

## EDITOR'S CHOICE

**A 21st century brain atlas**

As I read this extraordinary article in Nature, I imagined all the great neuroanatomists of the past, from Vesalius onwards, drooling. For in this first report of a massive project (GENSAT: Gene Expression Nervous System Atlas), all modern molecular gismos have been harnessed to produce an atlas of brain gene expression of classical beauty.

Unfortunately it is an atlas of mouse not human brain. This is to exploit the fact that the mouse genome has been sequenced in large chunks (called bacterial artificial chromosomes, BAC). This means –very importantly- that the BAC containing your target gene is very likely to also contain the genes influencing its expression. So, if you slip that particular BAC into a mouse egg (by standard transgenic technology) and label your gene target (with a reporter sequence that encodes green fluorescent protein) you should be able to track the normal expression of your gene using conventional fluorescence microscopy.

This all American team are systematically making transgenics for all the genes they can, doing the histology on developing mouse brain and reporting their results on a public web database available to all. As an example of the power of this technology, consider the *gooseoid* gene, found to be deficient in DiGeorge syndrome. This gene was first expressed on embryonic day 10 in just two cells in the ventricular border of the developing mesencephalon. Five days later *gooseoid* cells were seen in the developing interpenduncular nucleus and, by day 7 postpartum, neuronal expression of *gooseoid* is seen in a subpopulation of cells in the interpenduncular nucleus and in the axons of cells in the tegmental nucleus, which receives a projection from the interpenduncular nucleus.

If you like Cajal's drawings of Golgi's silver stains, you will love the pictures generated by this project. Not only are they stunning aesthetically, they are a huge resource for all neuroscientists. -AJC

*A gene expression atlas of the central nervous system based on bacterial artificial chromosomes.*

Gong S, Zheng C, Doughty ML, Losos K, Didkovsky N, Schambra UB, Nowak NJ, Joyner A, Leblanc G, Hatten ME, Heintz N.

NATURE  
2003;425: 917-25

**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  
**Tom Foltynie**, 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)  
**Andrew Larner**, Consultant Neurologist, Walton Centre for Neurology & Neurosurgery, Liverpool  
**Simon J G Lewis**, Honorary Clinical Research Fellow, Cambridge Centre for Brain Repair  
**Mark Manford**, Consultant Neurologist, Addenbrooke's Hospital, Cambridge, and Bedford Hospital  
**Peter Martin**, Consultant Neurologist, Addenbrooke's Hospital, Cambridge  
**John MacFarlane**, SpR in Rehabilitation Medicine, National Rehabilitation Hospital, County Dublin  
**Brian McNamara**, Consultant Neurophysiologist, Cork, Ireland  
**Andrew Michell**, Neurology Research Registrar, Addenbrooke's Hospital, Cambridge  
**Wojtek Rakowicz**, SpR Neurology, National Hospital for Neurology and Neurosurgery, London  
**Julian Ray**, Consultant Neurophysiologist, Addenbrooke's Hospital, Cambridge and Queen Elizabeth Hospital, Kings Lynn  
**Robert Redfern**, Consultant Neurosurgeon, Morrision 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](mailto:AdvancesinCNR@aol.com) or **Tel.** [Rachael Hansford on 0131 477 2335](tel:01314772335).

**EPILEPSY****Obstructive sleep apnoea in epilepsy**

In this series the authors collected two hundred and eighty-three consecutive patients with epilepsy but no other medical problems. They were asked about snoring, assessed on the Epworth sleepiness scale and where there was a clinical suspicion, they underwent sleep polysomnography. A fairly loose definition of sleep-related epilepsy was used; more than half of seizures in sleep. Obstructive apnoea was diagnosed when an airflow arrest >10seconds was associated with persistent thoraco-abdominal movements and a hypopnoea with >50% decrease in airflow and >4% reduction in SaO<sub>2</sub>. Standard criteria were used to define OSA and it was graded as mild, moderate or severe. Forty patients underwent polysomnography, of whom 29 were diagnosed with OSA. Unfortunately EEG was not recorded so nocturnal seizures on the night of recording could not be excluded. The table shows the key differences in those with and without OSA who underwent polysomnography.

