

EDITOR'S CHOICE

PPAR γ agonists for Alzheimer's Disease?

It is well-recognised from epidemiological studies that NSAIDs reduce the risk of developing Alzheimer's disease (AD). The mechanism of this effect is uncertain; the possibility that it is mediated via cyclo-oxygenases (COX) must be weighed against the ineffectiveness of selective COX2 inhibitors in treating established disease. Activation of the nuclear receptor peroxisome proliferation-activated receptor- γ (PPAR γ), leading to inhibition of pro-inflammatory gene expression, is another possibility, examined in this paper. APPV717I transgenic mice, which develop amyloid deposits and glia-mediated inflammatory responses typical of AD around 10 months of age, were fed with rodent chow supplemented with ibuprofen (62.5mg/kg/day) or pioglitazone (40mg/kg/day) for 7 days before sacrifice. The latter is a thiazolidinedione, a highly specific PPAR γ agonist, used in the treatment of type 2 diabetes (although it had no effect on blood glucose levels in these animals). Treated animals showed:

- reduced number of activated microglia and reactive astrocytes in brain cortex and hippocampus;
- reduced expression of proinflammatory enzymes (COX2 in microglia, iNOS in astrocytes);
- reduced expression at both mRNA and protein level of BACE1, a key enzyme in the APP processing pathway;
- reduced A β 1-42-immunopositive plaque area and staining intensity;
- reduced soluble A β 1-42 peptide (pioglitazone only).

These findings suggest that brief oral treatment with these agents acts rapidly to inhibit inflammatory responses in brain, so modulating amyloidogenesis. The authors suggest that PPAR γ agonists might be explored in the treatment of AD. Obviously, however, given the clinical experience with NSAIDs in AD, there must be misgivings about the efficacy of PPAR γ agonists in clinical practice. - *AJL*

Heneka MT, Sastre M, Dumitrescu-Ozimek L, Hanke A, Dewachter I, Kuiperi C, O'Banion K, Klockgether T, Van Leuven F, Landreth GE. Acute treatment with the PPAR γ agonist pioglitazone and ibuprofen reduces glial inflammation and A β 1-42 levels in APPV717I transgenic mice.

BRAIN

2005;128(6):1442-53.

HEAD INJURY: Roids no good

Sometimes it takes a huge effort to answer a simple question, in this case does early treatment with corticosteroids improve the outcome of head injury? The answer is no. In fact they may make things worse.... Top marks for the trial acronym, CRASH, which stands for corticosteroid randomisation after significant head injury! In this MRC trial 10,008 adults with head injury and a Glasgow Coma Scale score of 14 or less, within 8 hours of injury, were randomised to a 48-h infusion of corticosteroid (methylprednisolone) or placebo. The follow-up was impressive: at six months they had data from 9,673 (96.7%) patients. The risk of severe disability and/or death was higher in the corticosteroid groups by statistically significant, but rather small, differences. For those who like these things, the stats were: risk of death higher in the corticosteroid group (1,248 [25.7%] vs 1,075 [22.3%]; relative risk 1.15, 95% CI 1.07-1.24; p=0.0001); and the risk death or severe disability (1,828 [38.1%] vs 1,728 [36.3%] dead or severely disabled; 1.05, 0.99-1.10; p=0.079). Subgroup analysis by injury severity or time since injury did not reveal any useful differences. This is a very useful trial. I wonder if it will have any influence on the use of corticosteroids for spinal cord injury, which seems to be prevalent. Or are we going to have to randomise 10,000 people with that condition in the CRASS trial!?! - *AJC*

CRASH trial collaborators.

Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months.

LANCET

2005;365(9475):1957-9.

