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ABN Abstracts

Proceedings of Clinical Neurosciences, Torquay, Devon, 7–9 September 2005; neurology abstracts only

ABN Medallist 2005

Charles Warlow has been a major influence on international neurology over the last 25 years, especially on stroke neurology. His first recorded publication (*The Lancet*, 1969) was on ''burns encephalopathy'' in children, but soon his interests turned towards haematological factors in thrombosis and embolism. Finally, with the advent of aspirin as an antithrombotic agent, the emphasis in his research shifted from the venous to the arterial side of the circulation.

In the early 1980s Charles Warlow grew into his role of a leader in stroke research by organising clinical trials. It all started with the UK-TIA aspirin trial, which compared two different doses of aspirin with placebo. Out of this collaboration grew his most conspicuous research accomplishment, the European Carotid Surgery Trial. In hindsight this was a hazardous undertaking – initially only UK centres collaborated and there was little funding, while the resistance from vascular surgeons was formidable. Nevertheless Charles managed to spread the ''light of doubt'' across his own country and continental Europe. His 1984 review article in *Stroke* ''Carotid endarterectomy: does it work?'' shows all the elements of the mature Warlow style: comprehensive, persuasive, slightly provocative, and peppered with irony. Once it became clear the European study would provide useful answers a similar but heavily funded ''steamroller trial'' from North America was launched; it was no small feat of diplomacy from the part of Charles Warlow that the two studies were eventually welded into a single, solid block of clinical evidence.

It is a fortuitous combination of personal characteristics that has resulted in Charles Warlow's continuing success: his vision to collaborate with Richard Peto in applying epidemiological principles to clinical neurology before this became a common mantra; his capacity for hard work (a PubMed search – for what it is worth – provided 314 hits by the end of August 2005; even more notable is that of the latest 100 publications he was the first author in 15); his efficiency in getting so much important research done with limited means; his love of teaching, reflected in the Advanced Clinical Neurology Course that was started during his time in Oxford and continued in Edinburgh (this year the 27th course was held); his anti-authoritarian attitude, which he also managed to pass on to his collaborators, at least three of whom became professors in their own right; and finally his unconventionality – instead of accepting the editorship of an existing journal he preferred to start a new one, ''Practical Neurology'', in his own style. That achievement also serves to prove that he is more than a great ''strokologist'' – as is his growing interest in the borderland between neurology and psychiatry.

British Neurology has known quite a few stars since Willis and his Oxford circle; Charles Warlow is unquestionably one of them.

Jan van Gijn, University Medical Centre, Utrecht, The Netherlands, September 2005

001 SPONTANEOUS LOW CSF VOLUME HEADACHE WITH ABDUCENS NERVE PALSY

K. Krolikowski, A. Y. Al-Memar, O. J. Foster, S. M. Omer. *Dept Neurology, Atkinson Morley Wing, St George's Hospital, London, UK*

The syndrome of spontaneous low CSF volume headache is caused by spontaneous or traumatic leaks of the CSF from the subarachnoid space. The CSF hypovolaemia causes sagging of the brain and traction of cranial nerves leading sometimes to overt cranial nerve palsies. We report three cases of this syndrome, in which abducens nerve palsy developed after postural headache in two patients, and neck ache in the third. In one patient, symptoms started after a mild head injury. Head MRI showed typical dural thickening and enhancement in all and bilateral subdural hygromas, and downward displacement of cerebellar tonsils in two patients. Epidural blood patch was performed in one patient, and produced significant improvement of symptoms within hours of the procedure. The diagnosis of spontaneous low CSF volume headache should be considered in patients who present with abducens nerve palsy in association with headache and or neck ache, especially if the headache is postural.

002 INVESTIGATING B12 DEFICIENCY AMONGST NEUROLOGICAL PATIENTS

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Background: B12 deficiency is potentially relevant in several neurological presentations. There is wide variation in the clinical response to low B12 results.
Aim: To define current practice of B12 testing in a regional neurology service.
Methods: A retrospective case-note review of patients with a low serum B12 over a 6 month period. Mean follow up 12 months.
Results: Out of 544 tests, 38 (7%) had a low B12 level (median B12 135 mmol/l, range 64–166), of whom 30 had available case records. The test indication was neuropathy or myelopathy in 20 (67%). Three (10%) were anaemic, five (17%) were macrocytic. Eight cases had untreated repeat B12 measurements – two were normal. Investigation of cause was performed in two (7%). Treatment was initiated or suggested in six (20%). Sixteen cases (53%) had no further investigation or treatment. B12 deficiency was considered causative of the neurological presentation in four cases, all of whom were treated.
Conclusions: The majority of low B12 readings identified in neurology patients are not considered relevant to the clinical neurological diagnosis, resulting in low levels of further intervention. The benefits of investigating and treating low B12, which is judged unrelated to current presentation, are unknown and merit further investigation.

003 TELENEUROLOGY BY TELEPHONE: IMPACT OF THE NHS DIRECT TELEPHONE HELPLINE IN THE NEUROLOGY OUTPATIENT CLINIC, 2001–2005

A. J. Larner. *Walton Centre for Neurology & Neurosurgery, Liverpool, UK*

Objective: To report use of the NHS Direct telephone helpline by consecutive new neurological referrals.
Setting: Two district general hospital general neurology outpatient clinics in north-west England, first quarter of 2001–2005 inclusive.
Results: There was a large increase in NHS Direct use between 2001, shortly after the service was introduced in the region (4%), and 2002 (12%; $p<0.01$ chi-squared test). In the period 2002–2005, of 867 patients seen, 483 (55.7%) were aware of NHS Direct and 137 (15.8%) had used it; only five patients volunteered use before being asked. A slightly greater proportion of women than men were aware of (58% vs 53%) and had used (17% vs 14%) NHS Direct (both $p>0.1$, chi-squared test). The highest proportional use was in the 21–30 and 31–40 year age groups (26–27%). However, only 37 of the 137 reported calls to NHS Direct were related to the reason for neurological referral (27%).
Discussion/Conclusion: In this study, more than half of neurology outpatients were aware of NHS Direct; around 1 in 6 had used it, but in only 1 in 23 did this relate to the reason for referral. Hence, the role of NHS Direct in the health information seeking behaviour of new neurological outpatient referrals is small.

004 RECOMMENDATIONS FOR RESPIRATORY CARE OF ADULTS WITH MUSCLE DISORDERS

T. Shahrizaila. *Muscular Dystrophy Campaign Working Group*

As part of a muscular dystrophy campaign sponsored workshop, recommendations were drawn up on the management of respiratory problems in adults with muscle disorders. The workshop participants are listed below. The aim was to provide an expert review of the topic, grade the available evidence, and prepare management guidelines for use around the UK. The key questions that were discussed by the panel were

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as follow: (1) in which muscle diseases do respiratory complications arise in adults?; (2) what measurements of respiratory function should be made and how often?; (3) what can be done to delay the development of respiratory complications?; (4) what interventions are effective in the treatment of respiratory complications? Each recommendation was allocated a level of evidence as well as a grade of recommendation. Workshop participants: Dr Robert Bullock, Consultant Anaesthetist, Newcastle-Upon-Tyne; Dr Michelle Eagle, Physiotherapy Research Practitioner in NMD, Muscle Centre, Newcastle; Dr David Hilton-Jones, Consultant Neurologist, Oxford; Dr Robin Howard, Consultant Neurologist, Queen's Square, London; Dr William Kinnear, Consultant in Respiratory Medicine, Nottingham (chair); Dr Margaret Phillips, Consultant Rehabilitation Medicine, Nottingham; Dr Tina Shahrizaila, Specialist Registrar in Neurology, Nottingham (secretary); Dr Anita Simonds, Consultant in Respiratory Medicine, London

005 TEACHING NEUROLOGY IN AFRICA

S. A. Cooper, W. Whiteley, P. Newman. *Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK; Dept Clinical Neurosciences, Western General Hospital, Glasgow, UK; Middlesborough General Hospital, Middlesborough, UK*

Teacher: ''You are very keen''. African Student: '' We are very needy''. Since 2003, the ABN with the support of UCB Pharma has awarded annual travelling fellowships to fund short periods of neurology teaching in Africa. As recipients of this grant we report on our experiences teaching medical students in Malawi and Tanzania. Poor access to medical care (including drugs and investigation facilities) and an abundance of neurological problems provide the backdrop for an intensive neurology course. Topics covered include epilepsy, stroke, coma, headache, and HIV neurology along with history and examination techniques. The knowledge level of students varies widely but enthusiasm is high and feedback positive. Lecture-based work is supplemented with bedside and clinic teaching. Teaching for a short time in Africa provides exposure to a healthcare setting struggling with the burden of HIV, other infectious disease, and poverty. Neurological problems are common and neurologists scarce. The experiences taught us to be creative in communicating across cultural barriers whilst presenting neurology in a practically relevant way. We maintain links with the hospitals through ongoing visits. Colleagues are encouraged to apply for this grant in the future and enjoy the mutual benefits of teaching neurology in an African setting.

006 DELIVERING EFFECTIVE NEUROLOGY TEACHING BY PROBLEM-BASED LEARNING (PBL)

A. J. Wills. *Queens Medical Centre, Nottingham, UK*

Objective: To determine whether a PBL based method of teaching neurology is as efficacious as traditional teaching methods.
Design: Twelve medical students were taught on two neurological topics (epilepsy and neuropathy) by traditional techniques. The neuropathy component was then taught to an additional 12 students but altered to a PBL method—the tutor acting as facilitator rather than teacher. Knowledge was assessed by means of an MCQ and students satisfaction measured by means of a questionnaire in both groups. Subjects: 24 medical students partaking of a special study module in neurology.
Outcome Measures: Five point rating scale measuring satisfaction (0 worst to 5 best) and an MCQ in best of five format (BOF), 20 questions.
Results: Knowledge based assessment showed no significant differences between the PBL and traditionally taught groups; epilepsy score 60% in both groups, neuropathy score 65% vs 70%. Satisfaction scores were higher in the PBL group (4.6 vs 4.0).
Conclusions: PBL techniques are similarly effective to traditional teaching methods in imparting knowledge but students' satisfaction is greater with PBL methods. However, this is associated with a doubling of tutor time with potential economic consequences.

007 EEG-fMRI AND MR TRACTOGRAPHY. ADVANCED STRUCTURAL AND FUNCTIONAL IMAGING IN A PATIENT WITH REFRACTORY TEMPORAL LOBE EPILEPSY

K. Hamandi, H. W. R. Powell, A. Salek-Haddadi, P. A. Boulby, L. Lemiux, G. J. M. Parker, M. R. Symms, D. R. Fish, J. D. Duncan. *Dept Clinical & Experimental Epilepsy, Institute of Neurology, London, UK; Imaging Science & Biomedical Engineering, University of Manchester, Manchester, UK*

EEG-fMRI allows the localisation of the haemodynamic correlates of interictal epileptiform discharges (IEDs) recorded on surface EEG, in selected patients. MR tractography provides a method for studying white matter tracts in vivo. Combining these advanced imaging techniques offers an opportunity to study the relationship between brain structure and function. We studied a patient with refractory temporal lobe epilepsy, left hippocampal sclerosis, and frequent left temporal interictal spikes with both EEG-fMRI and diffusion tractography. Left temporal spikes were visually identified and used in an event related analysis of the fMRI. EEG-fMRI activations were used as seed points for MR tractography. Significant EEG-fMRI activations were seen in the left temporal lobe, involving hippocampus, lateral and inferior temporal lobe, in addition to widespread activations bilaterally in occipital lobes. Using the left temporal activations as seed points, diffusion tractography demonstrated connections to the left occipital and frontal lobes. We used the emerging techniques of EEG-fMRI and MR tractography to image the haemodynamic correlates of IEDs and the white matter connections of regions so identified. Despite current limitations related to spatial resolution and co-registration these techniques have the potential to study, non-invasively, epileptogenic areas and contribute to pre-surgical planning.

008 HAPLOTYPE STRUCTURE IN ABC TRANSPORTER GENES AND ASSOCIATION OF GENETIC VARIATION IN ABCB1, ABCC1, ABCC2, ABCC5, AND ABCB4 WITH EPILEPSY OUTCOME

G. D. Leschziner, M. Pirmohamed, P. Williamson, A. Marson, C. Middleditch, A. J. Coffey, D. B. Bentley, M. R. Johnson. *Imperial College London, London, UK; Wellcome Trust Sanger Institute, Cambridge, UK; University of Liverpool, Liverpool, UK*

ABCB1 is a putative mechanism for drug resistance in epilepsy. Previous studies have found associations between drug resistance and three SNPs in this gene, but others have been unable to replicate these findings. We aimed to identify associations between seizure outcomes and SNPs in ABCB1 and four other transporter genes (ABCC1, ABCC2, ABCC5, and ABCB4). Five hundred and two SNPs identified from public databases and extensive re-sequencing were genotyped in three populations. Linkage disequilibrium patterns were analysed in 192 unrelated normal Caucasian subjects with Haploview, and a subset of 71 tagging SNPs across the five genes was defined for future studies. Analysis of genotypes in patients with retrospectively defined seizure outcomes showed no significant associations in 76 drug resistant and 77 drug responsive patients. However, a subgroup analysis uncovered a significant association between a cluster of five SNPs in ABCB1 centred on C1236T ($p = 0.0058–0.0097$, $OR = 4.27$) in patients with lesional drug resistant epilepsy. This putative association is currently undergoing further analysis in 447 patients with prospectively validated seizure outcomes, using Cox regression models and time to event outcomes. These findings suggest that ABCB1 may have a role in drug resistance in lesional but not non-lesional epilepsy, which may explain previous discordant findings.

009 BRAIN ''IMAGING'' IN THE RENAISSANCE

A. Paluzzi, A. Belli, P. Bain, L. Viva. *Division of Neurosciences, Charing Cross Hospital, London, UK; Dept Radiology, James Cook University Hospital, Middlesbrough, UK*

A renaissance painter, the Church, and neuroanatomy: what do they have in common? Many would think not much, perhaps not least Raphael himself until the end of a glorious career that brought him fortune and fame all over Europe. But did he try to hide a message in the Transfiguration of Christ, his last and arguably most famous painting? Was this a deliberate attempt to rationalise deity through science or a tongue-in-cheek send up of religious themes in the face of a pompous and self-important clergy? Here we show how the painting may contain some striking neuroanatomical features, too detailed and accurate to have arisen by chance. The brain must have been a fascinating mystery to a Renaissance artist but some speculation existed at that time on the function of its parts. We suggest that Raphael used this knowledge in the Transfiguration of Christ and offer some historical perspective on the artist and the period in which he lived that may help unravel the enigma of its symbolism.