	Epilepsy + OSA (n=29)	Epilepsy only (n=11)
Age	45+/-15	33+/-12
BMI	28.5+/-3.6	23.3+/-3.7
Gender (male%)	83	46
Seizures in sleep (%)	47	26
More than one anticonvulsant	41	34
Patients under treatment	100	91
Treatment with valproate or phenobarbitone	23.5	24
Excessive daytime sleepiness	23.1	9

Unfortunately the numbers of controls are small but a pattern was suggested with older patients and later onset epilepsy tending to be associated with OSA. Unsurprisingly patients with OSA were more often male and were heavier, but not taking valproate more frequently than controls. Sleepiness was only present in a minority of those patients with OSA. Excessive daytime sleepiness is one of the cardinal symptoms of OSA and its absence in three quarters of patients makes one wonder how these patients were identified in the first place and if this was a typical OSA population. Seizures in sleep were somewhat more common. The study leaves me feeling that OSA may be commoner in patients with epilepsy and may be a significant problem, but I am not sure how I would screen for it in my epilepsy clinic. I think I shall rely on my standard clinical test of seeing if the patient dozes off before I do. -MRAM

*Obstructive sleep apnoea in a clinical series of adult epilepsy patients: frequency and features of the comorbidity.*

Manni R, Terzaghi, M, Arbasino, Sartori I, Galimberti CA, Tartara, A.

EPILEPSIA  
2003;44:836-40

**The neural correlates of laughter and humour**

At a time when laughs are perhaps harder to come by in the day-to-day practice of clinical neurology than was once the case, I wondered if this review article might suggest ways to cheer oneself up.

The study of laughter has been based on the classical lesion-based approach to symptomatic laughter, as in syndromes such as gelastic epilepsy, *fou rire prodromique*, and circumscribed brain lesions of vascular, inflammatory (MS) or neurodegenerative aetiology, supplemented in more recent times by brain stimulation techniques (most often in the context of epilepsy surgery) and noninvasive functional brain imaging. The neuroanatomical model developed to account for the observations from these different approaches proposes two partially independent pathways, viz.:

- an involuntary, emotionally driven, pathway involving the amygdala, hypothalamic and subthalamic areas, and the dorsal tegmental brainstem, activation of which causes cessation of cortical frontal inhibition;
- a voluntary pathway, sequentially involving premotor/frontal opercular areas, motor cortex, pyramidal tract and ventral brainstem.

A laughter-coordinating centre in the dorsal upper pottine mesencephalon coordinates these two pathways. Pathological laughter is therefore characterised as a consequence of subcortical disinhibition, triggered by normally inadequate stimuli.

Humour is more difficult to study, not least because it is hard to define what it is and what its components are. It has long been a subject of inquiry for philosophers: Plato, Aristotle, and Kant, to name but three. Nonetheless, the evidence-base indicates a special role for the right hemisphere in the comprehension of humour, including the right frontal cortex, medial ventral pre-

frontal cortex, right and left posterior (middle and inferior) temporal regions, and possibly the cerebellum.

Of course, many questions remain concerning these topics, but this is an excellent review of the state-of-the-art. An analogous review of crying and misery would be of interest. -AJL

*Neural correlates of laughter and humour [Review].*

Wild B, Rodden FA, Grodd W, Ruch W.

BRAIN

2003;126(10):2121-2138

## PRION DISEASE

### Prions in the spleen

Creutzfeldt Jakob disease (CJD) is the most common human prion disease, which occurs in sporadic, familial, iatrogenic and variant forms. Until now, accumulation of the disease-associated isoform of the prion protein, PrP<sup>Sc</sup>, has been limited to the central nervous system and olfactory nerve tissue in sporadic CJD. Only the new variant form, which results from the transmission of bovine spongiform encephalopathy, appeared to involve peripheral tissues. A detailed pathological study of 36 Swiss sporadic CJD patients resulted in the detection of PrP<sup>Sc</sup> in the spleen and skeletal muscle of one third of the patients. Such extraneural PrP<sup>Sc</sup> detection was made possible by use of a highly sensitive method that preferentially concentrates PrP<sup>Sc</sup> with sodium phosphotungstic acid, thus enhancing the sensitivity of Western Blots by up to three orders of magnitude. Patients with extraneural PrP<sup>Sc</sup> deposits had a much longer duration of disease and were more likely to have uncommon molecular variants of sCJD. These findings raise concern of iatrogenic transmission of sCJD following peripheral intervention from electromyography, and muscle biopsies, for example. However it seems unlikely that analysis of peripheral tissues will form the basis of a diagnostic test for sporadic CJD due to inhomogeneous peripheral distribution of PrP<sup>Sc</sup> deposits. -LMS & SJT

*Extraneural pathologic prion protein in sporadic Creutzfeldt-Jakob Disease.*

M.Glatzel, E.Abel, M.Maissen, A.Aguzzi.

