A s appears now to be the norm, the main conference was preceded by a one day Imaging Consortium. This is of mixed benefit, while the concentration of imaging talks benefits those researchers based principally in this field, there is repetition of the same material within presentations within the main conference.

Several groups presented updated results relating to molecular neuroimaging in Alzheimer’s disease (AD). One of the interesting aspects of the work described by the Klink and co-workers from Pittsburgh using Pittsburgh Compound B (PiB) was the longitudinal study involving amyloid imaging of patients with mild cognitive impairment (MCI); previous work has shown that around 50% of patients with MCI progress to AD within three years but there is also a significant proportion whose symptoms remain static or even improve. Analysis of the PiB-PET data reveals that 50-60% of “PiB-positive” MCI patients converted to AD over two years, whereas over the same period none of PiB-negative MCI cases progressed to AD and three out of ten PiB-negative cases reverted to normal (see also related paper in the May 2009 edition of Annals of Neurology). PiB-positivity was found to be highly correlated with reduced levels of Aβ42 in the CSF. These data were echoed by those of Chris Rowe from Melbourne, who presented evidence indicating that the presence of PiB-positivity in MCI patients was 87% predictive of progression to AD.

In addition to the PiB-related talks, mention was made of the 18F-related ligands with amyloid-labelling capability. They benefit from a longer half-life than the 11C-PiB, at present the usage of the latter is limited by its short half-life and so is essentially restricted to those centres with an in-house cyclotron. By comparison the 18F-ligands have the potential for widespread usage.

Cliff Jack of the Mayo Clinic presented a comparison of serial PiB and MRI data in controls, MCI and AD patients over a one year test period. There was little difference between the PiB and MRI in MCI and AD patient groups in terms of the change in degree of PiB labelling whereas there was a significant group difference with regard to rate of ventricular expansion (used as a measure of change in whole brain volume). Change in ventricular size, and not in PiB labelling, correlated with decline in cognitive and clinical state. The dissociation between the two sets of imaging data may provide an insight into the differing pathological processes in AD; in line with other investigators, it is proposed that deposition of amyloid occurs from a very early stage of the disease, with very little change in the rate of further deposition once an individual become symptomatic, whereas neurodegeneration (and associated brain parenchymal loss) is a manifestation of later stages of AD and parallels the cognitive decline. These findings have important implications for the use of these complementary techniques in tracking the disease at different stages.

Finally on the imaging front, Reisa Sperling and colleagues at Harvard demonstrated in cognitively normal and minimally impaired individuals that extracellular amyloid deposition as seen on PiB imaging is associated with a disruption of the normal pattern of activity within the “default resting network” of brain regions thought to be involved in successful memory encoding and retrieval, including the precuneus and retrosplenial cortex, as observed on fMRI. These early data suggest that amyloid deposition is related to dysfunction of brain regions subserving memory processes. However, it remains to be seen whether the relationship is causal, and these observations do not provide any clear explanation for the role of tau-related tangle pathology within the AD process (a criticism common to all PiB-based work).

Away from neuroimaging, Niklas Mattsson from Gothenburg presented data from a large scale longitudinal study of CSF biomarkers in MCI. A two year follow-up study of 750 MCI patients revealed that those patients converting to AD had lower CSF levels of Aβ42 and higher levels of tau and phosphorylated tau than non-converters with a positive predictive value of 62% and negative predictive value of 88%. This follows from the publication by Visser and colleagues concerning CSF profiles in patients with memory impairment who are at risk of progressing to AD which was accompanied by the challenging editorial which raised the issue of lumbar puncture as a potential routine investigation for patients presenting with memory impairment.

By comparison with ICAD 2008, the news on potential new drugs was relatively muted; to a large extent this was due to the fact that there was no major presentation detailing Phase II or Phase III study results. Following on from the presentation of Phase II data last year, the Phase III study of bapineuzumab (the monoclonal antibody directed against the N-terminus of Aβ42) is now in progress and provisional results will not be available until 2012. Aways from AD immunotherapy, there is interest in the antihistamine drug Dimebon, whose proponents suggest that it may have neuroprotective qualities related to the enhancement of mitochondrial function. While the promise of multiple future drugs with potential disease-modifying capability is undoubtedly exciting, several speakers rightly drew attention to potential difficulties. For instance, there is concern that the majority of drugs currently undergoing trial for AD are directed at “upstream” targets within the AD pathological process (such as β-secretase inhibitors) and as a result may have limited efficacy due to the lack of effect on the downstream processes that ultimately lead to neuronal dysfunction and death. Additionally, while there was a general consensus that drugs of this kind were likely to be of greatest benefit when applied early during the disease process, this will be problematic not least due to a) the difficulty of identifying patients in the earliest (effectively presymptomatic) stages of AD and b) the need for very large scale and prolonged trials to detect treatment effect of drugs applied at early stages of disease.

