

EDITOR'S CHOICE

MULTIPLE SCLEROSIS is more than one disease

For decades, people interested in multiple sclerosis have kicked this issue around: are we studying one disease or several? It is not a trivial question. Because the search for a unitary cause, genetic or environmental, is doomed if multiple sclerosis is a ragbag of different diseases. And, even more importantly, different forms of multiple sclerosis may require different treatments. In recent times, the collaboration between Claudia Lucchinetti and Brian Weinschenker of the Mayo Clinic and Hans Lassmann of the Centre for Brain Research in Vienna, has contributed several key papers that suggest multiple sclerosis is more than one disease. They showed that multiple sclerosis pathology can be divided into four types (I through to IV) [Lucchinetti C, *Ann Neurol*. 2000;47(6):707-17.] and that about half of patients with aggressive acute demyelinating syndromes respond to plasma exchange [Weinschenker BG, *Ann Neurol*. 1999;46(6):878-86.]. They now do the obvious thing: see whether those patients who respond to plasma exchange have distinctive pathology of their multiple sclerosis lesions. Obvious certainly, but not straight forward, as it is hardly usual practice for people with multiple sclerosis to undergo a brain biopsy! So this research letter in the *Lancet* focused on that rare group of patients who present with brain lesions which have to be biopsied because of diagnostic uncertainty... and who then do not respond to corticosteroids, making plasma exchange the next stage of treatment. They describe 19 such patients. Of these 10 patients responded to plasma exchange, of whom all had "Type II" pathology, which is characterised by immunoglobulin deposition and complement activation. In contrast, none of the 9 patients who failed to respond to plasma exchange had Type II pathology. Rather they had a mixture of Types I and III, neither of which include those hallmarks of antibody-mediated pathogenicity. This is neither a robust nor comprehensive study. Important details, such as CSF or radiology, are absent. Nonetheless, it is a spur to investigators to develop non-invasive techniques to distinguish the different forms of multiple sclerosis, to assist the scientist and clinician alike. -AJC

Keegan M, König F, McClelland R, Bruck W, Morales Y, Bitsch A, Panitch H, Lassmann H, Weinschenker B, Rodriguez M, Parisi J, Lucchinetti CF.

Relation between humoral pathological changes in multiple sclerosis and response to therapeutic plasma exchange.

LANCET

2005 Aug 13-19;366(9485):579-82.

DEMENTIA: and brain biopsy

★★★ RECOMMENDED

The antemortem diagnosis of dementia is almost invariably clinical, and at least as far as Alzheimer's disease (AD) is concerned this is usually corroborated post-mortem, in 80-90% of cases in the best hands. Occasionally, however, the need for tissue diagnosis in a patient experiencing cognitive decline is felt to outweigh the potential surgical risks of brain biopsy. How useful is this investigation? This retrospective study looked at 90 consecutive brain biopsies performed for dementia at the National Hospital, Queen Square, a tertiary referral centre, over a 14 year period (1989-2003), hence around 7 biopsies per year. All were undertaken to exclude a reversible (inflammatory or infectious) process. 90% were non-dominant frontal lobe biopsies, 6% produced inadequate samples, and 11% were associated with biopsy-related complications (seizures, infection, haemorrhage) but without lasting sequelae. Biopsy led to a specific diagnosis being made in 57% of cases, the most common diagnoses being AD, Creutzfeldt-Jakob disease (CJD), and inflammatory disorders. 10% of biopsies revealed a potentially reversible cause, mostly inflammatory but with one case of Whipple's disease. An elevated CSF cell count was a predictor, albeit not a very powerful one, of inflammatory pathology. In 11% of cases, treatment was directly determined by biopsy (increase or reduction in immunosuppression; antibiotics for Whipple's; cholinesterase inhibitors for AD). Outcomes were not recorded in detail, so it is not clear if any demented patient "reversed". The largest single category of biopsy diagnosis (37%) was non-specific gliosis variably affecting the cortex and white matter. The constellation of behavioural change, increased CSF protein and matched serum and CSF oligoclonal bands predicted this pathological finding. What relationship, if any, this non-specific gliosis has to progressive subcortical gliosis of Neumann (and whether it may have a specific neuroradiological/spectroscopic correlate; JNNP 2003;74:404) will require further investigation; three such cases coming to post-mortem had