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010 NEUROSARCOIDOSIS PRESENTING WITH COGNITIVE IMPAIRMENT: A SERIES OF FIVE CASES

J. M. Flowers, S. M. Omer, D. W. Wren, A. Y. Al-Memar. *Atkinson Morley Wing, St George's Hospital, London, UK*

Background: Clinically evident nervous system involvement occurs in 5–15% of patients with sarcoidosis. Presentation with prominent cognitive features directly resulting from neurosarcoidosis has rarely been reported.
Subjects: We describe the clinical, neuropsychological, CSF, and radiological features of five cases (age range 29–65 years; three male) of biopsy proven neurosarcoidosis in which cognitive impairment was a major presenting feature. The index case, a 29 year old male, presented with a 3 year history of impaired short term and spatial memory and difficulties with problem solving. Neuropsychometric assessment demonstrated significantly impaired mental tracking, concentration, cognitive speed, reduced spontaneous memory/memory retrieval, and subtle difficulties with expressive language. MRI brain showed abnormal enhancement of the leptomeninges and perivascular spaces, and patchy parenchymal signal change in the cerebral cortex and brain stem. CSF analysis showed a raised protein, low glucose, and normal cell counts, and was negative for organisms and acid fast bacilli. Biopsy confirmed non-caseating granulomata. The patient responded to treatment with pulsed intravenous methylprednisolone and oral prednisolone and methotrexate. Four further cases of neurosarcoidosis presenting with cognitive impairment will be discussed.
Conclusion: Neurosarcoidosis presenting with cognitive deficits may not be as rare as previously thought and represents a treatable cause of dementia.

011 NEGATIVE 14-3-3 CASES OF SPORADIC CJD

K. L. Murray, C. A. Heath, R. G. Will, R. S. G. Knight, A. J. E. Green. *National CJD Surveillance Unit, Western General Hospital, Edinburgh, UK*

Introduction: Cerebrospinal fluid (CSF) 14-3-3 test was introduced in December 1996 as a useful investigation into sporadic CJD (sCJD). However, occasionally the test is negative, potentially delaying correct diagnosis. This study describes all 14-3-3 negative, confirmed sCJD cases in the UK.
Methods: The National CJD Surveillance Unit archives were used to identify all pathologically proven sCJD cases with negative 14-3-3 results between December 1996 and December 2004. Clinical and pathological data was obtained via retrospective case note analysis. Their characteristics were compared with a general sCJD reference group.
Results: Twenty-six patients were identified from 371 definite cases. Mean age at referral was significantly younger (59.8 vs 66.7 years; $p=0.01$). Mean disease duration was prolonged (15.4 vs 7.2 months; $p<0.001$). Onset more frequently included unsteadiness but visual onset was never seen ($p=0.004$). The usually rare sCJD subtypes, MM2 and MV2, were most common whereas MM1 and MV1 subtypes associated with classical sCJD phenotype were underrepresented. Pathology was as expected for codon 129-prion protein type.
Conclusion: Negative 14-3-3 sCJD cases are clinically and pathologically atypical, probably reflecting the underlying codon 129-protein type. A negative 14-3-3 does not exclude the diagnosis, particularly in young patients with unusual clinical presentations and a prolonged disease course.

012 THERAPEUTIC INTERVENTIONS IN HTLV-1-ASSOCIATED MYELOPATHY (HAM)

G. P. Taylor, S. Youshya, F. Martin, A. Fedina. *Imperial College, London, UK*

Approximately 3% of the 20 000 persons in England and Wales infected with HTLV-I will develop HAM. There is no consensus on the management of HAM. In Japan short courses of Interferon-α are recommended with short-term benefit. Elsewhere, corticosteroids are often prescribed. Since 1996 we have studied the potential of nucleoside analogues (that inhibit HTLV-I reverse transcriptase) in patients with HAM. In 1999 we reported that lamivudine reduced HTLV-I viral load (v/l) with clinical benefit in some patients but subsequently in a randomised, placebo controlled trial of lamivudine plus zidovudine no change in immunological, virological, or clinical parameters was found. We now present data on the in vivo efficacy of tenofovir, the most potent HTLV-I RT inhibitor in vitro and on pulsed corticosteroids. Treatment for up to 6 months was associated with a small reduction in v/l in two, a small increase in two, and no change in a fifth patient and no clinical improvement. These results probably reflect natural variation in v/l. Conversely, 1 g Methylprednisolone daily for 3 days has measurably improved pain and gait for up to 3 months in patients with chronic HAM without altering v/l. An international randomised trial of corticosteroids in acute HAM is planned.

013 BILATERAL SEQUENTIAL ALIEN LIMB IN A PATHOLOGICALLY CONFIRMED CASE OF CREUTZFELDT-JAKOB DISEASE (sCJD)

T. Webb, S. Pal, D. Siddique, S. Brandner, S. Wroe, J. Collinge. *National Prion Clinic, NHNN, University College London Hospital NHS Trust, London, UK; MRC Prion Clinic, Dept Neurodegenerative Disease, Institute of Neurology, Queen Square, London, UK*

We report a case of pathologically confirmed sporadic Creutzfeldt-Jakob disease (sCJD) presenting with a bilateral sequential alien limb phenomenon. A 62 year old lady presented with a month's history of noticing her left hand moving about and waving in her field of view involuntarily. She was oblivious to her hand knocking objects and resting in her plate of food. Subsequently her left arm became immobile and she began to neglect the left side. Her right arm then began to demonstrate signs of alien limb. She deteriorated following admission with cognitive impairment and visual disorientation, dying shortly afterwards. MRI brain demonstrated widespread cortical atrophy; EEG was non-specific. CSF examination revealed raised 14-3-3 and s100 with no other significant abnormalities. A post-mortem demonstrated typical features of sCJD with evidence of spongiform encephalopathy. Immunostaining was positive for abnormal prion protein. Bilateral sequential alien limb has not been reported previously in prion disease. The progression seen in this case may relate to the underlying degenerative process and indicates that this sign can evolve as lesions progress. This case highlights that alien limb may be a presenting feature for sCJD and should be considered in the differential diagnosis.

014 SMELL TESTS COMPARED TO DOPAMINE TRANSPORTER IMAGING IN DIAGNOSIS OF IDIOPATHIC PARKINSON'S DISEASE: A PILOT STUDY

J. Deeb, L. J. Findley, M. Shah, N. Muhammed, C. H. Hawkes. *Essex Neuroscience Centre, Romford, UK*

Background: There is no specific test for idiopathic Parkinson's disease (IPD) and errors of diagnosis may occur in 10–20%. Dopamine transporter imaging (DaTScan) has high sensitivity for IPD but cannot distinguish parkinsonian syndromes. Olfactory identification is impaired in about 80% of patients with IPD but likewise has low specificity.
Methods: We tested 11 patients with IPD all conforming to the UK PD Brain Bank criteria and scoring 27/30 or greater on the Minimental Test. The following procedures were used: (1) University of Pennsylvania Smell Identification Test (UPSIT; range 0–40); (2) olfactory evoked potentials (OEP) to hydrogen sulphide using the Burghart OM2 Olfactometer; and (3) [123]I FP-CIT DaTScan. For controls we used our database of 245 healthy subjects for UPSIT and 70 of these for OEP. A value exceeding two standard deviations from the mean, adjusted for age was considered abnormal.
Results: Abnormal DaTScan imaging was found in 10/11 IPD. UPSIT results were abnormal (anosmic range) also in 10/11 IPD. Two patients had discrepancy between DaTScan and UPSIT tests. OEP latency was delayed in 8/11 while OEP amplitude was low in 3/11.
Conclusion: This preliminary analysis suggests that DaTScan and UPSIT are of approximately equal diagnostic value but they may measure different aspects of IPD.

015 ACETAZOLAMIDE RESPONSIVE PAROXYSMAL OCULAR TILT REACTION SYNCHRONISED WITH FOCAL LIMB DYSTONIA: DISCUSSION OF THE LIKELY ANATOMICAL SUBSTRATE

A. Petzold, M. A. Paine, P. Riordan-Eva, M. A. Gresty, G. T. Plant. *NHNN, London, UK; St Vincent's Hospital, Melbourne, Australia; King's College Hospital, London, UK; Imperial College, London, UK*

Acetazolamide has been used successfully in a range of paroxysmal disorders. Here we describe the 21 year follow up of a previously presented patient (10 year follow up, EUNOS 2005). This 52 year old lady suffered from a brainstem haemorrhage due to a right sided cavernoma at the age of 31 years. She initially presented with dizziness, diplopia, and a left haemiparesis that resolved. She then developed a paroxysmal disorder consisting of diplopia and left haemidystonia. The symptoms persisted for 10 years when our detailed examination

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revealed that the paroxysmal movements of the left arm (EMG) occurred synchronously with the paroxysmal left over right skew deviation and clockwise conjugate ocular torsion. She has been attack-free for 10 years on acetazolamide (250 mg/d). Each attempt to discontinue acetazolamide has led to recurrence of her attacks. We will describe the 21 year follow up investigations in this patient whilst off acetazolamide. On the background of recent intraoperative data following deep brain stimulation of the subthalamic region (*J Neurol* 2005;**252**:457) we speculate that the cavernoma causes the paroxysmal neuronal activity, which probably via ephaptic transmission, synchronously stimulates anatomically adjacent pathways causing OTR and haemidystonia.

016 A POPULATION BASED STUDY OF YOUNG ONSET PARKINSON'S DISEASE IN SOUTH WALES

M. M. Wickremaratchi, A. Jones, N. P. Robertson, Y. Ben-Shlomo, H. R. Morris. *School of Medicine, Cardiff University, Cardiff, Wales, UK*

Although the incidence of Parkinson's disease (PD) increases with age, 10–15% of patients with PD develop disease at less than 50 years of age. We are undertaking a novel nested community based study of young onset Parkinson's disease (YOPD) in South Wales. To date we have identified 46 patients with YOPD and disease onset of 55 years or younger (mean age was 43.8 years, range 29–55 years, 13 patients under 40 years). The majority were male (34% female) and resident outside the city of Cardiff (59%). Most YOPD patients were diagnosed to have PD within the neurology service (83.5% neurology; 5.5% geriatrics; 5.5% GP; 5.5% general medicine). The mean on state UPDRS motor score was 16/108, and the mean MMSE was 29/30. One-third of our YOPD cases have a family history of PD (95% CI 20 to 46). Over half of the patients have motor fluctuations (54%, 95% CI 39 to 69), which is comparable with late onset disease. However, dystonia is more common occurring in 43% (95% CI 29 to 59) at some point (including at disease onset and during exercise) compared with previous reports of between 0–10% in the late onset group. Our preliminary data confirms differences between YOPD and late onset Parkinson's disease (LOPD).

017 RELATIONSHIP BETWEEN AMYLOID DEPOSITION AND ATROPHY RATES IN ALZHEIMER'S DISEASE USING ^{11}C-PIB RADIOTRACER

H. A. Archer, P. Edison, N. C. Fox, J. Barnes, C. Frost, T. Yeatman, D. J. Brooks, M. N. Rossor. *Institute of Neurology, London, UK*

^{11}C-PIB is a novel PET tracer that binds to cerebral amyloid. Uptake has been shown to be increased in Alzheimer's disease (AD) subjects over controls. The rate of cerebral atrophy also increases in AD; this rate varies between individuals. We aimed to assess the relationship between amyloid deposition measured with ^{11}C-PIB and the rate of cerebral atrophy measured with serial MR scans.
Methods: Eight AD subjects (MMSE 16–26) underwent ^{11}C-PIB PET scanning and serial volumetric MR imaging. The PET images of ^{11}C-PIB tracer uptake were analysed with a probabilistic region of interest atlas and Statistical Parametric Mapping. The Brain Boundary Shift Integral calculated from registered serial MR scans was used to determine the annual rates of atrophy.
Results: Regression analysis revealed a positive correlation between rates of whole brain atrophy and cortical association area amyloid deposition ($p=0.025$). Rates of atrophy were also correlated with frontal, parietal and occipital lobes, and the anterior and posterior cingulate. However, these deposition rates were all highly correlated and the only statistically significant independent predictor of the rate of cerebral atrophy was posterior cingulate ^{11}C-PIB deposition ($p=0.013$).
Conclusions: There is a positive correlation between cortical grey matter amyloid load and cerebral atrophy.

018 SPATIAL WORKING MEMORY AND SPATIAL NAVIGATION IMPAIRMENT IN THE MILD STAGE OF FRONTOTEMPORAL DEMENTIA, ALZHEIMER'S DISEASE, AND VASCULAR DEMENTIA

J. Laczo, J. Hort, K. Vlcek, M. Vyhnalek, M. Bojar, J. Bures. *Dept Neurology, Second Faculty of Medicine, Charles University in Prague, Czech Republic; Dept Neurophysiology of Memory, Institute of Physiology, Czech Academy of Sciences, Czech Republic*

We used two tests to compare spatial working memory (SWM) and spatial navigation impairment in the mild stage of frontotemporal dementia (FTD), Alzheimer's disease (AD), and vascular dementia (VD). In spatial memory task (SMT), aimed at SWM, subjects should remember and than recall position of 2, 4, and 6 locations in the presentation order. In hidden goal task (HGT), testing navigation, subjects should locate a hidden goal in the arena in five subtests. Depending on the subtest, start position and/or cues are used for navigation. Both tests consisted of real space and computer version. Fifty subjects were divided into four groups: FTD, AD, VD, and controls. Diagnosis was based on NINCDS–ADRDA, NINCDS–AIREN and DSM-IV criteria, and supported by neuropsychological examination. Larger differences were found in HGT task. The AD group was impaired in all subtests, while VD group was impaired only in allothetic navigation. In SMT task we found similar impairment of AD and VD groups. The FTD group was not impaired in any of the tests. Our results suggest SWM impairment in AD and VD and more general spatial navigation impairment in AD than in VD. Supported by GACR grant 309/05/0693.

019 GDAP1 GENE MUTATIONS IN FIVE CZECH CMT FAMILIES WITH EARLY ONSET AXONAL HMSN

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Charcot-Marie-Tooth type 4A (CMT4A) neuropathy is the most common recessively inherited motor and sensory peripheral neuropathy (HMSN) of either axonal or demyelinating type, severely affecting the patients in infancy. It is caused by mutations in ganglioside-induced differentiation-associated protein 1 (GDAP1) gene. We describe the first findings of mutations in GDAP1 gene in Czech CMT patients and their phenotypes. We sequenced the gene in 70 patients from 65 families with disease onset in the first decade and without the most common CMT mutations. All pedigrees were compatible with autosomal recessive (AR) inheritance. Patients with both axonal and demyelinating CMT types were included. We detected two mutations (Leu239Phe and Arg191stop), one of which is novel, in six patients from five families. The disease was manifested in all patients before the age of six years mostly by foot deformity or tripping. On physical examination upper extremities were variably affected in all except for one 39 year old man. Nerve conduction studies in the patients aged 8–40 years showed axonal neuropathy. GDAP1 gene mutations represent a significant cause −7,7% of CMT in Czech families (AR or sporadic cases) with early onset CMT and with excluded CMT1A. Supported by IGA MZCR 1A8254

020 TO SNEEZE OR NOT TO SNEEZE: A LITERATURE REVIEW OF PHOTOPTAMOSIS

A. Cheesman. *Royal London Hospital, London, UK*

Francis Bacon observed in 1635 that ''Looking against the Sunne, doth induce Sneezing''. The photic sneeze reflex is present in perhaps 25% of the population yet is only occasionally discussed and remains partially understood. This may reflect its benign nature, although it is potentially hazardous for drivers emerging from tunnels into bright sunlight or pilots turning to face into the sun. The documented history, neuroanatomy, and physiology of the photic sneeze reflex will be discussed and allied phenomena of sneezing in response to other triggers reviewed.