MOTOR NEURON DISEASE: Interfering with silencers

*** RECOMMENDED

The identification of genetic causes of neurodegenerative disorders of the CNS has led to the development of therapeutic approaches which attempt to silence the disease causing gene product. This has perhaps been most studied using small interfering RNA (siRNA), that promote specific endonucleolytic cleavage of the mRNA targets of the mutant gene/protein. Adopting this strategy has proven successful in vitro, although it has proved difficult to completely silence the relevant element. Nevertheless the problem in vivo is even more problematic, in that there are issues of delivery – how do you get siRNA into all relevant cells with long term silencing? One approach around this has been to use viral vectors, which have a long history in the experimental delivery of therapeutic agents (especially growth factors) for CNS disorders. The favoured viral vector has changed over time, but of late much interest has focused on lentiviruses, because of the efficiency with which these viruses can infect neural cells. In this paper, Patrick Aebischer and colleagues explore this approach in vitro and then in vivo with the SOD1^{G93A} transgenic mouse model of familial motor neuron disease/amyotrophic lateral sclerosis (ALS). Mutations in Cu/Zn superoxide dismutase (SOD) have been known for over 10 years to cause rare familial forms of ALS, through a proposed toxic gain of function. Transgenic mice containing the mutant form of this gene develop a progressive ALS like illness over about a 6 month period. Using these mice, Aebischer et al show that intraspinal lumbar injection of a lentiviral delivery system for siRNA to SOD1, slows down the onset of disease and its progression in hindlimb muscles and related behaviours. This is an exciting study and comes hot on the heels of a study last year using a similar approach with transgenic SCA mice (see Caplan NJ (2004) Nature Medicine 10:775-776), which gives weight to the validity of this approach. There are though still a number of unresolved issues, including the most appropriate target of the siRNA as many neurogenetic diseases have multiple causative mutations. In addition, issues of delivery are still very real. In this study only lumbar regions were injected, although in the case of ALS one could argue for targeted delivery as there are clearly some motorneural pools that are more important than others (such as those innervating the bulbar/respiratory musculature). Nevertheless this work once more shows how far we have come in the treatment of neurological disorders through studies of rare genetic causes of common neurodegenerative diseases of the CNS - *RAB*.

Raoul C, Abbas-Terki T, Bensadoun JC, Guillot S, Haase G, Szulc J, Henderson CE, Aebischer P.

Lentiviral-mediated silencing of SOD1 through RNA interference retards disease onset and progression in a mouse model of ALS.

NATURE MEDICINE

2005;11:423-8.

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
Alasdair Coles	Lecturer, Cambridge University
Rhys Davis	Research Registrar, Addenbrooke's Hospital, Cambridge
Dan Healy	Neurology SPR, National Hospital, Queens Square, London
David Lythgoe	Centre for neuroimaging sciences, Institute of Psychiatry, London
Mark Manford	Consultant Neurologist, Addenbrooke's Hospital, Cambridge, and Bedford Hospital
Andrew Michell	Neurology Research Registrar, Addenbrooke's Hospital, Cambridge
Wendy Phillips	Research Registrar, Addenbrooke's Hospital, Cambridge
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
Ailie Turton	Research Fellow, Burden Neurological Institute, Bristol

Would you like to join ACNR's reviewer's panel and submit reviews to our popular journal reviews section?

For more information,
Email Rachael@acnr.co.uk or telephone 0131 477 2335.

