

## EDITOR'S CHOICE

**Adult neural precursor cells and brain repair**

The role and capabilities of the endogenous adult neural precursor cells have been debated in recent years but a number of papers in the last couple of months are starting to provide clear answers. Two papers have now clearly shown that adult neural precursor cells (npc) in the rat brain can respond to ischaemic lesions involving the striatum and hippocampus. Arvidsson and colleagues in Lund in a paper in *Nature Medicine* have shown that middle cerebral occlusion induces npc migration into the striatum (although interestingly not the overlying cortex) where they differentiate into the appropriate neuronal phenotype. However, it is not clear how successful such a reparative response is, in terms of the number of neurons generated and whether this is sufficient to alter behaviour.

The second paper is in *Cell* by Nakatomi *et al* and is a real tour de force, demonstrating that adult npc can lead to the regeneration of hippocampal pyramidal cells after an ischaemic insult (although other neurons were seen at other sites). These authors demonstrate that the cells can migrate to the hippocampus where they differentiate into the new neurons as evidenced by morphology, connectivity and neurophysiologically and that this has a functional consequence to the animal. Furthermore manipulation of the system using neurotrophic factors and anti-mitotic agents influences this response. This paper therefore demonstrates the capacity of adult npc to respond to ischaemic insults using a range of different methods and approaches and thus sets a new standard for such studies as well as offering hope for the future as a therapeutic approach.

Finally a paper by Theo Palmer *et al* has shown that neuro-

genesis can be adversely affected by cranial irradiation, probably by altering the environment in which the npc finds itself. This in turn may have consequences for understanding the sequelae of childhood irradiation and systemic chemotherapy in terms of cognitive deficits - a point that at the present time remains conjectural and unproven.

Therefore it is becoming clear that adult npc can respond to some injuries and mediate repair and that preventing their normal turnover may have significant consequences, although the extent to which this applies to man and the range of insults that the adult CNS is subject to remains to be discovered. - **RAB Arvidsson A, Collin T, Kirik D, Lindvall O.**

**Neuronal replacement from endogenous precursors in the adult brain after stroke.**

**NATURE MEDICINE**  
8:963-970.

**Nakatomi H, Kuriu T, Okabe S *et al*.**

**Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors.**

**CELL**  
2002 110:429-441.

**Monje ML, Mizumatsu S, Fike JR, Palmer TD.**

**Irradiation induces neural precursor-cell dysfunction.**

**NATURE MEDICINE**  
2002 Sep;8(9):955-62.

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## NEUROTOXINS

**Nanging and Neurology**

A case report from New Zealand provides an additional cause for sub acute combined degeneration of the spinal cord. This condition arises as a result of vitamin B12 deficiency, which leads to deficient production of myelin phospholipids. The dorsal columns bear the brunt of the insult but other components of the spinal cord and peripheral nerves are also involved leading to myelopathy, peripheral axonal neuropathy, with parasthesiae, gait ataxia, sphincter disturbance and pyramidal weakness. Cognition and levels of anxiety may also be affected. These were the features that the subject of this case report presented with. The eventual cause of the Vitamin B12 deficiency in this 37-year-old man, after other possible causes were excluded, was excessive inhalation of nitrous oxide. Replacement treatment with parental vitamin B12 produced resolution of the symptoms.

What is interesting with this case report is the insight into nitrous oxide inhalation, which is the commonest inhaled agent of abuse. A common source of the nitrous oxide is capsules used to produce whipped cream, which are readily available from supermarkets and hardware stores. The sound distortions produced after inhaling nitrous oxide are referred to as "nanging". The cobalt atom in vitamin B12 is irreversibly oxidised by nitrous oxide effectively producing a Vitamin B12 deficiency. -**TH**

**Ng J, and Frith R.**

**Nanging.**

**LANCET**  
2002; 360:384

## ALZHEIMER'S DISEASE

## ☆☆☆ RECOMMENDED

**IVIg for Alzheimer's disease?**

Intravenous immunoglobulin (IVIg) is used in the treatment of several neurological disorders presumed to have immune-mediated pathogenesis. This paper suggests that Alzheimer's disease (AD)

might join the list. Previous studies by these authors have shown that human serum and CSF contains IgG antibodies directed against the amyloid  $\beta$ -peptide (A $\beta$  which accumulates in plaques in AD brain. The role of such antibodies is uncertain, but they may contribute to immune-mediated clearance of A $\beta$ , which is itself a normal constituent of CSF with possible physiological roles. AD patients have lower levels of anti-A $\beta$  antibodies compared to controls.