THE NEW ENGLAND JOURNAL OF MEDICINE

2003; 349:1812-1820

## NEURAL DEVELOPMENT

### Neurogenesis in the substantia nigra

It used to be believed that new neurones could not be formed in the adult brain but relatively recently the concept of adult neurogenesis has become established. Constitutive adult neurogenesis has been demonstrated in the subventricular zone (SVZ) and the dentate gyrus (DG) in animals and humans. More controversially, it has been suggested that neurogenesis occurs constitutively in the cortex. Zhao *et al* suggest that neurogenesis also occurs constitutively in the adult mammalian substantia nigra. This would obviously have implications for Parkinson's disease as newly generated neurones could replace those lost to the neurodegenerative process. The authors suggest that this may be the case, using data obtained from partial MPTP lesioning. Alternatively the pathogenesis of the disease progression might include impaired neurogenesis.

Mice were used for the experiments, and proliferating cells were labelled using BrdU (a nucleotide analogue), [3H]-thymidine, and intraventricular infusion of a dye (DiI). They demonstrated, using immunohistochemistry and electron microscopy a few individually scattered cells in the substantia nigra double labelled for a proliferative marker and TH (thus there were newly born dopaminergic neurones). They showed that these cells projected to the striatum and integrated into synaptic circuits using a fluorescent retrogradely transported tracer. Thus, projection neurones were formed (neurogenesis in the SVZ and DG produce interneurons). They postulated that neurogenesis arises from the cells lining the ventricular extension in the midbrain, as individual DiI labelled subependymal layer cells grew neurospheres in vitro which could differentiate into neurones, astrocytes and oligodendrocytes (i.e. are neural stem cells), although none spontaneously acquired a dopaminergic phenotype. As neurogenesis increased two-fold following partial MPTP lesioning, the authors concluded that substantia nigra neurogenesis could be upregulated following an acute insult; again with implications for substantia nigra pathology (although one must of course bear in mind that MPTP lesioning is an acute insult as opposed to chronic neurodegeneration).

The degree of neurogenesis demonstrated in this study was very small indeed, although the authors pointed out that during the lifetime of a mouse, this process could replace all nigral dopaminergic neurones. Other laboratories have been unable to reproduce this work, but this may be due to methodological differences, bearing in mind the sensitivity required to pick up such

small numbers of new neurones. Also, despite demonstrating synaptic connectivity, the functionality of these new neurones remains to be established. More work is therefore required to explore nigral neurogenesis but the intriguing possibility has been raised, with all its attendant implications for Parkinson's disease. -WP

*Evidence for neurogenesis in the adult mammalian substantia nigra.*

Zhao MZ, Momma S, Delfani K, Carlen M, Cassidy RM, Johansson CB, Brismar H, Shupliakov O, Erisen J, Janson AM.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

2003;100 (13): 7925-7930

## ☆☆☆ RECOMMENDED

### Changing identity or just sticking together – What can stem cells do?

The ability of stem cells from one tissue to transdifferentiate into cells of other organs has generated much press of late, and indeed is discussed in this issue of ACNR by Josef Priller. The original papers purporting this have been pored over, and last year two papers appeared in Nature claiming that the result was not one of transdifferentiation but simply cell fusion. A new paper from the laboratory of Alvarez-Buylla that has just appeared in Nature further supports this claim. In this study the authors demonstrated that bone marrow derived cells (BMDCs) could fuse with neural progenitor cells in vitro and a range of cells in vivo, including Purkinje cells in the cerebellum. This study adopted a novel technique involving LacZ expression and a Cre/lox system to detect cell fusion events. This technique was validated in vitro before a transplant study was undertaken into irradiated mice. This latter study showed no examples of transdifferentiation using BMDCs, but cell fusion events involving hepatocytes, Purkinje cells in the cerebellum and cardiac muscle only (no other tissue compartments contained these cells).

This is a clever study but what this means is far from clear. For example does this happen normally and if so what does this achieve? Furthermore what does this mean for the stem cell therapies in neurological diseases? ....who knows, but this is clearly an area that will continue to generate many controversial studies. -RAB

*Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes.*

Alvarez-Dolado M, Pardal R, Garcia-Verdugo JM, Fike JR, Lee HO, Pfeffer K, Lois C, Morrison SJ, Alvarez-Buylla.

NATURE

2003; 425:969-973

## REHABILITATION

### Living with locked-in syndrome

Many of us have had only brief contact with patients who are "locked-in" unable to respond verbally or to move after a brainstem stroke, trauma or tumour. Perhaps we expect that most locked-in patients die within a few months or years and may see this as a blessing for quality of life for a locked-in person is low. An extraordinary longitudinal study of a cohort of 29 people living with locked-in syndrome refutes these views. This group of locked-in people live in United States and have been locked-in for over a decade. The latest study, reported in Journal of Head Trauma Rehabilitation, describes a telephone interview study conducted with 11 carers and one patient who communicated via a computer.

