Unn Ljøstad and Åse Mygland
Lyme Neuroborreliosis in Adults: Clinical Aspects

Jone Furlund Owe and Nils Erik Gilhus
Myasthenia Gravis and the Heart

Justin Cross
NEW NEURORADIOLOGY SECTION
Computed Tomography in Neurology

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Adults and elderly:

Use and handling.

B only and are not relevant to preparations of Botulinum Toxin Type A. See SPC for instructions for experienced physicians. When low doses are required, it must be diluted before use with preservative-free saline for injection for patients with neuromuscular disorders or chronic dystonia. Patients with neuromuscular disorders, e.g. myasthenia gravis, may experience antibody formation to the therapeutic substance. Antibodies may develop and persist for months or years after repeated administration. Spontaneous reports of dysphagia, aspiration, and potential risk in humans is unknown. Co-administration of Botulinum Toxin Type B with aminoglycosides or agents interfering with neuromuscular transmission (e.g. curare-like compounds) should be considered with caution.

Drug Interactions:

No specific interaction studies. Effect of co-administration with other botulinum toxin preparations of Botulinum Toxin Type A/B have not been totally excluded. Dosage units are specific to Botulinum Toxin Type B only and are not relevant to preparations of Botulinum Toxin Type A. See SPC for instructions for use and handling.

Children and adolescents under 18 years:

Not recommended.

Contra-Indications:

Hypersensitivity to Botulinum Toxin Type B or any excipient. Individuals with disorders affecting neuromuscular transmission or neuromuscular junctional disorders.

Patients with renal or hepatic impairment:

No dose adjustment required. (see SPC)

Patients with bleeding disorders:

Caution should be used in patients with bleeding disorders or receiving anticoagulant therapy.

NeuroBloc® is excreted in breast milk. Do not use during lactation unless clearly necessary as it is unknown whether Botulinum Toxin Type B contains human albumin and therefore the possibility of transmitting infectious agents cannot be totally excluded. Changes occur in the cervical musculature, including dysphagia, aspiration, pneumonia and/or potentially fatal respiratory disease, after treatment with Botulinum Toxin Type A/B have been reported. There is an increased risk of side effects in patients with underlying neuromuscular disease and swallowing disorders.

Electro-physiological jitter, which is not associated with clinical effects, has been reported. Events characterized by muscle weakness or other electrophysiological abnormalities, may be experienced in some distant muscles. There have been post-marketing reports of exaggerated muscle weakness, dysphagia, aspiration, pneumonia with fatal outcome in some cases. Abnormal accommodation, ptosis, vomiting, constipation, flu-like symptoms, and asthenia.

Post-marketing surveillance:

There have been rare reports of post-marketing adverse reactions, including dysphagia, aspiration, pneumonia with fatal outcome in some cases. Abnormal accommodation, ptosis, vomiting, constipation, flu-like symptoms, and asthenia.

References:


Information about adverse event reporting can be found in the adverse event section.

Adverse events should also be reported to Eisai Ltd on 0208 600 1400 or Lmedinfo@eisai.net

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Eisai Ltd, Hammersmit
yme disease of the central nervous system is relatively rare, although not uncommonly considered in the differential diagnosis of patients with an array of neurological problems including facial palsy and a radiculitis. In this clear article by Unn Ljøstad and Åse Mygland, we are taken through the common clinical features of this condition and how it can be diagnosed. This article contains a couple of really useful tables summarising the main points, which overall makes for an extremely succinct, up to date account, of this condition.

Jone Furland Owe and Nils Erik Gilhus discuss an unusual aspect of myasthenia gravis – namely how it affects the heart. They conclude that “there is good evidence for myocardial pathology in MG patients, including a diversity of heart-reactive autoantibodies and focal inflammation with cellular infiltrates and myocardial necrosis. On the other hand, any firm clinical correlates to these findings have yet to be established”. Interesting.

On the theme of epilepsy, Paul Johns and Maria Thom discuss in our neuropathology article the relationship between hippocampal sclerosis (HS) and epilepsy. It is well known that the two are associated but it is not clear whether one causes the other. In this article, the competing theories are discussed in particular whether seizures, especially early in life, cause HS or whether HS is consequent to a developmental problem which then causes seizures.