In the current study, a specific ELISA was used to show that antibodies recognising A $\beta$  were present in two commercially available IVIg preparations. Patients (n = 7) who received IVIg for a variety of neurological indications (MS, peripheral neuropathy, LEMS, dermatomyositis) were shown to have reduced CSF total A $\beta$  and A $\beta_{42}$  and increased CSF anti-A $\beta$  antibodies after treatment as compared to baseline. Serum total A $\beta$  and anti-A $\beta$  antibodies both increased, with a non-significant trend toward increased serum A $\beta_{42}$ , after treatment, suggesting the possibility of increased antibody-mediated clearance of A $\beta$  from CSF to serum.

Although very preliminary, these findings do tally with observations in AD transgenic mice, where anti-A $\beta$  antibodies given passively or following immunisation with A $\beta$  have been shown to reduce A $\beta$  deposition and prevent decline in some aspects of (mouse) cognitive function. Whether such a therapeutic approach will translate to the clinical arena remains to be seen. -AJL

**Dodel R, Hampel H, Depboylu C et al.**

**Human antibodies against amyloid  $\beta$ -peptide: a potential treatment for Alzheimer's disease.**

**ANNALS OF NEUROLOGY**  
2002;52(2):253-256

## STUTTERING

### Persistent stuttering: a neuro-anatomical explanation

Up to 5% of all children suffer from stuttering but the vast majority of these cases resolve spontaneously. In the 1% of people suffering from stuttering that does not spontaneously remit during puberty very little has been known about the anatomy of this disorder. Diffusion tensor imaging (DTI), a MRI technique, uses the diffusion properties of water to determine the orientation of white matter tracts. Using powerful analysis techniques associated with DTI such as fractional anisotropy of diffusion and voxel based morphometry white matter tract myelination abnormalities have been detected in patients with multiple sclerosis. So using DTI, this current study tried to define the anatomical pathology of persistent stuttering. DTI of 15 patients with persistent stuttering was compared with images of 15 normal controls. Of all the participants only one patient in the stuttering group was left-handed. A significant difference between the two groups was observed in the area immediately below the laryngeal and tongue representation in the left sensorimotor cortex. This area has fibre tracts, which connect the premotor cortex (planning motor aspects of speech) with the sensorimotor representation of the oropharynx (articulation). Therefore the authors suggest that the normal temporal pattern of activation from the premotor to the motor cortex is disrupted. Previous PET studies on persistent stutterers have demonstrated an overactivation in the right hemisphere. In this study no structural abnormalities in the right hemisphere were demonstrated therefore allowing the authors to further speculate that this activation is not a cause of the stuttering but rather compensation for the structural damage in the left hemisphere. Such compensation has been demonstrated in aphasia. -TH

**Sommer M, Koch M, Paulus W, Weiller C, Buchel C.**

**Disconnection Of Speech-Relevant Brain Areas In Persistent Developmental Stuttering.**

**LANCET**  
2002;360: 380-83

## EPILEPSY

### ☆☆☆ RECOMMENDED

### Hairy stories about antiepileptic drugs in pregnancy

If doctors are worried about the teratogenic effects of anti-epileptic drugs, it is nothing to what patients feel. It has long been suspected that women becoming pregnant stop medication and that this is a major cause of loss of control of epilepsy during pregnancy. This is no trivial issue since in the last confidential enquiry into maternal deaths, epilepsy was the second commonest cause (19 of 134 deaths).

Hair from the vertex grows at 1 cm per month. Drugs are sequestered into hair from the circulation and leech out from the hair in a linear and predictable fashion over time. In this study Williams *et al* took (cut not pulled) samples of hair from the vertex of 26 pregnant and 13 control patients. They cut them into 1 cm segments, corresponding to months of gestation and analysed them for lamotrigine and carbamazepine. They saw three patterns. First normal, minor fluctuations in drug levels. Second major variability suggesting fluctuating compliance and third withdrawal pattern in which levels declined as pregnancy progressed. Self-discontinuation affected 15% but was not generally associated with withdrawal seizures or deteriorating control. Patients usually denied altering intake.