THE TEMPORAL LOBE: Musical Offering

This paper in *Brain* takes as its topic the basis of scary music. This is an interesting topic as all film goers will testify...after all if you watch the predatory giant shark in *Jaws* about to attack without the music (as was once shown on Nationwide several decades ago!!), then the dramatic impact is greatly diminished. So how does music do this - where in the brain could music mediate such an effect? One obvious target would be the amygdala, given its close association with fearful stimuli - both experimentally in animals and in the clinic. In this study, 16 right handed patients with either a right OR left medial temporal lobectomy were studied using an emotional recognition task involving instrumental music. The patients had all had surgery for intractable temporal lobe epilepsy, of non-tumour origin. This music was categorised into fearful, peaceful, happy or sad and the subjects had to score these emotional impressions out of 10 - similar in many ways to the facial grading tests of emotion. Each subject was tested with 56 stimuli and careful attention was paid to ensure that any deficits were specific for the emotional content of the music. Interestingly, the study showed a relatively selective deficit in the recognition of scary music, with the other musical emotions being unaffected, irrespective of whether the patient had had a right or left temporal lobe resection. The authors therefore conclude that "These findings suggest that the anteromedial temporal lobe (including the amygdala) plays a role in the recognition of danger in a musical context". Although no evidence can be provided that the amygdala really is the source of this aspect of musical emotional processing, it would nevertheless seem the most likely candidate given its known role in the processing of fearful stimuli through other sensory modalities. Thus once more emphasising that structures involved in these forms of high level sensory processing, do so for a specific emotion but independently of the exact mode of sensory stimulation...Now who has turned the sound down on my television and what is all the fuss about that man stabbing at the shower curtain. - **RAB**

Gosselin N, Peretz I, Noulhiane M, Hasboun D, Beckett C, Baulac M, Samson S.

Impaired recognition of scary music following unilateral temporal lobe resection.

BRAIN

2005;128: 628-640.

AMYGDALA: Look into my eyes... and be fearful

*** RECOMMENDED

SM, a 38-year-old woman, has selective lesions of the amygdala bilaterally. She had previously been shown to lack normal fear responses and her interpersonal conduct is indiscriminately trusting and friendly. The experimental paradigm here consisted of a remarkable 3000 presentations of faces expressing either happiness or fear. However, only a small area (a random 'bubble') of any face was visible at each presentation, the remainder being obscured. In comparison with controls, SM required more bubbles to identify facial expressions reliably. Regression analysis of bubble locations contributing to fear recognition showed, in controls, the eye region to be most critical. By contrast, only bubbles around the mouth region seemed to influence SM's responses. Gaze monitoring, furthermore, found that SM consistently failed to fixate on the eyes of presented faces. Curiously, on the control task of deciding the sex of presented faces, not only did SM perform within the normal range but her visual scanning of the presented images was also normal. The implication is that perception links into emotional processes and ordinary object recognition in different ways. Most strikingly, when SM was instructed specifically to look at the eyes of the presented faces she attained normal fear recognition. This elegant case study therefore suggests that the amygdala engages in emotion recognition by influencing visual fixation and perception. The theory is both novel and intuitively plausible, given the proximity of the amygdala to multimodal sensory association cortices in the anterior temporal lobe and the increasing appreciation that perceptual processes merge seamlessly with other neural functions as disparate as memory and movement. Although the single instruction to SM that she should 'look at the eyes' failed to resolve permanently her impaired emotion recognition, the possibility is raised of rehabilitating patients with similar behavioural problems. As well as occasional patients with focal lesions, this might include patients with neurodegenerative disease and those with autistic-spectrum disorders. - **RD**

Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR.

A mechanism for impaired fear recognition after amygdala damage.

NATURE

2005;433(7021):68-72.

NEURODEGENERATION: antibiotics are the answer

Unlocking the full potential of existing pharmaceutical agents, given the enormous expense of developing new compounds, seems an ever more attractive proposition. Such endeavors encompass drugs for which years of investment and favourable initial safety studies ended with disappointing efficacy trials, as well as drugs listed in current formularies perhaps with unsuspected virtues. This paper describes a series of experiments whereby beta-lactam antibiotics show promise in the context of glutamate excitotoxicity, a pathogenetic mechanism implicated in several neurological diseases, including motor neuron disease. The foundation of the study was a screen of over 1000 currently licensed drugs that involved immunoblotting GLT1 (the receptor responsible for glutamate reuptake) on rat spinal cord slices exposed to one of the myriad drugs. Beta-lactam agents as a group were found to increase expression of GLT1 and this led to further experiments focusing specifically on ceftriaxone. In doses similar to those achieved during treatment of infectious diseases, ceftriaxone activated the human GLT1 promoter in cell culture and, in vivo, induced long-lasting increases in rat brain GLT1 expression. Neuroprotective properties were shown both in cultured neurons and in neural tissue preparations. Crucially, administration of ceftriaxone in a mouse model of motor neuron disease delayed the onset of clinical signs and prolonged survival. The initiative of Rothstein and colleagues is especially welcome given the various factors that conspire to limit pharmaceutical investment in neurodegenerative diseases generally. It is to be hoped that their specific findings will be substantiated by further work. - **RD**

Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Dykes Hoberg M, Vidensky S, Chung DS, Toan SV, Brijini LI, Su ZZ, Gupta P, Fisher PB.

Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression.

NATURE

2005;433(7021):73-7.

DEMENTIA: Painkillers kill neurons

*** RECOMMENDED

Traditional pain medication has been associated with protection from Alzheimer's disease. However, a recent study by Kukar and colleagues, published in *Nature Medicine*, suggests that non-steroidal anti-inflammatory drugs (NSAIDs) may in fact be detrimental to Alzheimer's disease. Several lines of evidence have indicated that NSAIDs would be useful in treating Alzheimer's disease. First, epidemiological studies suggest that long-term NSAID therapy reduces the risk of developing Alzheimer's disease. Second, inflammatory processes are activated in Alzheimer's disease. Third, Kukar has previously shown that NSAIDs are able to lower A β 42 production. A β 42 is a neurotoxic peptide that readily aggregates into fibrils and deposits as plaques in Alzheimer's disease brain. It is believed to be the initiating molecule in the pathogenesis of Alzheimer's disease. The initial aim of this cell-based screen was to identify NSAID-like compounds that reduced A β 42 production but had little effect on the COX enzymes. COX enzymes are the targets of NSAIDs, which convert arachidonic acid to prostaglandin H₂ in the first step of prostanoid production. There are two classes, COX-1, which is constitutively expressed and COX-2, which is expressed only during inflammation and is responsible for the production of pro-inflammatory prostanoids. Due to its constitutive expression, inhibitors of the COX-1 enzyme are associated with detrimental side-effects. The results of Kukar's screen of hundreds of NSAIDs and their analogues were both surprising and disappointing. Just a single compound was identified that lowered A β 42 production and lacked COX activity. Numerous compounds, principally the COX-2 selective NSAIDs, were found to promote A β 42 production in vitro and in vivo. Three-day oral treatment of mice with the COX-2 inhibitor, celecoxib, raised A β 42 production 2-fold. Alzheimer's disease-causing mutations in presenilin-1 and presenilin-2 and in amyloid precursor protein (APP) only increase A β 42 production by 30-100%. Despite the curious association between COX-2 selectivity of NSAIDs and propensity for A β 42-raising, the effect was independent of COX-2 binding. Like the A β 42-lowering NSAIDs, these compounds were shown to target the γ -secretase complex, which cleaves APP to generate A β 42. It is proposed that these compounds alter APP cleavage via allosteric modulation of the enzyme complex. The authors are wary of extrapolating their findings to humans because the concentrations of the A β 42-raising compounds in vitro were higher than those found in humans. The concentrations in mice were more similar to those found in humans but pharmacokinetic differences between the species must be taken into account. The main implication of the study is that exogenous com-

pounds or even alterations of endogenous isoprenoids could increase A β 42 production and in this way represent a novel risk factor for Alzheimer's disease development. Greater understanding of the mode of action of these γ -secretase modulators may aid in the design of new inhibitors of A β 42 production and improve Alzheimer's disease therapy. It still remains unclear if the beneficial effects of NSAIDs on inflammation in Alzheimer's disease outweigh the harmful effects. - *LMS & SJT*

Kukar T, Murphy MP, Eriksen JL, Sagi SA, Weggen S, Smith TE, Ladd T, Khan MA, Kache R, Beard J, Dodson M, Merit S, Ozols VV, Anastasiadis, Das P, Fauq A, Koo EH, Golde TE.

