

# American Epilepsy Society Annual Meeting

Washington, USA, 2-6 December, 2005.

The 2005 meeting of the American Epilepsy Society, usually the highlight of the epilepsy year, was like its venue in Washington DC, big but uninspiring. The meeting was at least congenial, whereas the city planners were given the remit to make DC intimidating to visitors. The area around the White House and the Capitol contains a plethora of neoclassical federal department buildings, each of which takes several minutes to walk past, which are imposing but unattractive; the park they surround is enormous and its best features a small lake and the Washington monument, the tallest free-standing stone structure in the world, elegant and needle-like from a distance, it has walls that are 15 feet thick at their base. In Georgetown one sees another side of the city. Site of the race riots of the late 1960s, it has out-Islingtoned Islington in upper middle class renaissance and antiques shops. The national museums of Washington are the highlight and are free, from the National Gallery of Art to the Space Museum.

What about the meeting? The 25th annual Merritt Putnam symposium was about the issue of pharmacoresistance, which though interesting remains speculative and the next few years will hopefully establish its clinical importance. Expression of drug transporters such as P-glycoprotein, important in phenytoin disposition, may be different in epileptic and normal brains and can be influenced by verapamil, a P-gp inhibitor. In other models there may be changes in the targets of AEDs such as sodium channels or GABA<sub>A</sub> reducing the effectiveness of medications and underlying this changes in mRNA may be detectable. In the meantime new drugs continue to be developed and there was a call from Marc Dichter of Pennsylvania for new ways of evaluating efficacy and new types of study which would allow us to evaluate new medication more speedily.

The annual course was a pragmatic one for clinicians, covering a number of issues including diagnosis and the value of EEG, long term cognitive outcome of epilepsy and women's issues. The format was varied and stimulating, using case studies, formal presentations and debates to highlight the issues, but much of the content was revision rather than revolution. Lawrence Hirsch from Columbia argued entertainingly and cogently that there is no evidence to support the aggressive management of anaesthetising

patients with non-convulsive status epilepticus to EEG burst-suppression. On this issue I came away with a clear feeling of uncertainty, which is probably intellectually healthy if not clinically useful.

The MESS study, published in the Lancet last Summer,<sup>1</sup> looked at 1443 patients with early epilepsy or single seizures who were randomised to immediate or deferred treatment. In essence, early treatment improved seizure outcome at 1-2 years but not at 3-5 years and there was no difference in major morbidity or mortality. In his platform presentation, David Chadwick presented an algorithm developed from this study which can be used to quantify the risk of recurrence and help decide whether to treat straight away (Table 1).

His study on behalf of the MRC of drug withdrawal is now 15 years old but remains a standard and has also given rise to a more complex algorithm (Table 2) for the risk of recurrence. If these algorithms are reliable in clinical practice then they will be helpful for clinicians and patients in planning when to start and stop medication. I await a pharmaceutical company initiative for a handy pen/seizure recurrence calculator/built in USB memory stick and laser pointer.

There were a variety of evening symposia, one on consciousness in epilepsy, which at 7.30pm was variably reflected in the consciousness of the audience. David McCormick (Yale) reviewed thalamocortical mechanisms in the generation of generalised spike-wave discharges and showed how the short loop between thalamus and thalamic reticular nucleus is responsible for normal sleep spindles, whereas the long loop from thalamus to cortex creates abnormal spike and wave discharges. Inhibitory cells are implicated with the spindle discharges, but blocking them with bicuculline seems to release an abnormal 2-3Hz discharge.

Neuropsychological assessment reflects clinical experience that absence is a variable phenomenon with different degrees of altered awareness in complex partial seizures versus 3Hz spike-wave

absences. In addition, the idea that spike wave causes loss of awareness is simplistic as the alteration in awareness starts before a spike-wave burst and increases towards a spike wave burst in association with the development of harmonics of the burst on the EEG. In addition there are genetic effects on awareness with female probands and relatives, being differently affected from males. This area has been ripe for fMRI study suggesting, amongst other things that complex partial seizures may propagate from mesial temporal structures to inhibit arousal mechanisms.