Of the initial 29 patients, 15 had died, 13 were alive and one although believed to be alive, was lost. The investigators took great trouble to find individuals. They even hired a private investigator to help trace two of them. The interview covered impairments, care, participation in activities and life satisfaction as perceived by the carers. 8 of the participants were living with family, 3 in care facilities and one in a hospital and one, for reasons that were not explained, in a school. Although the participants' movements and speech were largely unchanged their care had become simpler over the years. There was less use of tracheostomies, feeding tubes and indwelling urinary catheters. Most of the participants communicated through eye or facial movements though four used computers consistently.

The caregiver burden was very substantial; none of the carers felt able to leave their locked-in person alone for more than two hours. There were examples of supreme efforts to keep the person active in work and leisure. It was also apparent that the person was involved in making family decisions.

The most difficult question to answer in using telephone interviews was whether the locked-in survivors were satisfied with life. According to the carers 7 were satisfied with life in general, five were occasionally depressed. 7 had not discussed euthanasia, 6 had considered it in the past and one wanted to die. None had a "do not resuscitate" order. Clearly this is a difficult question for carers to answer on behalf of their lock-in person. With the increasing use of computer based communication more lock-in people will be able to

answer for themselves in the future. The authors of the study argue that disease and impairment do not equate with quality of life and caution against the prejudices of able bodied health care workers. -AJT

*Impairment, activity, participation, life satisfaction and survival in persons with locked-in syndrome for over a decade.*

Doble JE, Haig AJ, Anderson C, Katz R.

JOURNAL OF HEAD TRAUMA REHABILITATION

2003; 18: 435-444

### Coaching hints for skill learning after middle cerebral artery (MCA) stroke

There are differences of opinion in how motor skills should be trained in stroke rehabilitation. Some therapists take training strategies from sports science and give very explicit information to the patient about how they can improve their movements. Others work on the basis that patient's movements should not be brought to consciousness and try to elicit improvements in performance as a consequence of manipulating sensory information. These differences in approach are all too often based on the therapist's preferences and experience rather than on characteristics of the patient such as lesion site. An experiment reported by Lara Boyd and Carolee Winstein goes some way towards informing therapists about the importance of considering lesion site some way in determining appropriate strategies for training motor skills. They investigated the use of explicit information for helping patients to learn a motor sequencing task.

Boyd and Winstein used a serial reaction time task (SRTT), which was practised over 3 days to determine learning in stroke patients with middle cerebral artery lesions and in healthy subjects. In the SRTT task, on each trial a stimulus is presented in one of several possible locations and the task of the participant is to press the response button that corresponds to the location of the stimulus. The stroke patients were asked to respond using the hand ipsilateral to the lesion. Unknown to the subject, the target locations are sometimes determined by a repeating sequence and other times targets appear randomly. With practice, reaction time progressively decreases. However, when the sequence of stimulus locations follows a repeating pattern, due to the learning effect, the RT shortening becomes markedly increased in comparison to the condition when stimuli locations are determined randomly.

Patients and healthy subjects in the intervention group were told on day one to respond as fast as possible, on day two they were told that there was a sequence and on day three they were told what the sequence was and were allowed time to study it. The control group were asked each day just to respond as fast as possible.

Change in reaction times on days 2 and 3 and on a retention test on day 4 showed that as expected healthy subjects benefited from the explicit information about the sequence, but rather surprisingly the stroke patients did better without it. The explicit information interfered with their learning. Explicit learning involves memory for which the dorsolateral prefrontal cortex is important. The authors suggest that damage to brain areas such as the basal ganglia and premotor cortex that interconnect with dorsolateral prefrontal cortex, may disrupt the integration of explicit information into planned movement sequences.

This laboratory study demonstrates how important it is to consider lesion site in determining strategies for therapy. Some more ecological studies are needed before changing clinical practice but therapists may have to develop more imaginative ways to shape their patient's behaviour. Rather than using instruction, use of implicit cues such as the placement of objects in the training environment may result in greater benefit to stroke patients with MCA lesions. -AJT

*Impact of explicit information on implicit motor sequence learning following middle cerebral artery stroke.*

Boyd LA and Winstein CJ.

PHYSICAL THERAPY

2003; 83: 976-989

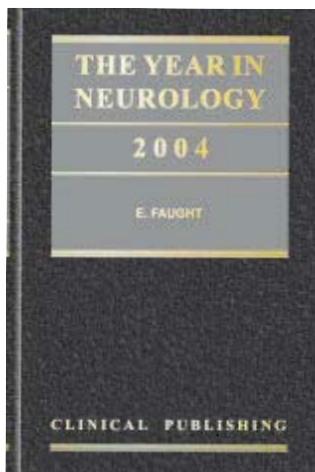
## AMYOTROPHIC LATERAL SCLEROSIS

☆☆☆ RECOMMENDED

### Reduced VEGF expression is a risk factor for ALS

Sporadic amyotrophic lateral sclerosis (SALS) is of unknown aetiology and pathogenesis, and represents 90-95% of total ALS cases. It seems likely that the disease is multifactorial, with a combination of largely unidentified modifying genes and environmental agents leading to its clinical manifestations.