Plaha and colleagues in their article for the Neurosurgery series consider chronic subdural haematoma. They begin by discussing how such lesions come about and how the patient may present, before considering how to optimally treat it. An issue that is far from clear cut! This is an easy to read account which represents a measured and pragmatic approach to this relatively common neurological problem.

Michael Turner reports on the guidelines and stipulations for jockeys engaged in different types of horse racing and the consequences to them of a fall and a head injury. This is not an uncommon event as there are approximately 110,000 rides a year and “Amateur jockeys fall every 7.9 rides, Jump jockeys fall every 7.9 rides, Jump jockeys fall every 15.8 rides and Flat jockeys fall every 200-250 rides. It is therefore not surprising that horse racing has some of the highest rates of injury seen in any sport, including the highest rates of concussion and fatal accidents in the published literature. Concussion rates are in fact six times greater than in Australian Rules Football – the sport with the closest incidence of concussion.” I think I will continue to walk and ride my bike.

In the first of our new series on Neuroradiology edited by Justin Cross we are treated to a sumptuously illustrated account on CT. In this first article by Justin we are introduced to the Compston effect and Hounsfield Units as well as having partial volume effects explained. This is a wonderful article that gives just the right amount of background physics and technical detail whilst also illustrating the role and value of this imaging modality to neurological practice in 2008.

In our Neurology and Literature series, Dr Pearce takes us through the Charles Bonnet syndrome and how it came to be called this and what exactly is meant by it. This article with a liberal sprinkling of original quotations from Dr Bonnet follows on from the earlier article we featured by Dominic Fytyche in ACNR 4.2 on visual hallucinations and optical illusions.

Heather Angus-Leppan gives us a picture of where the ABN is going (as opposed to where it has come from (see ACNR 7.5). We are also pleased to announce that Heather will be joining the editorial team of ACNR, helping to keep us abreast of developments within the ABN. Finally we have all our usual journal, conference and book reviews. Do enjoy and if you would like to become a part of the reviewing team just let us know by email to Rachael@acnr.co.uk.

Roger Barker, Co-Editor, Email: roger@acnr.co.uk

Sadly we report that Dr Raymond D Adams passed away on the 18th October, aged 97. He made a colossal contribution to neurology. We were fortunate enough to be the recipient of some of that knowledge in the article he wrote for ACNR in issue 6.5 (Nov/Dec 2006).

