

EPDA's 10th Anniversary Conference

30–31 May 2002, Ljubljana, Slovenia

This conference focused on the importance of partnership and collaboration and the first day concentrated upon the 'Team Approach' in the management of Parkinson's disease.

Mary G Baker, EPDA President, questioned whether health services knew what families needed and she highlighted the importance of:

- The need to focus more closely on families affected by neurological diseases so that their requirements could be met more appropriately.
- That people with neurological diseases be referred to a doctor with a special interest in their illness to ensure that they receive an accurate diagnosis.
- Patients should be referred to a multidisciplinary team sooner rather than later and should receive continuous care.
- Patients should also be encouraged to play an active part in the management of their illness.

Zvezdan Pirtosek (Slovenia) discussed the results of his History of PD search for possible descriptions of Parkinsonism in centuries before James Parkinson's seminal description in 1817. Fragmentary references were found in the:

- Text of an Egyptian papyrus (c. 1350–1200 BC)
- Bible (Ecclesiastes)
- Sanskrit Ayurvedic medical texts
- Chinese classical works 'Nei Jing' and 'Chan Zen', and clinical observations of Galen

He commented that Rembrandt and Leonardo da Vinci might have suffered from PD.

Both Laszlo Vecsei (Hungary) and Maja Relja (Croatia) addressed The Role of Drugs in the management of PD and it was reported that:

- Liquid preparations of levodopa provide more rapid absorption and can be used in an attempt to control complex patients who are very sensitive to even minor changes in levodopa dosage. Methyl ester and ethyl ester, water-soluble formulations of levodopa are also rapidly absorbed and are now under investigation for use in PD.

A *Multidisciplinary Approach* included presentations from Lidija Ocepek, PDNS (Slovenia) about the Slovenian 'model'. Mariella Graziano (Luxembourg) emphasised the importance of physiotherapy and addressed four core areas:

gait, balance, posture, and transfers whilst Jelka Jansa (Slovenia), Occupational Therapist, stressed the importance of environmental influences, which can either constrain or facilitate everyday functioning for people with PD.

In *Sexuality and PD*, Gila Bronner (Israel) reported that the Movement Disorder Unit in Tel Aviv is offering in-house counselling services for patients and spouses to discuss sexual issues. The sexual treatment is based on a short-term intervention (usually two to

four sessions), which proved to be effective for many patients, and 80% of the patients treated with this approach were satisfied.

In his presentation *Re-emergence of Surgery* Alberto Albanese (Italy) reported the latest data on the long-term follow-up of subthalamic nucleus stimulation in 22 patients with PD, which registered that in seven patients followed-up for 1 year, medication could be reduced by 65%.

Vladimir Kostic (Serbia), Irena Rektorová (Czech Republic) and Erwin Ott (Austria) in the session *Cognitive and Behavioural Dimensions of PD* covering Depression, Cognitive Disturbance and Dementia, and Pathophysiology and Treatment of Psychosis reported that:

- Depression and anxiety are the most common and frequently disabling psychiatric conditions that accompany PD, but also, that there is no doubt that depression in PD is a treatable, albeit under-treated, condition.
- The risk for developing dementia is two to six times higher in people with PD than in people without PD. Risk factors for developing dementia include age, severity of Parkinsonism, low education, family history of dementia and, possibly, depression.
- Parkinsonian/dopaminomimetic psychosis is a relatively slow, gradually progressing condition. It should be differentiated from a toxic confusional state, an acute condition characterised by disorientation, impaired concentration, alterations of sleep and usually caused by infection, dehydration or certain drugs. If Parkinsonian psychosis is mild, treatment may not be necessary. Drug management should be initiated when symptoms start to interfere with the patient's daily life.

The second day focused on the EPDA projects including:

Past:

- Participation in Life Survey (Mary Baker, UK)
- Global Parkinson's disease Survey (GPDS) (Leslie Findley, UK)
- Economic and Emotional Cost of Care (Clive Bowman, UK)

Present:

- PD Life (Drug Profiling) (David Burn, UK)
- PD Med (Carl Clarke, UK)
- INFOPark (Pirkko Routasalo, Finland)
- Multilingual Website (Dan Coene, the Netherlands)
- Parkinson's In Europe (Young People and what is needed to improve Quality of Life) (Dinah Gould, UK)
- Centres of Excellence (Nir Giladi, Israel)

Future:

- Complementary Therapies – Conductive Education (Mel Brown, UK)
- Deep Brain Stimulation (DBS) (Giuseppe Carbone, Italy and Mike Robins, UK)
- The REAL-PET Study (Example of Information the new Media Guide will disseminate) (Alan Whone, UK)
- WHO Working Group on Parkinson's disease (Aleksandar Janca, Australia)
- The Role of Phenomenology in Medical Education (Matthew Menken, USA)
- Strategic Alliances – The Global Declaration (Mary Baker, UK)

Lizzie Grabam, EPDA Liaison/Project Manager



Francoise Lucas, Branko Smid and Mary Baker deep in discussion at the conference

Abbreviated Prescribing Information Botox®

Presentation: Contains 100 units (U) of *Clostridium botulinum* type A neurotoxin complex (900kD). **Uses:** BOTOX® is indicated for focal spasticity, including the treatment of dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older and wrist and hand disability due to upper limb spasticity associated with stroke in adults.