Clinical Publishing / Atlas Medical Publishing Oxford



## The Year in Neurology 2004

Editor: **E Fought**, UAB Medical Center, Birmingham, Alabama, USA.

Now for the third year, *The Year in Neurology 2004* retains the tried and tested structure of previous volumes where an expert team of authors comments 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 makes sure that the busy clinician is able to 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 a thoroughly up-to-date working guide.

**CONTENTS AND CONTRIBUTORS:** PART I Neurological

disorders: 1. Epilepsy, *E Ben-Menachem*; 2. Cerebrovascular diseases, *N Bornstein and AY Gur*; 3. Neuro-oncology, *E Dropcho*; 4. Infectious diseases, *J Greenlee*; 5. Neuromuscular disease, *Y Harati*; 6. Neuro-immunology, *R Naismith and A Cross*; 7. Movement disorders, *A Nicholas and P Atchinson*; 8. Inherited disorders of skeletal muscle, *K North*; 9. Headache, *R Slaughter*; Alzheimer's disease, *E Zamrini*. PART II Investigation and management: 11. Cognitive neurology, *A Chatterjee*; 12. Clinical neurophysiology, *C Epstein*; 13. Epilepsy imaging, *R Knowlton*; 14. Neurological critical care, *T Bleck*.

#### READERSHIP:

Specialists in neurology and internal medicine; doctors in training.

#### BOOK DETAILS:

ISBN 1 904392 22 9;  
ISSN 1477-8106;  
384pp; 234 x 156mm;  
illustrations; hardback;  
publication February  
2004; price: £59.99/  
US\$104.95.

**TO ORDER:** Post, Fax, Phone or Email to:

T&F, ITPS, Cheriton House, North Way, Andover, Hants, SP10 5BE, UK Tel: +44(0) 1264 343070 or Fax: +44(0) 1264 343025  
Email: [uk.tandf@thomsonpublishingservices.co.uk](mailto:uk.tandf@thomsonpublishingservices.co.uk) or: [International.tandf@thomsonpublishingservices.co.uk](mailto:International.tandf@thomsonpublishingservices.co.uk)

The link between vascular endothelial growth factor (VEGF) and ALS was a very unexpected discovery during the development of a mouse model (*Vegfa $\Delta$ / $\Delta$* ) to investigate VEGF regulation. The expression of VEGF, an angiogenic cytokine, is induced by hypoxia and the binding of oxygen-sensitive transcription factors to the hypoxia response element (HRE) of the VEGF gene promoter. On deletion of the HRE by cre-loxP-mediated gene-targeting, Carmeliet and colleagues not only noted that reduced VEGF expression impaired angiogenesis but also that the *Vegfa $\Delta$ / $\Delta$*  mice developed an ALS-like motoneurone degeneration, which occurred in adulthood and was progressive in nature.

This finding prompted a study to determine if reduced VEGF expression played a role in the human condition of ALS. The VEGF alleles of nearly 600 ALS patients and 1000 controls originating from Sweden, Belgium and England were sequenced. Three single nucleotide polymorphisms (SNPs) in the VEGF promoter and 5' untranslated region (UTR), known to down-regulate VEGF expression, were investigated. A comprehensive haplotype analysis showed that the two recessive SNP haplotypes AAG/AAG and AGG/AGG were highly predictive of ALS risk and were not associated with any other neurological disease. Those individuals carrying "at risk" genotypes also exhibited a marked reduction in circulating plasma levels of VEGF.

The *Vegfa $\Delta$ / $\Delta$*  mice were used to demonstrate the biological importance of VEGF on motoneuron survival. In response to a minor ischemic insult (a proposed pathogenic mechanism in ALS) in the spinal cord, wild-type mice showed a transient clinical deficit, however the *Vegfa $\Delta$ / $\Delta$*  mice remained paralysed throughout the duration of the experiment due to their lower expression of VEGF. Moreover, SOD1 mice (an established ALS mouse model), which had been intercrossed with *Vegfa $\Delta$ / $\Delta$*  mice, exhibited a much more severe ALS phenotype and died earlier than the SOD-1 mice. Direct administration of VEGF to wild-type mice during the ischemic insult was shown to actively protect those motoneurons most susceptible to cell death. This paper corroborates earlier findings in a mouse model that low VEGF levels increase susceptibility of motoneurons to cell death. It also identifies the VEGF pathway as an important therapeutic target in ALS, and raises the possibility that long-term VEGF treatment may delay onset or slow the progression of motoneuron degeneration in this group of diseases. *-LMS & SJT VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans and protects motoneurons against ischemic death.*