final diagnoses of CJD, multiple sclerosis and CADASIL. As the authors state, the risk:benefit analysis for brain biopsy for dementia is finely balanced. It might also be questioned whether the findings of a tertiary referral centre may be generalised: at a regional neuroscience centre, I have not requested a brain biopsy for dementia after nearly 6 years in post. A prospective, preferably multi-centre, study is required. - AJL

Warren JD, Schott JM, Fox NC, Thom M, Revesz T, Holton JL, Scaravilli F, Thomas DG, Plant GT, Rudge P, Rossor MN.

Brain biopsy in dementia.

BRAIN

2005;128(9):2016-2025.

PARKINSON'S DISEASE: When divided they fall? Effects of dual-tasking on attention and gait

Dual task paradigms measure how performance of one task is affected by performance of another. When a task is cognitively demanding performance of a simultaneous second task is thought to put extra strain on existing resources. This paper looks into the relationship between cognitive functioning and gait, and compares the effects of dual tasking on features of gait in people who have Parkinson's disease, and in controls. There were 30 patients and 28 demographically matched healthy controls. The patient group were known to have poorer balance than the control group and had fallen significantly more frequently during the previous six months. Inhibitory control and response switching were assessed in all individuals prior to the dual task research using standard tests of executive functioning. While executive functioning was significantly worse in the patient group, preliminary memory tests did not differ significantly between the two groups. When interpreting the results that follow, perhaps these initial investigations were relatively more fatiguing to the patients than to the controls. Measures of executive function correlated significantly with variability of gait during performance of dual tasks, but not during ordinary walking. Gait speed was decreased in both patients and controls when they performed dual tasks. Gait variability during dual tasks was increased in patients when compared to ordinary walking. The authors suggest that while attention may be necessary in all individuals to maintain some aspects of gait, like speed of walking, other aspects, like regulating gait variability, may also become cognitively demanding in Parkinson's disease patients. This could partially explain patients' tendencies to fall in the real world where multiple demands are placed on a person's attention. The authors also suggest researching whether cognitive enhancing therapies would have beneficial effects on gait control and whether there is rehabilitation value in encouraging patients to maintain their stability during walking by focusing their attention on gait. The paper provides some tentative evidence to support the value of patients sitting down when performing complex tasks, specifically those requiring listening comprehension. Does paucity of gait hinder aspects of cognitive function through diversion of resources? Because gait is so useful to neurologists in illuminating aspects of health, disease and disability, it will be vital that clinicians and other scientists combine their knowledge in order to extract the array of questions interesting research like this poses. - LAJ

Yogev G, Giladi N, Peretz C, Springer S, Simon E S, Hausdorff J M.

Dual Tasking, gait, rhythmicity, and Parkinson's disease: which aspects of gait

are attention demanding?

EUROPEAN JOURNAL OF NEUROSCIENCE

2005;22:1248-56.

STROKE: Infarcts in migraineurs

★★★ RECOMMENDED

Migraineurs are at risk of silent posterior circulation (PC) infarcts, particularly in the cerebellum (Kruit et al, 2004). The present study aimed to characterise the neuroimaging topography of PC infarcts in migraineurs. Using a population based survey of 6491 Dutch adults aged 20-60 years from the Genetic Epidemiology of Migraine (GEM) study, 863 cases of migraine were identified. From this group, 134 cases of migraine without aura (MO), and 161 cases of migraine with aura (MA) were selected. Matched controls were selected from the GEM cohort, making a total of 435 subjects in the whole study. Each subject was subject to a telephone interview, MRI of the brain, drawing of blood (for cholesterol, but not thrombophilia screens), and a physical examination. 8.1% of MA, 2.2% of MO and 0.7% of controls had clinically silent PC territory infarcts. In total, 60 infarcts were identified: 81% were in the PC territory in the MA group, 47% were in the PC territory in the MO group and 41% were in the PC territory in the control group. Most PC territory infarcts were located in the cerebellum, and most were junctional as opposed to territorial, particularly in the MA group. Eleven subjects had multiple infarcts (59% of migraine cases, 25% of controls). Multiple PC lesions were exclusively in migraineurs. In