Dosage and Administration: BOTOX® is reconstituted prior to use with sterile unpreserved normal saline (0.9% sodium chloride for injection). **Doses recommended for BOTOX® are not interchangeable with other preparations of botulinum toxin. Paediatric cerebral palsy:** Diluted BOTOX® is injected using a sterile 23-26 gauge needle. It is administered into each of two sites in the medial and lateral heads of the affected gastrocnemius muscle. The recommended total dose is 4 units/kg body weight. When both lower limbs are to be injected on the same occasion this dose should be divided between the two limbs. Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes, but not more frequently than every two months. **Focal Spasticity associated with stroke:** Reconstituted BOTOX® is injected using a sterile 25, 27 or 30 gauge needle for superficial muscles, and a longer needle for deeper musculature. Localisation of involved muscles with EMG guidance or nerve stimulation may be useful. Multiple injection sites may allow BOTOX® to have more uniform contact with the innervation areas of the muscle, especially in larger muscles. The exact dosage and number of injection sites may be tailored to the individual based on size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness. (See SPC for dosage recommendations). **Contra-indications:** BOTOX® is contra-indicated, a) in individuals with a known hypersensitivity to any component of the formulation; b) when there are generalised disorders of muscle activity (e.g. myasthenia gravis); c) when aminoglycoside antibiotics or spectinomycin are already being used or are likely to be used; d) when there are bleeding disorders of any type, in case of anticoagulant therapy and whenever there is any reason to avoid intramuscular injections and e) during pregnancy or lactation. **Warnings and special precautions:** The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX®. Extra caution should be paid in the case of injection sites close to structures such as the carotid artery and pleural apices. The recommended dosages and frequencies of administration of BOTOX® should not be exceeded. Adrenaline and other anaphylactic measures should be available. **Reconstituted Botox® is for intramuscular injection ONLY. Focal Spasticity associated with paediatric cerebral palsy and stroke:** BOTOX® is a treatment for focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX® is not likely to be effective in improving range of motion at a joint affected by a fixed contracture. **Side effects:** Side effects may occur from misplaced injections of BOTOX® temporarily paralysing nearby muscle groups. Excessive doses may cause paralysis in muscles distant to the injection site. In cerebral palsy all treatment-related adverse events were mild-to-moderate in severity. The adverse reaction most frequently reported include falling, leg pain, leg (local) weakness, general weakness and localised pain at injection site. In focal upper limb spasticity the most commonly reported adverse reactions were ecchymosis, purpura, injection site haemorrhage, arm pain, muscle weakness, hypertonia and injection site burning. Less frequent events reported included hyperesthesia, arthralgia, pain, bursitis, dermatitis, headache, injection site hypersensitivity, malaise, nausea, paresthesia, postural hypotension, pruritus, rash, incoordination, amnesia, circumoral paresthesia, depression, insomnia, peripheral oedema, vertigo. Some of the uncommon events may be disease related. **Interactions:** The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or any other drugs that interfere with neuromuscular transmission e.g. tubocurarine-type muscle relaxants. Concomitant use of BOTOX® with aminoglycosides or spectinomycin is contra-indicated. Polymyxins, tetracyclines, lincomycin and muscle relaxants should be used with caution. **Pharmaceutical precautions:** Unopened vials should be stored either at 2°C-8°C (in a refrigerator), or in a freezer at or below -5°C. After reconstitution BOTOX® may be stored in a refrigerator (2-8°C) for up to 4 hours prior to use. Cost: £128.93 per vial (excl VAT). POM. PLO426/0074. Date of preparation: May 2002. Allergan, Coronation Road, High Wycombe, Bucks HP12 3SH. Further information available on request.

7th European Congress of Neuropathology

13-16 July 2002, Helsinki, Finland.