D.Lambrechts, E.Storkebaum, M.Morimoto, J.Del-Favero, F.Desmet, S.Marklund, S.Wyns, V.Thijs, J.Anderssen, I.van Marion, A.Al-Chalabi, S.Bornes, R.Musson, V.Hansen, L.Beckman, R.Adolfsson, H.Singh Pall, H.Prats, S.Vermeire, P.Rutgeerts, S.Katayama, T.Awata, N.Leigh, L.Lang-Lazdunski, M.Dewerchin, C.Shaw, L.Moons, R.Vlietinck, K.Morrison, W.Robberecht, C.Van Broeckhoven, D.Collen, P.Andersen, P.Carmeliet.

NATURE GENETICS  
2003;34:4:383-394

## Febrile convulsions and the hippocampus

Mesial temporal sclerosis (MTS) is the commonest cause of refractory focal epilepsy and studies suggest that its development is preceded by febrile convulsions (FC) in about half of cases. The average febrile convulsion is a benign event but certain "complex" features, including duration, focal features and postictal deficit confer a multiplicative increase in the risk of later MTS. Recent studies have shown that MTS is associated with some dysplastic changes in the temporal lobes. Is MTS present before the febrile convulsion, causing the complex febrile convulsion or does it arise after the febrile convulsion? The only way to study this is longitudinally, following patients with febrile convulsion, from as soon as possible after the event and this is what this group are trying to do. They recently published the early MRI data showing that the hippocampus appears large with prolonged T2 relaxation time, if studied within 48 hours of prolonged FC and from 2-5 days the relaxation time returns to normal but the hippocampus still appears large. In the current study, they repeated the scans in 14 patients, 4-8 months after prolonged febrile convulsion. At this stage, hippocampi were smaller than on the previous scans but no different from age-matched controls. Although there was no increase in asymmetry in patients compared to controls, there was an increase in the asymmetry of the hippocampi on the second scan compared to the acute scans after prolonged FC. One child in this cohort has developed non-febrile seizures and developmental delay but this child did not have MTS. The authors point out that it may be that there was hippocampal asymmetry prior to the first scans, which was obscured by the swelling seen early on but re-manifest as the swelling settled.

So what does all this mean? It seems clear that prolonged FC commonly affect the hippocampi in humans. How this translates into later pathology or seizure susceptibility is unclear. This cohort needs to be followed with repeat imaging over the years and even then I fear it may be too small to answer the question as the prognosis of prolonged FC is that about 7% will develop temporal lobe epilepsy; only one out of a cohort of 14. One patient had asymmetric hippocampi right from the word go. Will they be the one or will the

asymmetry progressively increase in the others with the development of seizures? I await further data with interest. *-MRAM*

*Hippocampal abnormalities after prolonged febrile convulsions: a longitudinal MRI study.*

Scott RC, King MD, Gadian DG, Neville BGR, Connelly A.  
BRAIN

2003;126:2551-57

## Cannabis in multiple sclerosis

☆☆☆ RECOMMENDED

For patients with MS, their carers and a growing element in the media the use of cannabis is clearly a very emotive subject. So the CAMS study (Cannabis in Multiple Sclerosis) comes at a time when debate about its use and legal status needs to move into the informed arena of objective evidence based medicine. The CAMS study was a multicentre placebo controlled study involving 630 patients randomised to either receive oral cannabis extract or D9-tetrahydrocannabinol. Placebo was also given, but because the two active ingredients could not be formulated to look the same, there were two placebo arms. The trial lasted 15 weeks. The primary outcome measure was the effect on spasticity using an objective measure of spasticity (Ashworth Scale) which showed no significant difference between the groups. However from the patients' point of view there was a subjective improvement in both pain and spasticity scores as result of the cannabinoid ingestion. Although many steps were taken to blind the participants to which treatment was being administered it was obvious to some patients and neurologists which treatment they were receiving thus reducing the significance of the self reported beneficial effects of cannabis. Side effects were as predicted for using cannabis or patients with MS.

Several conclusions might be drawn (and have been in the media): that cannabis does not help spasticity, that the Ashworth scale is too insensitive to show a real treatment difference, that oral administration makes cannabis less bioactive than smoking, or that cannabis is helpful to people with multiple sclerosis but not in spasticity. Two further studies allied to the CAMS study assessing the effect of cannabis on urinary tract symptoms (CAMS-LUTS) and psychology (CAMS-PEC) are eagerly awaited and will certainly further inform the debate on the use of cannabis in general and specifically for certain aspect of the MS symptom complex. *-TH*

Zajicek, J; Fox, P; Sanders, H; Wright, D; Vickery, J; Nunn, A; Thompson, A, on behalf of the UK MS Research Group

*Cannabinoids for the treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial.*

LANCET  
2003; 362:1517-26

## Ximelagatran: the new warfarin?

☆☆☆ RECOMMENDED

Imagine a drug which has a predictable pharmacokinetic profile, is unaffected by age, sex, bodyweight or ethnic origin, is stable over time, has a low potential for drug or food interaction, is rapid in its onset of action and is not metabolised by hepatic P450, does not require drug monitoring and is an oral anticoagulant: imagine ximelagatran.

