; Genoa, Italy
Fax. 00 39 0 103 762 322, E. ANR2004Genoa@neuroblastoma.org

Neurovascular Update: Intracranial Aneurysms
17-18 June, Boston, US
Fax. 617-384-8686,
E. hms-cme@hms.harvard.edu

BSCN Scientific Meeting
18 June, 2004; Cardiff, UK
E. bscn@secretariat.freesserve.co.uk

ENABLE: Can Technology Help People with Dementia?
21-23 June, 2004; Oslo, Norway
Fax. 00 47 33 33 21 53,
E. post@nordemens.no

Rethinking Rehabilitation
21-24 June, 2004; Oslo, Norway
Tel. +47 24 10 24 00
E. grete.hjermstad@ri-norway.no

5th World Stroke Congress
23-26 June, 2004
Tel. 00972 3 5140000,
E. stroke2004@kenes.com

International Symposium on Coma and Impaired Consciousness (satellite to ASSC8)
24 June, 2004; Antwerp, Belgium
www.ruca.ua.ac.be/assc8/satellite.html

Standardised Assessment in OT - special emphasis on neurology, part 2
24-25 June, 2004; London, UK
Tel. 020 7834 3181

8th Annual Meeting of the Association for the Scientific Study of Consciousness
25-28 June, 2004; Antwerp, Belgium
www.ruca.ua.ac.be/assc8

14th Meeting of the European Neurological Society
26-30 June, 2004; Barcelona, Spain
E. gerard.said@bct.ap-hop-paris.fr

July

Motor Disabilities: Assessment, Rehabilitation And Neurophysiological Support'
1-10 July, 2004; Marseille, France
Prof A Delarque, Service de Rééducation, CHU La Timone, 92 rue Auguste Blanqui, 13005 Marseille, France

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

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

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

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

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

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



SITS INTERNATIONAL

Fourth BASP Thrombolysis Training Day, Nottingham, 6th May 2004

Organised by Professor Kennedy Lees and Professor Gary Ford, in conjunction with BASP, to assist centres who plan to treat acute ischaemic stroke patients with intravenous thrombolysis following introduction of the UK licence for alteplase.

Alteplase is approved for administration within three hours after a stroke but approval is conditional on safety monitoring of treated patients, co-ordinated within the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST). Centres wishing to provide thrombolytic treatment need to meet certain criteria for inclusion in SITS-MOST. The training day will cover conditions of the licence and practical aspects of offering thrombolysis. To book a place, E-Mail: pcn1w@clinmed.gla.ac.uk, telephone 0141 211 2176.



EDITOR'S CHOICE

MEMORY: A role for prions in long-term memory storage

Prions are proteins that are able to adopt two functionally distinct conformations, one of which is self-perpetuating. They are usually associated with a family of mammalian neurodegenerative diseases called transmissible spongiform encephalopathies, which include CJD. In yeast, prions are non-pathogenic and are thought to explain the non-nuclear inheritance of a new phenotype. This paper reports the possession of prion-like properties in the neuronal CPEB (cytoplasmic polyadenylation element binding) protein from the sea slug, *Aplysia californica*. This protein facilitates messenger RNA (mRNA) translation by polyadenylating the tails of dormant mRNAs. Prion-like properties may allow the protein to produce the localised synaptic strengthening thought to be important in memory storage.

The study demonstrates that, in many respects, CPEB behaves like yeast prions. It possesses an amino terminal domain rich in polar glutamine residues and possesses conformational flexibility that allows it to switch into a self-perpetuating form. Moreover, when the amino terminal domain of CPEB is fused to a reporter protein in yeast, it induces a dominant conformational change that is transmissible along cell lines. Finally, like yeast prion propagation, the switching of CPEB conformation is influenced by heat shock proteins. Unlike normal prions, it was surprising to find that it was the self-perpetuating, aggregated form of CPEB that represents the active state of the protein.

Despite the fact CPEB has yet to be found in different conformational states in *Aplysia* neurons in vivo, the authors propose a model to explain how the prion-like state may contribute to the long-term synapse-specific changes involved in long-term memory formation. Pulses of the neurotransmitter serotonin, which simulate long-term memory training, upregulate CPEB levels at the active synapse in *Aplysia* neurons. It may be the neurotransmitter itself or the elevated level of protein that leads to the switch of CPEB to its active "prion" state. The CPEB in the active synapse triggers local translation of dormant mRNAs, associated with structural and regulatory molecules leading to strengthening of specific synaptic connections. The self-perpetuating nature of CPEB in its "prion" state means it can sustain the altered rate of translation on a long-term basis with minimal energy expenditure, compared to phosphorylation.

CPEB is present in post-synaptic regions of vertebrates and higher mammals, but it is unclear at present whether this prion mechanism contributes to long-term memory storage in such organisms and work is currently underway to investigate this. -LMS, SJT

A Neuronal Isoform of the Aplysia CPEB Has Prion-Like Properties.

Si K, Lindquist S, Kandel ER.