The 7th European Congress of Neuropathology was organised by Dr Matti Haltia, Dr Hanno Kalimo and the Scandinavian Neuropathological Society under the auspices of the European Confederation of Neuropathological Societies (EuroCNS). The abstracts will be published in *Clinical Neuropathology*. EuroCNS seeks to unify standards of education, diagnosis and research in Neuropathology throughout Europe. To this end, the main Congress was preceded by four-day course on the Pathology of Central Nervous System Tumours brilliantly organised by Dr Dirk Troost (Amsterdam).

Both the Course and the Congress were held in the modern Biomedicum at the University Hospital. Helsinki is a delightful city with beautiful architecture and a distinct maritime air that was enhanced by a week of sunny, warm weather making this Congress one of the most enjoyable of the year.

The scientific sessions of the Congress were composed of 8 plenary lectures, an interactive slide seminar, 18 workshops and 233 posters, 98 of which were on neurodegenerative diseases and 59 on tumours. Some 400 delegates from countries world-wide attended.

Three of the plenary lectures were focused on CNS tumours. V. Peter Collins (Cambridge UK) reviewed the roles of cell cycle pathways in the oncogenesis of astrocytic tumours emphasising how deregulation of p53 occurred in 70% of all astrocytic tumours whereas abnormalities of PTEN and EGFR were more common in glioblastomas. David N Louis (Boston USA) emphasised the impact of molecular genetics on the classification and treatment of CNS tumours. Concentrating mainly upon oligodendrogliomas, he discussed how loss of chromosomes 1p and 19q is associated with a good response to chemotherapy and a favourable prognosis. Optimism was expressed that the combination of histological and molecular genetic techniques would lead to many further bene-

fits for the therapy of CNS tumours. Such work will be greatly aided by the microarray techniques reviewed by Olli-P Kallioniemi (Bethesda USA). Angiogenesis is a hot topic and Karl H Plate (Frankfurt Germany) explored the multiple functions of VEGF in relation to tumours, hypoxia and ontogenesis. Hans Lassmann (Vienna, Austria) showed how Multiple Sclerosis is characterised by an underlying immune attack by cytotoxic T-cells on the CNS with the add-on effects of antibodies, complement, ischaemia-like disturbances of oligodendrocytes and axonal degeneration determining the variations in clinical and pathological picture. Combining his unique experience of the clinical aspects and pathology of muscle diseases, George Karpati (Canada) gave an excellent update on the molecular basis of genetic muscle diseases. Neurodegenerative diseases were a major focus of the Congress; John Hardy (Bethesda, USA) graphically dissected the genetic bases of tau and α -synuclein-related disorders and presented a framework gathering the tau, synuclein and parkin into a single group of related disorders. Explicit molecular models did much to clarify the relationships between presenilins, β -amyloid and its precursor APP. Charles Weissmann (London, UK) gave the final lecture of the Congress in which he analysed the evidence for the protein (prion) theory of CJD and other transmissible spongiform encephalopathies.

The workshops covered a wide variety of Neurological disorders concentrating upon the relationships of Neuropathology to other basic and clinical Neuroscience disciplines. There were thorough reviews and discussions on recent advances in the study of CNS tumours and of dementias including prion diseases. Discussions of the new technologies of genetic analysis and proteomics in relation to neuromorphological techniques arose in all fields and in specific workshops. In addition to workshops on trauma, infections, angiogenesis, stem cell research, demyelination, paediatric neuropathology, muscle and nerve diseases, issues such as safety, the legal aspects of Neuropathology and the impact of genetics on the diagnosis and management of Neurological disease were hotly debated.

Posters were the life-blood of the Congress and there was ample time to digest and discuss the contents with presenters. Twenty-two posters were selected for special commendation. Three were awarded prizes: A. Kulla *et al* (Tartu, Estonia and Bonn, Germany) solved the long disputed origin of blood vessels in glioblastomas. They isolated both vessels and tumour from paraffin sections and then by tissue arrays and DNA sequencing showed that TP53 mutations did not correspond. These results suggest that the tumour vasculature is derived from pre-exist-



The Waterfront in Helsinki with the City Hall in the background and the Lutheran Cathedral towering above.



Dr Matti Haltia, President of the EuroCNS Congress (left), talking to Dr Sam Ludwin, President of the International Society of Neuropathology during the Congress Dinner in the Suomenlinna Sea Fortress.

ing normal vessels rather than via transdifferentiation from primitive glioblastoma cells. This has important implications for

tumour therapies directed at angiogenesis. J.F.Poduslo *et al* (Rochester MN and NYU) demonstrated an elegant method for imaging β -amyloid (A β) plaques by MRI in transgenic mice. They used a gadolinium-labelled putrescine probe that crosses the blood-brain barrier and binds to A β with high affinity. This technique has great potential for assessing A β load in human Alzheimer's disease and for monitoring therapy. P.Lamont *et al* (Australia and the Netherlands) characterised a myopathy in a family of Dutch descent with late onset progressive limb weakness and the presence of rod-bodies and cores in muscle fibres. Linkage to chromosome 15q was obtained. This study demonstrated beautifully how knowledge of muscle disease advances through a careful multidisciplinary clinical, pathological and genetic approach.