There is a bitter irony in this study that discontinuation after the patient realises they are pregnant will not prevent the more major malformations from occurring, although more minor developmental and cognitive consequences of these drugs remain open to question. In one tragic case, a woman suffered a sudden unexplained death in epilepsy (SUDEP) during pregnancy. Analysis of her hair, including at post mortem revealed that she had been taking her medication consistently; further evidence that SUDEP is generally not due to poor compliance. -MM

**J Williams, V Myson, S Steward, G Jones, JF Wilson, MP Kerr, PEM Smith.**

**Self-discontinuation of antiepileptic medication in pregnancy: detection by hair analysis.**

**EPILEPSIA**  
2002;43:824-31

## PARKINSON'S DISEASE

### A novel approach to treating parkinson's disease

A fascinating and provocative paper in Science uses a gene therapy approach to change the phenotype of neurons in the subthalamic nucleus and by so doing not only ameliorate features of PD in the animal model but appears to convey neuroprotection. In this study Luo *et al* injected adeno-associated viral vectors containing the gene for glutamic acid decarboxylase (GAD), the enzyme involved in the synthesis of GABA, into the subthalamic nucleus (STN) of rats. This was not associated with any host immune response several months after injection when the gene was still present, but was associated with a successful switch in phenotype of the STN neurons from glutamergic to GABAergic. This structure is the major nucleus driving the outflow of the basal ganglia (see ACNR 2.4., pp9-10) and in Parkinson's disease (PD) the STN is thought to be overactive which explains the beneficial effects of deep brain stimulators and lesioning of this nucleus in advanced cases of this condition. Thus by changing the output from this nucleus from an excitation to inhibition, one would expect a benefit in terms of the signs of experimental PD - and this is indeed the case. So far so good, but this study has made one other observation and that is, that this change in phenotype actually protects nigral dopaminergic neurons from toxic damage with 6-OHDA - something that is not seen in cases where the STN is actually destroyed. In other words an inhibitory input from the STN to the substantia nigra protects cells, whilst an input - or if

you like, the lack of an excitatory input is without effect, suggesting that inhibition is necessary for cell rescue. This is remarkable, and although no explanation is given to account for this it is nevertheless of great interest. Thus this paper takes a well researched approach using viral vectors but uses a novel target and strategy which produces unexpected results...and as such may have profound implications for how we think about neuroprotecting the parkinsonian brain -*RAB*

**Luo J, Kaplitt MG, Fitzsimons HL et al (2002)**  
*Subthalamic GAD gene therapy in a Parkinson's disease rat model.*

**SCIENCE**  
**2002 298: 425-429.**

## REHABILITATION

### Good vibrations for the treatment of unilateral neglect

Unilateral neglect hinders the rehabilitation of many people with right hemisphere brain damage. As treatment, therapists often try to encourage patients to look left and practice visual scanning tasks. However such training tends to be very task specific with gains shown only in the practiced tasks and even these improvements are only seen when patients have some awareness of their problem. Recently new treatments, which challenge the integration of vision, and other orienting systems that use proprioceptive or vestibular inputs, have reported successful results in the literature. It is thought that these treatments somehow recalibrate the ego-centric coordinate system that is responsible for the localisation of the body in space and of object position in relation to the body. One such treatment is neck muscle vibration, which perturbs both proprioceptive inputs and vestibular inputs that are important for building up representations of head position. A crossover study reported in the *Journal of Neurology, Neurosurgery and Psychiatry* by Schindler *et al.* has shown beneficial effects that generalised beyond the tasks practiced and were long lasting.

After a three week baseline 20 patients with unilateral neglect were given visual exploration training using a computer for 30 sessions. For the first 15 sessions half of the patients had their posterior neck muscles on the contralesional side stimulated with a vibrating disc while they were doing the training programme; the other half had visual exploration training only. After that the groups swapped treatments for the next 15 sessions. Perception of midline and exploration deficits in both visual and tactile modalities were tested. In addition patients were assessed on a reading task and their carers were given a questionnaire to rate the incidence of everyday problems relating to neglect. Reduction in symptoms of neglect was achieved in both the trained visual and untrained tactile exploration mode after training combined with neck vibration. Reading performance improved and the incidence of everyday problems also reduced. The improvement was still evident two months after completion of the treatment. In contrast visual exploration training alone resulted in only small benefits in visual exploration. There was no significant transfer effect to other tasks.