Finally, from a UK perspective it was gratifying to witness the presentation of a Lifetime Achievement Award to Professor Martin Rossor of the Dementia Research Centre, London. Professor Rossor’s work in the field of dementia now spans nearly a quarter of a century and takes in such notable achievements as the identification of the first pathogenic mutations in familial AD. The timing of the award is particularly appropriate given the increasing international emphasis on the management of dementia, exemplified nationally by the introduction of the National Dementia Strategy.

REFERENCES


New Developments in Clinical Trials in Neuroscience & Psychiatry

**Conference details:** 10 June, 2009; Edinburgh, UK. **Reviewed by:** Professor Peter Sandercock, Edinburgh, UK.

**New Developments in Clinical Trials in Neuroscience & Psychiatry**

Translational neuroscience offers enormous potential, but has yet to deliver real benefits for patients with the disorders of the nervous system that cause such a large burden of disability: stroke, dementia, neurodegenerative diseases and the major psychiatric disorders. This meeting sought to take a step back to examine the strengths and weaknesses of translational research in the field to identify key barriers and potential solutions. Gordon Murray, Professor of Medical Statistics at The University of Edinburgh gave the opening lecture which set the scene. He drew a sharp contrast between cardiology and neuroscience. In cardiology the availability of useful and reliable surrogate markers (coronary artery patency, left ventricular function, blood pressure) had underpinned the development of large-scale trials able to detect effects on major clinical outcomes. These trials then established the benefits of aspirin, beta blockers, angiotensin converting enzyme inhibitors and thrombolysis, just to name a few. By contrast, in acute stroke, thrombolysis had skipped the translational pathway and was developed in stroke ‘on the back of’ experience in cardiology. Neuroprotection, which had shown so much promise in animals, has yet to show benefits in man. Very presciently Professor Murray outlined the themes that many of the speakers would return to during the afternoon. The most important of these was the need for careful methodological development of better surrogate markers, both of the underlying biological processes, but also of the clinical outcomes those processes were mostly likely to influence. Professor Joanna Wardlaw then went on to outline the rather chequered history of imaging as a surrogate outcome in acute stroke research. One illustrative example which she drew on, was the use of advanced neuroimaging to outline cerebral tissue that was ischaemic but potentially rescueable by therapy. Whilst it is relatively straightforward to produce attractive colour-rendered pictures of cerebral perfusion it has become clear that the use of different measurement algorithms can produce radically different results. In brief, there is a need for much greater methodological rigour in the development and application of such techniques and the research community needs to reach consensus on an optimal and standardised approach. Several of the themes of her talk are reflected in a recent editorial in the journal ‘Stroke’.

Next on the podium was Professor Stephen Lawrie, Professor of Psychiatry and Neuroimaging at The University of Edinburgh, who outlined the promises and challenges of neuroimaging in major psychiatric disorders. His talk ran along the theme that although there were undoubtedly structural and functional changes in the brain in people at risk of, or with established psychotic disorders, there were many challenges in measuring these changes precisely or understanding their underlying biological substrate. Multicentre imaging studies offer greater statistical power to help detect and clarify the nature of the subtle structural and functional changes that occur in the brain. Neurogrid, Neuropygird and the Scotland-wide SINAPSE collaboration certainly seem to be forging ahead, developing the technological advances needed that will facilitate multicentre imaging studies to help take the field further forward.

Dr Roger Staff from the University of Aberdeen showed results of work in progress on the use of SPECT and PET imaging in dementia and Alzheimer’s disease. The techniques do seem to show promise as useful surrogate outcomes and the promising results in a small phase II trial are now being tested on a larger scale in a phase III trial of a therapeutic agent for this major group of diseases.

Dr Carl Counsell moved away from imaging to consider how to improve the clinical assessment of outcome in Parkinson’s Disease and neurodegenerative disorders. His talk was a reminder that while biomarkers (imaging, molecular biology and genetic) have some role in the assessment of new treatments for Parkinson’s Disease and in neurodegeneration, in parallel with those developments, the science of clinical measurement needs to be applied to assess the impact of disease on the patient and their life. He outlined the path forward that developments in clinimetrics would need to take to achieve this goal.