Given that most contacts are made at social events, the superb receptions in the Senate House and City Hall, the boat trip and Dinner in the off shore Suomenlinna Sea Fortress ensured the success of the Congress.

*Professor Roy O. Weller,
Southampton, UK.*

12th Meeting of the European Neurological Society

June 22-26 2002, Berlin, Germany

To anyone who recalls those iconic images of the Berlin Wall being broken down, the opportunity to visit that romantic city, with its exotic associations of espionage and cabaret, would be hard to resist. Too hard apparently for the 3500 neurologists who visited this June under cover of the 12th meeting of the European Neurological Society. They were rewarded with good weather, an excellent meeting and a conference banquet in the Russian Embassy. But above all, this ENS will be remembered for the football. The speakers in one memorable afternoon session had to address a near-empty room, competing with loud reactions to the shifting fortunes of the Germany-South Korea match, watched on a large screen hastily erected at one of the pharmaceutical stalls. As the President pointed out, this was the first time data presented at a pharmaceutical stand were accepted without criticism or the call for meta-analysis from all delegates – South Koreans excepted.

Plenty of work was done as well. My personal prize for the best poster goes to the team from Kragujevac Hospital, Yugoslavia, who carefully documented all 387 cases of Bell's palsy in their region from March 1998 to December 2001. 77 (20%) of these occurred in the three months (March 24th to Jun 23rd 1999) of NATO air strikes. The authors attribute this to the stress of combat or a change in the environment as people took to their basements.

MULTIPLE SCLEROSIS. The meeting was dominated by multiple sclerosis, both in the academic sessions and the parallel symposia. It was apparent, informally, that (whilst understanding the nature of economic forces) not all delegates favour this emphasis or feel comfortable with the bunching up of satellite symposia with the more academics sessions. Alastair Compston, who took over as President of the ENS on the first day of this meeting, organised a captivating symposium on the clinical science of demyelinating disease. He introduced the provisional results of the **GAMES** project: the

European-wide search for susceptibility genes in multiple sclerosis. His team have narrowed the search down to nine areas of the genome for more detailed study taking forward a story that has remained stubbornly recalcitrant for nearly three decades. In this session, Ken Smith (London) gave one of the most elegant talks of the conference. He proposed that axonal death in demyelinating disease results from unhappy coincidence of the need for increased energy to prevent the accumulation of sodium ions within axons (since sodium channels redistribute themselves along the demyelinated axon), and the presence of metabolic inhibitors (like nitric oxide). The therapeutic conclusion is that sodium channel blockade might protect axons; for which reason he and Raj Kapoor are trying to establish a trial of flecainide in secondary progressive multiple sclerosis. The Queen Square MRI unit reported on the MRI effects of 6 months' treatment with **natalizumab** (Antegren) in 213 patients in the US, Canada, and UK. T2 and T1 hypointense lesion volumes increased in the placebo group, but decreased in the natalizumab groups, from months 0-6. However, six months after all therapy stopped, there was no difference between the groups. The use of **intravenous immunoglobulin** in multiple sclerosis received a severe blow when the European multi-centre trial of IVIG in secondary progressive patients (presented by Otto Hommes) showed not only that IVIG failed to reduce the accumulation of disability, but also that the previously reported claim for significant reduction in relapse rate seen in the phase II study could not be replicated. Curiously IVIG did reduce the rate of cerebral atrophy on MRI.



Rudolf Virchow (1821-1902) was educated at the University of Berlin, then was Professor of Pathology at Wurzburg and then Berlin. He was the first person to describe neuroglia.

in the phase II study could not be replicated. Curiously IVIG did reduce the rate of cerebral atrophy on MRI.

GUILLAIN-BARRÉ SYNDROME. The Dutch GBS Study Group showed – against orthodoxy – that **intravenous methylprednisolone** 500mg daily for five days is useful in GBS. In a placebo-controlled study of 225 patients unable to walk independently, and



Professor Alastair Compston, new President of the ENS

treated within 14 days after onset of weakness, the addition of steroids to standard IVIG significantly improved the outcome at 4 weeks. (Steroid patients were three times more likely than placebo patients to have improved on the Hughes' scale.) The longer-term outcome was not reported.