CELL

2003; 115: 879-91

Panel of Reviewers

Roger Barker, Honorary Consultant in Neurology, Cambridge Centre of Brain Repair
Richard Body, Lecturer, Department of Human Communication Sciences, University of Sheffield

Patrick F Chinnery, Senior Lecturer in Neurogenetics and Honorary Consultant Neurologist, University of Newcastle upon Tyne and Newcastle Hospitals NHS Trust
Alasdair Coles, Wellcome Advanced Fellow, Dunn School of Pathology, Oxford and Dept of Neurology, Cambridge

Amanda Cox, Research Registrar, Addenbrooke's Hospital, Cambridge

Rhys Davies, Research Registrar, Addenbrooke's Hospital, Cambridge

Tom Foltynic, Neurology Research Registrar, Cambridge

Richard Hardie, Consultant Neurologist and Director of Neurorehabilitation, Headley Court Medical Rehab Unit

Tim Harrower, SpR in Neurology, Addenbrooke's Hospital

Lucy Anne Jones, Research Associate (Cognitive Neuroscience)

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Mark Manfred, Consultant Neurologist, Addenbrooke's Hospital, Cambridge, and Bedford Hospital

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Andrew Mitchell, Neurology Research Registrar, Addenbrooke's Hospital, Cambridge

Wendy Phillips, Research Registrar, Addenbrooke's Hospital, Cambridge

Julian Ray, Consultant Neurophysiologist, Addenbrooke's Hospital, Cambridge and Queen Elizabeth Hospital, Kings Lynn

Robert Redfern, Consultant Neurosurgeon, Morriston Hospital, Swansea

Liza Sutton, UCL PhD Student, Institute of Neurology

Sarah J Tabrizi, DoH Clinician Scientist and Clinical Senior Lecturer, Institute of Neurology

John Thorpe, Consultant Neurologist, Addenbrooke's Hospital, Cambridge, and Peterborough

Ailie Turton, Research Fellow, Burden Neurological Institute, Bristol

Andrew Worthington, Brain Injury Rehabilitation Trust, Birmingham

For more information on joining our panel of reviewers,

E-Mail AdvancesinCNR@aol.com or Tel. [Rachael Hansford on 0131 477 2335](tel:01314772335).

NEUROLOGICAL DRUGS**How does intravenous immunoglobulin work?**

There are dozens of suggested answers to this question, possibly different in different diseases. The most robust come from electrophysiological studies of autoimmune peripheral nerve diseases. We reported last year on Klaus Toyka's *Annals* paper showing the neutralisation of blocking antibodies in Guillain-Barré syndrome by IVIG.

Now Hugh Willison's group in Glasgow have produced similar results in Miller Fisher syndrome, that variant of Guillain-Barré syndrome characterised by ophthalmoplegia, ataxia and areflexia associated with anti-GQ1b antibodies. This group has developed a system for assaying the "latrotoxin-like" (a spider toxin) effects of anti-GQ1b antibodies on mice diaphragm muscle strips: application of Miller Fisher serum produces miniature end plate potentials that summate to produce visible twitches and complement is deposited at the neuromuscular junction. IVIG blocked the binding of serum anti-GQ1b antibodies to the GQ1b ganglioside in an ELISA; furthermore IVIG was able to partially displace anti-GQ1b antibodies already bound to GQ1b ganglioside. When applied to muscle strips, IVIG reduced the latrotoxin-like effects of serum containing anti-GQ1b antibodies. However, if serum was applied first and then IVIG later, latrotoxin-like effects were still seen. The conclusion is that IVIG works in this model by preventing, or reversing, the binding of anti-GQ1b antibodies to their target, but does not influence downstream effects.

Whilst such a mechanism nicely explains why IVIG sometimes has such rapid clinical effects, it does not account for its prolonged action, well beyond its half-life in serum, in diseases such as multifocal motor neuropathy. -AJC
Immunoglobulins inhibit pathophysiological effects of anti-GQ1b-positive sera at motor nerve terminals through inhibition of antibody binding.

Jacobs BC, O'Hanlon GM, Bullens RW, Veitch J, Plomp JJ, Willison HJ.

BRAIN

2003;126:2220-34

☆☆☆ RECOMMENDED

MEMORY: Sleeping on it: solutions from sleep

When our parents told us that "it would all be clearer in the morning", they may just have been right. This fantastic experiment tests our ability to solve problems during sleep. The design was very simple: people were given a problem to solve and then given 8 hours of either night time sleep, night time wakefulness or daytime wakefulness. They were then re-exposed to the problem: those who had slept had more that double the chance of solving it than the other groups. The task was crafty. Subjects had to process a string of numbers by two rather laborious rules to get a final answer. But there was a shortcut, which the subjects had to discover for themselves. The endpoint of the test was the number of people who spotted and used this shortcut in each group.

One interpretation of this result might be that the refreshment of sleep improves cognitive performance. But the authors, from Germany, tested different subjects on this task after sleep, without previous exposure. This group performed at the same levels as the "wake" groups in the first experiment. This suggests that there was processing of the task's rules during sleep following exposure to the task. Another important confound was excluded by studying the subject's reaction time. Normally, the reaction times to stimuli in the second test were shorter than those in the first. But amongst those subjects in the sleep group who solved the problem, reaction times actually slowed between trials. This might suggest some competition for the mechanism underlying sleep-time learning between motor planning and problem solving! -AJC

Sleep inspires insight.

Wagner U, Gais S, Haider H, Verleger R, Born J.

NATURE

2004 Jan 22;427(6972):352-5


PARKINSON'S: Improved understanding of alpha-synuclein biology and pathobiology

Alpha-synuclein is a protein abundantly expressed throughout the brain at nerve terminals. It is implicated in a number of neurodegenerative diseases, particularly Parkinson's disease, where it accumulates in ubiquitinated cytoplasmic inclusions called Lewy bodies. Its normal function remains unclear. In vitro data have suggested a role for alpha-synuclein in cellular lipid metabolism and synaptic vesicle trafficking. It is also thought to be important in development, learning and plasticity.