migraineurs, cardiovascular risk factors were not higher in the infarct group. In migraineurs with PC infarcts, the highest risk was in MA patients with a high attack frequency (at least 1 per month), odds ratio 15.8. In summary, MA patients with a high attack frequency were at risk from border zone cerebellar infarcts. Cerebellar dysfunction has been recognised previously in migraineurs but a structural basis has not been identified. Border zone infarcts were postulated to result from decreased perfusion pressure and subsequent emboli formation, furthering low blood flow. Low cerebral blood flow during and up to a day after a migraine attack has been described, possibly due to cortical spreading depression, coagulopathy or release of vasoactive peptides. SCA watershed zones were particularly vulnerable perhaps due to the longer course of the SCA branches compared with PICA and AICA branches. Because of the predominance of junctional zone infarcts, lack of small vessel disease (as identified by deep white matter lesions and periventricular white matter lesions) and the lack of association of infarcts with cardiovascular risk factors in migraineurs, the pathophysiology of such infarcts is more likely due to low cerebral blood flow than ischaemic vessel disease. - WAP

Kruik MC, Launer LJ, Ferrari MD, van Buchem MA.

Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study.

BRAIN

2005;128: 2068-77.

Kruik MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD.

Migraine as a risk factor for subclinical brain lesions.

JAMA

2004;291: 427-34.

EPILEPSY: Are seizures dangerous to a baby in utero?

Teratogenicity is a thorny issue in the management of epilepsy in women of childbearing age. For most patients with mild epilepsy, I have taken a reassuring line about the epilepsy at least and not fussed too much about the occasional patient with mild partial seizures who abandon their tablets, openly or covertly. These authors describe a woman with mild partial seizures, comprising twitching of the right side, pallor and sweating, occurring only 6 times per year. In the seventh month of her pregnancy she presented with two consecutive seizures leading to a fall. She had a further seizure whilst being monitored associated with a tachycardia. Her baby experienced a bradycardia from a baseline of 150-160 down to 70 per minute in the absence of uterine contractions. Whilst the significance of the change is unclear, it contradicts conventional wisdom that seizures where oxygenation is maintained have no significant effect on the foetus and raises the possibility that mild epilepsy can affect a baby. The contrary evidence comes from epidemiological studies in which pregnancies in patients on no medication fared just as well as controls. I shan't change my advice on the basis of this one case, although autonomic effects of seizures are common.....-MRAM

Sahoo S, Klein P.

Maternal complex partial seizure associated with fetal distress.

ARCHIVES OF NEUROLOGY

2005;62:1304-5.

REHABILITATION: Keep moving is best for hemiplegic shoulders

Recovery of upper limb function is notoriously poor after stroke. One of the reasons for this is the loss of integrity at the shoulder. During the early weeks following stroke when the arm is immobilised due to weakness, the muscles and soft tissue structures that normally keep the head of the humerus tight in the glenoid fossa lengthen under the weight of the arm. Once this has occurred it is difficult for patients, who may be recovering muscle activity, to regain shoulder stability and to move the shoulder effectively. Functional electrical stimulation is used to prevent and to remediate shoulder subluxation in some centres but in most places in the UK treatment is conservative and therapists rely on slings, shoulder supports and positioning. Now a group in New York have found some benefit in using a tool that is normally used after orthopaedic surgery: Continuous Passive Motion (CPM). Occupational therapists and physiotherapists do not usually use CPM with stroke patients. Although some do advocate regular passive movement, in practice little time is given to this in stroke rehabilitation. In their study (n= 35), Lynch et al. randomly assigned stroke patients with very weak arms to daily CPM for twenty days or to a daily range of motion group in addition to their normal therapy programme. The affected arm of the patients in the CPM group was supported in a rigid brace while the shoulder was ranged to 90° of abduction for 15 minutes and 80° of external rotation for 10 minutes each day. The control group ranged their own arm in a daily group