STROKE. A team in Frankfurt reported their experience of treating 205 patients with high-grade carotid stenosis using **carotid angioplasty and stent implantation** since 1994. They concluded that the results were no different to endarterectomy. A rather depressing presentation from the European SAFEII investigators revealed that, of 300 consecutive patients with **stroke and atrial fibrillation** who should have been put on warfarin – by agreed guidelines, only 60 in fact were anti-coagulated. The explanation, it seems, is ignorance. Oh dear.

PARKINSON'S DISEASE. **Sleep attacks** occurring on dopamine agonists were much discussed a couple of years ago. A German group has surveyed 2952 patients, of whom 171 were found to have developed sudden irresistible sleep attacks during activity. They occurred equally commonly with all the dopamine agonists, less frequently with L-dopa alone, and not at all with selegiline and amantadine. The **REAL-PET study** of 186 new Parkinson's disease

patients studied over two years showed that **ropinirole** was associated with less reduction of 18F-dopa signal in the putamen and nigra than occurred with L-dopa. Unsurprisingly, L-dopa induced better changes on clinical motor scores, but also more dyskinesias (27% versus 3%).

EPILEPSY. The new anticonvulsant drug, **levetiracetam**, received much attention during the conference. Its mechanism of action remains unknown. In a pragmatic study of efficacy, O'Rourke reported on its use as add-on therapy in adults with mental retardation and epilepsy. Levetiracetam rendered 14% of punters seizure-free and gave a 64% seizure reduction by > 50%. These figures are higher than for topiramate and gabapentin in the same population, but not as good as lamotrigine (21% and 25% respectively). Tim Betts from Birmingham reported an "impressive result" from an open-label study of its use in juvenile myoclonic epilepsy.

NEURO-OPHTHALMOLOGY. In an epidemiological study, some Berlin neurologists found that **benign positional vertigo** tended to last for three years, during which patients had 2.4 episodes of vertigo. In only 4% had the Epley manoeuvre been tried, which is almost criminal given that it is the most successful of all neurological treatments for this horrible symptom. Would a survey in the UK give any better results? Thomas Brandt's team reported a case that should also worry us: a patient with apparent "**idiopathic vestibulopathy**" who turned out to have autoantibodies against the inner ear structures and who improved on immunosuppressive therapy.

DEMENTIA. There were no less than seven posters on galantamine, a novel acetylcholinesterase inhibitor that also acts as an agonist at nicotinic acetylcholine receptors. Perhaps the most interesting was from Helsinki, indicating that galantamine maintains cognitive function for a year in patients with both Alzheimer's disease and vascular dementia, as well as those diagnosed with vascular dementia alone.

The next meeting of the ENS is in June 14-18, 2003 in Istanbul. Early signs are that it will be just as stimulating and enjoyable as this one was. Get it in your diary!

Alasdair Coles & Alastair Compston

LETTERS

We welcome your letters and comments about ACNR. Please write to The Editors, ACNR magazine, c/o 7 Alderbank Terrace, Edinburgh EH11 1SX, or e-mail. AdvancesinCNR@aol.com

Dear Dr Coles

In your recent cerebellar pontine angle anatomy primer (pg 16-17, vol 2, issue 3, July/Aug. 2002), your introduction declares that amongst other signs, an acoustic neuroma classically gives rise to ipsilateral facial palsy. I can only imagine that this was a slip of the pen for an ipsilateral facial palsy is an excessively rare presentation of the lesion and is almost always the stamp of therapeutic intervention.

Yours sincerely

Charles G H West
Consultant Neurological Surgeon
Royal Manchester Children's Hospital

Inaugural meeting at new UK epilepsy assessment centre

25 April, 2002, Buckinghamshire, UK

The world's leading medical centre for assessing and treating people with epilepsy was officially opened at The National Society for Epilepsy in Chalfont, Buckinghamshire, on Thursday 25 April 2002 by HRH the Duchess of Gloucester.



HRH the Duchess of Gloucester unveiling the plaque at the opening of the Sir William Gowers Centre, NSE, Chalfont, Buckinghamshire.

The Sir William Gowers Centre

This purpose-built Assessment Centre providing 26 beds and five outpatient rooms at the National Society for Epilepsy (NSE) is linked to the state-of-the art MRI Unit, which was completed in 1995. The Sir William Gowers Centre – named after one of the 19th century founders of the NSE, to commemorate his role in establishing modern understanding of epilepsy and its treatment – is the first centre anywhere in the world where an MRI scan can be performed immediately after a seizure. The proximity of patients 'on site' minimises the time between seizure occurrence and scan, providing exciting new possibilities for scientific understanding of ictal activity. Other facilities at the centre include EEG and pharmacology laboratories, video-EEG telemetry, neuropsychological testing and occupational therapy. Patients are referred for a number of reasons such as clarification of their diagnosis, classification of seizure type, supervised optimisation of antiepileptic drug (AED) treatment and formulation of a longer term social and medical care plan.