This paper employs a yeast model, which has a highly-conserved protein quality control and membrane trafficking mechanism, to investigate normal and abnormal alpha-synuclein biology in vivo. Wild-type alpha-synuclein and two mutant forms (A53T and A30P), both associated with early onset

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Tel: 01676 521000 • Fax: 01676 521200 • Email: octapharma@octapharma.co.uk
www.octapharma.com*

References:

1. Sewell WAC et al J Neurol Neurosurg Psychiatry 1997; 63: 106-109.

February 2004 Code OGM/04/01

octapharma

familial Parkinson's disease, were expressed in yeast.

In an attempt to mimic aging neurons, in which misfolded proteins accumulate due to a compromised protein quality control system, the three constructs were over-expressed by two-fold. This doubling in expression levels had severe consequences at the cellular level. First, it severely inhibited yeast cell growth. Second, the wild-type and A53T mutant proteins, which are normally localised specifically to the plasma membrane, had been recruited into large cytoplasmic inclusions. The A30P mutant exhibited impaired membrane-binding capacity. Thirdly, over-expression of all three forms of alpha-synuclein lead to their ubiquitylation, which indicated they were misfolded and were destined for degradation by the proteasome. Finally, these misfolded proteins were demonstrated to directly impair proteasome function.

Alpha-synuclein has also been reported to share biophysical properties with fatty acid binding proteins. The study proceeded to investigate the proposed role of alpha-synuclein in lipid metabolism and synaptic vesicle trafficking. Alpha-synuclein was shown to inhibit phospholipase D (PLD) in vivo, promote lipid accumulation and to disrupt synaptic vesicle membranes causing the release of neurotransmitter into the cytoplasm.

This paper clearly demonstrates how minimal disruption in protein quality control mechanisms and subsequent accumulation of alpha-synuclein can have devastating effects on cellular function. The confirmation of the involvement of alpha-synuclein in lipid metabolism and vesicle trafficking is important, and such findings suggest these may be primary pathogenic pathways in Parkinson's disease. This data is also supported by clinico-genetic observations. It has recently been reported by John Hardy's group that a triplication at the alpha-synuclein locus, causing a doubling of wild-type gene expression, causes premature onset of PD in humans. This supports the notion that a small change in the expression of alpha-synuclein relative to the cell's quality control systems causes disease-related toxicity. -LMS, SJT

Yeast Cells Provide Insight into Alpha-Synuclein Biology and Pathobiology.

Outeiro TF and Lindquist S.

SCIENCE

2003;302:5651:1772-1775

HUNTINGTON'S: The sweet taste of success in treating Huntington's disease

This is yet another paper suggesting a possible treatment for Huntington's disease, but unlike some other compounds this agent is simple, non-toxic and easy to administer orally. In this study Tanaka and colleagues began by using an in vitro screening strategy involving a mutant sperm whale myoglobin! This assay involved screening for inhibitors of polyglutamine-mediated protein aggregation and showed that a disaccharide TREHALOSE caused a significant and dose dependent reduction in this aggregation. This is a property of a number of disaccharides and it appears to work through stabilisation of the proteins containing the expanded polyglutamine. They then demonstrated that trehalose decreased aggregate formation in a transfected neuroblastoma cell line and increased cell viability in a dose dependent fashion. Finally the group tried their compound in the R6/2 transgenic mouse model of HD and showed that it was effective in terms of reducing weight loss but not the development of diabetes (common features of this mouse model of HD), improved motor performance and decreased pathology - both the degree of atrophy and number of inclusions. Finally in this model the compound increased the average life span of the mice from ~97 to 108 days.

This is another interesting study, given its simplicity and thus the obvious translation into the clinical arena. However clearly more work needs to be done before clinical trials can be done, especially given the relative reduced life span of their R6/2 mice. Indeed a better test for the compound may involve the use of the newer better mouse models of HD using full length huntingtin and knock-in strategies. -RAB

Trehalose alleviates polyglutamine-mediated pathology in a mouse model of Huntington Disease.

Tanaka M, Machida Y, Niu S, Ikeda T, Jana NR, Doi H, Kurosawa M, Nekooki M, Nukina N.

NATURE MEDICINE

Published online 18th Jan 2004

☆☆☆ RECOMMENDED

BIH: Venous stenting for idiopathic (benign) intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a syndrome characterised by visual disturbance and headache. Papilloedema is common but not invariable. A variety of terms have been used to describe the syndrome including pseudo-tumour cerebri, benign intracranial hypertension and, as first described by Quincke in 1897, serous meningitis. Ventricular size is not increased but CSF pressure is raised. CSF examination is normal, other than raised pressure. Various causes have been implicated, including middle ear

infection, obesity, various drugs, and venous sinus thrombosis. Management has hitherto been somewhat empirical, relying initially on serial lumbar punctures sometimes combined with the administration of the carbonic anhydrase inhibitor, acetazolamide. For resistant cases CSF diversion strategies, for instance lumboperitoneal shunts, have been employed. When this fails cranial decompression procedures or optic nerve sheath decompression have been used rather as a last resort.