021 LEUCODYSTROPHY, CEREBRAL CALCIFICATION, AND CYSTS (LCC): REFINEMENT OF A NEW CLINICAL PHENOTYPE

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Leucodystrophy, cerebral calcification, and cysts (LCC) is a rare syndrome, recently described in six unrelated patients. A disorder of childhood onset, patients exhibit pyramidal, extrapyramidal, and cerebellar signs, as well as cognitive impairment and seizures. We describe a sibling pair with LCC. Both patients had onset of seizures in infancy, mild learning difficulty, ataxia, and parkinsonism. Cranial CT imaging revealed extensive bilateral and asymmetrical coarse calcification in the dentate nuclei, basal ganglia, thalamus, and periventricular white matter in both cases. Magnetic resonance imaging demonstrated extensive abnormal high signal in the white matter on T2 weighted images with relative sparing of the corpus callosum and subcortical U fibres as well as small CSF dense cysts in the white matter. CSF results were normal. Magnetic resonance spectroscopy placed on abnormal parieto-occipital grey and white matter demonstrated loss of white

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matter neuroaxonal tissue without significant gliosis. The parents were clinically and radiographically normal. In one case, a new large cyst and a number of small cysts were identified with serial imaging indicating that white matter cysts are not an essential requirement for the phenotype. The occurrence in a sibling pair, with unaffected parents suggests an autosomal recessive aetiology.

022 VIDEO-ASSISTED THORACOSCOPIC THYMECTOMY FOR SURGICAL TREATMENT OF MYASTHENIA GRAVIS

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Video-assisted thoracoscopic surgery (VATS) is an attractive alternative to conventional sternotomy for thymectomy for myasthenia gravis (MG). Potential benefits include improved cosmesis, faster recovery, and minimal chest wall disruption but doubts exist about its efficacy. We describe our initial experience with T-2 ''classic'' VATS thymectomy.
Methods: Under GA and single-lung ventilation, full mediastinal dissection was performed through three 3 cm incisions. Ten cases (five male, five female), mean age 60.2 years (30–83), were undertaken from 1999–2005. Preoperative staging and status at follow up was assessed by MGFA Clinical and Postintervention Status.
Results: Histologically, five patients had thymoma (Masaoka 1-2a), three hyperplastic thymus, and one thymic carcinoma. Median operation time was 150 minutes, drain removal 1.5 days, and hospital stay 4 days. There was no mortality or morbidity including conversion to open surgery or phrenic nerve damage. At mean follow up of 40 months overall improvement was observed in 87% (6/7) patients; 2/7 (29%) reported complete stable remission (CSR), and 4/7 (57%) minimal manifestations (MM-3).
Conclusion: ''Classic'' T-2 VATS is a safe and effective approach for MG with real benefits over open surgery. This may influence referral practice, especially in UK where the Thoracic Register shows only 13% mediastinal excisions are through VATS.

023 EFFECT OF SILDENAFIL CITRATE (VIAGRA) ON CEREBRAL BLOOD FLOW IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background: Sildenafil citrate (Viagra) causes nitric oxide (NO) dependent vasodilatation by selectively inhibiting phosphodiesterase type 5. Multiple sclerosis (MS) patients show evidence of reduced cerebral blood flow (CBF), particularly in the grey matter, and this is thought to be linked with cognitive dysfunction. Because of elevated levels of NO precursors in the MS brain due to pathological activity, we have postulated that sildenafil could be influential in increasing CBF in MS patients.
Methods: Six SPMS patients, five healthy controls and seven diabetic subjects participated in this study. Subjects were scanned twice; before and an hour after taking sildenafil. Perfusion arterial spin labelling scans were acquired to quantify resting CBF pre- and post-sildenafil. For analysis, data was segmented into grey and white matter.
Results: Estimated CBF was significantly increased by sildenafil in both grey matter (mean increase 25%, $p=0.03$) and white matter (mean increase 28%, $p=0.01$) in all the SPMS patients, but not in the healthy controls or the diabetic subjects.
Conclusions: Sildenafil citrate appears to have a specific effect on CBF in MS patients when compared to controls or diabetic subjects. It is possible that sildenafil could have clinical implications in increasing CBF and reducing cognitive impairment in MS patients.

024 NOGO-A AND NOGO-66 RECEPTOR IN MULTIPLE SCLEROSIS AND AMYOTROPHIC LATERAL SCLEROSIS SPINAL CORD AND INJURED HUMAN PERIPHERAL NERVES

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Myelin associated proteins have inhibitory effects on axonal regeneration, particularly Nogo-A, which binds to the Nogo-66 receptor. We have studied their changes by immuno-histochemistry in post-mortem multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) spinal cord, and injured human peripheral nerves. The number and intensity of Nogo-A and Nogo-66 receptor positive motoneurones were significantly increased in MS and ALS spinal cord (eg for Nogo-A in MS $70\%\pm5\%$; ALS $66\pm8\%$; controls $33\pm3\%$; $p<0.02$ for both MS, ALS). Dense Nogo-A immunostaining was observed in sensory neurones in control human dorsal root ganglia (DRG), axons in dorsal and ventral roots, and peripheral nerves. The number of Nogo-A positive large sensory neurones was decreased after acute avulsion injury in DRG (control $83\pm4\%$; avulsed $68\pm6\%$; $p<0.05$). Nogo-A was unchanged in injured peripheral nerves, suggesting translocation from the cell body, and Nogo-66 receptor levels were generally very low in intact and injured nerves. The data supports blockade of Nogo-A and its receptor as being potentially therapeutic in neurodegenerative and neuro-inflammatory disorders. The marked presence of Nogo-A with low Nogo-66 receptor levels in peripheral nerves indicate additional roles, such as axonal guidance, in the developing, adult, and regenerating peripheral nervous system.

025 RAISED WHITE MATTER MYO-INOSITOL AFTER A CLINICALLY ISOLATED SYNDROME IS ASSOCIATED WITH THE SUBSEQUENT DEVELOPMENT OF MULTIPLE SCLEROSIS

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On proton MR spectroscopy (1H-MRS), myo-inositol (Ins) is significantly raised in the normal appearing white matter (NAWM) of patients presenting with clinically isolated syndromes (CIS) suggestive of multiple sclerosis (MS). The aim of this study was to investigate if this increase is related to the subsequent development of clinically definite MS (CDMS). Single voxel 1H-MRS (PRESS with TR 3000 ms, TE 30 ms) was performed on the NAWM of 76 patients (66 optic neuritis, five brainstem, five spinal cord syndromes; 49 female, 27 male; median age 32 years) a mean of 19 weeks after a CIS and in 46 healthy controls (24 female, 22 male; median age 36 years). Patients were followed up for 3 years. Ins was significantly higher in the NAWM of the CIS patients who developed CDMS (mean 4.02 mM, SD1.03) when compared with controls (mean 3.31 mM, SD 0.84, $p=0.00008$) and with patients who did not have CDMS after 3 years (mean 3.36 mM, SD 0.77, $p=0.001$). CIS patients with high levels of Ins where more likely to convert to CDMS and at a faster rate than those with lower levels. Ins appears to be an in vivo marker of clinically important pathological abnormality in the NAWM.

026 SENSITIVITY OF HIGH RESOLUTION MRI FOR DETECTING GREY MATTER DEMYELINATION IN THE SPINAL CORD IN MULTIPLE SCLEROSIS: A POST-MORTEM MRI HISTOPATHOLOGICAL CORRELATIVE STUDY

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Aim: To evaluate the sensitivity of high resolution magnetic resonance imaging (MRI) for detecting grey matter (GM) demyelination in the spinal cord in multiple sclerosis (MS).
Methods: Proton Density (PD) images were acquired at 4.7 Tesla using formalin-fixed spinal cord autopsy material from 11 MS patients. Tissue sections from the cervical or thoracic cord were stained for Proteolipid protein and assessed histopathologically. Analysis of the corresponding PD images was performed with observers blinded to the histopathological findings.
Results: On histopathological analysis a mean 19.7% of the white matter (WM) was completely demyelinated and 11.4% showed reduced myelin density. 21.3% of the GM was completely demyelinated and 7.2% had reduced myelin density. All GM lesions were mixed GM/WM lesions. In two cases the MR images were of poor quality and were excluded from the analysis. MRI analysis of the remaining nine cases detected 94.6% of completely demyelinated WM lesions (in comparison to histopathological analysis) and 75% of WM areas with reduced myelin density. In the GM 87.5% of completely demyelinated lesions and 33.3% of areas of reduced myelin density were visible.
Conclusion: Post-mortem imaging at 4.7 Tesla is highly sensitive for detecting GM demyelination in the spinal cord in MS.

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027 THE MULTIPLE SCLEROSIS IMPACT SCALE (MSIS-29) AS A MEASURE OF QUALITY OF LIFE IN MULTIPLE SCLEROSIS

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Objectives: To investigate the relationship between functional ability and quality of life in patients with multiple sclerosis (MS).
Methods: A population based study identified patients with definite MS within the north-east region of Northern Ireland, who were asked to complete the multiple sclerosis impact scale -29 (MSIS-29) questionnaire. Their functional ability was measured by the Kurtzke expanded disability status scale (EDSS). Patients were classified as having mild (EDSS 0–3.0), moderate (EDSS 3.5–5.5) or severe (EDSS 6.0–9.5) MS.
Results: The 191 participants (65 male, 126 female) had a mean age of 48.5 (SD 12.5) and were a mean 15 years since onset of symptoms (SD 11.72). EDSS ranged from 0 to 8.0 (median 6.0). The MSIS-29 revealed mean physical and psychological scores of 47.5 and 41.8 respectively. There was a significant difference in mean physical scores with EDSS (mild 26.9, moderate 49.2, and severe 61.5) and years after onset. Mean psychological scores were greatest in the moderately disabled group (mild 35.7, moderate 50.1, and severe 43.87).
Conclusions: There was a clear correlation between physical score of the MSIS-29 and Kurtzke EDSS. Psychological impact score was greatest in patients with early progressive MS.

028 RAISED PREVALENCE OF HERPES SIMPLEX TYPE-2 ANTIBODY IN MULTIPLE SCLEROSIS

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Introduction: Earlier small studies have suggested an association of multiple sclerosis (MS) with herpes-simplex virus type 2 (HSV-2; genital herpes). Seropositivity to HSV-2 correlates with sexual partner number.
Methods: 571 stored serum samples (1995–2002) from patients with clinically definite MS were compared by age and gender to general population samples from public health laboratories (n = 3 646) and London blood donors (n = 1 494). HSV-2 assay was by specific monoclonal antibody blocking ELISA or Western Blots.
Results: HSV-2 seroprevalence in older (35–64 years) MS patients was raised compared to the general population in an unadjusted comparison (17.2% vs 11.5%; χ^2 6.86, p = 0.009). HSV-2 seroprevalence was also higher in MS patients than in blood donors (16–34 years, 11.5% vs 6.1%, χ^2 4.54, p = 0.03; 35–64 years, 20.7% vs 10.1%; χ^2 13.8, $p<0.001$. In logistic regression analyses increased age, female sex, and MS positive status each contributed significantly to the model using likelihood ratio testing, each independently increasing the odds of HSV-2 seropositivity. The adjusted odds ratio for having MS was 1.61 (95% CI 1.09 to 2.37).
Conclusion: HSV-2 seropositivity is elevated in our sample of clinically definite MS patients from England and Wales. This may be non-specific, but if correct has implications for environmental exposure.

029 REMISSION OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY AFTER TREATMENT WITH ALEMTUZUMAB (CAMPATH 1-H)

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is thought to be an immune mediated disorder characterised by a progressive or relapsing course. We discuss a patient with intravenous immunoglobulin (IVIg) dependant relapsing CIDP, who achieved remission following treatment with alemtuzumab. A 19 year old female presented with distal paraesthesia and weakness. Investigations supported a diagnosis of CIDP. She was successfully treated with intravenous immunoglobulin (IVIg). After the forth relapse she started steroids and later azathioprine with marginal benefit. Eighteen months after onset the patient had experienced 11 relapses, with an average interval of seven weeks between IVIg treatments. She was treated with alemtuzumab. Two further relapses occurred, at 5 weeks and 8.5 weeks post treatment, both successfully treated with IVIg. Oral prednisolone and azathioprine were withdrawn. The patient had no relapses for 16 months following alemtuzumab, but then suffered a further relapse with distal weakness and numbness developing over 3 weeks. She was treated with IVIg with good response. A further course of aletuzumab is planned. Alemtuzumab is a monoclonal antibody that targets CD52 antigen and is thought to have some role in immune modulation. This case demonstrates the potential use of monoclonal antibodies as a novel treatment for severe relapsing CIDP

030 GETTING THE MEASURE OF SPASTICITY IN MS: THE MULTIPLE SCLEROSIS SPASTICITY SCALE (MSSS-88)

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Background: Spasticity can be measured through electrophysiological, biomechanical, and clinical evaluation (typically using Ashworth scale). None of these techniques incorporate the patient's experience of spasticity, nor how it affects their daily lives.
Objective: To construct a rating scale quantifying the impact of spasticity on people with multiple sclerosis (PwMS).
Methods: Qualitative methods (patient interviews, focus groups, expert opinion, literature review) were used to develop a conceptual framework of spasticity impact, and items to convert this framework into a rating scale. A preliminary scale was administered to PwMS and spasticity. Guided by Rasch analysis, we constructed and validated a rating scale for each component of the conceptual framework.
Results: The conceptual model had eight components addressing symptoms (muscle stiffness, pain and discomfort, muscle spasms), physical impact (activities of daily living, walking, body movements), and psychosocial impact (emotional health, social functioning). Two postal surveys (n = 272; n = 259) led to the construction and validation of an 88-item instrument.
Conclusions: The MS Spasticity Scale (MSSS-88) is a reliable and valid patient-based measure of the impact of spasticity in PwMS. It has the potential to advance outcomes measurement in clinical trials and clinical practice, and provides a new perspective in the clinical evaluation of spasticity.