These results are good news especially since the treatment is easy and inexpensive to apply and does not require patients to have awareness of their condition. -*AJT*

**Schindler I, Kerkhoff G, Karnath H-O, Keller I, Goldenberg G**  
*Neck muscle vibration induces lasting recovery in spatial neglect.*

**JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY**  
**2002: 73: 412-419**

### Good Posture

Postural muscles are constantly battling against the relentless effects of gravity whenever we decide to stand upright. This balancing act has to contend with any motor action we may decide to perform, always maintaining the postural equilibrium.

Movements that threaten our stability are commonly accompanied by anticipatory changes in the activity of postural muscles and the CNS generates these patterns in a feed forward manner before the onset of the perturbation. Studies of these anticipatory postural adjustments (APAs) have been shown in healthy individuals to be affected by 3 major factors: expected magnitude and direction of the perturbation, voluntary action associated with the perturbation, and current postural state. These anticipatory and compensatory mechanisms have been shown to be impaired in patients with stroke. Slijper and colleagues have confirmed this in their recent study but have also addressed the influence of a light manual support and the effects of changing the direction of the perturbation. A heterogeneous group of stroke patients including cortical and subcortical lesions were studied against a group of age-matched controls. All patients had their stroke at least 6 months prior to the test. Subjects were required to release a weight held in the extended arm, either in front of them or to the side. Surface electrodes measured the activity of muscles in the limbs and trunk. Experiments with a light manual support, a touchpad to rest the paretic hand upon, were compared without such aids. APAs were asymmetric in the stroke group with reduced activity on the paretic side, but perhaps of more interest were the signs of ineffective modulation of APAs on the 'non-paretic' side. Support conditions did not seem to improve matters. It appears to be the case that the CNS in the patient with a hemiparesis avoids excessive use of muscles in the affected limb even when the task requires it, i.e. when subjects released the weight from the contralateral side. Successful rehabilitation needs to consider optimising these APAs, which if not corrected may in time become maladaptive, making the patient less able to cope with an ever-changing environment. -*JLR*

**Slijper H, Latsh ML, Rao N and Aruin AS.**

*Task-specific modulation of anticipatory postural adjustments in individuals with hemiparesis.*

**CLINICAL NEUROPHYSIOLOGY**

**2002: 113: 642-655**

## STROKE

### How to find the hole in the heart?

Ten to 30% of the normal population harbours a patent foramen ovale (PFO). In young (<55 yrs of age) patients with ischaemic stroke a significant proportion are "cryptogenic", ie after an adequate search no definite cause for the stroke was found. Of these up to 40-50% may have a PFO - but it is uncertain whether the PFO was relevant or not.

We now know, from a carefully-designed European prospective follow up study of patients with cryptogenic stroke, that the risk of recurrent stroke (whilst taking aspirin) with an isolated PFO is around 0.5% per annum, and that if there is an associated atrial septal aneurysm (ASA) the risk rises to about 4% per annum. As yet we do not have clinical trial evidence to guide us as to whether antiplatelet therapy, anticoagulation or endovascular closure are the best and safest ways of preventing stroke recurrence. Trials are in the process of being set up.

The historical "gold standard" for detecting PFOs has been transoesophageal echocardiography (TOE) with echocontrast and a right to left shunt may be demonstrated during the Valsalva manoeuvre. However it is often difficult for the stroke patient to perform a Valsalva when they have a TOE camera down their throat. False negative tests may thus result.

The alternative is to use transcranial Doppler (TCD) with echocontrast and monitoring for air microembolic signals in the middle cerebral artery (MCA) during Valsalva. This approach gets around the mechanical problem of Valsalva during TOE but is less specific in that there is no direct visualisation of the shunt at cardiac level. The operator must follow strict guidance on the appearance of MCA microembolic signals within 10-15 cardiac cycles. Appearance of signals beyond this time is suggestive of shunting

at another site (usually a pulmonary arteriovenous fistula).