Two recent studies, a report of a single case in Newcastle, and a series of 12 patients reported from Cambridge, emphasise the importance of stenosis of the lateral venous sinus as a possible patho-aetiological mechanism. In both studies treatment was with venous stenting. The background to these studies is recent evidence which suggests that in some patients with IIH the raised intracranial pressure (ICP) may be the result of focal stenotic lesions of the lateral sinus. In Cambridge 12 female patients with IIH, all with raised CSF pressure (> 25cm H2O), intractable headaches and visual disturbance, underwent invasive monitoring of lateral venous sinus pressure and were treated with venous sinus stenting via percutaneous jugular puncture. Follow-up was undertaken at 8-12 weeks. Initially, 5 patients were rendered asymptomatic and 2 showed some improvement but had residual headache. None of these patients showed clinical deterioration over a further follow-up of 9-24 months.

In the case report from Newcastle a diagnosis of benign intracranial hypertension was made on clinical and radiological grounds and phase contrast MR venography (MRV) showed evidence of reduced flow within the left transverse sinus which was felt to be congenitally narrowed or occluded. A significant pressure gradient was recorded across the stenosed segment. At follow-up evaluation, 3 months and 6 months following stenting, symptoms had completely resolved and there was reduction in the severity of pre-treatment papilloedema. Cerebral angiography at 12 months was satisfactory, as were interval repeat MRVs.

The relationship between raised ICP in IIH and possible lateral venous sinus stenotic lesions is not clear-cut. Not only is radiological interpretation complicated by variations in normal anatomy but also raised ICP itself may result in secondary collapse of the lateral sinuses, a reversible phenomenon. Furthermore, removing CSF during venography has been found to reduce or eliminate pressure gradients in the lateral venous sinuses and reduce intracranial venous hypertension. However, with the hypothesis that venous outflow obstruction results from lateral sinus stenosis in mind, venous stenting seems logical and, to the extent that a number of patients thus treated have gained prolonged symptomatic improvement, justified. The question remains as to whether this iterative loop of raised intracranial pressure is the result of a physical, anatomical variant (venous stenosis) or to a physiological phenomenon (venous collapse). Even if selection difficulties can be overcome it remains to be seen whether or not medium-term symptomatic relief in some of these patients is maintained or whether venous obstruction at the site of stenting will recur. - RMR

Endovascular stenting of the transverse sinus in a patient presenting with benign intracranial hypertension.

Ogungbo B, Roy D, Gholkar A, Mendelow AD.

BRITISH JOURNAL OF NEUROSURGERY

2003;17(6):565-8

Idiopathic intracranial hypertension : 12 cases treated by venous sinus stenting.

Higgins JNP, Cousins C, Owler BK, Sarkies N, Pickard JD.

JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY

2003 ;74:1662-6

REHABILITATION: A picture to improve arm recovery after stroke

This winter many England rugby fans were on the edge of their seats while Jonny Wilkinson played a mental movie to himself in preparation for the kick that won the world championship. The power of mental practice is well known in the world of sport. Over the last five years these sports science methods have become of interest for retraining movement in patients following stroke and benefits have been demonstrated in a few small studies.

One such study is reported in the first issue of Clinical Rehabilitation this year. The authors of this study were interested to see if mental practice would help patients in a stroke unit. 10 patients were given daily mental practice for two weeks and their rate of improvement on the Motricity index score for the upper limb was compared before, during and after the two weeks mental practice.

The rate of recovery was increased over the intervention phase in eight of the patients, in one patient no change was seen and change in the remaining patient was not analysed because performance over the baseline phase was not stable. The study has limitations: it is small and there is an inherent difficulty in checking compliance to mental practice. Patients were their own controls rather than there being a control group and the status of the asses-

sor (blinded or not to the phase of study) was not reported. However the results of this pilot study are very promising and if substantiated mental practice may provide a simple and inexpensive means of supplementing therapy. Even in stroke units patients have little opportunity to carry out real practice so with adequate training those who are cognitively able may at least be able to do mental practice while they sit by their beds. -AJT

The adjunctive role of mental practice in the rehabilitation of the upper limb after hemiplegic stroke.

Crosbie JH, McDonough SM, Gilmore DH, Wiggam MI

CLINICAL REHABILITATION

2004; 18: 60-68

SPEECH: Treating aphasia

Two rather distinct approaches to aphasia therapy have emerged over recent years. The first, based on strong cognitive neuropsychological models, focuses on a specific aspect of the language impairment, e.g. semantic processing, with little direct attention to generalisation into everyday communication. The second has a much broader perspective, in which language is viewed as only one aspect of overall communicative ability. It has been easier to demonstrate improvements using the first approach but a query remains over the extent to which this really helps people. Conversely, the second approach, while firmly rooted in real communication, is much more difficult to measure.

This study (the second in a series of three) contributes to what is as yet a very small literature where the two approaches have been investigated together. In the full study six patients were taken through two baseline assessments, and two major periods of therapy, one termed 'lexical therapy' and the other 'communicative'. The previous paper reported the results of the lexical therapy; this paper has a focus on the combination of lexical and communicative therapy, in which tasks moved gradually from picture naming, to exercises involving the transmission of specific information and on to natural conversation. Within the broad range of results there were different patterns of gain across the lexical and communicative therapy phases. One participant did not benefit from the communicative therapy (but had from the earlier lexical therapy) while the pattern was reversed in another. The authors were able to conclude that overall gains were made via the combined therapy for five of the six participants.