The arrival of the thrombin inhibitor - ximelagatran - as an alternative to warfarin is being heralded by data from the SPORTIF III trial (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation). This large (n=3410) multicentre randomised open labelled, parallel group trial directly compared ximelagatran with the well known and trusted anticoagulant, warfarin (INR 2.0-3.0) for patients with atrial fibrillation with one or more risk factors for stroke.

There was no significant difference between the groups in terms of primary events (stroke or systemic embolism). Furthermore disabling or fatal strokes, mortality and major bleeding similarly were observed at similar rates in the two treatment groups. However a significant advantage in terms of combined major and minor haemorrhages was observed for the ximelagatran group. An elevation in serum alanine aminotransferase was more common with ximelagatran - the significance of which may only become evident further down the development pathway of this promising alternative to warfarin. (Data from SPORTIF V, a similar study is yet to be published.)

The new drug is therefore as effective as the old warhorse warfarin and has the distinct advantage of not requiring blood monitoring but -presumably- will cost much more than £13 a year for warfarin treatment. Oh dear, another one for NICE. *-TH*

*Executive steering Committee on behalf of the SPORTIF III Investigators*

*Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial.*

LANCET  
2003; 362:1691-98

## HUNTINGTON'S DISEASE

### Funny sensations in Huntington's disease

Research in neurophysiology often involves the application of a single test pulse or cue (electrical, magnetic, auditory or visual) to a neurological structure and measuring a response (electrical or magnetic), usually in terms of amplitude and latency. Increasing the pulse strength allows further exploration of a target population of neurons. To dig deeper, two pulses are given. The first pulse is much smaller than the second, often subthreshold, so only a small response or no response is initially seen. This would be a pointless exercise if the response amplitude following the second standard pulse were the same from that obtained by applying a single pulse. However, depending on the timing of the first pulse, the second pulse response will often increase or decrease, implying that the target population have been conditioned. To achieve this change either inhibitory or facilitatory pathways have been brought into the equation. This principle is applied in a host of experimental paradigms.

Munoz *et al* have used this method to explore facial chorea movements (FCM) in patient's with Huntington's disease (HD); the hypothesis being that sensory processing in HD is impaired which may as a consequence impair motor reflexes.

Genetically proven HD patients with and without FCM were compared with age matched controls. Spontaneous blink rates were measured, these varied between excessively high or low, and did not correlate with the presence of FCM, indicating the heterogenous nature of HD. Blink reflexes, measuring EMG twitches in orbicularis oculi, were performed in response to both auditory and electrical stimulation (supraorbital nerve) and included dual pulse studies. The inhibitory effect, utilising a conditioning pulse, that is normally seen, was clearly lacking in HD subjects. This was observed with both auditory and electrical stimuli in all HD patients. Patients with FCM had statistically significant greater disinhibition compared with patients without FCM. Therefore FCM in HD may well be an expression of a disturbance of motor control secondary to abnormal sensory processing. This abnormality may relate to delay of sensory information processing at the brainstem level. Perhaps therapeutic procedures should be attempted to resynchronise the sensory and motor pathways. -JR

*Neurophysiology study of facial chorea in patients with Huntington's disease.*

Munoz E, Cervera A, and Valls-Sole J.  
CLINICAL NEUROPHYSIOLOGY  
2003; 7;1246-1252

### New treatment trials in Huntington's disease - attacking the histones

The development of transgenic models of Huntington's disease has led to a better understanding of the pathogenic pathways and with this the development of novel therapies. Of late the experimental emphasis has been on histone deacetylase inhibitors, which modulate transcription. The first major paper reporting this approach in mammals appeared in PNAS in February from the group of Gill Bates. In this study seberoynilide hydroxamic acid (SAHA) was administered to the R6/2 transgenic mouse model of HD from 4 weeks of age until death and was shown to cross the blood-brain barrier and increases histone acetylation. In addition the drug appeared to mediate some behavioural effects in terms of latency to fall off the rotorod, although many other measures did not improve and that included brain pathology and inclusion formation.