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Consult Summary of Product Characteristics before prescribing. **Uses:** The treatment of disabling motor fluctuations (“on-off” phenomena) in patients with Parkinson’s disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an “off” episode which is refractory to other treatments. **HCl** should be given to the term of treatment, **Domperidone** (typical dosage 30mg three times a day) before and during **apo** treatment is essential. The optimal dose of apomorphine **HCl** has to be determined on an individual patient bases; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 16 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be extended to all patients with cardiac disease or who are taking vasodepressor drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. **APO-go** should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson’s disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists. **Side Effects:** Local induration and nodules usually asymptomatic often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesia during “on” periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intermittent. Persistent sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when **apo**-treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs’ tests and haemolytic anaemia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine **HCl**. Patients treated with dopamine agonists, including apomorphine, have been reported with disabling signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Breathing difficulties have been reported. **Prescribers should consult the Summary of Product Characteristics in relation to other side effects.** **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 1mg/ml, as follows: 20mg in 2ml – basic NHS cost £3.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £7.11 per carton of 5 ampoules. Apo-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £12.91 per carton of 5 pens. Apo-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **References:** 1. Pietz K, Hagell P, Odin P, 1998. Subcutaneous apomorphine in late stage Parkinson’s disease: a long term follow up. J Neurol Neurosurg Psychiatry. 65:709-716. 2. Lees A, Turner K. 2002. Apomorphine for Parkinson’s Disease. Practical Neurology. 2:280-287. 3. Deleu D, Hanssens J, Nuytstra M G, 2004. Subcutaneous Apomorphine: An Evidence-Based Review of its Use in Parkinson’s Disease. Drugs Aging. 21(11), 687-709. 4. Hallschmid M, Schmied C. 1997. Use of Apomorphine in Parkinsonian Patients with Neuropsychiatric Complications to Oral Treatment. Parkinsonism & Related Disorders, 3 (2), 103-107. **Marketing Authorisation Numbers:** Apo-go Ampoules: PL04483/0064 Apo-go Pens: PL04483/0065 Apo-go Pre-filled syringes: PL05928/0025 **Legal Category:** POM **Date of last revision:** July 2008 **For further information please contact:** Britania Pharmaceuticals Limited, 41-51 Brighton Road, Redhill, Surrey RH1 6YS. **Adverse events should be reported.** Reporting forms and information can be found at www.yellowcard.gov.uk. **Adverse events should also be reported to Medical Information at Britania at the above address or telephone 01737 773741 or e-mail: drugsafety@britannia-pharm.com **Abbreviated Prescribing Information** **Editorial board and contributors** Roger Barker is co-editor of ACNR, and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular Parkinson’s and Huntington’s disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants. Alasdair Coles is co-editor of ACNR. He is a University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis. Stephen Kirkor is the editor of the Rehabilitation Section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke’s NHS Trust, Cambridge. He trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation. David JBurn is the editor of our Conference News Section and is Professor in Movement Disorder Neurology & Honorary Consultant, Newcastle General Hospital. He runs Movement Disorders clinics in Newcastle-upon-Tyne. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson’s Disease. Andrew Lamer is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries’ Lecturer in the History of Medicine at the University of Liverpool. Alastair Willkins is our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis. Nicki Cohen is ACNR’s Neuropathology Editor. She is a Specialist Registrar in Neuropathology at Southampton and has a DPhil in Neuroscience. Her research interests lie in CNS stem cell biology, and the brain’s response to injury. Peter Whitfield is ACNR’s Neurosurgery Editor. He is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery. Heather Angus-Leppan is ACNR’s ABN representative on the Editorial Board. She is Head of the Neurology Department at Barnet Hospital and Consultant Neurologist, Honorary Senior Lecturer and Epilepsy Lead at the Royal Free Hospital, London, UK. She is the Honorary Assistant Secretary of the Association of British Neurologists, Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and President Chair of the Map of Medicine Epilepsy Group, UK. **International editorial liaison committee** Professor Riccardo Soffietti, Italy: Chair of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital. Professor Klaus Berek, Austria: Head of the Neurological Department of the KH Kufstein. Professor Hermann Stefan, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nurnberg. Professor Nils Erik Gillius, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.
Lyme Neuroborreliosis in Adults: Clinical Aspects

Lyme neuroborreliosis is caused by the tick-borne spirochete Borrelia burgdorferi (Bb) sensu lato. The Bb sensu lato complex consists of at least three human pathogenic species; Bb sensu stricto, B. garinii and B. afzelii. All are endemic in Europe, whereas Bb sensu stricto is the only species detected in North America. This may account for clinical differences in American and European neuroborreliosis. In this short review we convey basic facts, our own experience and some new knowledge of clinical manifestations, diagnostics, treatment and prognosis of Lyme neuroborreliosis in European adult patients.

Clinical manifestations
At least 80% of European patients with neuroborreliosis present with facial weakness due to facial neuritis, or lancinating pain, numbness and sometimes weakness in an extremity, the chest or abdomen due to spinal radiculitis, or a combination of these (Bannwarth’s syndrome). More unusual symptoms are diplopia due to oculomotor, trochlear- or abducens neuritis, visual loss due to retrobulbar optic neuritis, hearing loss due to acoustic neuritis, visual loss due to vestibular neuritis, shortness of breath due to diaphragmatic paralysis, and isolated muscle weakness and fasciculations due to selective involvement of motor neurons and motor roots. A recent report describes a patient with an autoimmune-mediated motor neuropathy with conduction blocks and GM1 antibodies concomitant to, and probably triggered by infection with Bb. Symptoms from the central nervous system are rare, but some patients may present with weakness and clumsiness of both legs due to myelitis, or memory loss, confusion, unsteadiness, parkinsonism, or opoclonus myoclonus due to focal encephalitis. Vascularitis may account for acute stroke like or relapsing symptoms with hemiparesis and aphasia. Most patients with Lyme neuroborreliosis suffer from constitutional symptoms in addition to their neurological complaints, but it should be emphasized that headache, fatigue, paresthesias or malaise alone are not typical symptoms of Lyme neuroborreliosis.

The onset of Lyme neuroborreliosis is usually subacute with progression over weeks, so-called early or stage I Lyme neuroborreliosis. Some cases are self-limiting, even without treatment. Less than 10% of untreated cases progress slowly over months and years, so-called late, or stage III, Lyme neuroborreliosis.