This exciting and fruitful symposium was rounded off by a lecture from Dr Walter Koroshetz, Deputy Director of the National Institute of Neurologic Disorders and Stroke, at the National Institutes of Health, Bethesda, USA. He outlined themes that were all too familiar to the audience: the difficulties of moving successfully from identifying a potential therapeutic target, selecting an agent that might act on that target and then establishing its effects in animals and subsequently in humans. In parallel with the challenges of scientific development of agents, there is also a difficulty – on both sides of the Atlantic – of developing the careers of the next generation of clinical trialists. They will need stamina to overcome the bureaucratic and organisational hurdles to clinical trials and combine it with the scientific vision and charisma that are needed to lead the large collaborative groups to undertake multicentres international clinical trials. He ended on a note of optimism. Whilst these problems are significant, they are all potentially soluble and we must work on them one step at a time.

This well-attended meeting was supported by the following academic institutions, research groups and NHS research networks: The University of Edinburgh Centre for Clinical Brain Sciences, Edinburgh Neuroscience, the Edinburgh Clinical Trials Unit Collaboration, the Scottish Collaboration of Trialists, the Scottish disease-specific research networks in stroke, mental health and neuro-degenerative disorders, the SFC Brain Imaging Centre and a grant from The Royal Society of Edinburgh.

The lectures are available on-line at http://www.ccbs.ed.ac.uk/bcm.html
This year’s International Epilepsy Congress was a very special one as the International League against Epilepsy (ILAE) is celebrating its first 100 years. The ILAE meeting was held on 30 August 1909 at a meeting in Budapest, the same city where the organisation was founded. The League is the oldest international subspecialist organisation in the field of neurology and one of the oldest in medicine.

During the Presidential Symposium Peter Wolf from Denmark, President of the League, expressed his hopes for the future. “We expect that ILAE and IBE together will make progress toward a world where nobody needs to suffer from epilepsy or its consequences because they don’t have access to the existing diagnostic and therapeutic possibilities.” Furthermore, he was confident that both diagnostics and therapies, pharmacological and other, will become still more effective in the future. “If we achieve remission in 90% of patients instead of the current 70%, we will have achieved a lot.”

Promising future

One of the new drugs which will hopefully help to achieve higher remission rates in the future is lacosamide. It has recently been approved in the US and EU for the adjunctive treatment of partial-onset seizures in adults. Lacosamide appears to selectively enhance slow inactivation of voltage-gated sodium channels without affecting fast inactivation. Preliminary in vitro studies suggest a potential interaction of lacosamide with collapsin-response mediator protein 2 (CRMP-2), a protein involved in neuronal differentiation, polarization and neurotrophin-induced axonal outgrowth. Lacosamide has quite a favourable pharmacokinetic profile. It is rapidly and completely absorbed (bioavailability of 100%), has a half-life of 13 hours permitting a twice daily dosing schedule and a low protein binding (under 15%).

The safety and efficacy of this new drug have been evaluated in three well-controlled Phase II/III clinical trials. Individual and pooled data from these trials were used to evaluate lacosamide efficacy across the 200 – 600mg/day dose range studied. The pooled analysis, presented by Elinor Ben-Menachem (Goteborg/Sweden) showed a reduction of the median seizure frequency by more than 40%. This is particularly remarkable considering that 77% of the patients included had tried four or more lifetime antiepileptic drugs before entering the trial. A further advantage of lacosamide is that its efficacy seems to be independent of the concomitant antiepileptic treatment. Lacosamide was generally well tolerated, with dizziness, nausea, headache and diplopia being the most common side effects.

REFERENCES

The 13th International Congress of Parkinson’s Disease and Movement Disorders was held on June 7th-11th 2009 at Le Palais des Congrès in Paris. Despite overcast Parisian skies, the event was an overwhelming success with more than 4,600 participants from 39 countries. The 5-day event comprised various plenaries, parallel sessions and poster workshops and discussions in the format of ‘video olympics’ and a lively debate on some controversies in movement disorders. A variety of poster sessions attracted impressive participation from various groups around the world. This year’s special theme was Anatomy, physiology and pathology of the basal ganglia.