The small number of previous studies involving both approaches to therapy is at least partly attributable to the complexity of issues involved. This study produces interesting and informative results in its own right and advances some of the methodological issues to promote more work in the field. -RB

Combining lexical and interactional approaches to therapy for word finding deficits in aphasia.

Herbert R, Best W, Hickin J, Howard D and Osborne F.

APHASIOLOGY

2003; 17: 1163-1186

REHABILITATION: A "holistic wellness program" for people with spinal cord injury

This interesting study from a US university centre demonstrated the benefit of a 7 month "wellness programme" for patients with spinal cord injuries (SCI), many of the features of which seem to constitute an integral part of "the standard" rehabilitation programme offered by centres this side of the Atlantic. This was a randomised controlled trial for patients with SCI of a series of six 4-hr (outpatient) workshop sessions over a 3 month period with telephone follow-up and support for the following four months. The study group were a mean of 14 years since their injury and 43 out of 67 starters completed the 7-month trial. Though difficult to ascertain exactly the content and how the sessions were conducted, it consisted of four modules which were "didactic & experiential": lifestyle management, physical activity, nutrition and prevention of secondary complications. The workshops were facilitated by two staff members with SCI and there were individual coaching sessions by the teachers for 3 of the 4 modules.

They based the design of their programme on Stuijbergen's self-efficacy model, defined as the "degree of confidence that one can successfully perform a specific behaviour". Their outcome measures included Self-Rated Abilities for Health Practice and other such scales to assess this model. The other outcome measures related to the modules described above and a standard ASIA neurological examination conducted at entry, at 2 weeks and 4 months after the workshops. Using regression analysis the standardised measures for each of health-related self efficacy, nutritional awareness and behaviour, stress management and physical fitness as well as secondary conditions all showed significant improvements with the intervention, supporting their model. However there were no changes in physiological (some may say more objective) measures which the authors attributed to the short time frame involved.

As usual for a rehabilitation study it was limited by small sample size and

heterogeneity of the sample but did achieve statistical significance in a number of areas with high satisfaction ratings from participants. Whilst acknowledging Prof. Derek Wade's concerns about opening the "black box of rehabilitation" this study adds some evidence to understanding the vital components of a comprehensive rehabilitation programme. It would be interesting to compare the outcomes (including economic) of the "short-sharp" sub-acute rehabilitation programmes commonly on offer in the US along with this programme, with "the standard" programmes on offer in the British Isles and Europe. - JJMACF

Assessment of a Holistic Wellness Program for Persons with Spinal Cord Injury.

Zemper ED, Tate DG, Roller S, Forchheimer M, Chiodo A, Nelson VS, Scelza W.

AMERICAN JOURNAL OF PHYSICAL AND MEDICAL REHABILITATION
2003;82:957-968

GUILLAIN-BARRÉ SYNDROME: What lies between GBS and CIDP?

By definition, patients with Guillain-Barré syndrome reach their worst point within four weeks from the start of their neurological symptoms, and people with chronic inflammatory demyelinating polyneuropathy have a progressive decline (with or without relapses) over months. However not every case fits these criteria and there has always been some debate about whether an additional entity, subacute inflammatory demyelinating polyneuropathy (SIDP), exists. In this paper Oh and colleagues examined patients with SIDP based on their history (progression with nadir between 4 and 8 weeks from onset with no relapse on follow-up) and neurophysiology. Using these criteria they identified 16 definite and 13 probable cases, and showed that cranial nerve involvement and respiratory failure were rare features and that most responded to steroids with complete recovery in two thirds of cases. They therefore suggested that SIDP was more like CIDP than GBS, but that there was a higher rate of antecedent infection and a higher recovery rate in SIDP.

This paper claims to show that SIDP is different from CIDP and GBS, but to my mind this claim remains unproven. Nevertheless on a pragmatic level it does suggest that patients progressing beyond 4 weeks with "GBS" might well benefit from steroid treatment. -RAB

Subacute Inflammatory Demyelinating Polyneuropathy.

Oh SJ, Kurokawa K, de Almeida DE, Ryan HE, Claussen GC.

NEUROLOGY

2003; 61: 1507-1512.

GUILLAIN-BARRÉ SYNDROME: Steroids along with IVIG for GBS?

I clearly remember the conclusion of the presentation of the Dutch GBS group at the ENS in 2002: IV methylprednisolone combined with IVIG improved the outcome of GBS when compared to IVIG alone. I even reported this result in ACNR. However, by the time their work was acceptable to the Lancet reviewers, the researchers' claims had sobered up: steroids offered no significant increased efficacy to IVIG treatment. The study involved 233 people with GBS who were unable to walk independently. There was no difference between the groups in the primary outcome measure: disability at 4 weeks. However, if the results were adjusted for age and disability, factors which were unbalanced at baseline, a treatment effect emerged although even then the stats are unimpressive. There is the usual plea in the last paragraph for more trials, but few people can share their enthusiasm, as Richard Hughes's commentary amply demonstrates. - AJC

Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial.

van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA; Dutch GBS study group.