Laboratory confirmation
Due to the low yield from culture and polymerase chain reaction (PCR) in Lyme neuroborreliosis, we are left with indirect laboratory diagnostic methods. Both an elevated cell count in the cerebrospinal fluid (CSF) and elevated CSF-to-serum Bb antibody index, indicating intrathecal Bb antibody production, have to be present to confirm definite Lyme neuroborreliosis.

In day to day practice, however, diagnostics may be a challenge because the CSF Bb antibody index has a low sensitivity (about 75%) in patients with a symptom duration of less than six weeks, and the CSF cell count may be normal in rare patients infected with certain genotypes of Bb. It therefore seems reasonable to introduce the term possible Lyme neuroborreliosis. Suggested case definitions with two levels of diagnostic accuracy are presented in Table 1.

Different other laboratory tests such as CSF CXCL13, LTT MELISA, and Bb specific immune complexes may in the future be helpful diagnostic markers, but they need further validation.

Antibiotic treatment
All patients with Lyme neuroborreliosis should be treated with antibiotics to achieve rapid resolution of symptoms, and, theoretically, to prevent further dissemination of the infection. Table 2 shows the suggested treatment guidelines.

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Dr Unn Ljøstad is a consultant clinical neurologist based at Sørlandet Hospital, Kristiansand, Norway. She will present her doctoral thesis on ‘Lyme neuroborreliosis, diagnostics and treatment in European adult patients’ later this year.

Dr Åse Mygland is Consultant Neurologist at Sørlandet Hospital Kristiansand and Assistant Professor at the Institute of Clinical Medicine, University of Bergen, Norway. She has a special interest in managing patients with neuromuscular and inflammatory neurological disorders.

Table 1: Suggested case definitions

<table>
<thead>
<tr>
<th>Definite neuroborreliosis</th>
<th>Possible neuroborreliosis</th>
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<tbody>
<tr>
<td>All three criteria fulfilled</td>
<td>1. Neurological symptoms suggestive of Lyme neuroborreliosis without other obvious reasons</td>
</tr>
<tr>
<td>1. Neurological symptoms suggestive of Lyme neuroborreliosis without other obvious reasons</td>
<td>2. CSF pleocytosis (&gt;5 leucocytes/mm³)</td>
</tr>
<tr>
<td>3. Intrathecal Bb antibody production</td>
<td>4. Intrathecal Bb antibody production</td>
</tr>
<tr>
<td>1. CSF pleocytosis (&gt;5 leucocytes/mm³)</td>
<td>b. Intrathecal Bb antibody production</td>
</tr>
<tr>
<td>a.</td>
<td>c. Bb antibodies in serum</td>
</tr>
<tr>
<td>d. Erythema migrans during the last four months</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Suggested treatment guidelines for European adult patients with Lyme neuroborreliosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment duration</th>
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<tr>
<td>• First choice:</td>
<td>2-4 weeks</td>
</tr>
<tr>
<td>o Oral doxycycline 200 mg daily</td>
<td></td>
</tr>
<tr>
<td>• Alternative choices:</td>
<td></td>
</tr>
<tr>
<td>o IV ceftriaxone 2 g daily</td>
<td></td>
</tr>
<tr>
<td>o IV penicillin G 3 g X 3-4</td>
<td></td>
</tr>
<tr>
<td>o IV cefotaxime 2 g X 3</td>
<td></td>
</tr>
</tbody>
</table>

| Repeated course with a different drug | Should be restricted to patients with definite Lyme neuroborreliosis who do not improve after first course (exceptionally rare) |

| Post Lyme disease syndrome | Symptomatic treatment |
Review Article

How to handle ‘possible’ Lyme neuroborreliosis

In our opinion patients who fulfill the criteria for possible Lyme neuroborreliosis should be offered one, but not repeated courses of antibiotic treatment. If one course does not lead to lasting improvement, a search for other causes of the symptoms should be sought.