031 INTRODUCING THE SOUTH WEST IMPACT OF MULTIPLE SCLEROSIS (SWIMS) PROJECT: A POPULATION-BASED NATURAL HISTORY PROJECT TO ACQUIRE PATIENT-ORIENTATED INFORMATION ABOUT THE IMPACT OF MULTIPLE SCLEROSIS

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Background: To develop better services and treatments for multiple sclerosis (MS) we need to understand how the full spectrum of the disease affects people's lives. The SWIMS project aims to do this, using a range of measurement techniques. Natural history studies of MS have traditionally been based on physician-orientated data, predominantly the expanded disability status score (EDSS). Because of the limitations of the EDSS, the SWIMS project also incorporates patient-focussed outcomes.
Objective: To create a natural history database of physician- and patient-based measures in MS, including clinically isolated syndromes (CIS). This will be used to develop outcome measures for clinical trials and inform clinical practice.
Methods: Selected measurement instruments are administered by postal questionnaire every 6–12 months to patients with MS or CIS in Devon and Cornwall. Items enabling the longitudinal profiling of medication use, service use, relapse rate, and perceived disease progression are included. EDSS is collected at routine appointments.
Results: We report baseline data on the first 200 participants, including patient-reported relapse rate, MS course; symptom, medication, service use profiles; intervals between first symptom, GP visit and diagnosis. Currently recruitment is >70% (n = 393) and compliance is >90% (n = 269).
Conclusion: The SWIMS project is generating important data enabling comparison of patient and physician-orientated measures.

032 SUBTLE BLOOD BRAIN BARRIER DISRUPTION IN CHRONIC NON-ENHANCING LESIONS IN MS

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Objective: To use contrast enhanced imaging to find evidence of blood brain barrier (BBB) disruption in chronic non-enhancing lesions – both T1-hypointense and isointense – of patients with relapsing remitting (RR) and secondary progressive (SP) MS.

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Methods: Serial T1 relaxation time (T1-RT) maps were obtained before and at three time points up to one hour after administering Gd-DTPA (0.3 mmol/kg). Paired regions of interest (ROI) were placed around non-enhancing lesions and contralateral normal appearing brain tissue (NABT). T1 relaxation rate (T1-RR) rise per unit time post contrast, where T1-RR is defined as the inverse of T1-RT, was used to quantify BBB leakage.
Results: Nineteen patients were scanned (10 SPMS, 9 RRMS). The time averaged T1-RR rise was 8% in lesions and 4% in NABT. Greater T1-RR rise was observed in lesions than in NABT ($p<0.001$ at all timepoints). The T1-RR rise was not different in T1-hypointense vs T1-isointense lesions ($p=0.86$, 0.44, and 0.14 for respective timepoints), or between RR and SP MS ($p=0.96$, 0.67, and 0.89 for respective timepoints).
Conclusion: Low grade BBB leakage is a consistent feature of chronic, non-enhancing lesions in MS. The BBB leakage is apparent in all clinical and lesion subtypes studied.

033 SLEEP AND FATIGUE IN MULTIPLE SCLEROSIS

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Objective: This study aimed to describe the frequency and pattern of sleep disturbance in a group of outpatients with multiple sclerosis (MS), examine self-reported reasons for sleeps difficulties, and explore the relationship between sleep quality and fatigue.
Method: Sixty patients with MS were recruited from an outpatient clinic. Subjects completed self-rating scales to measure fatigue and somnolence and kept a sleep diary for 7 days.
Results: Fatigue and daytime somnolence were both common in this group of patients (64% and 32%). Sleep problems were common including initial insomnia (sleep latency >30 minutes at least two nights per week in 42%), middle insomnia (two or more awakenings at least two nights per week in 53%), and terminal insomnia (waking early than desired at least twice per week in 58%). The reasons cited for different types of insomnia varied, with pain/discomfort and anxiety being the commonest causes of initial insomnia and nocturia the commonest cause of nocturnal awakenings. Middle insomnia was significantly correlated with fatigue during the day.
Conclusions: Sleep problems are common in MS, and are frequently associated with treatable symptoms including pain and nocturia. Sleep problems may be an important factor contributing to fatigue in patients with MS.

034 CAMS REVISITED: AN EFFICIENT BAYESIAN ANALYSIS OF ASHWORTH AND RIVERMEAD DATA

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Background: Established methods for analysis of data from instruments like the Ashworth Spasticity Scale and Rivermead Mobility Index are inefficient. Modern Computationally Intensive Bayesian methodology provides a model based framework for assessment of change giving more insight into the effects of treatments.
Objective: To demonstrate Bayesian model based approaches to the analysis of discrete choice data arising in clinical trials.
Methods: A model incorporating longitudinal change in patient state and treatment effects is fitted to data from the cannabinoids in multiple sclerosis (CAMS) trial. A Bayesian approach to inference is applied using Markov chain Monte Carlo methodology. Precision and power properties are assessed using computer simulation.
Results: The Bayesian modelling gives more precise inferences of treatment effects. Superior power and precision is confirmed by means of computer simulation.
Conclusion: Modern Bayesian methodology provides an efficient alternative to established techniques applied in clinical trials giving benefits in terms of greater statistical precision and better insight into patient change and treatment effects.

035 THE OPHTHALMODESMOSES: THE OCCULAR MANIFESTATIONS OF THE DISTAL ARTHROGRYPOSES

S. R. Irani, J. L. Holton, G. T. Plant. *NHNN, London, UK*

Objective: To report the clinical features and novel muscle histology of a father-and-son with identical ocular manifestations of distal arthrogryposis, and review the literature surrounding this association.
Participants and Methods: Ophthalmological and neurological examinations were performed for two subjects. In addition, electromyography, nerve conduction studies, orbital imaging, muscle biopsy, and mitochondrial genome analysis, were performed for the father.
Results: Father-and-son demonstrated classical core features of distal arthrogryposis. They also showed identical restrictive clinical ocular motility examinations with features of Brown's syndrome bilaterally. Muscle biopsy revealed sub-sarcolemmal accumulation of mitochondria, of abnormal morphology, containing type II paracrystalline inclusions. Mitochondrial genome mutation screen was negative.
Conclusions: This is the first reported case of a mitochondrial myopathy in the distal arthrogryposes, and the first report of a mitochondrial myopathy mimicking a restrictive ophthalmoplegia and a Brown's syndrome. It extends the spectrum of mitochondrial disease. The transmission from father-to-son suggests autosomal dominant inheritance of nuclear DNA involved in mitochondrial function. A review of the previously reported ocular features in distal arthrogryposis is presented and concludes that these, potentially treatable, cases are under recognised. To increase awareness of this association we name the ocular manifestations of the distal arthrogryposes: the ophthalmodesmoses.

036 BILATERAL LOSS OF VISION FROM HYPOPERFUSION

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A 74 year old man presented with sudden loss of vision in the left eye due to cilioretinal artery occlusion. He had a history of systemic hypertension, cardiovascular disease, carotid endarterectomy, and bilateral stable open-angle glaucoma. One day before the episode his antihypertensive medication was changed and the patient lost his vision following a single dose of candersartan, an angiotensin II receptor antagonist. His blood pressure was 80/60 mm hg on presentation and candersartan was discontinued. Five days later a 24 hour blood pressure monitoring was carried out and his blood pressure was found to be persistently around 180/90 mm hg. He was therefore started on valasartan, another angiotensin ii receptor antagonist. Due to pre-existing congestive cardiac failure, he was already on diuretics. Following a single dose of valasartan, he developed cilioretinal artery occlusion in the right eye. Flourescein angiography performed within 48 hours showed delayed arterial filling and gross hypoperfusion in both eyes. The synergistic interaction of the diuretic and the angiotensin receptor antagonists induced hypoperfusion of the cilioretinal arteries, which in an already compromised retinal circulation (due to long standing glaucoma and carotid artery stenosis) lead to infarction, which was demonstrated in the fundus fluorescein angiogram.

037 EFFECT OF REVERSIBLE ACUTE EXTERNAL OPHTHALMOPLEGIA IN MILLER-FISHER SYNDROME (MFS) ON PERCEPTUAL AND OCULOMOTOR VESTIBULAR PROCESSING

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During head movements, the vestibulo-ocular reflex (VOR) stabilises gaze, and a brainstem mechanism, the ''velocity storage'' (VS) mechanism, optimises the VOR during low frequency movements. The VS mechanism may be demonstrated by stopping after prolonged spinning on the spot; the engendered vertigo and associated nystagmus is prolonged by VS from 20s (ie endolymph motion duration) to circa 60s duration. The time constants of exponential decline in VOR slow-phase velocity and perceived angular velocity (normal value for both ≈15s) are well correlated suggestive of fidelitous perceptual processing of ascending vestibular brainstem signals. In chronic (not acute) external ophthalmoplegia (EO), patients do not complain of head-motion induced oscillopsia despite excessive retinal slip. Chronic EO possess increased visual motion perception thresholds and deficient VS that together help to reduce sensations of dizziness from visual-motion or inertial signals. During the evolution of an acute but recovering ophthalmolpegia (from MFS), we serially assessed oculomotor and perceptual VS time constants and were respectively as follows post-EO zenith in recovery: (1) 2 wks – 6.2s & 7.6; (2) 2.5 wks – 6.3s & 7.7; (3) 6 wks – 8.6 & 15.3. This shows asynchronous recovery of perceptual and oculomotor vestibular mechanisms, implying a differential processing of perceptual vestibular signals from (ascending) brainstem signals.

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038 LAUGHING ALL THE WAY TO THE ITEM BANK: HOW TO IMPROVE YOUR TREATMENT EFFECT BY IMPROVING YOUR OUTCOME MEASUREMENT

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Background: Patient completed rating scales are increasingly used as outcome measures in clinical trials. Some scales measure a wide range of functioning but have poor precision and poor responsiveness. Others have superior precision and responsiveness, but over a limited range with inevitable floor and ceiling effects. Both cases risk treatment effects being underestimated. New psychometric methods allow the development of ''item banks'' that achieve measurement precision over a wide range. Moreover, patients need only answer a few items. We are developing an item bank to measure physical functioning in multiple sclerosis (MS).
Method: Physical functioning items were generated from comprehensive literature review, examination of existing scales, and semi-structured interviews with MS patients.
Results: A total of 150 physical functioning items were generated. The first survey (n=100) is underway. Rasch analysis will be used to construct the item bank. We will report the results of the initial and validating (n=350) surveys.
Conclusions: New methods enable clinicians to solve the main problems of existing scales without increasing patient burden. Item banks are not subject to floor and ceiling effects, are highly sensitive to change across the spectrum of disability, and will be invaluable tools for measuring patient outcomes in future clinical trials.

039 MEANINGLESS STATISTICS AND THE ILLUSION OF FATIGUE

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Background: More than 30 rating scales purport to measure fatigue. Psychometric evaluation can help determine whether scales provide reliable and valid measurements. However, these statistical analyses can only be interpreted if the variable to be measured has been defined, and the scale items form a clinically meaningful and conformable set.
Objective: To assess the psychometric properties of the widely used 30-item fatigue impact scale (FIS), and the conceptual basis of its development.
Method: FIS data from 200 people with MS were analysed. Reliability and validity of the total score and three subscale scores (cognitive, physical, social) were assessed using traditional and new (Rasch analysis) statistical methods.
Results: Both types of analysis suggest the FIS is a reliable and valid measure. However, no clear conceptual grounding or construct definition underpinned scale development. A close examination of the items shows they concern outcomes ''distal'' to fatigue. As such, measurement is confounded and validity non-specific.
Conclusion: Results demonstrate how statistics can mislead investigators. In this case they give the illusion that fatigue is being measured rigorously. This problem is common to most fatigue scales, and highlights the fundamental importance of rigorous qualitative work in the development of clinically meaningful rating scales.

040 INTERNATIONAL CO-OPERATIVE ATAXIA RATING SCALE (ICARS): SUITABLE FOR CLINICAL PRACTICE AND TREATMENT TRIALS IN FRIEDREICH'S ATAXIA?

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Background: Developments in our understanding of Friedreich's ataxia (FDRA) have led to treatments aimed at slowing disease progression. Accurate evaluation of these treatments is dependent on rigorous measurement of clinical outcomes.
Objectives: This study evaluated the suitability, in measurement terms, of the international co-operative ataxia rating scale (ICARS) for clinical trials in FRDA.
Methods: Seventy seven people with genetically confirmed FRDA were measured using the ICARS. We tested two assumptions fundamental to its use: is it legitimate to report ICARS total and subscale scores in FRDA?; are ICARS total and subscale scores acceptable, reliable and valid?
Results: The ICARS total score effectively satisfied all psychometric criteria tested, but the extent to which it validly represents ataxia remains uncertain. One of three subscales (posture and gait) performed well. The other three subscales failed to satisfy tests of scaling assumptions, reliability, and validity.
Conclusions: Although the ICARS offers clinicians a method of quantifying ataxia, our findings raise important questions concerning the validity of inferences made from its subscales. This research emphasises the importance of fully testing measures before neurologists and researchers use them in clinical practice and trials, and make clinical and policy decisions on the results they generate.

041 THE FRIEDREICH'S ATAXIA IMPACT SCALE (FAIS) MEETS THE NEEDS OF TODAY'S CLINICAL STUDIES

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Background: Studies of Friedreich's Ataxia (FRDA) require rigorous patient-based outcome measures that meet different needs. Some studies typically need high precision in one or two specific areas. Others need measurement across the full spectrum of disease impact.
Objective: To develop a rating scale for FRDA that meets the differing needs of clinical trials, observational studies, and audit, whilst guaranteeing rigorous measurement.
Methods: Patient interviews, expert opinion, and literature review generated a conceptual model of impact of FRDA, and the items necessary to construct a scale. A preliminary scale sent to 307 patients (65% response rate). Rasch analysis guided scale development.
Results: The conceptual model has eight domains (body movement, speech and swallowing, upper limb functioning, lower limb functioning, ADL, isolation, mood, self perceptions). Data analyses led to the construction of two fully equitable versions of the scale, with subscales measuring all eight domains. A longer version of the FAIS for clinical trials, and a short version for observational studies, and audit.
Conclusions: The FAIS allows neurologists to measure patients' perceptions of their own health, and complements existing clinical based scales. The two fully interchangeable versions provide the measurement flexibility required by the demands of today's studies.