LANCET

2004 Jan 17;363(9404):192-6.

☆☆☆ RECOMMENDED

ALZHEIMER'S: the role of APP in A β toxicity

It is now 20 years since the first characterisation of amyloid β -peptides (A β) from Alzheimer's disease (AD) brain. Although evidently toxic in cell culture, the precise role of A β in AD pathogenesis has remained uncertain, one consequence of which has been the sometimes acrimonious debate surrounding the use of so-called A β vaccines for the treatment of AD. That A β toxicity may depend in some way on its parent molecule, amyloid precursor protein (APP), a transmembrane protein which might have an intracellular signalling function, has been postulated (the "reciprocity hypothesis"; BioEssays 1995; 17: 819-24). Certainly A β toxicity is attenuated in APP deficient neurones (Nature Neuroscience 2000; 3: 460-4)

In the series of experiments reported in this paper, it is shown that soluble

A β potentiates APP homodimerization, forming A β /APP dimer complexes. This step does not require the cytoplasmic (C-terminal) domain of APP. Caspase-8 is then recruited to the complex, cleaving APP at position 664, leading to the generation of cytotoxic C-terminal APP peptides including C31, known to be proapoptotic. The time course of these binding and cleavage processes correlates with cell death. Furthermore, a preliminary study of AD brains (n = 3) showed a correlation between levels of caspase-cleaved APP fragments and soluble A β .

These findings suggest that soluble A β -induced multimerization of APP at the cell surface may transduce a cell death signal, through recruitment and activation of caspase-8. Since it is increasingly appreciated that soluble A β , rather than the fibrillar species in plaques, best correlates with the severity of AD, this mechanism may be of relevance to AD pathogenesis and suggests possible points for therapeutic intervention. These might include not only anti-apoptotic agents but also small molecules antagonising Ab-APP binding. -AJL

Amyloid β protein toxicity mediated by the formation of amyloid- β protein precursor complexes.

Lu DC, Shaked GM, Malsiah E, Bredesen DE, Koo EH.

ANNALS OF NEUROLOGY

2003;54(12):781-789

EPILEPSY: Steroids for parasites in the brain?

There is something particularly horrible about a parasite growing in your brain, but it remains probably the most common cause of epilepsy in places where the pork tapeworm is found. In the UK cases are seen regularly in centres where travel to endemic areas is common, particularly among the Asian community. Surprisingly, although treatment is indicated in certain situations, it is not clearly established whether it affects the development of epilepsy in those with from one to a few parenchymal cysts. The first two randomised trials of treatment and the effect on seizures have just been published. In the study by Garcia *et al*, 120 patients were selected. They all had a history of seizures for less than 10 years and all had evidence of viable *Taenia Solium* cysts on CT or MRI, some with signs of inflammation. Patients were randomised to albendazole plus dexamethasone or placebo and followed for 30 months. The number of patients with partial seizures was similar in the two groups but treatment significantly reduced secondarily generalised seizures (23% of treated patients and 37% of placebo patients). Patients who had no active lesions at 6 months had 62% fewer seizures than those who had active lesions. In the placebo group, nearly all the non-inflamed viable cysts persisted whereas in the treatment group, less than half persisted. The authors argue that these results support treatment although they do not establish whether the effective agent was albendazole or steroids.

Mall *et al* studied a slightly different group of 97 patients with new onset seizures (<11 days) and a single cyst. They randomised patients to prednisolone 1mg/kg for 10 days or placebo and followed up clinically and with neuroimaging at 1 and 6 months. Both groups received anti-epileptic drugs. After 6 months, lesions had disappeared in 88% of prednisolone-treated patients but only in 52% of placebo patients. Seizure recurrence was associated with abnormal CT scans in 81%, including persisting lesions and calcified or regressed lesions. So steroids seem to help scan resolution, and scan resolution is associated with lower seizure recurrence in both studies. Does this mean that it was actually the steroids that were effective in the Garcia study? The patient groups were different so it is difficult to be sure. A study of albendazole plus steroids versus steroids would clearly answer the question. Worries about a Herxheimer type reaction mean that albendazole is rarely used alone. -MRAM

A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. Garcia H.

Pretell EJ, Gilman RH *et al*.

NEW ENGLAND JOURNAL OF MEDICINE

2004;350:249-257.

Short course of Prednisolone in Indian patients with solitary cysticercus granuloma and new-onset seizures.

Mall RK, Agarwal A, Garg RK, Kar AM, Shukla R.

EPILEPSIA

2003;44:1397-1401

EPILEPSY: PET of DNETs?

Dysembryoplastic neuroepithelial tumours are increasingly recognised as a cause of refractory epilepsy. They are benign lesions and are difficult to diagnose with certainty with conventional radiological techniques. Follow-up scans are usually needed to help exclude low grade gliomas. Resection of DNETs results in a high (80-90%) rate of seizure remission in some series. A method of distinguishing them from progressive lesions would be very valuable. In this small study of 7 patients with benign temporal lobe lesions and

epilepsy, the authors used [11C]Methionine PET and related them to histological diagnosis after resection. Four patients with DNET all had low uptake in the lesions, whereas 3 patients with other lesions (low grade astrocytoma, pleomorphic astrocytoma and ganglioglioma) all had high uptake. If this finding is confirmed, it may prove a useful ancillary investigation for this small group of patients. -MRAM

Usefulness of [11C]Methionine PET in the diagnosis of dysembryoplastic neuroepithelial tumor with temporal lobe epilepsy.

Maehara T, Nariai T, Kawai K, Shimuzu H, Ishii K, Ishiwata K, Ohno K.