led by an Occupational Therapist. The exercises focused on the shoulder, elbow and hand for ten minutes each. A therapist who was blinded to group allocation assessed shoulder stability, motor impairment, muscle tone and pain before and after the treatment. CPM treated patients showed more improved shoulder joint stability than the control group. This result did not quite reach significance. No differences in the other variables were found. This was a small study investigating a new treatment and extension of this work to a larger trial would be worthwhile. It would also be interesting to find out why CPM might improve shoulder stability. Is the improvement due solely to sensory stimulation or are the patients inadvertently being provided with a low level of activity-assisted practice? The positions achieved in the support of the CPM machine are impossible for patients to achieve without assistance. Is it the amount of repetition, the extent of the ranging or the position in which it is done that is important? There are many questions to answer in further investigations of this promising therapy, not least is: Why are we so slow in taking principles from orthopaedics and applying them in neurological rehabilitation. - AJT

Lynch D, Ferraro M, Krol J, Trudell CM, Christos P, Volpe BT.

Continuous passive motion improves shoulder joint integrity following stroke.

CLINICAL REHABILITATION

2005;19: 594-9.

STROKE: to clip or coil?

This is a serious trial, by anyone's standards: comparing endovascular or surgical treatment of intracranial aneurysms in 2143 patients with subarachnoid haemorrhage. The results are well known because the trial was stopped early. At an interim analysis, looking at death and dependency at one year, there was a significant benefit for coiling. This was reported in the Lancet in 2002, causing much debate and ruffling of partisan feathers. Now, in the same journal three years later, we have the complete report of all the one-year data and some long-term follow-up (with c. 100 patients in each arm at 7 years). The chance of death or dependency at one year after an aneurysmal subarachnoid is 24% with coiling and 31% with clipping, an absolute risk reduction of 7%. In other words, for every 1000 patients treated with an endovascular approach, 74 patients avoid death or dependency. This early survival advantage is maintained for up to seven years. And another point in favour of coiling was that there was a significantly reduced risk of epilepsy compared to the surgical procedure. Although the numbers of patients having re-bleeds after either procedure was low (28 in total), these usually occurred after coiling. Game and match. Step aside clippers for the coilers.... - WAP

Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group.

International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion.

LANCET

2005 Sep 3-9;366(9488):809-17.

DEMENCIA: The pathological basis of semantic dementia

*** RECOMMENDED

The nosology of frontotemporal dementia (FTD), the blanket term under which SD falls, is somewhat confusing, and the clinical classification does not parallel the pathological classification. Furthermore, many patients evolve from one clinical diagnosis to another with time. Finally, it can be difficult to distinguish with certainty the different diagnoses, and the precise definitions of some clinical diagnoses have been questioned. Traditionally, tauopathies consist of largely Pick's disease (part of the FTD classification), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), or neurofibrillary tangle dementia. Ubiquitin-positive inclusions exclusively, are found predominantly in motor neuron disease dementia (FTD-MND). Rhys Davies [an ACNR reviewer!] and colleagues describe, in a relatively large pathological case series of SD, the predominant pathological features, as well as the pathological distribution and a retrospective review of case notes. Thirteen of 18 cases were ubiquitin-positive only (motor neuron disease inclusion dementia, MNDID) although one case also had Alzheimer's disease (AD) pathology, 3 had Pick bodies, and 2 had AD pathology. All cases, by inclusion had semantic impairment, and all had bilateral frontotemporal atrophy on imaging. Eight had behavioural disturbance and motor symptoms were infrequent although patients were not routinely assessed once global dementia occurred. One of the MNDID cases developed MND one year before death, and one had dysphagia and dysphonia ante-mortem and one had a family history of MND. Five MNDID cases also had pathology in the motor system. One of the AD cases had ubiquitin-positive inclusions exclusively in the inferior olivary nucleus. Interestingly, of the MNDID cases, 6 had inclu-