042 IS IT RASCH TO COMPARE THEE ON ANOTHER SCALE?

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Introduction: Patient completed rating scales are increasingly the outcome measures in clinical trials. Unfortunately, results from different scales cannot be compared, even when they clearly measure a common health construct (eg physical functioning). This longstanding problem, which prevents comparisons of studies and meta analyses, was solved by the development of sophisticated psychometric methods.
Objective: To determine if four scales purporting to measure physical functioning could be equated, so their results can be compared directly.
Methods: Data were Rasch analysed from 563 people with multiple sclerosis (MS) who completed: the physical functioning scales of the MS impact scale (MSIS-29) and short form 36 health survey (SF-36), functional assessment of MS (FAMS) mobility scale, and self report Barthel index (BI).
Results: The four scales measure a common construct, but at different places and across different ranges of the physical functioning variable. A table equating all possible scores from all four scales was produced.
Conclusion: The four scales studied measure physical functioning. Their results have been equated. Sophisticated methods offer investigators the opportunity to overcome the limitations of rating scales and advance outcomes measurement for clinical trials of neurological diseases. State of the art clinical trials will benefit from these methods.

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043 DOES THE GHQ-30 LEAVE ROOM FOR CHANGE?

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Background: Self-report scales are frequently used as primary outcome measures in clinical trials and practice. As such, their ability to detect change is crucial. The South West impact of multiple sclerosis (SWIMS) project with longitudinal data on MS patients over a decade, utilises the general health questionnaire (GHQ-30) as one of several scales administered biannually. This study investigates its suitability for that task.
Methods: The scale was administered to a sample of 200 people with MS (PwMS). Data were Rasch analysed from the first 200 patients; standard criteria were used to evaluate reliability and validity (person separation index, ordering of response options, item-person interactions, item-trait interactions, and item characteristic curves).
Results: Reliability was high (PSI = 0.942). Validity was supported by empirical support for response options, items forming a statistically conformable set, and fit of the observed data to the measurement model. Targeting was good and there was room for change on the variable.
Conclusions: The GHQ-30 is a reliable and valid indicator of general psychological health for PwMS. Evidence supports its suitability for use in a longitudinal study.

044 SEVERE ULNAR NEUROPATHY WITH PRESERVED HAND FUNCTION

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A 28 year old patient sustained a laceration on the medial side of the left arm 5 cm above the medial epicondyle with subsequent hypoesthesia in ulnar nerve distribution but with no hand wasting or weakness. Four years later, he presented with a small tender lump beneath the scar. Tapping the nodule produced tingling along the ulnar nerve distribution. MRI scan of the ulnar nerve showed a 6 mm×10 mm long soft tissue mass involving the ulnar nerve that has the typical MRI appearance of a neuroma. He had surgery and was found to have a large neuroma causing severe ulnar neuropathy with only about 10% of fibres in continuity. This was surprising to the surgeon as the patient had an excellent hand function. Nerve conduction study showed a significant median to ulnar (Martin-Gruber) anastomosis. The ulnar intrinsic hand muscles were innervated by fibres travelling along the median nerve. Variation in anatomy has saved the hand in a devastating injury to the ulnar nerve.

045 USE OF THE NOVEL CONTACT HEAT EVOKED POTENTIAL STIMULATOR (CHEPS) FOR THE DIAGNOSIS OF SMALL FIBRE NEUROPATHY

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The novel contact heat evoked potential stimulator (CHEPS) delivers rapid heat pulses to selectively stimulate Aδ or C fibres. Cerebral evoked potentials (EPs) can be recorded to provide a simple and quick method to detect small sensory fibre dysfunction. We have studied 13 patients with undiagnosed small fibre neuropathy using CHEPS, then validated findings by other tests such as skin biopsies, and report CHEPS abnormalities even in those with minimal or no change in thermal perception thresholds. To illustrate, a 43 year old patient reported constant pain and episodic redness in his feet, suggesting primary erythromelalgia or small fibre neuropathy. There were no abnormalities on clinical examination, or tests including monofilament, vibration, thermal perception thresholds, and nerve conduction studies. Aδ EPs from the vertex (Cz) using CHEPS (Medoc Ltd, Ramat Yishai, Israel) were of reduced amplitude and longer latencies from his face and arm in comparison with controls, and absent from his calf. This evidence of small fibre neuropathy was corroborated by a significantly reduced calf skin flare response (14.5 cm^2, controls mean 23.8 cm^2) and loss of intra-epidermal nerve fibres in his calf skin biopsy. CHEPS provides a sensitive non-invasive objective method to differentiate neuropathy from other chronic pain states.

046 ADVANCES IN SKIN BIOPSY DIAGNOSIS OF PERIPHERAL NEUROPATHY WITH MARKERS OF NOVEL SENSORY RECEPTORS

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Skin biopsies are particularly helpful in the objective diagnosis of small fibre sensory neuropathy, where clinical examination and nerve conduction studies may be normal, and thermal thresholds usually elevated. The discovery of novel sensory receptors and ion channels may advance skin biopsy diagnosis in patients with idiopathic painful neuropathy who have normal or decreased thermal thresholds. Punch skin biopsies ($\leqslant$4 mm) were taken from the calf of patients with established diabetic neuropathy with elevated thermal thresholds (n = 8), idiopathic painful small fibre neuropathy with minimal changes in thermal thresholds or hypersensitivity (n = 12), and control subjects (n = 8). Structural innervation was measured using the pan-neuronal marker (PGP9.5) or small fibre marker peripherin (PPN), and neurochemical studies performed, including immunostaining the heat and capsaicin receptor TRPV1. In diabetic skin, TRPV1 sub-epidermal and intra-epidermal fibres and their ratios to structural markers were decreased ($p<0.01$). In contrast, while painful idiopathic neuropathy patients showed overall reduced PGP9.5-immunoreactive intra-epidermal fibres ($p<0.04$), TRPV1 fibres were not significantly decreased, and in three biopsies appeared increased. Changes in sensory receptor levels observed in these skin biopsies provide a molecular basis for symptoms, and represent novel targets for neuropathic pain and idiopathic hypersensitivity disorders.

047 SENSORY RECOVERY AND PAIN PHENOMENA FOLLOWING BRACHIAL PLEXUS AVULSION INJURY AND SURGICAL REPAIRS

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Root avulsions from the spinal cord in brachial plexus traction injury may lead to intractable de-afferentation pain. Seventy six patients with brachial plexus avulsion injuries were studied using pain questionnaires and quantitative sensory testing. There was significant correlation between pain intensity (current visual analogue score) and number of roots avulsed, prior to surgery ($p = 0.0004$). Successful surgical repairs were associated with pain relief, including a new method which re-connected avulsed spinal nerve roots directly to the spinal cord. Sensory recovery was observed to thermal stimuli in the C5 dermatome. Allodynia to mechanical and thermal stimuli was observed mainly in border-zone of affected and unaffected dermatomes, in 18% of patients studied at early (<6 months) and 37% patients at later stages. Pain and sensation referred to the original source of the afferents occurred at a later stage (>6 months, 12% patients), and was related to indicators of nerve regeneration (eg Tinel's sign), whereas ''wrong-way'' referred sensations (eg referral of pain down the affected arm while shaving or drinking cold fluids) often occurred early and was transient (<6 months, 44% patients), suggesting CNS plasticity. Understanding these sensory mechanisms will help advance treatments for severe brachial plexus injury.

048 AN INVESTIGATION INTO PROTECTIVE AUTOIMMUNITY AFTER TRAUMATIC HEAD INJURY

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We undertook a pilot study to assess the immunological changes that occur following traumatic brain injury (TBI). We hypothesised that the exposure of lymphocytes to unusually large quantities of myelin antigens would stimulate autoimmune type activation of myelin specific lymphocytes. Ten patients were recruited to the study within 72 hours of sustaining severe TBI (median GCS 7). Blood was sampled within 72 hours (baseline), and 10 days thereafter. A significant increase in myelin specific lymphocytes and the extent to which they proliferated was demonstrated. The response was heterogeneous; four individuals demonstrated a dramatic increase (mean 5336%) in myelin reactivity ($p<0.001$); six demonstrated little or no increase. Reactivity inversely correlated with age. There was no difference in severity of TBI, infections,

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use of steroids or other medical interventions between the two groups, although more reactive patients required barbiturates and surgical decompression. There was a non-significant trend for myelin reactive patients to have more favourable outcomes (GOS). We explored the nature of interactions between myelin specific T lymphocytes and myelin basic protein ex vivo to determine whether auto-reactivity in a non-autoimmune setting could be protective. Such information could guide the management of head injury and the development of neuroprotective agents.

049 FULL-LENGTH AORTIC DISSECTION PRESENTING AN ISCHAEMIC STROKE WITHOUT CLASSICAL SYMPTOMS OF DISSECTION

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Acute aortic dissection is a potentially fatal condition, in which prompt diagnosis and treatment can be lifesaving. Diagnostic delay is common in atypical cases. We describe a patient with full length aortic dissection presenting as stroke, without classical symptomatology. This case stresses the clinical relevance and necessity of an urgent aetiological stroke diagnosis to prevent catastrophal outcome.

050 CT VENOGRAPHY IN THE DIAGNOSIS OF CEREBRAL VENOUS SINUS THROMBOSIS

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Cerebral venous sinus thrombosis (CVST) is an important cause of neurological morbidity. Recognised acute neurological presentations include acute thunderclap headache, new onset focal neurological syndromes with or without secondarily generalised seizures and headache, acute neurological syndromes suggestive of raised intracranial pressure and acute encephalopathy. Magnetic resonance imaging (MRI) with venography (MRV) has largely replaced the previous gold standard of catheter angiography for radiological confirmation of CVST in suspected cases. Computer tomographic venography (CTV) is a recently introduced imaging modality that is reportedly as sensitive as MRV in identifying CVST. We describe a series of six out of 38 patients admitted to the University Hospital North Staffordshire acute Neurology service between April 2003 to October 2004 with syndromes suggestive of acute CVST and draw attention to the use of CTV as opposed to MRI/MRV in the diagnosis. We illustrate practical cases where CTV has limitations in the assessment of suspected CVST. From our experience with this imaging modality we discuss the benefits of CTV for an acute neurology service over MRV. Advantages of CTV specifically include ease of access to the Accident and Emergency department, use in the critically ill patient and for hospitals where 24 hour access to MRI is not available. We also highlight potential pitfalls in the use of CTV.

051 PROSPECTIVE STUDY OF SPEECH AND LANGUAGE DEFICITS IN ACUTE ISCHAEMIC STROKE: PRELIMINARY FINDINGS IN 10 PATIENTS

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Background: Apraxia of speech (AOS) is one of many speech and language deficits that may occur following stroke. Deficits lead to problems in timing and duration of utterances that are considered integral components of speech prosody.
Objectives: To determine the prevalence of AOS and dysprosody in patients with acute hemisphere stroke, the association between orofacial apraxia and AOS, and whether there is any frequency difference in AOS and dysprosody between patients with right and left hemisphere strokes.
Methods: Patients admitted with acute ischaemic hemispheral stroke were recruited and screened. The test battery consisted of a 30 question comprehension test, 40 word/non-word repetition task, Apraxia Battery for Adults, and prosodic identification/discrimination test. This was administered after admission and at a 2–3 day interval.
Results: Preliminary data from the initial 10 patients shows that half the patients demonstrated AOS. Three of seven patients had evidence of linguistic dysprosody. There was a dissociation between orofacial apraxia and AOS. All patients with AOS and linguistic dysprosody had L hemisphere strokes.
Conclusions: Our findings suggest that AOS and dysprosody occur frequently following stroke. Our data supports the observation of left hemisphere involvement as an important part of prosodic processing.

052 DOES APOLIPOPROTEIN E (APOE) GENOTYPE INFLUENCE THE RISK OF THE PATHOLOGICAL TYPES AND SUBTYPES OF STROKE? SYSTEMATIC REVIEW AND META-ANALYSES OF 31 STUDIES IN 5961 CASES AND 17 965 CONTROLS

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ApoE genotype may affect risk of both ischaemic and haemorrhagic stroke, but studies to date have produced conflicting results. We conducted meta-analyses of the association of apoE genotype with ischaemic stroke (IS), intracerebral haemorrhage (ICH), and subarachnoid haemorrhage (SAH). We analysed data from 31 eligible studies (26 IS, 6 ICH, 3 SAH) in 5961 cases and 17 965 controls. ϵ4 allele-containing (ϵ4+) genotypes were significantly associated with IS (OR 1.11, 95% CI 1.01 to 1.22) and SAH (OR 1.42, 95% CI 1.01 to 1.99), and non-significantly with ICH (OR 1.16, 95% CI 0.93 to 1.44), while ϵ2+ genotypes were associated with ICH (OR 1.32, 95% CI 1.01 to 1.74). Associations were stronger: between ϵ4+ genotypes and large artery IS than with other IS subtypes, and for Asian compared with white populations; between ϵ2+ genotypes and lobar than with deep haemorrhages. However, we found no association between ϵ4+ genotypes and IS when we analysed only studies without control selection bias (OR 0.99, 95% CI 0.85 to 1.17) or only larger studies (>200 cases) (OR 0.99, 95% CI 0.88 to 1.11. Selection and publication biases make existing studies of apoE genotype and stroke unreliable. Further, very large, methodologically rigorous studies are needed.

053 INFORMED CONSENT IN A RANDOMISED TRIAL OF DECOMPRESSIVE SURGERY FOR SPACE-OCCUPYING INFARCTION

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Background: Non-randomised studies have suggested that decompressive surgery in patients with space-occupying infarction may reduce mortality from 78 to 16%. Randomised treatment allocation in clinical trials evaluating surgical treatment for space-occupying infarction may therefore be considered unethical and unacceptable by the patients' legal representatives.
Methods: We recorded the number of representatives who refused participation in HAMLET, an ongoing randomised trial of decompressive surgery in space-occupying infarction. In addition, we interviewed representatives of the first 15 patients one year after inclusion in this trial.
Results: Of the 37 representatives asked for participation of a relative in HAMLET up to 1 May 2005, three refused, only to avoid survival with a severe disability. Twelve (80%) of the 15 interviewed representatives spontaneously recalled participation of their relative in a clinical trial. Prior to giving informed consent, 13 representatives (87%) had considered the outcome of the randomisation procedure a matter of life or death. Eleven (73%) felt in retrospect that participation in a randomised trial was acceptable and only one (7%) regretted having given permission for participation. In this small sample, treatment allocation had no effect on recall, understanding, and satisfaction with the informed consent procedure.
Conclusion: Inclusion of patients in a randomised trial of surgical decompression for space-occupying infarction is feasible and generally considered acceptable by the patients' legal representatives.