Diverse compounds mimic Alzheimer disease-causing mutations by augmenting A β 42 production.

NATURE MEDICINE

2005;11(5):545-50.

PAIN: rTMS can provide long lasting relief from neuropathic pain

Electrical stimulation of motor cortex using surgically implanted electrodes provides pain relief for some but not all people with medication resistant neurogenic pain. The implantation surgery is expensive and there has been no way of determining which patients could benefit from the treatment. Recently a non-invasive method of cortical stimulation using rapid rate Transcranial Magnetic stimulation (rTMS) has been shown to provide transient pain relief in some patients suffering from neurogenic pain. Now a paper in JNNP reports that a course of rTMS over five days can result in prolonged and significant pain relief. This raises the possibility that response to treatment with rTMS could be a useful and inexpensive predictor of the effectiveness of direct motor cortex stimulation. In a randomised controlled trial of 48 patients Khedr et al compared rTMS treatment with sham rTMS. Twenty-four of the patients had trigeminal neuralgia and 24 had post stroke pain mostly affecting face upper limb and trunk. Fourteen patients with each diagnosis were treated with 10 minutes of real TMS over the hand area of motor cortex (20 Hz, 10 x 10s trains with stimulator intensity at 80% of motor threshold). The stimulation was given every day for five consecutive days. The control group received sham stimulation of the same duration. Pain was assessed with the Leeds Assessment of Neuropathic Symptoms and Signs and by Visual Analogue Scale. Compared with the sham treated group, the group treated with real rTMS showed a statistically significant and clinically meaningful reduction in pain. The effect appeared to be cumulative over the first four days and lasted at least until the final assessment at two weeks after the last treatment session. Distributions of rating scores among the patients showed that not all patients with either diagnosis responded to the real rTMS. In addition to the promise of rTMS as a predictor of which patients might benefit from implanted electrodes, the results of this study show that stimulating over the hand area of motor cortex can reduce pain in the face as well as the upper limb; presumably because of spread of the effects to adjacent cortical representations. Since it is easy to determine the stimulation intensity needed from the motor threshold of small hand muscles, this means that in future patients on the waiting list for motor cortex implanted electrodes and those who do not want to undergo surgery could be offered courses of rTMS in the clinic. - *AJT*

Khedr EM, Kotb H, Kamel NE, Ahmed MA, Sadek R, Rothwell JC.

Long lasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain.

JOURNAL NEUROLOGY, NEUROSURGERY & PSYCHIATRY

2005;76:833-8.

MULTIPLE SCLEROSIS: Bad things may happen when rescuers are turned back at the gates

*** RECOMMENDED

So, at last, we have some published data on the much-discussed complication of progressive multifocal leucoencephalopathy (PML) with the new drug, natalizumab (Antegren or Tysabri). Amazingly, and surely wrongly, this drug was licensed as a treatment for relapsing remitting MS on the basis of an interim analysis of two phase III trials, which have yet to be published: AFFIRM (natalizumab alone) and SENTINEL (natalizumab in combination with interferon-beta-1a). Natalizumab is a monoclonal antibody that binds to the α 4-integrins on lymphocytes and prevents their entry to gut and brain. Press releases from the manufacturers of natalizumab, Biogen, had claimed that, in the recent two-year results from the AFFIRM trial, natalizumab reduced relapse rate by 67% and reduced progression of disability by 42% compared to placebo over two years. These results represent a very

significant improvement on the currently available disease modifying therapies for multiple sclerosis, which offer at best a third reduction in relapse rate.