sions in the inferior olivary nucleus and two of these had inclusions exclusively in the inferior olive (i.e. not in the usual site of the cortex and dentate gyrus). This study shows that the pathological hallmark of SD is MNDID. It was suggested that MND and SD may lie on a spectrum, with a predilection of ubiquitin-positive inclusions for the corticospinal tracts and the anteroinferomedial temporal lobe, respectively. The anteroinferomedial temporal focus for SD, predicted from imaging, pathological and animal studies, was confirmed. Due to this relatively well-circumscribed predilection, clinical features rarely overlap, or do so only in subtle ways or at the end stage of the disease. Interestingly, one of the two cases with exclusively inferior olivary inclusions was the case with MND. It may be that inferior olivary pathology is predictive of MND. The authors concluded that SD cases may be predicted to have MNDID, pathologically. - *WAP*
Davies RR, Hodges JR, Kril JJ, Patterson K, Halliday GM, Xuereb JH.

The pathological basis of semantic dementia.

BRAIN

2005;128; 84-1995.

EPILEPSY: Shaker or faker?

Epilepsy or non-epileptic seizure (NES)? We all get caught out from time to time and the quest for the infallible test continues. This study reviews some of the things that people have done to try and diagnose patients. The authors tried to be as scientific as possible in selecting only papers where sensitivity and specificity of the technique in question could be measured. They looked at various measures including psychometric assessment, seizure semiology or post-ictal symptoms, seizure induction techniques and prolactin levels. They found 33 studies they could measure. If you can trigger a seizure by saline injection or hypnosis, then the specificity for NES approaches 100%. Is this ethical? Is it more important to be ethical and wrong or use a questionable technique and get the right answer and treatment for your patient? We all know that prolactin levels are most helpful in tonic-clonic seizures so this, and the timing of the sample, needs to be considered in interpreting the results. SPECT scanning had a sensitivity of 70% and specificity of 80% - so much for modern imaging. The presence of pre-ictal pseudosleep requires EEG diagnosis but was 100% specific for NES (only 23% sensitive). If a patient has a convulsive seizure then the absence of synchronised movements of upper and lower limbs and the absence of vocalisation at the beginning or end of a seizure had 96% sensitivity and 96% specificity for NES. Home videoing may be of value even without EEG. Most other ictal features are relatively unhelpful - particularly when compared against frontal lobe attacks. Of course the bottom line is that without the gold standard of video-EEG telemetry we will always make mistakes. But for those of us without ready access to gold, there are some things that can provide additional support to a diagnosis that often has to be made by sixth sense. - *MRAM*
Cuthill FM, Espie CA.

Sensitivity and specificity of procedures for the differential diagnosis of epileptic and non-epileptic seizures.

SEIZURE

2005;14:293-303.

REPAIR: Functional neurons from the adult brain

*** RECOMMENDED

Neurogenesis persists into adulthood in the mammalian brain in the subventricular zone (SVZ) and dentate gyrus (DG) of the hippocampus in many species including humans. The extent to which neurogenesis occurs in humans is the subject of debate, particularly as it is difficult to fate map proliferating cells in humans. Neural precursor cells (NPC) have been isolated in vitro from human brain, from resection specimens and post-mortem, but it is unclear whether these cells are relevant to brain function or whether they are artefacts of culture. It has been shown that NPC from humans can form cells which express neuron specific markers, and also that these possess some characteristics of neurons, namely excitability, although this can also occur in developing glia. Thus, the ability of NPC to form functional neurons have not yet been demonstrated in humans in vitro. Moe et al (2005) have cultured NPC from the SVZ, from temporal lobe resection specimens on patients with epilepsy, and characterised their properties in vitro, using a combination of electrophysiology and channel blockers. NPC can be grown in culture as neurospheres. Neurospheres are aggregates of cells, and with time in culture, it is those cells that can self renew that are selected for. Neurospheres can be dissociated into single cells and the cells differentiate after removal of mitogens and addition of serum. They show that during the first week of differentiation in vitro, some cells express neuronal markers. During the second week, they express voltage gated-K⁺ channels and then voltage gated Ca²⁺ channels, which produce small action potentials (AP). It was suggested that the repolarising currents mediated by the K⁺ channels were required to offset excess Ca²⁺ entry to the developing neurons or, more likely, that these