This article is a succinct review of the pros and cons of looking for PFOs using either method. This is becoming an increasingly important consideration and given how simple the TCD method is to perform it would seem reasonable to use TCD for screening and TOE perhaps for confirmation in TCD positive cases. -*PJM*  
**Baguet JP, Besson G, Tremel F, Mangin L, Richardot C, Mallion JM.**

***Should one use Echocardiography or Contrast Transcranial Doppler Ultrasound for the detection of Patent Foramen Ovale after an Ischaemic Cerebrovascular Accident?***  
**CEREBROVASCULAR DISEASES**  
**2001;12:318-324**

### **Botox for stroke spasticity**

It stands to reason that if spasticity in the muscles of the wrist and fingers after stroke contributes to disability then local treatment with intra-muscular botulinum toxin type A (Botox) should provide improvement. But the evidence base for this is limited. In a multicenter randomised double blind placebo-controlled trial comparing once-off set of Botox injections (200-240 units) into the wrist and finger muscles with placebo involving 126 patients, this issue was addressed. Patient eligibility in this study was a stroke, at least six months prior to randomisation, resulting in increased flexor tone in the hand or finger. Baseline assessment included patient choice of the most personally relevant disability (choice of 4 possibilities: pain, personal hygiene, dressing and limb position), and investigator rating of flexor tone. At six weeks post injection 62% of patients in the Botox group reported a significant improvement in their chosen disability compared to 27% improvement in the placebo group. This observed benefit was sustained for at least 12 weeks and in an open label extension phase of this study the Botox benefit persisted with subsequent injections and lasted for up to 24 weeks in some patients. Investigator-observed spasticity also differed between the experimental groups providing evidence that the Botox was physiologically active. So with the observed decrease in spasticity, and reported improvement in ability, the working hypothesis has been shown to hold true. No adverse events were noted. Interestingly one of the patients in the Botox group who did not experience any improvement had Botox neutralising antibodies in post treatment serological analysis. Unfortunately baseline levels of the neutralising antibodies in this patient were not determined eliminating the obvious physiological explanation for the observed treatment failure. This study goes a long way to offer hope that some help to relieve disability can be offered to patients with significant spasticity of the hand after stroke. -*TH*

**Brashear, A, Gordon, M, Elovic, E, Kasscieh, D, Marciniak, C,**

**Do, M, Lee, C, Jenkins, S, Turkel, C for the Botox Post-Stroke Spasticity Study Group.**

***Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke.***  
**NEW ENGLAND JOURNAL OF MEDICINE**  
**2002; 347:395-400**

### **Sexual Intercourse and the risk of Stroke**

There has been little good science investigating whether sexual activity can cause stroke either acutely or over a long period of time. Some reports have linked haemorrhagic stroke with sexual activity, and there have been reports of increased risk of sudden death following vigorous exertion, although there is hitherto little known about the relationship between increased sexual activity and risks of ischaemic stroke.

Whether increased frequency of sexual intercourse increased or decreased risk for ischaemic stroke and coronary heart disease (CHD) was examined in this study. The Caerphilly study is an ongoing cohort study which has collected prospective information regarding multiple known and putative cardiovascular risk factors at the outset and recorded cardiovascular events over the subsequent 20 years. Men aged 45-59 were divided into 3 groups on the basis of their frequency of sexual intercourse at the start of the study. Less than once a month was described as 'low frequency'; twice or more a week was described as 'high frequency', and the remaining men were put into an 'intermediate' group. Disappointingly, rates of ischaemic stroke were slightly lower for those men engaging in less frequent sexual intercourse, although no significant pattern was seen after adjustment for age, and known cardiovascular risk factors.

Interestingly, stroke was most common among those men who did not respond to the question on sexual activity, and these men tended to be older, shorter, and had a higher level of CHD at the start of the study. In contrast however, fatal heart attacks were observed more commonly among men with infrequent sexual activity. (Data regarding haemorrhagic stroke was not described presumably due to low numbers).

Although this study cannot explore the relationship between sexual activity and the triggering of an acute stroke, it should provide some reassurance for middle aged men that sexual activity is not a strong risk factor for ischaemic stroke, and may even protect against heart attacks. -*TF*

**Ebrahim S, May M, Ben Shlomo Y, McCarron P, Frankel S, Yarnell J, Davey, Smith G.**

***Sexual intercourse and the risk of ischaemic stroke and coronary heart disease: the Caerphilly study.***  
**JOURNAL OF EPIDEMIOLOGY AND COMMUNITY HEALTH**  
**(2002) 56:99-102**

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