054 SOURCES OF BIAS IN ANIMAL MODELS OF NEUROLOGICAL DISEASE

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Background: Animal models are used extensively in the preclinical testing of candidate drugs for neurological disease. However, there is often substantial discordance between the results of such studies and efficacy in clinical trial. One potential explanation for this discrepancy is bias introduced in the conduct and reporting of such animal studies

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which has the effect of overstating drug efficacy. We have set out to determine the evidence for such a bias in the experimental stroke literature.
Method: Stratified meta-analysis of data identified from systematic reviews of eight candidate neuroprotective drugs in animal models of cerebral ischaemia.
Results: Data were available from 257 comparisons describing outcome in 3 860 experimental animals. Partitioning comparisons by study quality explained a significant proportion of the between-comparison heterogeneity ($p<10–17$). Increased efficacy was seen in studies using ketamine anaesthesia (41% vs 31%, $p<10–11$) and reporting random allocation to group (36% vs 31%, $p<10–4$), and reduced efficacy was seen where hypertensive or diabetic animals were used (17% vs 34%, $p<10–24$).
Conclusion: Higher quality studies tended to give lower estimates of efficacy, and the quality items most strongly associated with the estimate of outcome were ketamine anaesthesia, randomisation, and the use of animals with co-morbidities.

055 BASELINE CT CHARACTERISTICS OF THE FIRST 137 PATIENTS IN THE START-UP PHASE OF THE MRC THIRD INTERNATIONAL STROKE TRIAL (IST-3)

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Introduction: Intravenous recombinant tissue plasminogen activator (rt-PA) is approved for the treatment of selected patients with acute ischaemic stroke. MRC IST-3 is a large scale randomised controlled trial of iv rt-PA within 6 hours of onset in 6000 patients, which seeks to determine whether a wider variety of patients may benefit.
Aim: To determine whether appropriate patients were recruited in the early ''start-up'' phase of the trial.
Methods: Blinded review of CT scans by an expert neuroradiologist.
Results: We assessed the pre-randomisation CT appearances of the first 317 patients in the trial. Attenuation patterns consistent with early changes of acute cerebral ischaemia (often subtle) were present in 73% and the hyperdense artery sign (indicative of a clot in the relevant cerebral vessel) in 44%. Other CT changes were common: atrophy in 63% and periventricular lucencies in 40%, reflecting the age distribution of patients recruited. No major protocol violations (ie no cases of non-stroke lesions or ''missed intracerebral haematomas'' as the cause of the initial neurological deficit) were found.
Conclusions: These data confirm that appropriate patients with acute ischaemic stroke are being entered into the trial. The Independent Data Monitoring Committee confirms it is now appropriate to increase recruitment to meet the target.

056 THE EARLY PROGNOSIS FOR DEATH AND HAEMORRHAGE FOR ADULTS WITH ARTERIOVENOUS MALFORMATIONS (AVMS) OF THE BRAIN: PROSPECTIVE, POPULATION-BASED STUDY

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Background: There are no prospective, population-based data about whether brain AVM presentation with intracranial haemorrhage confers a higher risk of subsequent haemorrhage than other modes of presentation.
Methods: We prospectively recruited a population-based cohort of adults in Scotland, first diagnosed with a brain AVM between 1999–2003. Individuals were observed (from the time of presentation that led to AVM diagnosis) for future occurrence of death or haemorrhage, and were censored at the time of first interventional treatment or latest follow up. Radiological diagnosis and clinical outcome were independently validated.
Results: 229 adults (55% male, median age 47 years) were followed for a total of 736 patient-years (median 3.2 years, range 0 to 6.4 years, completeness 88%), during which time there were 16 deaths and 10 brain AVM haemorrhages. Of the 115 adults (50%) who had presented with haemorrhage, nine died within 30 days (eight due to haemorrhage, two of which were re-bleeds) giving a 30-day case fatality of 8% (95% CI 5 to 13%). During follow up, AVM haemorrhage at initial presentation conferred a higher risk of subsequent haemorrhage (nine bleeds) than other modes of presentation (two bleeds), especially in the first 6 months (log rank = 9.7, $p = 0.002$).
Conclusion: Brain AVM haemorrhage rates during untreated follow up appear higher among adults who first present with haemorrhage than those who present with other symptoms.

057 BLOOD-BRAIN BARRIER DYSFUNCTION IN PARKINSON'S DISEASE: A CAUSATIVE MECHANISM?

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Objective: To demonstrate blood-brain barrier (BBB) dysfunction in Parkinson's disease (PD).
Background: Both genetic and environmental toxic theories have been proposed as explanation for the slowly progressive decline of the catecholaminergic neurones (in particular the dopaminergic neurones) in the midbrain of patients with PD. Genetic mutations can explain only a very small proportion of cases in particular families. Parkinsonism due to toxins is well known but usually related to rare causes, occurring only in a minority of cases. Here we introduce a new concept that might combine both genetic and toxic components in an explanation of PD disease causation. A faulty BBB function on the basis of genetic predisposition might in the course of the years allow toxic compounds – or normally in the blood circulating compounds not passing the BBB – to enter the brain in certain regions and damage vulnerable cells like the catecholaminergic neurones in the brain stem. The P-glycoprotein system is normally present in the BBB in a very high concentration. That system serves to remove unwanted substances out of the endothelial cell back into the blood. Recently it has become possible to measure Pgp activity in the brain in man in vivo semi-quantitatively using positron emission tomography (PET).
Methods: Using PET and the radiotracer [C-11]-verapamil, a substrate for the P-glycoprotein, brain uptake was measured in five medicated patients with PD (UPDRS-III mean (SD): 20.2 (7.9)) and five age-matched healthy controls. After data acquisition, volume of distribution images were calculated with Logan method and normalisation and smoothing steps undertaken. Using SPM the two groups of subjects were compared and t-contrasts were calculated at a threshold of an uncorrected $p<0.001$.
Results: The SPM distribution of significant voxels yielded a cluster only in the midbrain region. Brain penetration of [C-11]-verapamil was elevated by 18% in the midbrains of the PD patients relative to the healthy controls ($p = 0.02$). All patients showed a higher uptake value compared to any of the controls.
Conclusions: This pilot study demonstrates that the midbrain of PD patients has a defective BBB in respect to the P-glycoprotein molecular efflux pump. This suggests that toxic substances can accumulate more easily in the brain of PD patients than in healthy controls.

058 A RANDOMISED CONTROLLED TRIAL OF NON-INVASIVE VENTILATION (NIV) IN MOTOR NEURONE DISEASE (MND)

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Background: In Europe and the USA most MND patients do not receive NIV, reflecting uncertainty about its role in this condition. We have conducted a randomised trial of NIV to determine its effect upon quality of life (QoL) and survival.
Method: To ensure the trial assessed the general applicability of NIV in MND, all eligible patients attending a regional MND care centre were offered enrolment and most participated. Exclusion criteria were age >75 years, cognitive impairment or inability to communicate. Subjects were monitored regularly and later randomised to NIV or best supportive care only if and when they met predefined criteria: orthopnoea with Pimax <60% predicted or symptomatic daytime hypercapnia. Randomisation was stratified by bulbar function using a simple clinical scale. Survival and QoL were analysed by intention to treat using generalised Wilcoxon test.
Results: Of 92 subjects enrolled, 41 met one or both criteria for randomisation during the period of surveillance (NIV = 22, standard care = 19). Compared to standard care, NIV improved survival and QoL

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both in the total group and in the subgroup (n = 20) with normal or only moderately impaired bulbar function. Subjects with severe bulbar impairment showed no survival or QoL benefit.

059 FURTHER INSIGHTS INTO HSP AND SPASTIN: SEVERE COMPLICATED PHENOTYPES AND EVIDENCE OF LOWER MOTOR NEURONE DYSFUNCTION

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Background: Mutations in the spastin gene are the commonest cause of hereditary spastic paraparesis (HSP) accounting for approximately 40% of autosomal dominant cases. The phenotype associated with HSP due to mutation in the spastin gene (SPG4) tends to be pure HSP.
Objective: To further characterise genetically and phenotypically a large cohort of patients with spastin mutations.
Methods: Patients were screened for spastin mutation by direct sequencing of all exons.
Results: We have identified in 61 patients 47 different spastin mutations of which 25 are novel. These mutations were scattered throughout the gene with a particular hot spot in exon 1. Three patients were identified with two separate mutations within the spastin gene. The phenotype in the majority of patients was of pure HSP. However, in a number of individuals the phenotype stood out as being particularly severe and complicated. Additional features observed included progressive bulbar dysfunction, respiratory insufficiency, prominent upper limb involvement, contractures, and the presence of denervation on neurophysiological assessment suggesting lower motor neurone involvement.
Discussion: These findings add to the number of spastin mutations identified and demonstrate the importance of screening the whole gene given the possibility of double mutations. The apparent hot spot for spastin mutation identified in exon 1 suggests an important functional role for this region of spastin, which requires further investigation. These results broaden the phenotype associated with spastin mutation.

060 INTRADURAL EXTRAMEDULLARY ANAPLASTIC EPENDYMOMA WITH PRESUMED DROP METASTASIS

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The authors describe a 29 year old woman who presented with progressive neck pain and weakness in both arms. Magnetic resonance imaging (MRI) of the cervical spine revealed a tumour compressing the spinal cord. During surgery an intradural extramedullary tumour was found. Unexpectedly, further imaging showed a second lumbar tumour. Microscopy of both tumours was consistent with anaplastic ependymoma, which is very rare at the spinal level. We hypothesise that the lumbar anaplastic ependymoma was possibly a drop metastasis of the cervical ependymoma.

061 EXTENDING THE PHENOTYPE OF ALS: WHITHER THE SENSORY NERVES?

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Clinically evident sensory involvement is thought not to be a feature of amyotrophic lateral sclerosis. However, electrophysiological studies suggest that sub-clinical sensory dysfunction may be present in as many as 60% of sporadic ALS patients. We therefore hypothesised that in a proportion of ALS cases a sensory neuropathy would be clinically apparent. In the King's MND clinic we have identified four cases of sporadic ALS with neurophysiological evidence of sensory neuropathy, in three of which there was also clinically evident sensory involvement. In none of these individuals was an alternative cause for the neuropathy identified. In cases where nerve biopsy was performed this demonstrated axonal degeneration without inflammatory features. We propose that sensory axonal neuropathy be added to the list of non-motor pathologies that can be seen in sporadic ALS. This is supported by the relatively high incidence of sensory neuropathy in familial ALS due to SOD1 mutations. As average disease duration increases due to advances in supportive care and pharmacology, we anticipate that the true spectrum of pathology in ALS will become more clinically evident necessitating a revision in the standard clinical descriptions of the disease.

062 FUNCTIONAL WEAKNESS: WHY WEAKNESS AND NOT SOME OTHER SYMPTOM? THE ROLE OF PANIC, DISSOCIATION, PAIN, AND PHYSICAL INJURY IN ONSET

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Background: Functional weakness, also called motor conversion disorder or psychogenic weakness, is common in neurological practice but poorly understood. Current psychological theories about the cause of functional weakness fail to explain why weakness, and not some other symptom, develops in individual patients.
Methods: 107 consecutive patients with recent onset functional weakness were interviewed about the onset of their weakness as part of a larger study.
Results: 48% had a sudden onset, 13% developed weakness on waking, and the rest developed weakness gradually. The following factors were found at onset: symptoms of panic (37%); dissociative symptoms (31%); pain (21%); physical injury immediately prior to onset (16%); migraine (7%); sleep paralysis (5%); general anaesthetic (2%); symptoms noticed by others first (6%). A gradual onset with fatigue, sleep disturbance, and progressive asymmetrical limb heaviness was common.
Conclusion: Panic, dissociation, pain, and physical injury appear to have an important and neglected role in the onset of functional weakness. As many neurologists recognised over a century ago, there are plausible reasons for these associations, which may shed light on why weakness, and not some other symptom, develops in individual patients. Further controlled study is required.

063 RATING SCALES FOR NEUROLOGICAL DISEASES: LESSONS FROM RASCH ANALYSIS

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Background: Rating scales are increasingly the primary outcome measures for clinical trials. As such, they are the central dependent variables on which treatment decisions are based, and every effort should be made to maximise their scientific quality. Although more sophisticated methods of scale analysis have become recently available their role is uncertain.
Objective: To determine how a scale developed using traditional methods, the multiple sclerosis impact scale (MSIS-29), measures up to more sophisticated examination.
Methods: MSIS-29 data from n = 2526 people were analysed to determine the extent to which it satisfies Rasch's criteria for rigorous measurement.
Results: Rasch analysis largely supported the scientific soundness of the MSIS-29. However, analyses highlighted that: more reliable measurement is achieved if the item response options are reduced; more valid measurement could have been achieved if the scales had been constructed on the basis of strong conceptual definitions rather than the factor analysis of an item pool; more responsive measurement could have been achieved if the items had been better spread across the disability continuum.
Conclusions: The application of new psychometric methods can improve the quality of outcome measures for clinical trials, and change the way scales are developed.

064 REVALIDATION OF THE WORLD HEALTH ORGANISATION (WHO) DIAGNOSTIC CRITERIA FOR VARIANT CJD (VCJD)

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Introduction: In 2001, following recognition of variant CJD (vCJD), the World Health Organisation (WHO) developed diagnostic criteria providing a standard framework for case definition. A formal revalidation of the WHO diagnostic criteria has been carried out.
Method: ''Suspect'' cases of variant CJD were identified from the archives of the National CJD Surveillance unit (NCJDSU). Autopsy provided a definitive diagnosis. A retrospective case note analysis provided details of the clinical and investigative features.
Results: One hundred and six pathologically confirmed cases were identified. Eighty-eight cases were retrospectively classified as probable cases in life, six were classified as possible cases, and 12 did not fulfil the diagnostic criteria. Of the 88 probable cases, 85 fulfilled the criteria on clinical features and a ''positive'' MRI brain scan with only 3/88

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requiring a tonsil biopsy for diagnostic classification as ''probable''. The mean time from onset to classification as a probable case was 9.5 months. Thirty-three pathologically confirmed ''not cases'' were identified, none fulfilling the criteria for a ''probable'' case.
Conclusion: The WHO diagnostic criteria for variant CJD are sensitive and specific. These data suggest invasive procedures are indicated only if cases do not fulfil the diagnostic criteria for a probable case following appropriate neuroimaging, consistent with the current WHO guidelines.

065 IMAGING ACTIVATED MICROGLIA IN PRESYMPTOMATIC HUNTINGTON'S DISEASE GENE CARRIERS: AN 11C-PK11195 PET STUDY

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Animal studies have implicated activated microglia in the pathogenesis of Huntington's disease (HD). Using 11C-(R)-PK11195 (PK) positron emission tomography (PET), we have recently shown significant microglial activation in HD brain which correlated with disease severity. The aims of the current study are to investigate microglial activation in presymptomatic HD gene carriers (PSGC) and its role in HD pathogenesis. Six PSGC (age 39.8 ± 4.1 years; CAG repeats length 43.5 ± 3.6; mean $\pm$ SD) and 10 normal controls underwent PK PET. Mean striatal PK binding potential (BP) of PSGC was significantly higher than that of controls ($p<0.005$). Four PSGC, all with $\leqslant 3$ years to predicted disease onset (PDO) (Brinkman *et al*, 1997), showed increased striatal PK BP (>2 SDs above control mean). The other two PSGC with normal striatal PK BP had >10 years to PDO. The PSGC striatal PK BP correlated with time to PDO ($r=-0.89$, $p<0.05$), and disease load measured by CAG index ($r=0.89$, $p<0.05$). This is the first in vivo demonstration of microglial activation in PSGC. It supports the notion that microglial activation is an early event in HD pathogenesis and is associated with subclinical disease progression. This has important therapeutic implications as agents that inhibit microglial activation may be trialled to delay disease onset.