There was a vast number of poster information nuggets to view. Donepezil does not help memory in epilepsy – surprised? Patients who suffer cognitive decline from their epilepsy tend to be those with lower IQ, longer duration of epilepsy, more abnormal hippocampal volume and more cerebral atrophy. Temporal lobe drop attacks, which sometimes develop later in the course of the illness may be ictal asystole. Four patients were reported with severe unilateral hippocampal sclerosis whose seizure onset was in the opposite hippocampus. Presumably the atrophy was so severe that there were not the neuronal circuits needed for seizure generation. Postictal whispering or feeble speech rather than aphasia is a sign of non-epileptic seizures. One episode of ictal aggression was described in a patient with a right temporal lobe tumour. He got out of bed turned towards his wife and motioned as to shoot her with a bow and arrow, whilst making a shooting noise and then briefly tried to strangle her. The EEG confirmed a right temporal seizure discharge – honest m'lud! The Columbia University group described 6 critically ill patients with encephalopathy who suffered focal motor seizures when exposed to alerting stimuli; something to be remembered when nursing patients on ITU. Subtle white matter lines on MRI may be a marker for tuberose sclerosis. If teachers know that a student has epilepsy then they tend to rate their performance lower on teacher assessment

Simplified model	Score
One seizure prior to presentation	0
Two seizures prior to presentation	1
>2 seizures prior to presentation	2
Neurological disorder / deficit, learning disability or developmental delay	+1
Abnormal EEG	+1
	Final score
Low risk	0
Medium risk	1
High risk	2-4

Factor	
1. Starting score for all patients	-175
Age >16	45
Taking more than 1 AED	50
Seizures occurring after start of treatment	35
Any TCS	35
Myoclonus	50
EEG while in remission	
Not done	15
Abnormal	20
Duration of seizure-free period =D	200/D
2. Total score	T
3. Exponentiate $Z=e^{T/100}$	Z

	Probability of seizure recurrence	
	By 1 year	By 2 years
On continued treatment	1-0.89 <sup>Z</sup>	1-0.79 <sup>Z</sup>
On slow withdrawal of treatment	1-0.69 <sup>Z</sup>	1-0.60 <sup>Z</sup>

than they achieve on objective academic assessments, whereas this is not the case if they do not know that they have epilepsy. Ethosuximide (now only one preparation available in the UK) is traditionally only used in absence epilepsy. One study reported its efficacy in epileptic negative myoclonus in 10 patients. A reminder that topiramate can cause hypohydrosis and hyperthermia. Two studies looked at the effect of cooling the cortex, one using a thermoelectric device in animals and the other using a cooling helmet in

humans. In one man, this reduced core temperature by 0.24°C and scalp temperature by 14.3°C for 1 hour each week. He had no seizures during the 4 week trial period compared to 0.75 per week in the rest of the study.

My most unforgettable time in DC was in the Holocaust Museum, which leaves you at once traumatised through the depiction of horror and uplifted by stories of resilience and selfless acts of heroism. A most potent reminder of vital personal, religious and political freedoms. I disapprove

of what you say but I will defend to the death your right to say it – Voltaire.

Mark Manford,  
Consultant Neurologist, Norwich.

1. Marson A, Jacoby A, Johnson A, Kim L et al. *Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial.* *Lancet* 2005;365:2007-13.

## British Society For Immunology Annual Meeting

Harrogate, UK, 6-9 December, 2005.

### Cleanliness causes depression

The "hygiene hypothesis" explains why allergy and autoimmunity are on the increase. The increasing cleanliness of industrialised society reduces the opportunities to encounter trivial or harmless infections. So we have fewer chronic infections. Yet the immune system has evolved to live with, or even depend upon, such infections. For they induce release of cytokines such as IL-10 which promote regulatory T cells that suppress allergic and autoimmune responses. Without commensals, the immune system is tipped towards a pro-inflammatory and pro-allergic state. So far, so good.

Graham Rook, from UCL, has taken this further. He hypothesised that the hygiene hypothesis might also explain depression. Experimentally, he demonstrated that mice infected with *Mycobacterium vaccae*, which induces regulatory T cells and suppresses allergic responses, had increased serotonergic staining in localised CNS pathways and swim for longer in the "forced swim test" of depression. He argues that perhaps depression is an abnormally prolonged form of the "sickness behaviour" that accompanies the release of pro-inflammatory cytokines. Now I know why cleaning the kitchen makes me so unhappy.