currents are required for migration. In the third week, the cells developed voltage gated Na⁺ channels, which mediated a broad high-threshold AP. These evolved into short-lasting low-threshold repetitive AP seen in mature cortical neurons. Furthermore, by the end of the fourth week of differentiation, GABAergic and glutamatergic post-synaptic currents were observed, indicating synaptic connectivity. The authors thus demonstrated that functional neurons can be produced from NPC isolated from the adult human brain. This observation provides an essential step in the therapeutic application of such cells, as well as the suggestion that functional neurogenesis may occur in the adult human brain. - *WAP*

Moe MC, Varghese M, Danilov AI, Westerlund U, Ramm-Petersen J, Brundin Svensson LM, Berg-Johnsen J, Langmoen IA.

Multipotent progenitor cells from the adult human brain: neurophysiological differentiation to mature neurons.

BRAIN

2005;128:2189-99.

GLIOMAS: How they attract haemopoietic stem cells

Many types of stem and progenitor cells are attracted to tumours, as well as other pathologies such as stroke and neurodegeneration. Because gliomas are deeply infiltrating and are relatively resistant to radio- and chemotherapy, an autologous cellular vector is an attractive option for therapy. Tabatabai and colleagues have elucidated the molecular mechanism of the tropism of haemopoietic precursor cells (HPC) to intracerebral gliomas. Granulocyte colony stimulating factor (G-CSF) was used to mobilise HPC, which were then harvested, labelled and injected intravenously into nude mice which had previously been transplanted with human glioma cells. The HPC were found in the gliomas but not elsewhere in the brain. The labelled HPC continued to express CD34 and did not express markers of neurons or glia, indicating that the label was specific and that the cells did not undergo phenotypic transformation. In vitro, HPC migrated towards supernatant from glioma cells, which was blocked by addition of a neutralising antibody to CXCL12. CXCL12 is the major cytokine for stem cell homing to bone marrow. Next, glioma cells in which expression of transforming growth factor b (TGFb) had been blocked by RNA interference, were transplanted into rat organotypic hippocampal slices. The disabling of TGFb reduced the migration of HPC towards the glioma. This TGFb-dependent attraction was found to be dependent on CXCL12, and, in parallel, matrix metalloproteinase (MMP-9) and stem cell factor (SCF). MMP-9 and SCF work in parallel to CXCL12 because they are unable to overcome CXCL12 neutralisation and MMP-9 does not increase CXCL12 levels. TGFb is upstream of these factors because addition of exogenous TGFb could not compensate for the loss of the other factors. Similarly, MMP-9 is up-stream of SCF. Additionally, CXCL12 is essential for chemotaxis because the other factors lose their chemoattractive ability when CXCL12 is neutralised, but CXCL12 can compensate for loss of SCF. The study shows that CXCL12 is the essential factor in chemoattraction of glioma cells to HPC, which is dependent on TGFb, with MMP-9 and SCF as synergistic agents. This finding has implications for the development of cellular vectors, which could target glioma cells. - *WAP*

Tabatabai G, Bahr O, Mohle R, Eyupoglu IY, Boehmler AM, Wischhusen J, Rieger J, Blumcke I, Weller M, Wick W.

Lessons from the bone marrow: how malignant glioma cells attract adult haemopoietic progenitor cells.

BRAIN

2005;128:2200-11.