However, in early March 2005, Biogen stopped distributing natalizumab. A fatal case of PML was diagnosed in a patient treated with the drug in combination with interferon-beta-1a. The pathology of this case has now been published. After three years of seemingly characteristic (if oligoclonal band negative) multiple sclerosis, and two years' treatment with interferon-beta-1a, she was entered into the SENTINEL study. Thirty months later she had developed new neurology, including a "decreased fund of information" (how ever did that nonsense get past the editors?) Three months later she was dead, after a clinical typical course for PML. For some reason, a MRI scan done seven months before the first PML symptoms was "not available" and the report was insufficiently clear to tell if there were pre-symptomatic PML lesions. The pathology of her case is scary: nearly every tissue section from both cerebral hemispheres had either macroscopic or microscopic PML lesions!

The second multiple sclerosis patient is the most instructive. He developed the first symptoms of PML 25 months after starting natalizumab. But, actually, a MRI scan the preceding month showed an odd lesion that - in retrospect - was the first sign of PML. The reason this is important is that there is a hint in this report that PML may not have the awful prognosis we all assume. The patient continued to deteriorate for three months after natalizumab was stopped. However, after that point, JC virus was no longer detectable in his blood. And his MRI lesions became enhancing, suggesting an inflammatory response (similar to the "immune reconstitution syndrome" seen in HIV patients with PML). This is not always a good thing: patients can deteriorate during this phase of the illness. However it does mean the blood-brain-barrier is breached and this can allow access to the brain for cytarabine. This is the only drug which kills JC virus in vitro, unlike cidofovir which is sometimes used in this condition. At all events, this patient received cytarabine and his condition improved somewhat. He remains very disabled... but he is alive and has survived PML which is no mean feat.

News of these two cases came to the attention of a Belgian group, who had looked after a man with Crohn's disease who had taken part in a trial of natalizumab for inflammatory bowel disease. 16 months after starting natalizumab, he presented to hospital with confusion and several large non-enhancing white matter lesions on a MRI scan. He deteriorated and died. At the time, he was thought to have an astrocytoma. But, when his pathology was re-examined, it was more compatible with PML. Furthermore, his serum contained measured JC virus DNA from 12 months onwards after treatment. An important point is that PML had not appeared at any time during his previous treatment with azathioprine or infliximab.

So what have we learnt about PML, the demyelinating central nervous system infection by the "JC virus"? 50-80% of the population are seropositive for JC. It is believed that the virus itself remains latent in the kidneys and the lymphoid organs. We associate its reactivation normally with devastating immune damage, particularly HIV infection. We now know that this need not be the case: natalizumab has - until all of this - seemed a rather benign drug, certainly no less toxic than azathioprine or infliximab. It seems that we are all poised to get PML... and only prevented from it by the quiet continuous trafficking of T lymphocytes through the brain. As the NEJM editorial puts it: "bad things may happen when rescuers are turned back at the gates".

And is this the end of natalizumab treatment of multiple sclerosis? The data, such as we have, suggests that it may be more efficacious than the current licensed drugs. First we need to know the risk of PML after natalizumab. Biogen are currently re-examining and imaging all 3000 pts who have received natalizumab for any condition. Then we need to ask if that risk is worth the benefit? Difficult decisions. - *AJC*

Van Assche G, Van Ranst M, Sciort R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P.

Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn's Disease.

NEW ENGLAND JOURNAL OF MEDICINE

2005;Jun 9; [Epub ahead of print].

Kleinschmidt-Demasters BK, Tyler KL.

Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis.

NEW ENGLAND JOURNAL OF MEDICINE

2005;Jun 9; [Epub ahead of print].

Langer-Gould A, Atlas SW, Bollen AW, Pelletier D.

Progressive Multifocal Leukoencephalopathy in a Patient Treated with Natalizumab.

NEW ENGLAND JOURNAL OF MEDICINE

2005;Jun 9; [Epub ahead of print].