### Reverse vaccinology for meningitis

The revolution in the management of meningitis passed me by. Did you realise that meningococcus A, C, Y and W are no longer? Since the UK introduced a vaccination policy in 1999 for everyone under the age of 18 (and we were the first country to do it), the number of cases has fallen precipitously. The scientist behind those vaccines was R Rappuloi, from Chiron Vaccines in Siena. Now the hunt is on to develop a vaccine against meningococcus B. It is proving difficult. By traditional vaccine technology, only one antigen can be detected on the surface of meningococcus B, of which there are many thousands of variants. Where only one strain exists (such as New Zealand) a vaccine is easy to create and it works. But for the rest of the world a "one fits all" vaccine is required... to find this, Rappuloi has developed the technique of "reverse vaccinology". He persuaded the scientific community to sequence the genome of meningococcus B and 18 months later he had identified 90 novel proteins expressed on the surface of meningococcus B, which he has whittled down to 5 vaccines now entering clinical trials. Pasteur would have been proud.

### Controlling pathogenic CNS – reactive T-cells: death and regulation

An effective immune system must be able to respond to all possible pathogens whilst maintaining tolerance to self. These twin requirements are finely balanced, with increased T-cell receptor (TCR) diversity resulting in an increased risk of autoaggression. Steve Anderton (Edinburgh) has demonstrated some of the niceties of this balance using EAE induced by the Ac1-9 peptide of myelin basic protein (MBP) in mice expressing a transgenic Ac1-9-reactive TCR. The peptide was subtly altered (single amino acid changes at key positions) to make a series of altered peptide ligands (APLs) with varying binding affinities to the TCR. Interestingly, EAE could only be induced by immunisation with the wild type peptide. Sub-agonist and surprisingly super-agonist APLs failed to induce disease. Super-agonists are defined by the ability to stimulate T-cells in vitro at significantly lower concentrations than the wild type peptide. Immunisation with the super-agonist led to the apoptotic elimination of super-activated cells in a Fas dependent manner. Only T-cells with very low affinity TCRs survived apoptotic cell death. These cells were unable to respond to wild type antigen at the concentration found in vivo, and were, therefore, unable to induce disease. In addition, immunisation with the sub-agonist activated T-regulatory cells thus preventing disease induction.

### The search for an endogenous agonist for Toll like receptor 3 (TLR), a repair mediator in the CNS

It would be extremely useful to be able to exploit repair mechanisms in the CNS to treat MS, but how could these repair mechanisms work? Jan van Noort (Netherlands) discussed TLR3 and its possible role. Activation of TLRs upregulates pro-inflammatory cytokines, some of which are relevant for tissue repair. In the MS lesion, TLR3 expression increases early in microglia and later on the surface of astrocytes; and in vitro TLR3 ligation causes astrocytes to release neurotrophic factors, anti-inflammatory cytokines and other factors important in repair. The only known agonist for human TLR3 is dsRNA. Van Noort and colleagues have found another ligand, preferentially expressed in the CNS, by screening tumour cell lines. High expression levels of this agonist were found in foetal development at axonal growth regions and developing dendrites and lev-

els decreased with age. Inflammation seemed to increase production of this agonist in neurones and oligodendrocytes. We will not get to know the identity of this agonist until the patent lawyers have had their say, but it sounds promising...

### TIM and galectins: Role in T cell differentiation, autoimmunity and tolerance

The T cell immunoglobulin mucin (Tim) proteins are type 1 membrane glycoproteins expressed on T cells. Tim-3 was first identified in VJ Kuchroo's Boston laboratory, and is expressed on terminally differentiated TH1 cells, which produce IFN-g and IL-2, and at low levels by TH1IL-17 cells. Kuchroo described how Tim-3 is an inhibitory molecule. Blocking Tim-3 with an immunoglobulin fusion protein resulted in hyperproliferation of TH1 cells and an increase in levels of IFN-g, and the abrogation of antigen-specific tolerance. This suggests that Tim-3 and its ligand are important regulators in peripheral tolerance and expansion of effector TH1 cells. Kuchroo's laboratory has also identified the ligand for Tim-3: galectin-9.