Although an assessment unit has existed at the NSE since 1972, previous accommodation was inadequate for the 280 inpatients and 2000 outpatients who are referred there each year. It took 10 years to plan, design, raise the necessary £2.4 million, build and complete the Sir William Gowers Centre. Funding for the new seminar room at the centre was donated by GlaxoSmithKline. The inaugural meeting in this room, attended by about 60 neurologists from the UK, took place on 26 April 2002.

*Professor John Duncan
Medical Director, National Society for Epilepsy*

National Society for Epilepsy: past, present and future

The NSE is integrated with the National Hospital for Neurology and Neurosurgery, London, and provides valuable inpatient and residential facilities. Professor Ley Sander (UCL Institute of Neurology, London) presented a fascinating insight into the history of the NSE and the links between the two establishments.

In the 19th century, people with epilepsy were regarded as being possessed by the Devil and were often consigned to poor-

houses, lunatic asylums or jails. By the mid-1880s physicians at Queen Square in London had recognised the existence of 'sane epileptics', and in 1892 William Gowers and others founded a society to provide employment for 'able epileptics'. An appeal was launched to establish a 'colony for the epileptics', and the current site at Chalfont opened in 1894. Junior physicians at Queen Square paid weekly visits there – a tradition that strengthened the medical and scientific standing of the establishment and that still continues today.



Sir William R Gowers, FRS (1845–1915) – one of the Founders of the National Society for Epilepsy

Early research at Chalfont (by Aldren Turner, 1894–1910) suggested that seizures were more likely between 10 pm and midnight and that salt deprivation decreased seizures by 30%. Current research is wide-ranging, covering areas such as neuroimaging, neurogenetics, epidemiology and pharmacology. Patients at the National Society for Epilepsy are often among the first to try new AEDs, and several experimental agents are currently under evaluation.

Emerging treatments for epilepsy

Professor Sander also presented a detailed review of current and pipeline drugs for epilepsy. Major goals of AED treatment are:

- complete seizure freedom
- no adverse effects (including cognitive effects and teratogenicity)
- maintenance of a normal lifestyle
- reduction in morbidity and mortality.

Conventional AEDs do not control seizures in 30% of patients. A number of 'new' AEDs have been licensed since 1990, but these drugs too have some limitations. In chronic epilepsy, the most successful new agents are Lamictal® (lamotrigine), Keppra™ (levetiracetam) and Topamax® (topiramate). In newly diagnosed epilepsy, the efficacy of new and conventional AEDs is comparable, but new AEDs are generally better tolerated. However, currently available treatments manage the seizures but not the underlying epilepsy, so there is an urgent need for 'curative', disease-modifying drugs.

The quest for potential new AEDs is not only revisiting old targets (the GABAergic system, NMDA receptors, ion channels) but also seeking to identify novel approaches to drug delivery, immunological targets, mechanisms of drug resistance, 'new' neurotransmitter systems (eg adenosine) and pharmacogenetic mechanisms. A large number of AEDs are currently in development – 4 in Phase I, 9 in Phase II and 4 in Phase III – and some of these are simultaneously being developed for other indications such as neuropathic pain, migraine, anxiety or mood stabilisation. A number of these pipeline AEDs – alongside recent genetic discoveries offer promising developments in treatment.

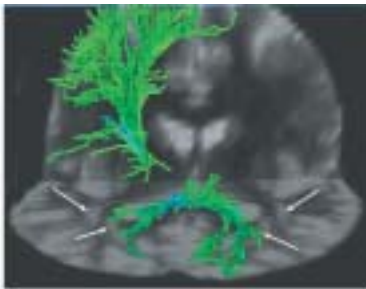
Professor Nicholas Wood (Institute of Neurology, London) explained how pharmacogenomics could provide more information on disease risk and drug responsiveness within the next 2 years. For Mendelian epilepsies, genes have been mapped at

more than 33 loci, including at least 10 genes for ligand- or voltage-gated ion channels. Mutations at these sites give rise to a variety of seizure types. For complex (non-Mendelian) traits, linkage disequilibrium mapping can help to localise large numbers of polymorphisms using a few markers.¹ Candidates for further investigation are all the Mendelian epilepsy genes, all 160 CNS-expressed ion channels, genes involved in signalling pathways (eg GABA) and sites of action of AEDs.