Some of the many highlights included Professor Stan Fahn’s plenary that provided a thorough overview of the various therapeutic agents currently used in the treatment of early Parkinson’s disease (PD) and also highlighted certain areas such as neuroprotective strategies. Evidence from therapeutic trials on monoamine oxidase B inhibitors (MAO-B) are supportive in slowing down disease progression (DATATOP, TEMPO, PRESTO, ADACIO studies) and delaying onset to freezing of gait (BLIND-DATE study).

Other important aspects of therapeutic intervention include the use of dopamine agonists that delay the need to use levodopa but do not prevent dyskinesia when used in combination with levodopa. The important potential side-effects of dopamine agonists such as impulse control disorders, somnolence and peripheral oedema were mentioned. There was also a brief mention of current trials involving potential neuroprotective agents such as the QES study (co-enzyme Q10) and creatine. Professor Fahn reiterated the need to always individualise treatment.

The management of motor complications following medical and surgical therapy was discussed by another group of international specialists. Professor Heinz Reichmann highlighted that the weak off-effect of levodopa that can occur as soon as 6 months after commencement. Motor fluctuations are thought to be due to fluctuating dopamine levels and ‘downstream changes’ within medium sized spiny striatal neurons. In the ELLDOPA study 17% of participants receiving levodopa experienced mild dyskinesia and 30% experienced wearing off approximately six months after commencement therapy. The panel also discussed the use of amantadine and its antidyskinetic effect that may be useful but decreases in efficacy over time. The use of surgical therapy, specifically deep brain stimulation (DBS), was also discussed by Dr Patricia Limousin-Dowsey and it was agreed that subthalamic nucleus (STN) stimulation can greatly improve motor symptoms in the ‘off’ phase such as tremor and dyskinesia. Importantly, STN stimulation is cost effective. Limited information is known about the effect of DBS on non-motor symptoms but some have observed improvement in hyperthermia, hyposmia, sleep and pain. Common adverse effects associated with DBS include weight gain and speech impairment. Other potential disabling side-effects include eyelid apraxia, dyskinesia and psychiatric changes (including suicidal ideation). Though STN stimulation is the most common performed type of DBS for PD, potential therapeutic benefits of globus pallidus interna (GPI) and thalamic (ventrals intermedius nucleus) stimulation were also discussed. The role of lesion therapy (e.g. unilateral pallidotomy, gamma knife thalamotomy) was also briefly discussed. Key points to be considered as selection criteria for surgical therapy include the patient’s general health, disability, cognition, speech, swallowing and their pre-operative expectations.

Dr Anette Schrag and Professor David Burn provided insights into the disease-related psychiatric and behavioural abnormalities of PD, as well as the assessment and management of cognitive impairment in Parkinson’s disease dementia (PDD). Among the useful cognitive screening tools currently utilised are the Montreal Cognitive Assessment (MoCA) and the Addenbrook’s Cognitive Examination – Revised (ACE-R). Professor Burn briefly touched on the use of antipsychotics in PDD and the potential benefit of cholinesterase inhibitors such as rivastigmine, donepezil and galantamine as well as glutamate antagonist, memantine, that is currently being studied by various groups. Emphasis on the importance of non-pharmacological approaches in the management of cognitive impairment in PD includes rehabilitation (e.g. auditory cueing and gait retraining), exercise and potential for ‘medical foods’.

The topic of new therapeutics in PD was touched on by Dr Richard Walker, Dr Njideka Okubadejo and Dr James Bower. Impressive results in drug therapy were demonstrated by Professor Christopher Goetz on ‘Jean-Martin Charcot and movement disorders’. This was followed up by the junior award lecture by Dr Helen Ling from the United Kingdom. Dr Ling reported diagnostic accuracy in pathologically confirmed corticobasal degeneration (CBD). The diagnostic accuracy of CBD presenting to movement disorder specialists was found to be much lower compared to progressive supranuclear palsy and multiple system atrophy. Dr Carlos Juri from Spain presented on the progression of MPTP induced Parkinsonism in monkeys via a multi-hit and gait PET study. Different hypometabolic patterns were illustrated and compared to PET findings in PD patients that revealed some contrary results and which may provide useful information in the development of putative neuroprotective strategies. The Presidential Lecture session was finished by the C David Marsden Lecture presented by Professor Richard Morimoto from the United States of America. His thought-provoking lecture was on the stress of misfolded proteins in ageing neurodegenerative disease. Among the science being unravelled by Professor Morimoto and his team are the regulation of the heat shock stress response via heat shock proteins and molecular chaperones.