Galectins are carbohydrate-binding proteins, which act as controllers, silencers and tuners of the immune system, and have a vital role in immune cell homeostasis. Galectin-9 inhibits IFN-g production by Tim-3 expressing TH1 cells in vivo and induces TH1 cell apoptosis in vitro. TH1 cells incubated with recombinant galectin-9 clumped together and underwent rapid cell death, however, when Tim-3 deficient TH1 cells were incubated with recombinant galectin-9, cell death was partially impaired suggesting that galectin-9-mediated cell death is both Tim-3 and contact dependent. C57BL/6J mice, immunised with myelin oligodendrocyte glycoprotein (MOG) to induce EAE, and injected with galectin-9 had a 50% decrease in IFN-g production by antigen specific IFN-g producing CD4+ T cells, indicating that galectin-9 targeted antigen-specific TH1 cells in vivo, but not other peripheral T cells. These mice had reduced disease severity and mortality. Kuchroo proposes that Tim-3 and its respective ligand, galectin-9 may be involved in regulating the fine balance between maintaining tolerance to self and defending the body from pathogens.

Alasdair Coles, Joanne Jones,  
Vicki Robertson, Sara Thompson, Cambridge.

# 16th International Symposium on ALS/MND

Dublin, UK, 8-10 December, 2005.

Pre-Christmas Dublin was the lively venue for the 16th International Symposium on ALS/MND organised by the Motor Neurone Disease Association in co-operation with the International Alliance of ALS/MND Associations. Over 850 clinicians, researchers and health care professionals along with patients and representatives attended the 3 day meeting. The sparkling Burlington Hotel could just about cope with the numbers with many of the parallel sessions full to capacity. The programme committee, chaired by Professor Pamela Shaw (Sheffield), managed to pack in sessions ranging from basic science and clinical research through to clinical care and support. The review below highlights some of the sessions I attended.

## Alternative medicine

The Opening Session began with a talk on 'Alternative medicine – hope or hype'. This was delivered, somewhat dryly and without visual aids, by Dr Steven Barrett (Pennsylvania, USA) who has established the website Quackwatch ([www.quackwatch.org](http://www.quackwatch.org)). From his opening salvo – “‘Quackery’ is a nasty term, and so is ‘complementary medicine’” – his choice of hype over hope was clear. He took issue with denoting the field as ‘complementary’ or ‘alternative’ saying that these terms give quackery a credibility and legitimacy it hasn't earned. He emphasised that ‘alternative’ therapies are not necessarily harmless, giving false hope and having negative effects on wider public health issues, even if not often physically detrimental. Whilst not agreeing with all he said, I found his talk challenging. We are so keen not to offend nor dash hope in our dealings with people with MND that it is all too easy to say that certain complementary therapies are unlikely to do physical harm and if patients report that such treatments make them feel better suggest they continue them. Is this really the best advice we can give?

In the second talk of this plenary session Nigel Leigh (King's, London) gave a clear overview of variation in ALS/MND, emphasising the heterogeneity of the disorder in term of phenotype and prognosis. A take home message was that a one-mechanism, one-prescription-for-all type of approach may not be appropriate.

## Lessons from other motor neuron disorders

I thought this was one of the best sessions of the meeting. A comprehensive talk on recent advances in the genetic understanding of distal hereditary motor neuropathies by Peter de Jonghe (Antwerp) was followed by a review of spinal muscular atrophy by Michael Sendtner (Wuerzburg). He detailed research suggesting that this is not caused by a primary defect in cell survival but rather with a defect in axonal growth and maintenance. He outlined various therapeutic possibilities including up-regulation of axonal mRNA transport and local protein synthesis at the presynapse. Martin Schwab (Zurich) gave an elegant account of axonal regeneration and functional recovery in adult injured mammalian spinal cord. He outlined the role of neurite

inhibitory growth factors and reviewed results of experiments administering neutralising antibodies to Nogo-A in rats and monkeys following acute cord injury. It's not yet clear if any of this work on treatment following acute cord injury will be relevant to ALS/MND, a disease where there is still no good early marker of disease.

## Protein folding and degradation defects

Heather Durham (Montreal) gave an overview of the proteasome and its role in cell regulation and neuromuscular disease. I hope that she will write the talk up as a review, as she presented much complex data in a very accessible way. Avijit Chakrabarty's short talk outlining the use of an antibody that specifically binds to misfolded SOD1 generated much interest. About 20% of autosomal dominant familial ALS cases are due to mutations in SOD1, an enzyme that normally functions as a homodimer. Mutant SOD1 is more aggregation prone than wild-type SOD1 in vitro and prior to aggregation SOD1 goes through a monomeric intermediate. The newly developed SEDI (SOD1 exposed dimer interface) antibody specifically recognises an epitope that is only exposed in monomeric SOD1, and lovely data was presented showing that the antibody binds to misfolded SOD1 in spinal cords of transgenic G93A and G37R SOD1 mice, binding not seen in non-transgenic littermates. It was also suggested that the antibody staining around vacuoles in motor neurones represented misfolded SOD1 in mitochondria, which fits well with the proposed pathogenic role for mitochondria in ALS/MND. Results on staining of only one surviving motor neurone in the spinal cord of a single ALS patient were presented. After the session many groups with human tissue offered to collaborate and future reports of the results in ALS/MND tissue are awaited.