EPILEPSY: Neuropsychiatric porphyria in patients with refractory epilepsy: report of three cases

"Would I have thought of it?" is the question that I always ask myself when I see reports like this. The first patient was a twenty year-old woman who developed tonic clonic seizures at the age of 12. She then developed recurrent bouts of abdominal pain and vomiting – phew, a smart handle I could probably spot! Epilepsy deteriorated with drop attacks and she developed disturbed sleep, weight loss and constipation and was found to have elevated urinary δ -aminolaevulinic acid and a metabolic defect in the hydroxymethylbilane synthase gene. She was treated with haem arginate and antiepileptic drugs were changed to gabapentin and clonazepam on which she has one seizure per year. The second patient was 40 with a 3 year history of refractory epilepsy and hyponatraemia around 119 mmol/L (I didn't know that). She had an episode of limb shaking during an EEG thought to be non-epileptic (oh dear, I'm in trouble!). She suffered with recurrent low back and left inguinal pain and constipation (no, I still wouldn't have got it). She had nocturia with dark, foul smelling urine and paraesthesiae in both hands and mentioned that she was sensitive to sunlight with occasional rashes (at last, perhaps the penny would have dropped, but I guess these were sought rather than volunteered). Urinary δ -aminolaevulinic acid was raised along with total faecal porphobilinogens and a mutation of protoporphyrinogen oxidase oxidase was found confirming a diagnosis of variegate porphyria. Phenytoin was changed to lamotrigine and seizures reduced to 2 per year, along with improvements in her biochemistry. The third case was a 27 year-old woman with an 18 year history of refractory epilepsy. She had had 3 tonic-clonic seizures at the onset but subsequent attacks were of shooting of pins and needles through her body, sometimes with shaking or weakness of the right side for a few seconds without loss of consciousness (this is looking tricky!). Telemetry showed epileptiform discharges during the attacks (that's better). She then developed tonic falls thought to be non-epileptic (Oh no, not again!). A wide variety of AED's was tried and finally she was started on topiramate with her carbamazepine. Four months later she was found collapsed on the ground and required intensive care. Standard investigations yielded no cause but her EEG showed a metabolic encephalopathy and then urine was noted to be dark (Bingo, but too late!). She had elevated urinary δ -aminolaevulinic acid and faecal protoporphyrin with a mutation in the protoporphyrinogen synthase gene. She was treated with haem arginate and medication was changed to gabapentin plus clobazam and then her seizures declined but she was left with a severe spastic quadriparesis, and dysarthria with preserved cognition. So, the important lessons are that refractory epilepsy can be the presentation and other features may only emerge years later. Seizures can be odd and may be mistaken for non-epileptic attacks. Severe constipation and hyponatraemia as well as abdominal pain should ring alarm bells and the colour of the urine needs to be asked for. How much porphyria are we missing? I confess I have never diagnosed a case. - **MRAM Winkler AS, Peters TJ and Elwes RDC.**

Neuropsychiatric porphyria in patients with refractory epilepsy: report of three cases.

JNNP

2005;76:380-3.

EPILEPSY: Removal of epileptogenic sequences from video material. The role of colour

565 children had a fit whilst watching Pokémon on Japanese TV in one showing in the 1990's. Personally, having endured my son watching Pokémon videos and swapping Pokémon cards, I can understand this as a valid critical response. However, the Japanese medical community felt it was pathological and worthy of investigation. The authors of this paper assessed whether specific components of the broadcast could be modified to alter the EEG response to transmission rather than my favoured but less scientific approach of chucking a brick at the telly. (Fuddy-duddies of the world unite!) In this transmission, a particular property of colour modulation, especially flicker transitions between red and blue were critical in generating seizures, a property termed chromatosenitivity. The authors took 25 patients with clear photosensitive epilepsy and measured the range of frequencies of flash to which they were photosensitive. The most epileptogenic sequence was embedded in 12 seconds of cartoon. Different colours were altered separately to reduce the colour modulation, with as little effect on the cartoon content as possible.