A new study employing a similar approach has now just appeared in the Journal of Neuroscience by Bob Ferrantes' group. In this study the same transgenic strain of mouse was used but instead of SAHA, sodium butyrate was given intraperitoneally. This compound is known to alter transcription and it led to improved body weight and motor performance in a dose-dependent fashion, as well as life expectancy. In addition, the drug delayed the neuropathological abnormalities using a number of different parameters such as brain weight loss, ventricular dilatation and striatal atrophy although did not reduce huntingtin associated aggregates. The drug also appeared to protect against 3-NP toxicity (a specific striatal toxin). Furthermore this study also showed that the drug did affect acetylation without affecting the expression of mutant huntingtin but did affect a range of other gene products using microarrays.

This is therefore an impressive study, which has clearly shown that this approach could impact on the clinic, as there is evidence that the drug works both at the behavioural and pathological level. However whether this turns

out to be the case is unknown, as other claims of drug efficacy have not been sustained over time (e.g. minocycline - cf. Chen M *et al* (2000) Nature Medicine 6:797-801 versus Smith DL *et al* 2003 Ann.Neurol. 54:186-196 versus Bonelli RM *et al* 2003 Neurology 60:883-884) -RAB

Hockly E, Richon VM, Woodman B, Smith DL, Zhou X, Rosa E, Sathasivam K, Ghazi-Noori S, Mahal A, Lowden PA, Steffan JS, Marsh JL, Thompson LM, Lewis CM, Marks PA, Bates GP.

*Seberoynilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease.*

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES  
2003 100:2041-2046

Ferrante RJ, Kubilus JK, Lee J, Ryu H, Beesen A, Zucker B, Smith K, Kowall NW, Ratan RR, Luthi-Carter R, Hersch SM.

*Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice.*

JOURNAL OF NEUROSCIENCE  
2003 23:9418-9427

## ☆☆☆ RECOMMENDED

### Are Huntingtin fragments toxic?

There is some controversy as to whether N-terminal fragments of mutant huntingtin are toxic and contribute to the neuropathology of Huntington's disease. Previously, it had been shown that an abnormal phenotype (at 5 weeks) was demonstrated in knock-in mice before the pathological appearance of N-terminal fragments, and this was used as an argument against these fragments contributing to the disease process.

This paper shows that some antibodies do not label fragments in brain sections although they do on Western blots. Therefore in the aforementioned studies the fragments may have been present in the young brains prior to symptoms but, say due to conformational changes, they were not labelled. That these fragments appear before symptoms and could be contributing to neuropathology, has important implications for other mouse models, which have been subject to some criticism, namely the R6/2 mouse. This is a transgenic model, which expresses only the mutant N-terminal (in contrast to, say, the knock-in which expresses the whole length of the mutant protein).

The authors show that poly-Q (poly-glutamate, translated from CAG repeats) N-terminal fragments increase with age but are present from two weeks, i.e. before the mice display an abnormal phenotype.

Several lines of evidence, some more circumstantial than others, demonstrate that these fragments are toxic:

N-terminal fragments contain poly-Q

The accumulation of fragments correlates with disease progression

The fragments accumulate in the nucleus (unlike full length mutant huntingtin). Nuclear fractions of brain homogenates contained almost exclusively small fragments, and it was suggested that these are translocated to the nucleus where they interfere with transcription.

The accumulation of fragments in cells transfected with expanded polyglutamine tracts correlates with vulnerability to oxidative toxins

The toxicity of fragments has been demonstrated previously in transgenic mouse models

The ubiquitin-proteasome complex is responsible for degrading aberrant proteins including small poly-Q fragments. The authors demonstrated that proteasome activity decreases with age in both transfected human embryonic kidney cells, and knock in mice, and propose that this decline in proteasome function results in accumulation of toxic fragments and this is the basis for age related neurodegeneration. Experimental inhibition of proteasome function increases the amount of fragments in transfected cells, in vitro synthesised huntingtin and knock-in mice. Interestingly, after inhibition of proteasome function, 23Q transfected cells (a non-toxic length) did produce small fragments (non-toxic because not poly-Q). So, presumably, another degradation system was being employed. In contrast, in 120Q cells, toxic proteins of large molecular mass were produced (representing oligomers, or possibly conjugation). Of note, there was no difference in proteasome function between knock-in and wild type mice.

To summarise, this was a carefully planned and executed study which furthered the evidence that N-terminal fragments are cytotoxic and may contribute to neuropathological changes. Furthermore, they demonstrated an age related decline in proteasome function, which could contribute to their accumulation in Huntington's disease and provide the basis for the delayed onset neurodegeneration. -WP

Zho H, Cao F, Wang Z, Yu Z, Nguyen H, Evans J, Li S, Li X.

*Huntingtin forms toxic NH2-terminal fragment complexes that are promoted by the age dependent decrease in proteasome activity.*

THE JOURNAL OF CELL BIOLOGY  
2003; 163 (1); 109-118