## Preclinical therapeutic trials

A highlight here was the work presented by D Kieran (Dublin) on angiogenin. Work in recent years has shown that the hypoxia-inducible factors VEGF and IGF-1 are neuroprotective to motor neurons. At the ALS/MND Symposium in 2004 Orla Hardiman's Dublin group presented data showing that mutations in the gene encoding the hypoxia-responsive peptide angiogenin are associated with ALS. The paper in the current symposium built on this, showing that angio-

genin is expressed in cultured motor neurons, this expression increases during hypoxia and that co-treatment with angiogenin significantly increases motor neuron survival in cultures exposed to hypoxia or excitotoxicity. The role of hypoxia inducible factors in motor neuron degeneration and their potential as therapies is clearly a 'hot' research area in ALS/MND at present.

## Clinical trials

The session of the meeting that I'm most asked about by people with MND and their carers is that on clinical trials. "Was there anything new from the meeting that's going to help me now?" Sadly, no new positive clinical trial data was presented at the meeting. The negative results of the Phase II/III clinical trial of TCH 346, an anti-apoptotic agent, were presented by Bob Miller (San Francisco). The negative results of (another) study of creatine 5g once daily were presented by Dr Rosenfeld (Charlotte, USA). I was surprised that Dr Rosenfeld concluded his talk by saying that perhaps another study of creatine should be performed, using higher doses of the agent and looking at its effect combined with exercise. My take on the presentation of his data was that, despite the promising results in the SOD1 mouse model, creatine is not of benefit in human ALS/MND.

Elsewhere in the symposium safety data was presented from Phase I and II trials of compounds such as the manganoporphyrin AEOL10150, glatiramer acetate, tamoxifen and thalidomide. Novel trial designs such as futility trials, which allow smaller patient and control numbers, or trials based on selecting rapidly progressing patients were also discussed.

## Genetics sessions

Points I noted from the genetics sessions included: more families with ALS and frontotemporal dementia linked to chromosome 9p21 have been identified, but no gene has as yet been reported; spastin mutations are not found in primary lateral sclerosis; spastin mutations are occasionally found in both adult and juvenile onset ALS; mutations in VAPB, a protein that interacts with synaptobrevin to aid vesicular packaging and transfer have been found in about 2% of ALS patients (both familial and sporadic) and occasionally in controls.

## Conclusions

Although no 'big breakthroughs' were presented at the meeting, there was much to be encouraged by and I certainly left feeling upbeat about the prospects for ALS/MND care and research. Oh yes, I forgot to mention the social side of the proceedings. The Irish MND Association really do know how to host a meeting. Many thanks to Dr Hardiman and all the local MND workers for creating an excellent atmosphere throughout the meeting and for staging a great conference dinner, complete with Irish dancing. I don't think Riverdance has to fear from an influx of MND researchers just yet.

*Professor Karen E Morrison, Professor of Neurology, University of Birmingham.*



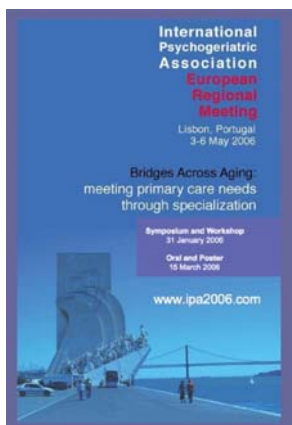
An MND patient using a nasal mask for assisted ventilation.

An MND patient using a communication device strapped to her foot.

## CONFERENCE PREVIEW: Bridges across Ageing: meeting primary care needs through specialisation. International Psychogeriatric Association European Regional Meeting

Lisbon, Portugal, 3-6 May, 2006.