Because the sequence was digitised at 25Hz, only a flicker frequency of 12.5Hz was assessed in the experiments. The cartoon was then played back on 50Hz and 100Hz televisions. and the maximal epileptogenic properties of the sequence, involving alternating red-blue flicker were suppressed. Twenty-three patients were sensitive to the Pokémon video and one of the others was colour-blind (deuteranope). One man taking valproate was not sensitive to standard flashes did show EEG changes to Pokémon. The responses of the 23 patients sensitive to the original cartoon were compared to the responses to the modified cartoon. The number of grade 4 photoparoxysmal responses (the worst grade) was 56% on the 50Hz TV and 41% on the 100Hz TV, reducing to 17% on the 50Hz and 4% on the 100Hz TV. A 100Hz TV may reduce the epileptogenic properties of mains flicker but will not protect against the epileptogenic effects of the most potent colour switching components of a cartoon. Cartoonists may need to take the colour composition into account in planning their cartoons but nothing works better than a brick. - **MM Parra J, Kalitzin SN, Stroink H, Dekker E, de Wit C, Lopes da Silva FH.**

Removal of epileptogenic sequences from video material. The role of colour. NEUROLOGY

2005;64:787-91.

EPILEPSY: Neuropsychological effects of exposure to anticonvulsant medication in utero

The authors contacted 547 women attending epilepsy clinics, of whom 219 agreed to participate in the study and 163 women had 256 children between the ages of 6 and 16. Of these, 249 underwent neuropsychometric assessment. Factors associated with a lower IQ were maternal IQ, exposure to valproate and more than 5 maternal seizures during pregnancy. Valproate was the only drug to show differences compared to children of women not exposed to AED. Verbal IQ of the 41 children born to mothers taking valproate was 84(77-89) compared to 94(90-99) for the 52 children born to women taking carbamazepine. Of valproate children 22% had VIQ<69 compared to 4-6% in the other groups. Polytherapy had no effect in this study, unless it included valproate, which differs from other studies. The results add to the authors' previous findings in a younger cohort also with a selective verbal IQ deficit attributable to valproate - making this trend increasingly worrying to those of us who regularly find that valproate is the only drug that works for some women. Apparently testosterone has selective effects on right and left hemisphere development; enhancing right and inhibiting the left. Valproate-induced rises in testosterone levels could in theory cause differential developmental effects through this mechanism. - **MRAM**

Vinten J, Adnab N, Kini U, Gorry J, Gregg J, Baker GA for the Liverpool and Manchester Neurodevelopment Study Group.**Neuropsychological effects of exposure to anticonvulsant medication in utero.**

NEUROLOGY

2005;64:949-54.

EPILEPSY: More tea vicar?

Ginseng contains a variety of ginsenosides, in the leaves, stems and roots. The proportion of the different types varies between plants; American ginseng (*Panax quiquefolius*) has a lower Rg1/Rb1 ratio than Asian ginseng (*Panax ginseng*). Rg1 is said to have excitatory properties and Rb1 inhibitory properties so in theory American ginseng is more likely to have antiepileptic effects. A variety of concentrated ginsenosides, with differing concentrations of key components such as an extract of Rb1, were given to rats before having seizures induced by pilocarpine, kainic acid or pentylenetetrazole (PTZ). The Rb1 extract was given in different doses. The latency to seizure onset was prolonged and seizure duration shortened in PTZ preparations by Rb1 in a dose-dependent manner. Mortality of the animals was reduced from around 30% to zero at higher doses of Rb1 and other ginsenosides also had a beneficial effect. Dose dependent changes were also seen with Rb1 in kainate preparations. In the pilocarpine animals Rb preparations improved various parameters. There was a dramatic reduction in heat-shock protein expression in treated animals, a measure of brain stress. Mortality was increased by unselected extracts of roots or leaves from American ginseng, when compared with control untreated animals. These have a lower proportion of Rb ginsenoside. So when the vicar comes to tea, find out what sort of epilepsy he has before you offer the ginseng. - **MRAM**

Xiao-Yuan Lian, Zhi-Zhen Zhang and Janet L Stringer.**Anticonvulsant activity of ginseng in seizures induced by chemical convulsants.**

EPILEPSIA

2005;46:15-22.