REPAIR: The old story of hippocampal neurogenesis, its regulation and significance

*** RECOMMENDED

There is no doubt that new neurons (neurogenesis) are constantly being born in the adult mammalian hippocampus, and that this gets less with ageing. Furthermore the functional significance of these new neurons is in the acquisition of certain forms of memory and exercise and environmental enrichment can both increase hippocampal neurogenesis and learning - ergo, what happens if you physically exercise the aged mammal in terms of neurogenesis and learning? Well obviously you can't study grandma on the treadmill, so Gage and colleagues have used the aged mouse, a running wheel and the Morris water maze. This study clearly shows that neurogenesis is increased in the aged mice with physical activity, and that the new born neurons have normal morphology and that this is associated with improved retention of information in the Morris water maze (but not causally proven to be). This occurs without any changes in angiogenesis - the latter often being thought of as going hand in hand with neurogenesis. This is an exciting study and suggests that keeping active in old age is

good for the hippocampus, if not the knees. This study comes on the back of another interesting paper, this time in Neuron by Tozuka et al. In this paper, the authors show that excitatory GABAergic stimulation of the transiently amplifying neuronal precursor cells in the dentate gyrus of the hippocampus is important in their neuronal differentiation. Furthermore this GABAergic input is from the hippocampal circuitry itself, suggesting that the level of electrical activity within the hippocampus controls the rate of neurogenesis. This suggests that using the hippocampus, through mental activities for example, may increase neurogenesis. So goodness knows what would happen if you thought hard whilst running! However apart from the obvious benefits that may be there for us all, these papers raise many questions not least about what happens in disease. For example, what does all this mean for the patient with temporal lobe epilepsy on treatment with drugs that interfere with GABAergic neurotransmission? Therefore we are once more challenged to think about how the brain behaves in a dynamic way in both normal ageing and in disease and how this may be harnessed to manipulate this network for clinical good. - *RAB*

Van Praag H, Shubert T, Zhao C, Gage FH.

Exercise enhances learning and hippocampal neurogenesis in aged mice.

JOURNAL OF NEUROSCIENCE

2005;25:8680-5.

Tozuka , Fukuda S, Namba T, Seki T, Hisatsune T.

GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells.

NEURON

2005;47:803-15.

EPILEPSY: Announcement for medicolegal practitioners

The authors describe three cases who had peripheral injuries and later developed epilepsy arising from the cortical representation of the affected part. The first was a 23 year old man who caught his right hand between mechanical rollers, sustaining soft tissue injuries. A day later he developed jerking movements of the

right hand 20 times daily and three months later started having nocturnal tonic clonic seizures. MRI and SSEP were normal. Video-EEG telemetry showed stereotyped supplementary motor type seizures and in the one localisable attack, onset was in the left parasagittal region. The second patient was a 27 year-old woman who had two maternal uncles with epilepsy. At the age of 19 she sustained a cigarette burn to medial surface of the left middle finger, causing blistering. Within 24 hours she started to have recurrent bouts of tingling affecting the tip of the burned finger which over the following months spread to affect the whole arm and upper torso and increased in duration to 30 seconds. After 5 months the pain became more intense and she would cry out and have clonic movements of the left side. She had sensory signs of bilateral carpal tunnel syndrome. She was treated with carbamazepine for a presumed pain syndrome, which was tapered during video-EEG telemetry. She had supplementary motor type seizures affecting the left side of her body, which secondarily generalised on one occasion. EEG was non-specific and MRI was normal but interictal PET showed hypometabolism in the right parietal lobe. The third patient was a thirty-seven year-old man who burned his right hand at the age of 4 and 6 months later developed sensory seizures affecting his right hand and evolving into hemi-clonic and occasionally generalised seizures. Investigations were non-localising. We are used to thinking of sensory stimuli as seizure triggers; simple such as photic stimulation or complex such as startle. But this is causation at a different level – epileptogenesis rather than trigger. The onset of seizures within 24 hours in two cases is persuasive but also means that much of the wiring for focal seizures was already present and relatively minor changes induced by altered sensory input could rapidly lead to seizures. Does the heightened sensory stimulus act as a form of kindling? I look forward to animal models that explain the mechanism. - *MRAM*

Spiller AE, Guberman, A, Bartolomei F, Zifkin B and Andermann F.

Epileptogenesis due to peripheral injury as a cause of focal epilepsy.

EPILEPSIA

2005;46:1252-5.

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