A programme of plenary sessions, symposia and workshops, poster presentations, as well as themed oral sessions for new research and satellite symposia supported by industry, will be the structure for this meeting, focused on bridging primary care with specialties to most effectively meet the mental health needs of the elderly. International speakers will bring knowledge and data appropriate to an audience of professionals including psychiatrists, primary care physicians, neurologists, internal medicine physicians, psychologists, social workers, nurses, occupational therapists and other colleagues with interests in geriatric mental health.



Topics include: Delivery of psychogeriatric services; Dementia; Depression and suicide; Medical aspects associated with AD; Mental health services in nursing homes; Mild cognitive impairment; Psychosis; Psychotherapies and cognitive training.

Recent advances in the field of Psychogeriatrics will be presented, especially in the areas of understanding basic neurobiology, diagnostics, therapeutics, and service development and delivery. Symposia will also be presented by the World Psychiatric Association, European Association for Geriatric Psychiatry and on the EDCON project.

Visit [www.ipa-online.org](http://www.ipa-online.org) to see the latest programme, speaker information and submission and registration details.

*Horácio Firmino, Meeting Chair.*

Portugal is a beautiful country known for its contrasts – from its outstanding landscapes of beaches and mountains to its rich history and exciting contemporary development. The same is true in its diverse ageing population. The distribution of the elderly population in Portugal is not homogeneous, reflecting the socio-economic diversities of each region. At this time, 17% of the Portuguese population lives beyond 65 years of age. The largest percentage of population over 65 resides in the central and southern regions of the country. According to a study of the National Institute of Statistics (2002), the population in Portugal over 65 years of age has doubled in the last 40 years, so that in about 30% of families, there is at least one elderly person and around half of these families are composed of elders.

The increase of this elderly population has led to the development of social policies to guarantee an ageing with quality of life. New solutions of home support and day centres help to maintain the elderly in their own residences, and provide options beyond nursing home placement. Portugal is a country with handicap access both socially and politically thus offering a peaceful and quality environment for the elderly.

## CONFERENCE PREVIEW: Brain Injury Social Work Group AGM (BISWG)

Birmingham, UK, 16 May, 2006.

The Annual General Meeting and case discussions take place at the British Association of Social Workers Head Office, 16 Kent Street, Birmingham B5 6RD.

BISWG exists to raise awareness and standards for the provision of resources to those people with a brain injury and their families and carers. The organisation aims



Patti Simonson, Chair, Brain Injury Social Work Group.

to bring together interested professionals who seek both to offer and to receive knowledge, education and skills in this specialised area.

Case Discussions will focus on the following areas – transition of young people to adult services and adults to older people's services, capacity, direct payments, supporting people and/or continuing health care fund-

ing, medico-legal cases where statutory assessments/services are being requested.

If you have any case summaries you feel would provide pertinent discussion in these areas, please send details to Guy Soulsby. This will not be an event where a panel provides expert guidance but one where we will share ideas/information amongst the group.

Contact: Guy Soulsby;  
Tel. 0151 250 6247,  
Email: [guy.soulsby@merseycare.nhs.uk](mailto:guy.soulsby@merseycare.nhs.uk)

## CONFERENCE PREVIEW: Primary Care Neurology Society 2006 Conferences

Primary Care Neurology 2006 will take place on the 11th May, at One Great George Street, Westminster, London and also in the North of England on the 12th October, at Cutler's Hall, Sheffield. The P-CNS are extremely grateful for all the excellent feedback they received from last year's conference, and have found it very helpful when formulating this year's programme. Topics include:

- Primary Care Neurology in the Psychiatrists Chair

- Fits Faints and Funny Turns
- Access to MS Services
- Development of Neurological Rehabilitation Services

It offers a programme of keynote lectures, an Interactive Question Time and clinical workshops which will focus on:

- Issues in Primary Care Dementias
- Diagnosis and Long-term Management Issues in Parkinson's Disease

- Establishing a Primary Care Epilepsy Service
- Identifying and managing mental health issue in neurology

### Speakers include:

Dr Mark Ashworth, Dr Alan Carson, Dr Andy Dowson, Dr Mike Footitt, Dr Helen Hosker, Dr Steve Iliffe, Marianne Peachey, Dr Greg Rogers, Amanda Scutt, Dr Chris Ward,

A booking form is available from the P-CNS website, [www.p-cns.org.uk](http://www.p-cns.org.uk)