EPILEPSIA

2004;45:41-45

THE BIZARRE: the neurology of out-of-body experiences

The pages of Brain are not the likeliest place for a discussion of the whacky and wonderful. But this is a truly classical account from Geneva of out-of-body experiences (where people feel they are outside of themselves and see their own body within the world) and autoscopia (the experience of remaining within one's body but seeing another copy of one's body outside of one self). 6 clinical cases are presented in which 4 definitely had epilepsy, one had hemiplegic migraine and one case was undiagnosable but certainly had migraine. In all but one, the experience was vivid and felt to be real at the time. In out-of-body experiences, the body lay on the bed whereas in autoscopia, the body was upright. This was accompanied usually by a feeling of dizziness or lightness and fear (although one patient reported joy). Three patients also experienced body part illusions (such as limb shortening). Combining anatomical and electrical lesion data, the authors suggest that these unusual experiences can arise from unilateral lesions in the temporo-parietal junction of either hemisphere. They go on to speculate on the mechanism. They argue that we assimilate multiple sensory sources into a representation of ourselves which is contained within our defined personal space. If this representation "escapes" the confines of cognitive personal space, then we see an illusory duplication of ourselves. A fantastic read. -AJC

Out-of-body experience and autoscopia of neurological origin.

Blanke O, Landis T, Spinelli L, Seeck M.

BRAIN

2004;127 (Pt 2):243-58.

☆☆☆ RECOMMENDED

MULTIPLE SCLEROSIS: brain plasticity and effect of cholinesterase inhibitors

Colleagues from the multiple sclerosis (MS) clinic occasionally ask me whether cholinesterase inhibitors (ChEI) might have a role in the treatment of cognitive problems in MS. My formulaic answer has been "there is no evidence", but this may change if the findings of this paper from Oxford are corroborated. Ten MS patients without significant neuropsychological impairment as assessed by a battery of tests, but with subjective complaints of poor concentration and memory, were studied along with 11 controls using fMRI whilst performing the counting Stroop test, performance of which is impaired with frontal lobe damage. The patients showed a distinct, and abnormal, pattern of brain activation relative to the controls, with reduced right inferior frontal (Brodmann area 45) and right basal ganglia activation, but increased left medial prefrontal (Brodmann areas 8, 9, 10) activation. The magnitude of these differences correlated with normalised parenchymal brain volume, a measure of disease burden. Since behavioural performance was similar in the two groups, the authors suggest that these activations reflect adaptive functional neuroplasticity in response to brain injury.

Double blind administration of the ChEI rivastigmine (3 mg), one of the licensed treatments for mild-to-moderate Alzheimer's disease, 150 minutes before fMRI, resulted in normalisation of the pattern of activation in all 5 MS patients tested, but had no effect in the 4 controls tested. No change in patients' behavioural performance was noted following rivastigmine, but numbers were small. These findings suggest that cholinergic agonism rapidly modulates functional changes, perhaps by facilitating processing associated with right prefrontal activation and consequently reducing adaptive left frontal responses, perhaps by unmasking latent pathways.

Of course, functional imaging is one thing and clinical neurology is quite another, but these findings do suggest that clinical trials of ChEI in cognitively impaired MS patients may be of interest. -AJL

Potentially adaptive functional changes in cognitive processing for patients with multiple sclerosis and their acute modulation by rivastigmine.

Parry AMM, Scott RB, Palace J, Smith S, Matthews PM.

BRAIN

2003; 126(12):2750-2760

Complete human anatomy in 3D

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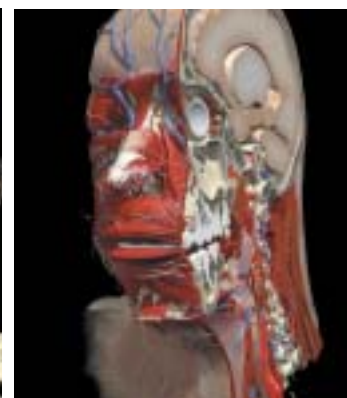
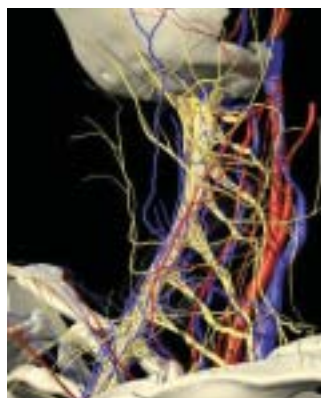
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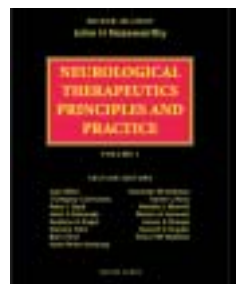
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Neurological Therapeutics: Principles and Practice



THIS 2-volume textbook, edited by John Noseworthy, addresses the treatment of patients with neurological disease. It is a comprehensive reference for adult and pediatric neurologists, trainees, and other physicians who treat neurological patients.

With 345 authors, 271 chapters in 14 sections, and over 3000 pages it is comprehensive in its scope. Chapters cover particular conditions, detailing epidemiology, aetiology, pathogenesis, genetics, clinical features, investigation findings and natural history, as well as therapeutics. It uses a systematic approach to the evidence base for treatment.

A companion volume, 656 pages containing 600 graphics from the book for ease of use is included.

For more information contact Martin Dunitz on Tel. 0207 842 2001, or see the web site, www.tandf.co.uk/books

From science to practice

THE ninth in the 'from science to practice' series BGS SIG Parkinson's disease conference, revisits two difficult areas for clinical practice - current research on why people with Parkinson's disease fall and what we can do about it, and palliative care, starting with the ethical and legal framework for end-of-life decisions.