066 A STUDY OF DISORGANISED CARE: A 3 YEAR INVESTIGATION OF ACUTE INPATIENT REHABILITATION AFTER HEAD INJURY IN A DISTRICT GENERAL HOSPITAL

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Background: Despite the Galasko (1999) recommendations on the management of patients after head injury (HI), acute rehabilitation (AR) services for these patients remain disorganised. Evidence for the effectiveness of organised acute care and rehabilitation after stroke is overwhelming, but few studies exist after HI.
Methods: We investigated the process of AR for patients admitted after HI to a district general hospital. We drew up guidelines from existing international guidelines for both stroke and acquired brain injury, categorised the items into 13 domains covering care from initial assessment through to discharge planning, and retrospectively audited care recorded in medical notes for 90 patients admitted after HI for more than 48 hours over 3 years.
Results: All patients were admitted to general wards (mean stay 8 days), 78 after mild HI (GCS13-15). Mean domain compliance was 33%, with only 2%, 22%, and 29% compliance in the acute initiation of rehabilitation, monitoring of progress, and discharge planning domains. Post-traumatic amnesia, cognition, and mood were monitored in 0%, 3%, and 33% respectively, and 80% of patients were not given written information about sequelae on discharge.
Conclusions: These results confirm the concerns of the Galasko report, highlighting the need for acute rehabilitation provision after HI.

067 IS ISOLATED APHASIA A TYPICAL PRESENTATION OF PRESUMED CARDIOEMBOLIC STROKE?

Th F. M. Fennis, M. Van den Broek, P. J. Koudstaal, A. Algra, P. J. Koehler.

Background: Previous studies have suggested that patients with isolated aphasia should be carefully screened for a cardiac source of embolism. Most of these publications, however, are case reports or small series.
Objectives: The purpose of the study was to study the relation between isolated aphasia and cardio embolic brain ischaemia within the setting of two large multicentre trials.
Method: The frequency of isolated aphasia was compared between patients with a TIA or minor ischaemic stroke either with (European Atrial Fibrillation Trial (EAFT), n=1007) or without ((Dutch TIA Trial (DTT), n=3150) atrial fibrillation. Logistic regression was used to adjust for differences between patients from the two trials.
Results: Of 4157 patients 210 had isolated aphasia, 109 patients from the EAFT and 101 from the DTT (odds ratio (OR) 3.7, 95% CI 2.8 to 4.9). Patients with isolated aphasia were older than those without (70.3 vs 66.8 years), more often female (OR 1.7; 1.4 to 2.5) and non-smokers (OR 2.2; 1.6 to 3.1), had more often diabetes (OR 1.7; 1.2 to 2.6) and hypercholesterolemia (OR 1.8; 1.1 to 3.0). After simultaneous adjustment for age, gender, diabetes, hypercholesterolemia, and smoking patients with isolated aphasia still had more often atrial fibrillation than patients without isolated aphasia (adjusted OR 2.9; 2.2 to 4.0).
Conclusion: Isolated aphasia is an independent sign of a cardiac source of embolism.

068 THIENOPYRIDINES OR ASPIRIN FOR SECONDARY PREVENTION OF VASCULAR EVENTS?

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Aspirin is the most widely used antiplatelet drug in secondary prevention of vascular disease, but there may be more effective alternatives. We did an updated Cochrane systematic review of randomised trials comparing a thienopyridine antiplatelet drug (ticlopidine or clopidogrel) with aspirin in patients with a history of ischaemic stroke or transient ischaemic attack (TIA), ischaemic heart disease, or peripheral arterial disease. We identified 10 relevant randomised trials in 27 000 patients (12 000 with an ischaemic stroke or TIA). Aspirin 325 mg daily was the commonest dose used. The thienopyridines prevented slightly more serious vascular events (stroke, myocardial infarction, or vascular death) than aspirin (OR 0.91, 95% CI 0.84 to 0.98; 10 events avoided per 1000 patients treated, 95% CI 0 to 20 events per 1000), but the wide confidence interval included the possibility of no additional benefit. Aspirin caused more upper gastrointestinal symptoms and gastrointestinal haemorrhage (but might not do so at a lower daily dose). The thienopyridines, particularly ticlopidine, caused more skin rash and diarrhoea. Ticlopidine, but not clopidogrel, produced a higher risk of haematological adverse effects. Clopidogrel appears to be as effective and as safe as aspirin but is far more expensive and so is not cost effective.

069 CAN WE PREDICT WHO IS AT HIGH RISK FROM ENDOVASCULAR CAROTID ARTERY INTERVENTION?

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Background: To identify clinical, angiographic, or procedural variables which are predictive of stroke/death following the endovascular treatment of carotid artery stenosis.
Methods: A multivariate analysis using logistic regression was performed on 487 consecutive patients undergoing endovascular treatment between 1993 and 2003.
Results: The risk of stroke/death following carotid intervention was increased in patients with atrial fibrillation, (OR=9.96, 95% C.I. 3.34 to 29.67), in those with a time independent indication for treatment (OR=5.35, 95% C.I. 1.12 to 25.60) and in patients with cortical rather than retinal symptoms (OR=2.97, 95% C.I. 1.04 to 8.49). The odds of stroke/death were decreased with the concomitant use of clopidogrel (OR=0.41, 95% C.I. 0.19 to 0.91) and in those patients who had a past history of myocardial infarction (OR=0.25, 95% C.I. 0.08 to 0.79).
Conclusions: Predictors for risk of procedural stroke/death were identified. These included clinical factors (AF, no past MI, no concomitant use of clopidogrel) and presenting symptoms (cortical rather than retinal symptoms and indications that were time independent). The latter group mainly included asymptomatic patients awaiting coronary surgery and patients with a contralateral symptomatic occlusion.

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070 HAMLET: HAEMICRANIECTOMY AFTER MIDDLE CEREBRAL ARTERY INFARCTION WITH LIFE-THREATENING OEDEMA TRIAL

The HAMLET Investigators. *UMC Utrecht, Academic Medical Centre, University Hospital Groningen, Leyenburg Hospital, University Hospital Maastricht, Medical Centre Haaglanden, University Hospital St Radboud, The Netherlands*

Background: Patients with massive space-occupying hemispheric infarction have a poor prognosis. Non-randomised studies suggest that decompressive surgery reduces mortality and improves functional outcome of survivors. HAMLET is an ongoing randomised controlled trial to study the efficacy of decompressive surgery to improve functional outcome in patients with supratentorial infarction and space-occupying oedema.
Methods: The study design is that of a multi-centre, open, randomised clinical trial, which will include 112 patients aged up to 60 years with a space-occupying infarct in the territory of the middle cerebral artery leading to a decrease in consciousness. Patients are randomised to either decompressive surgery, consisting of a large haemicraniectomy and a duraplasty, or conservative treatment. The primary outcome measure is functional outcome, as determined by the score on the modified Rankin Scale at one year.
Trial coordination: HAMLET is coordinated from the Trial Office Neurology at the University Medical Centre Utrecht, the Netherlands. Study coordinator: Jeannette Hofmeijer (j.hofmeijer@neuro.azu.nl); principal investigator: H. Bart van der Worp (h.b.vanderworp@neuro.azu.nl).
Trial status: HAMLET started in September 2002. Up to April 2005 34 patients have been included in seven centres in the Netherlands. New centres are invited to participate.
Funding: HAMLET is supported by the Netherlands Heart Foundation (2002B138).

071 PROSPECTIVE POPULATION BASED MORTALITY STUDY OF MULTIPLE SCLEROSIS IN SOUTH WALES OVER A 20 YEAR FOLLOW UP PERIOD

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Introduction: Mortality statistics are important in determining disease effects on survival. Most studies have been of selected populations and/or short duration. We present 20 year prospective population based mortality data of multiple sclerosis (MS) in South Wales.
Methods: A prevalence study in South Wales in 1985 identified 441 patients. Cases were flagged with the Office of Population Censuses and Surveys. Death certificates were collected prospectively and comparison made with national statistics, and standardised mortality figures determined.
Results: 206 patients had died, 215 were alive, and 20 untraceable. Mean age of death was 67 in females and 65 in males (range 33–99), compared with UK population 79.4 in females and 73.2 in males. 108 deaths (55%) were related to MS, 99 (44%) were unrelated and in 7 (3%) no cause was determined. MS was mentioned on certificates in 65.6%. Crude death rate was 30.12 deaths/1000/year, age standardised mortality ratio was 118(95% CI = 101.76 to 134.24), and excess death rate 3.5/1000/year. 38% of deaths were from pneumonia. 70.4% of deaths occurred in patients over 60 years.
Discussion: Over half of all patients die from the disease or its complications. Standardised mortality ratio shows an 18% increase in deaths compared to background Welsh population.

072 OPTIC NERVE ATROPHY AND RETINAL NERVE FIBRE LAYER THINNING FOLLOWING OPTIC NEURITIS: EVIDENCE THAT AXONAL LOSS IS A SUBSTRATE OF ATROPHY

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CNS atrophy is believed to reflect axonal loss in multiple sclerosis (MS) but direct evidence is lacking. Our hypothesis was that if the optic nerve atrophy that develops following optic neuritis is predominantly due to axonal loss, it would correlate with thinning of the retinal nerve fibre layer (RNFL), which can be measured non-invasively with optical coherence tomography (OCT). Twenty-five patients at least one year after a single unilateral attack of optic neuritis and 15 controls had (i) fast fluid-attenuated inversion recovery (fFLAIR) MRI to determine mean intraorbital optic nerve area, (ii) OCT measurement of mean RNFL thickness and macular volume (MV), (iii) quantitative visual testing, and (iv) electrophysiological examination. Optic nerve area, RNFL thickness, and MV were all significantly reduced in affected patient eyes compared to both control eyes and clinically unaffected fellow eyes ($p<0.001$). Within patients, using interocular differences, optic nerve area correlated with RNFL thickness ($r=0.66$, $p<0.001$), MV ($r=0.59$, $p=0.002$), visual acuity ($r=0.50$, $p=0.01$), and VEP amplitude ($r=0.40$, $p=0.05$). These findings suggest that axonal loss is a substrate of optic nerve atrophy following a single attack of optic neuritis. By inference, axonal loss in other inflammatory brain lesions in MS may contribute to the global measure of brain atrophy.

073 CORRELATIONS BETWEEN CANNABINOID LEVELS AND THE ASHWORTH SCORE SUPPORT RESULTS FROM THE CAMS TRIAL

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Objective: The CAMS study showed that over 52 weeks there was a significant improvement in spasticity in patients treated with Δ9THC compared to either cannabis extract (mainly containing both Δ9THC and the non-psychoactive cannabidiol) or placebo. There were also significant improvements in measures of disability.
Aims: To investigate whether the clinical effects of Δ9THC are related to serum level and at what level the difference between cannabis extract and Δ9THC occurred.
Methods: Cannabinoid levels were taken from 150 patients during the first 16 weeks of the CAMS trial and analysed.
Results: There is a weak correlation between clinical effect and increasing concentration of Δ9THC for the Δ9THC group but in the cannabis extract group increasing Δ9THC was associated with a decrease in clinical effect as is increasing cannabidiol concentration. Analysis of log concentrations shows a significant difference between the two treatment arms. Levels of 11-hydroxytetrahydrocannabinol (a metabolite of Δ9THC) are not different between the two groups.
Conclusion: The correlation between Δ9THC level and clinical effect reflects the results from the CAMS trial. The similarity between metabolite levels implies that the difference between the two treatments does not occur at the metabolic level.

074 A SURVEY OF AUTOIMMUNITY AFTER THERAPEUTIC LYMPHOCYTE DEPLETION IN THE TREATMENT OF MULTIPLE SCLEROSIS

A. L. Cox, J. L. Jones, S. J. Thompson, J. Deans, D. A. S. Compston, A. J. Coles. *Department of Clinical Neuroscience, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK*

We previously reported an increased incidence of autoimmune thyroid disease in a third of patients with multiple sclerosis treated with a single pulse of Campath-1H. In order to further define the emergence of autoimmunity after lymphocyte depletion, we surveyed all patients with multiple sclerosis treated with Campath-1H to date for autoimmune diseases. In total, 38 of the 97 patients treated (39%) have developed de novo autoimmunity following treatment with Camapth-1H. Fifty percent of these were restricted to the thyroid gland, and in a further 39%, emergence of non-thyroidal autoantibodies were seen without associated symptoms. The remaining 11% consisted of a single case each of autoimmune neutropaenia, Goodpasture's disease and erythema multiforme. The incidence of autoimmune disease has fallen since the introduction of second and third ''maintenance treatments'' with Campath-1H, which prolong the duration of lymphopaenia. This suggests that the emergence of autoimmunity requires significant replenishment of the peripheral lymphocyte pool. The development of autoimmunity was associated with unexpected patterns of lymphocyte reconstitution and heterogeneous abnormalities in cytokines involved in the homeostasis of peripheral immune system. We speculate that the same faulty mechanisms may be responsible for the pathogenesis of multiple sclerosis itself.

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075 EVALUATION OF MODIFIED MRI CRITERIA FOR MULTIPLE SCLEROSIS IN PATIENTS WITH CLINICALLY ISOLATED SYNDROMES

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An early and accurate diagnosis of multiple sclerosis (MS) enables patients to be counselled and assists with planning their future management. The McDonald criteria use MRI evidence for dissemination in space (DIS) and time (DIT) to diagnose MS in patients with a single clinically isolated syndrome (CIS) but they are insensitive in making the diagnosis with early follow up. We investigated modified MRI criteria for DIS and DIT to improve the accuracy of an early diagnosis. T2 and gadolinium-enhanced T1-weighted brain and cord MRIs were performed on 90 prospectively recruited CIS patients within 3 months of symptom onset. Brain MRI was repeated 3 months later. The modified criteria for DIS required ⩾1 lesion(s) in ⩾2 of 4 characteristic CNS locations: periventricular, juxtacortical, infratentorial, or spinal cord. The modified DIT criteria required ⩾1 new T2 lesion(s) at 3 month follow up. Patients were followed up for 3 years or until development of clinically definite (CD) MS. Both the McDonald and modified criteria had a high specificity for development of CDMS (94% and 92% respectively) but the modified criteria were more sensitive (77% compared with 46%) and accurate (86% vs 73%). The modified criteria are also easier to apply.