There was also a special session on the challenge of PD management in Africa. The difficulties in diagnosis and management of PD in a third world environment were discussed by Dr Richard Walker, Dr Njideka Okubadejo and Dr James Bower. Impressive results in drug therapy were demonstrated in patients who had been treatment naïve for years and only reinforced the need to improve provision of medication as a basic necessity to the population. Auditory cueing and rehabilitation also produced stark benefit in mobility of patients and once again, reminded us of the importance of non-pharmacological treatment.

The Wednesday night ‘Video Olympics’ was an entertaining and educational floor for interesting neurological cases and diagnostic conundrums to be presented to the expert panel. Among the cases presented were galac-
WCN 2009 World-Class Speakers, Compelling Issues

By: Dr Naraporn Prayoonwisit, MD, local chairperson of the WCN 2009 Scientific Program.

The scientific programs for the upcoming WCN 2009 are central to the congress being a success. Our aim is to deliver great insights and tangible value to all attendees. I would like to share with you some highlights of what we have planned for the scientific program of WCN 2009, which takes place October 24-30 in Bangkok.

The scientific program this year has the theme, ‘Innovation in Neurology’. With innovation and reference to the latest research firmly in mind, WCN 2009 will analyse the latest developments in stroke, epilepsy, neurogenetics, multiple sclerosis, dementia, movement disorders, headache and pain.

The organising committee is proud to announce that Nobel Laureate, Prof Stanley Prusiner, whose discovery of an extraordinary infectious protein called ‘prions’ will address the latest developments in a session on PRION disease.

The urgent requirement to bring good neurological care to needy people in developing countries will be addressed by Prof Johan Aari, the President of the World Federation of Neurology. Other advanced information on multiple sclerosis, epilepsy, neurogenetics, neuroimaging, etiological neurology, headache and pain will be presented by international experts.

Prof Vladimir Hachinski, the WFN Vice President and globally respected authority in the modern debate on stroke, will discuss the global agenda on stroke. This devastating condition affects a large proportion of the world’s population, particularly in Asian countries where access to prompt treatment is still quite limited.

Of course, we will address controversial issues. Theories, research and results from the latest research in neurology will be brought out into the open. For example, whether good old aspirin still holds the reputation of the ‘best antiplatelet for stroke prevention’ will be debated by Prof Peter Sandercock and Prof Louis Caplan.

The conflicting opinions on whether Devic disease, a common demyelinating disease in the East, is actually the same as its western counterpart, multiple sclerosis, will be investigated by Prof Alastair Compston and Prof Vanda Lennon.

A decision to do or not to do a genetic workup for epileptic patients should become clearer with the discussions provided by Prof Samuel Berkovic and Prof Michael Johnson.

The congress finale comprised a lively debate on controversies in movement disorders. The hot topics discussed were ‘The PPION is a promising target for treatment-resistant gait disorders in Parkinson’s disease’, ‘Do cholinesterase inhibitors make a meaningful difference in treating PDD?’, ‘Lewy bodies in grafted dopaminergic cells: Do they tell us anything about the pathogenesis of and the promise of cell replacement therapies in PD?’ and ‘Transcranial sonography: A useful diagnostic tool for movement disorders?’. As with most controversies, only time (and more research) will help us define the right from wrong.

Participants were given the opportunity to attend a variety of educational sessions held as parallel sessions throughout the duration of the congress. These sessions were chaired by experts in the field and robust discussion was always encouraged. I am sure that all participants will be looking forward to next year’s congress, to be held on 13th-17th June in Buenos Aires, Argentina.

Also, could a diagnosis of predementia, or mild cognitive impairment, be as simple as checking for a biomarker? Should neuropsychometric testing be more reliable? These topics will be analysed by Prof Serge Gautier and Prof Rachelle Doody.

Other compelling areas of neurology will be covered as well. In addition to the daily main themes on stroke, multiple sclerosis, epilepsy, neurodegenerative diseases, headache and pain, there will be parallel sessions on infections, imaging, neurooncology, stem cells, movement disorders, genetic diseases, neuropathy, myopathy and more. The relationship between neurology and the creative arts and artists, ethics and palliative care (e.g. in motor neuron disease) will also be explored at the WCN 2009.

Delegates will have the opportunity to contribute to the WCN 2009 scientific program through abstracts based on their accomplished research. In addition, there will be many platform presentations as well as abundant space for poster presentations.

There will be time for smiles as well as learning. Teams of neurologists can have fun as well as gain knowledge by participating in a WCN tournament, the third Tournament of the Minds. We will arrange a special prize for the tournament’s winning team.