Parkinson's disease nurse specialists have greatly improved the quality of life for patients and carers as well as hard-pressed medical staff. We will review where we are with this initiative and ask 'What are the threats and challenges for the future?'

For more information and to register for this conference, please contact MEP Ltd on 020 7561 5400 or info@mepltd.co.uk

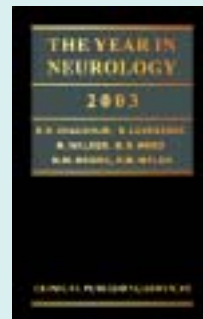
Competition winners

CONGRATULATIONS to Dr JH Tho, SPR in Clinical Neurophysiology, London, and Dr Ismael Mohammed Bin-Jaliah, Researcher, Birmingham, who each won a copy of The Year in Neurology 2004 in our competition last issue.

'The Year in Neurology 2004' was published on 29 February. Now in its third year, The Year in Neurology 2004 retains the tried and tested structure of previous volumes, whereby an expert team of authors comment on over 150 recent papers selected from the world's leading journals. Keeping abreast of the vast number of papers published in neurology is a difficult task - this title helps ensure that busy clinicians can gain access in one volume to many more journals than he or she can easily scan, is guided towards the landmark papers, and is given a view of their implications for his or her own clinical practice.

Concise and easy to read, the text reflects the rapid changes in this fast-moving field, providing all those working or training in the area of neurology with an up to date, working guide.

For further information contact: Anthony Gresford, Clinical Publishing Services, Tel: + 44 1865 811116 Fax: +44 1865 251550, E-Mail: info@clinicalpublishing.co.uk



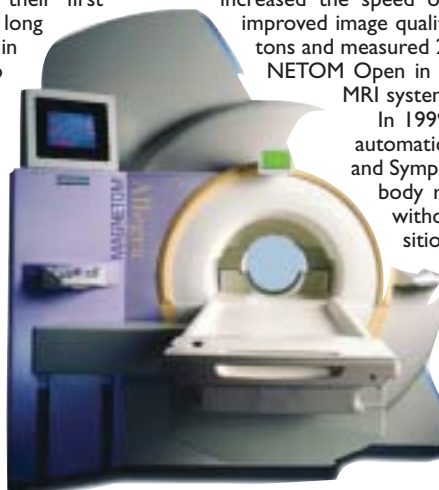
From a red pepper to a view inside the human brain

MORE than 25 years ago, scientists at Siemens made their first experiments in Magnetic Resonance Imaging (MRI). It is a long way from generating that first image of a red pepper in a wooden hut on the Siemens research facilities to introducing the Total imaging matrix (Tim) technology at this year's RSNA.

The first image of the head was generated in March 1980 requiring an acquisition time of eight minutes. The first clinical MRI by Siemens was installed in Germany in 1983 at the Medizinische Hochschule Hannover (Medical College in Hannover). At that time, a complete examination took as much as 1½ hours.

The development of super-conductive magnets

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increased the speed of image generation, simplified installation and improved image quality. However, the magnets weighed as much as 8 tons and measured 2.55 meters in length. The introduction of MAGNETOM Open in 1993 made Siemens the first to offer an open MRI system to benefit claustrophobic patients.

In 1999, Siemens coupled their IPA coil concept with automatic table movement for MAGNETOM Harmony and Symphony. Since then, complete examinations of large body regions - for example the spine - are possible without extensive and uncomfortable patient repositioning.

Advances in MRI scanners mean that today's neurologists, psychologists and neurosurgeons can gain new insights into the functions as well as metabolic processes of the brain using functional magnetic resonance imaging (fMRI) - particularly with the newer range of Ultra high field systems.

For more information please contact Mike Bell, Siemens Medical Solutions, Tel. 01344 396317, www.siemens.co.uk/medical

Going solo

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

- as carbamazepine when it is predominantly selected for partial-onset seizures¹
- as valproate when it is predominantly selected for generalised seizures.^{1*}



BECAUSE LIFE
WITHOUT SEIZURES
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*In a double-blind trial in newly diagnosed epilepsy, 49% overall and 63% of children on topiramate were seizure free for the last 6 months of the study^{1,2} +Topamax is indicated as monotherapy in adults and children aged six years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. Uses: Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years); generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. Dosage and Administration: Oral. Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3 – 6 mg/kg/day (two divided doses). Initiate at 0.5 – 1 mg/kg nightly with weekly or fortnightly increments of 0.5 – 1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5 - 9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1 – 3 mg/kg. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. Contra-indications: Hypersensitivity to any component. Precautions and Warnings: May cause sedation; so caution if driving or operating machinery. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). Acute

myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use. Requires discontinuation of Topamax and treatment of symptoms. Side Effects: Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diplopia, headache, hypoesthesia, fatigue, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma reported rarely. Pharmaceutical Precautions: Tablets: Do not store above 25°C. Keep container tightly closed. Sprinkle Capsules: Do not store above 25°C. Legal Category: Package Quantities and Prices: Bottles of 60 tablets. 25 mg (PL0242/0301) = £20.02; 50 mg (PL0242/0302) = £36.17; 100 mg (PL0242/0303) = £64.80; 200 mg (PL0242/0304) = £125.83. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.88, 25 mg (PL0242/0349) = £25.32, 50 mg (PL0242/0350) = £41.60. Product licence holder: Janssen-Cilag Limited, Saunderton, High Wycombe, Buckinghamshire HP14 4HJ, UK. Date of text revision: April 2003. APIVER100403.

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