076 THE ABN RELAPSE BASED MULTIPLE SCLEROSIS BETA-INTERFERON STOPPING CRITERION IS NOT CLINICALLY USEFUL

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Objective: To investigate whether the relapse-based ABN stopping criterion for beta-interferon (IFNB) in relapsing-remitting MS (RRMS) is predictive of disability progression.
Methods: 175 RRMS patients on IFNB were followed 6-monthly for a median of 5 years (range 2–10 years). Relapses and expanded disability status scale (EDSS) were measured yearly. Relapse-based treatment failure was two disabling relapses in one year (ABN criterion). IFNB failure due to progression was defined as a one-point increase in the baseline EDSS sustained for six months. Patients without EDSS progression were considered responders.
Results: Sixty patients (34%) had disability progression. Thirty-five (20%) met the ABN relapse-based stopping criterion. ABN relapse-based criterion in the first or second treatment year was an insensitive predictor of progression (sensitivity 10% and 7% respectively). Logistic regression defined predictive variables as a baseline EDSS of 2.0 or greater ($p=0.018$), a one-year pre-treatment relapse rate of 1.2 or less ($p=0.037$) and, most significantly, failure of IFNB to completely suppress relapses ($p=0.001$).
Conclusion: The ABN IFNB relapse based stopping criteria are not predictive of disability progression. Only those patients who remained relapse free on IFNB therapy are less likely to progress over a median of 5 years follow up.

077 SEIZURES IN MULTIPLE SCLEROSIS (MS): IS GREY MATTER DAMAGE THE CULPRIT?

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Background: The true incidence of seizures in MS is controversial, ranging from being no different from the general population to 7% in patients requiring baclofen pumps.
Aim: Since seizures are associated with neuronal dysfunction, we determined the extent of grey matter damage post-mortem in patients who had experienced seizures during life.
Methods: Clinical history was correlated with pathological quantification of grey matter damage (none, mild, moderate, or severe).
Results: Seizures occurred in 17 of 126 MS patients recruited to the United Kingdom MS Tissue Bank (13.5%). In this population 122 (97%) became wheelchair-users in life. Seizures occurred in 10 (59%) after they became wheelchair-users. Post-mortem examination of the extent of grey matter damage in 46 subjects revealed that 4 of 11 subjects (36%) that had moderate-to-severe grey matter damage experienced seizures during life whereas seizures were only experienced by 4 of 35 subjects (11%) that had no damage or mild grey matter damage.
Conclusion: Here we demonstrate that the frequency of seizures is increased in subjects with MS mainly occurring after they become wheelchair-bound and that an increased incidence of seizures is seen with increasing grey matter damage. This implicates the underlying disease process as an aetiological factor.

078 FUNCTIONAL MRI OF SPIKE WAVE ACTIVITY IN IDIOPATHIC AND SECONDARY GENERALISED EPILEPSY

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EEG-fMRI allows the study of the haemodynamic correlates of neural events detected on EEG. We used EEG-fMRI to study generalised spike wave activity (GSW) in a large series of patients. Thirty patients with idiopathic generalised epilepsy (IGE) and 16 patients with secondary generalised epilepsy (SGE) were included. SPM2 was used for all image pre-processing and statistical analyses. GSW epochs were visually identified and used to derive a boxcar model, to test for GSW-related fMRI changes. A second level multi-subject random effects group analyses was used to identify population specific fMRI changes. This was applied separately to IGE and SGE groups. GSW-related fMRI changes were seen in 25 patients, with thalamic signal change (15 patients), predominantly activations; and cortical signal change, involving symmetrical frontal (20 patients), posterior parietal (23 patients) and posterior cingulate (19 patients), predominantly deactivations. Individual fMRI analyses were not syndrome specific. Group analysis revealed thalamic activation and frontal, parietal, and posterior cingulate deactivation in IGE and thalamic and frontal changes in SGE. These findings are in keeping with current hypotheses based on neurophysiological findings, with involvement of thalamocortical networks. The distribution of cortical change resembled those seen in studies of vigilance suggesting involvement or disruption of processes in these networks during GSW.

079 OLFACTORY TESTS DISTINGUISH ESSENTIAL FROM PARKINSONIAN TREMOR. EVIDENCE OF ENHANCED DETECTION AND AGE RESISTANCE IN FAMILIAL ESSENTIAL TREMOR

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Background: It is unclear whether patients with essential tremor (ET) have intact sense of smell. If olfaction is normal it could help distinction from tremor-dominant Parkinson's disease (PD) where smell sense is usually impaired.
Methods: Fifty-nine patients with ET were compared to 245 controls by the 40 odour University of Pennsylvania smell identification test (UPSIT-40) and to 74 controls by olfactory event related potentials (OERP). Sixty-four patients with tremor dominant PD were also compared to the control group by UPSIT and OERP. Mean UPSIT scores were compared between groups using multiple regression of UPSIT on group indicators with gender, age, and age squared as covariates. Mean latency and amplitude was compared using multiple regression models with gender and a linear term in age as covariates.
Results: Controls and ET were indistinguishable when allowing for age, smoking, and gender ($p=0.016$). Mean values for ET and PD on both olfactory tests were markedly different ($p=<0.001$). Familial ET patients scored higher than controls on UPSIT ($p=<0.001$) and their age-related decline was slower ($p=0.035$).
Conclusion: These clear differences between tremor groups could be useful clinically. Normal olfaction in suspected PD or abnormal smell in suspected ET warrants diagnostic review. The superiority of familial ET and their resistance to aging suggests a protective mechanism.

080 SCREENING FOR UNDIAGNOSED PARKINSONISM IN A RANDOM COMMUNITY SAMPLE OF PEOPLE AGED 65 YEARS AND OVER

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Objectives: As part of an incidence study of parkinsonism in North-East Scotland (the PINE study), we performed community-based screening in order to: (1) identify the proportion of people aged 65 years and over with previously undiagnosed parkinsonism, or with newly diagnosed parkinsonism that had been missed by our case-finding methods; and (2)

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calculate the sensitivity and specificity of three questionnaires for identifying new parkinsonism.
Methods: A random sample of 2449 patients aged 65 years and over was screened for parkinsonism using a postal screening questionnaire, followed by neurological assessment.
Results: Amongst the 1556 (64%) patients who responded, four patients (0.26%, 95% CI 0.07%, 0.66%) with previously undiagnosed parkinsonism were identified. Only one further patient was identified who had been previously diagnosed and missed by the PINE study's case-finding methods. Using two simple screening questions we achieved a high sensitivity for newly diagnosed parkinsonism (95%), but a low specificity (28%). More detailed screening questionnaires offered better specificity than the two simple questions, but with lower sensitivity.
Conclusions: (1) Although only a small proportion of the population had undiagnosed parkinsonism, the numbers were sufficient to significantly increase the incidence of parkinsonism and Parkinson's disease. The case-finding methods of the PINE study were effective. (2) Simple questions were sensitive for screening for undiagnosed parkinsonism, and could be used in future incidence studies.

081 WHAT ARE THE DIFFERENCES BETWEEN PATIENTS WITH HEADACHE MANAGED BY GENERAL PRACTITIONERS (GPS) AND THOSE REFERRED TO NEUROLOGISTS?

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Introduction: Headache is the commonest new neurological problem seen by GPs and neurologists. We described and compared a group of patients consulting GPs for headache, with a group referred to neurologists.
Method: Eighteen practices, with 140 000 adults, recruited patients consulting with headache and migraine over 7 weeks, and patients referred for headache over one year. Outcome measures included headache impact (HIT-6), disability (MIDAS), anxiety and depression (HADS), illness perceptions (IPQ-R), consultation rates, and satisfaction.
Results: 489 patients consulted and were managed by GPs, and 81 were referred to specialists. Both groups reported very severe impact on functioning and severe disability. Those referred were significantly more likely to be men, to link more symptoms to their headache, to believe the cause of their problem was physical, to be more worried and afraid about their headaches, and to consult more frequently. There were no significant differences between GP-managed and referred groups in mean headache impact, disability, general anxiety, depression, or satisfaction.
Discussion: Extrapolating, the average GP may see one new patient with headache each week and refer one per year to a neurologist (2%). Referral is related more to social than to clinical factors. This may inform future management strategies.

082 LETTER FROM BOTSWANA

A. J. Wills. *Queens Medical Centre, Nottingham, UK*

Literature has the power to change lives and having read about the adventures of Mme Ramotswe, Botswana's only fictional female detective, and clutching a cheque for £1000 kindly provided by the ABN, I was inspired to visit the country of Mme Ramotswe's birth—almost unique amongst African nations by virtue of prolonged post-independence political stability. Demographic details and comparators are shown in the table.

	Population	Infant Mortality	Life expectancy
United Kingdom	60 m	5.2/1000	78
Botswana	1.6 m	59/1000	39

The reason for the appalling (and declining) life expectancy figures is, of course, AIDS. Prevalence rates of HIV infected individuals in the general population are 38%. There are no neurologists in Botswana, although there are limited neurological investigational facilities in Gaborone including a CT scanner, angiography, and myelography. AIDS has transformed the medical landscape in Botswana in a relatively short timescale. Bed occupancy on the medical wards runs at a staggering 200%. The majority (90%) of hospital medical inpatients have HIV-related conditions. The neurological complications of HIV are pervasive. Around 30% of HIV positive hospital inpatients have a neurological illness. These range from acute seroconversion syndromes (cerebellar ataxia, inflammatory neuropathies), through sub-acute (tuberculous/cryptococcal) and acute (pyogenic) meningitides to dementia, myelopathy and painful neuropathy associated with low CD4 counts.

083 HUGHLINGS JACKSON PLANS A RESEARCH PROJECT

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In 1893 Jackson, in the first three of a series of papers in the *Lancet*, under the general title Neurological Fragments, described his observations on the eyelids and pupils in two cases of progressive external ophthalmoplegia. He confirmed Mendel's hypothesis that the levator component of the orbicularis oculi is innervated by fibres from the third nerve, rather than the facial nerve, and addressed the innervation of the constrictor and dilator muscles of the pupils. His instructions to his house physician, Dr Wood, written on 10 July 1893 regarding this investigation have been discovered in the Archive. These are the only surviving clinical notes in Jackson's hand. We were able to identify Case 2 (JC) of the *Lancet* report in the diagnostic index for 1893 at The London Hospital. Jackson transferred JC to Queen Square, where the relevant inpatient records have survived. Jackson and his two house physicians tested the effect of cocaine on JC's pupils at the London Hospital and at Queen Square, and also tested the effect of Faradic stimulation on the peri-ocular muscles. This evidence documents Jackson's methods, and illustrates his detailed knowledge of contemporary literature and his utilisation of new techniques. Modern neurologists will be glad to learn that JC was discharged and cured, after a hospitalisation of 11 months. Neurological Fragments. *J Hughlings Jackson.* Published by Humphrey Milford at the Oxford University Press 1925 pp 65–75.

084 A PILOT STUDY OF A NEUROLOGY TEACHING PROGRAMME FOR MEDICAL STUDENTS

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Neurology is perceived to be a difficult subject by students, junior doctors, and general practitioners. The Government is aiming to increase the number of medical graduates that are likely to put increased strain on the existing educational system. This study aimed to assess effectiveness of a new neurology teaching programme and to assess students' perceptions of their abilities. Forty-five students were allocated to the programme compared to 133 students who received neurology teaching by traditional methods. The programme consisted of three large group introductory tutorials followed by 5 weekly bedside teaching sessions in small groups. Objective structured clinical examinations (OSCE) formed part of the final summative assessment. Students reported a subjective increase in knowledge of neurology post-attachment but still felt neurology was a difficult subject and were less confident in it. Students who participated in the teaching programme had a mean mark of 70.4% for their neurology OSCE station compared to a mean of 65.6% for the control group. There was no difference in mean marks for neurology and respiratory OSCE stations (70.4% vs 70.6%). This pilot study suggests that a relatively simple teaching programme can be effectively implemented and that students' anxieties regarding neurology do not reflect their abilities on objective skills testing.

085 THE FEMINISATION OF BRITISH NEUROLOGY – WHAT IS THE REAL IMPACT?

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Background: 33% of neurology SpRs and 12.5% of neurology consultants are female. This is likely to increase to 50% and 30% respectively within 10 years. To predict the impact of changing demographics on the neurology workforce it is necessary to determine what life choices future neurologists will make.
Methods: A questionnaire survey of life choices and working practice was administered to neurology consultants and trainees, SHOs, and medical students.

Downloaded from jnnp.bmj.com on 22 December 2006

Results: 345 responses were received (105 students, 44 SHOs, 69 registrars, 127 consultants). Of respondents, 3% of SpRs and 4.6% of consultants work part-time, largely accounted for by 9% and 37% of female SpRs and consultants respectively (approximately 44% of those with children). With unchanged working patterns, this would increase within 10 years to 4.5% of SpRs and 11% of consultants. However, 87% of female and 22% of male junior doctors plan to work part-time for on average 7.5 and 1.5 years respectively, as do 30% of consultants. 14.3% of SpRs, and 6% of consultants have taken a career break; 37.5% of SpRs and 18.2% of consultants are planning a career break.
Conclusions: The changing demands of both sexes will have greater impact on the neurology workforce than the increasing proportion of women alone.

086 SELECTING NEUROLOGY REGISTRARS BY STATION INTERVIEW

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Under Calman, registrar selection relies solely upon the application form and panel interview based on that form informal discussions are forbidden and written references are used post hoc to confirm (or not) the panel decisionare barely read. Interviews alone must therefore identify a candidate's capability and competence. We have piloted station interviews, which include a broader range of elements to select neurology specialist registrars. We conducted three specialist registrar interviews in 2004–5, each for six applicants (total = 18). Interviews comprised three 20-minute stations and assessed seven domains: curriculum vitae (CV) and clinical scenario discussion (Station 1); history taking and information giving using a simulated (actor) patient (Station 2); oral presentation on a teaching topic, and discussion of specified scenarios on audit and research (Station 3). Two or three interviewers at each station scored independently. Group discussion and reference reading occurred after overall scores were ranked submitted. Correlations with overall ranking were good for history taking ($r = 0.71$) and for research (0.66), but less good for information giving (0.56), emergency scenario (0.54), CV-based element interview (0.51), teaching presentation (0.49), and audit (0.46). Station interviews provide more assessment time for applicants and assessors, provide independent rankings of different elements, and seem more relevant to common elements in the person specification, and fair competency assessments, giving candidates more time, more assessors, and more independent scoring. Importantly, the CV-based interview elements (the centrepiece of conventional interviews) did not reliably predict overall performance. Neurology trainee interviews must assess a range of relevant competencies, but particularly history taking.