New imaging in epilepsy

MRI is used to establish the cause of epilepsy, assess its consequences, study the genetics and enhance surgical selection. It can identify structural abnormalities in 80% of cases of focal epilepsy. Dr Sanjay Sisodiya (Institute of Neurology, London) gave some specific examples of the use of new MRI sequences (diffusion tensor imaging [DTI], T2 mapping, magnetisation transfer ratio imaging and double inversion recovery) that can reveal subtle abnormalities in previously MRI-negative cases of epilepsy.

Imaging can increase our knowledge of the mechanisms underlying brain function, connectivity and biochemistry. Functional MRI (fMRI) combined with other types of imaging can give more information about function and structure. For example, tractography, an extension of DTI, can trace axon tracts within the human brain *in vivo* to reveal the putative distributed network that is contributing to epileptogenesis and identify the connections responsible for that network.



Tractography reveals the connections of the posterior corpus callosum and the pyramidal tracts in a patient with bilateral subcortical band heterotopia. The occipital region has been 'cut away' in this 3D reconstruction to show the forceps fibres of the corpus callosum passing through the splenium and into the occipital lobe. The axons traversing the heterotopic regions (white arrows) demonstrate the connections between the malformation and other parts of the brain.

Continuous EEG recording performed while a patient is undergoing fMRI scanning can help to pinpoint brain areas where there are signal changes associated with specific EEG discharges, providing additional localising information about seizures.

Teratogenic effects of antiepileptic drugs

About 3–4 pregnancies in every 1000 involve women with active epilepsy, giving a total of about 1800–2400 live births each year to women in the UK with the condition. AEDs administered during pregnancy can sometimes cause major malformations, minor abnormalities, and adversely affect psychomotor development and intra-uterine growth. Major malformations such as cleft palate and spina bifida occur in 1–2% of pregnancies not exposed to AEDs, but in AED-exposed pregnancies the overall risk for major malformations is thought to be around 2–3 times higher than the background rate. This estimate is based on several retrospective and prospective studies with varying methodologies. As such, it does not provide a firm basis on

which to make recommendations to women with epilepsy who are taking particular AEDs, either singly or in combination, and who are contemplating pregnancy.

Dr John Craig (Royal Victoria Hospital, Belfast) described how he and colleagues set up the UK Epilepsy and Pregnancy Register about 5 years ago, to obtain accurate information on the relative risks and types of major congenital malformations associated with specific AEDs, and the effects of modifying dosage. A primary objective of their study is to investigate whether some AEDs pose a lower risk in pregnancy than others. Animal studies indicate that lamotrigine and gabapentin appear to cause fewer abnormalities than other AEDs. However, more data from humans is essential before firm conclusions can be drawn or recommendations made. So far, almost 2500 pregnancies in epilepsy have been reported to the register, and full outcome data are available for around 1910 (73% receiving monotherapy, 21.5% polytherapy and 5.5% untreated with an AED). Dr Craig encourages doctors to register all new pregnancies in women with epilepsy by ringing Freephone 0800 389 1248.

Informed choice: medico-legal implications

Changing relationships between doctors and patients mean that cases where personal autonomy confronts paternalism can make headline news and sometimes cost the NHS millions of pounds in medical negligence settlements. David Evans (Middlesex), a specialist healthcare lawyer, gave a highly informative presentation covering some implications of the Human Rights Act and issues surrounding patient consent, including the definition of 'capacity' (or lack of it) to make health-related choices.

Obtaining consent prior to treatment helps to protect doctors against two potentially damaging allegations: trespass (touching or attempting to touch a patient without consent) and negligence. A number of classical cases have set medico-legal precedents. In *Bolam v. Friern Hospital Management Committee* (1957), a patient who received ECT treatment without a relaxant drug dislocated both his hips. However, because the use of sedatives was not commonplace in the early 1950s, the court eventually ruled that the duty of care had *not* been breached. Much criticism followed this case, however, and 40 years later the House of Lords ruled that a court is not bound to absolve a doctor of liability just because experts agree that treatment has been in accord with sound medical practice (*Bolitho v. City and Hackney Health Authority*, 1997). The expert opinion must be logically justifiable. Current best practice requires that patients receive adequate information prior to consent.

This presentation provoked much lively discussion, particularly in relation to the issue of AED-related teratogenicity. There was a consensus that appropriate information needs to be given regularly and should be well documented. A woman may be advised about the potential risks of one agent in pregnancy and be offered an alternative. However, if she decides that she wishes to continue taking her current medication, the audience suggested that the specialist should record this conversation in a letter to the GP, with a copy to the patient.

The need to keep up-to-date with new developments and to provide clearly written patient information leaflets and was stressed. This meeting certainly helped attendees to achieve the first of these objectives.

Reference

1. Jeffreys AJ, Kauppi L, Neumann R. *Intensely punctate meiotic recombination in the class II region of the major histocompatibility complex*. Nat Genet 2001 Oct 29;21:7–22.

We would like to thank GlaxoSmithKline for sponsoring this report

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Forum of European Neuroscience (FENS 2002)

13-17 July 2002 Paris, France

The 3rd Forum of European Neuroscience (FENS 2002) was hailed as a success. "It was a great meeting," said Pierre Magistretti, the new president of the Federation of European Neuroscience Societies. "And it can grow. FENS has been able to provide a new opportunity for European neuroscientists. It generates a synergy amongst societies."

Hosted this year by La Société des Neurosciences at Palais des Congrès in Paris, FENS 2002 brought together nearly 6000 people from around the world – the largest gathering yet. The previous two meetings were held in Berlin and Brighton with the aim of raising the status of neuroscience in Europe.

Delegates were not disappointed! There were around 3,500 sessions and posters covering a diverse range of topics:

- For people severely or partially paralysed the ability to communicate helps to improve their quality of life. For the first time, Professor Niels Birbaumer (Institute of Medical Psychology and Behavioural Neurobiology, Tuenbingen, Germany) has found a way to use the brain as an instrument with a 'thought translation' device operated by the patient's brain waves alone.
- The central ethical principle in human embryonic stem cells research is that of beneficence, said Professor John Harris (Manchester University, UK). A key aspect of ethical debates is the variety, diversity and strength of the various interests involved and the many stakeholders whose concerns require attention. According to Dr Glyn Stacey (National Institute for Biological Standards and Control, UK), the safety of stem cell therapy is as important as the ethical aspects. Regulatory guidance must be developed to ensure safety of stem cells intended for clinical application. Embryonic stem cell banks must be prepared and validated to provide a reproducible source of quality stem cells. Professor Patrick Brundin (Lund University, Sweden) believes that the future of stem cell grafting for Parkinson's disease is very promising. The criteria for selecting patients and the way the tissue is handled are among the factors to affect the outcome.
- Understanding the biology of drug addiction and relapse is important in helping to inform social and clinical strategies to treat these chronic disorders. The knock-out mouse model with a gene deleted involved with the dopamine – or reward – system of the brain indicates to Dr Beatriz Rocha (National Institute of Drug Abuse, USA) that cocaine is still able to induce its effects by interacting with other brain chemicals. Her research shows that new therapies must be more wide-ranging to take into account these and other psychiatric con-



The BNA stand in the exhibition hall



Pierre Magistretti, the new president of the FENS.

Picture: Duncan Banks

- ditions that reinforce cocaine addiction. Dr Taco De Vries (Vrije University, Amsterdam, The Netherlands) discovered recently that the cannabinoid system, which exists in the brain and regulates normal body and cognitive functions, also plays a role in relapse to cocaine and heroin abuse, possibly by altering the way nerve cells communicate with each other.
- The genetic variation involved in causing ADHD points the way towards the development of new drug treatment and related disorders based on the dopamine (the reward) system in the brain, according to Dr David Collier (Institute of Psychiatry, UK). Pharmacogenetics is the science of relating the reaction to a pharmaceutical treatment to the specific genetic make-up of a person and, said Professor Philip Gorwood (CNRS, Colombes, France), is beginning to show promise for some groups of patients with schizophrenia and other psychiatric disorders.
- Serotonin is essential for functions such as body temperature, arousal and satiety. Dr Annie Daszuta (INCF, Marseille, France) and her team have shown that the interaction of serotonin and estrogen could be significant in the treatment of depression and postmenopausal conditions.
- Professor Gareth Williams (Liverpool University, UK) has shown that orexins that partly regulate mood, appetite and sleep, are stimulated by low glucose in the body but when feeding is underway, they are switched off, thereby regulating short-term feeding habits. Narcolepsy is caused by a lack of orexins (also known as hypocretins) and affects around 1 in 2000 people and also affects certain breeds of dog. Dr Emmanuel Mignot (Stanford University, USA) has discovered that whereas in the Doberman dog there is a clear genetic link, in humans, the immune system plays a far more important role than genes and that narcolepsy appears to be an auto-immune disease. This knowledge could eventually lead to an entirely new approach to treatment.
- Around 2,500,000 people around the world have multiple sclerosis. Dr Robin Franklin (University of Cambridge, UK) has shown that there are changes in the inflammatory processes in response to MS and that repair of the damaged myelin sheath is best when the inflammatory processes are most active. This indicates that drugs that suppress inflammation could, in fact, hamper potential regeneration.

At a meeting such as this, national and European issues can be blended together. "There was a lot of positive energy this year at FENS and a good spirit for exchanges," said Professor Magistretti.

Elaine Snell