Outcome after treatment

Outcome after treatment for Lyme neuroborreliosis is debated. A Swedish questionnaire follow-up study found persistent complaints in 50% of patients who had experienced neuroborreliosis, as compared to 16% in control patients who had experienced erythema migrans. Most of the complaints were subjective such as headache, attention problems, memory difficulties, depression and paresthesia. The real burden of remaining symptoms and neurological abnormalities after treatment for Lyme neuroborreliosis, as well as the pathophysiological mechanisms of post-Lyme disease syndrome, should be better charted in well designed studies. It seems clear that additional prolonged antibiotic treatment does not give any benefit in post-Lyme disease syndrome, and it should be remembered that treatments continued for months carry substantial risk for the patients. Anecdotal reports of better response to long-term or repeated antibiotic treatment exist, but this could be due to placebo effect, which is known to occur in at least 30% of cases. A positive Bb antibody index may last for years and is not a suitable marker for treatment response.

Conclusion

We suggest two levels of diagnostic accuracy for clinical practice; definite and possible Lyme neuroborreliosis. Treatment with 2-4 weeks courses of IV ceftriaxone, penicilline or oral doxycycline are effective. We recommend oral doxycycline for two weeks as the first treatment choice. Patients with possible Lyme neuroborreliosis should be offered one, but not repeated courses of antibiotic treatment. Extensive antibiotic treatment is not recommended under any circumstances. The prognosis of neuroborreliosis and pathophysiology of post-treatment conditions need further studies.

We recommend oral doxycycline for two weeks as the first treatment choice. Enhanced therapeutic efficacy of extended treatment beyond two to three weeks is not well documented.

References

Myasthenia Gravis and the Heart

Myasthenia gravis (MG) is well established as an autoimmune disorder with specific autoantibodies directed against the nicotinic acetylcholine receptor (AChR) in the neuromuscular junction. Involvement of the heart has been claimed and reported, but a causal connection between MG and altered cardiac function has not been found. This review summarises what is known about the possibility of heart involvement in MG.

Immunology

Whereas the AChR-antibody is the mainstay of MG, several other antibodies can be found. Some of these antibodies have been shown to react with cardiac muscle, thus being termed skeletal and heart reactive autoantibodies, or striatal antibodies. A proportion of this striatal reactivity is due to antibodies against titin and the ryanodine receptor (RyR) found in the sarcoplasmic reticulum, whereas other antibodies are claimed to react with myosin, α-actin and actinin. Non-striatial antibodies have also been demonstrated in MG, directed against beta-adrenergic receptors and against AChR of the muscarinic type. Mylgland demonstrated that the existence of heart muscle antibodies was related to type of MG, in finding such antibodies in MG-patients with thymoma and late-onset MG, but not in early onset MG. These heart muscle antibodies were shown to be specific for MG. Lately, the discovery of antibodies to the muscle specific tyrosine kinase (MuSK) has identified a subgroup of MG patients with rather distinct clinical characteristics. Antibodies to MuSK inhibit agrin-induced AChR-clustering, indicating a potential effect on agrin-dependent maintenance of AChRs at the neuromuscular junction. Cardiac function has not been examined specifically in MuSK-positive MG-patients.

The existence of all these antibodies – and antibodies not yet characterised – offers theoretical mechanisms for cardiac involvement in MG, by interfering with contractility, cardiac conduction, autonomous regulation or by an immunological attack on the myocardium, involving complement activation, infiltrates of inflammatory cells and with consequent necrosis.

Giant-cell myocarditis (GCM) is a condition showing a clear association to thymoma and in some cases to MG. GCM is characterised by degeneration and necrosis of heart muscle, and has been linked to IgG anti-cardiomyocyte antibodies. GCM is however extremely rare, with only a few reported cases.

However, looking beyond the rare giant-cell myocarditis, the potential immunological mechanisms are at the present insufficiently correlated to clinical cardiological findings in MG patients.

Clinical findings

ECG

Changes in cardiac function as registered by changes in the ECG have been taken as a marker for MG-related cardiac disease. Hofstad found ECG abnormalities in 14 of the 124 patients (16%), regarding the findings in twelve of these patients to be directly MG-related. A larger study by Luomanmäki reported 97 MG-patients where 11% had abnormalities from concomitant heart disease, 9% had minor alterations (same rate as normal population) and 15% showed terminal notching of the QRS complex. Later, Büyükbüktürk reported a higher frequency of QT-prolongation, right bundle branch block, sinus tachycardia and arrhythmias than found in the normal population. Ashok found in 4 of 10 MG-patients flat to inverted T-waves, ST-depression and poor progression of R-waves in three precordial leads, all abnormalities reverting to normal following oral neostigmine. On the other hand, a clinical study by Kornfeld could not demonstrate any convincing ECG–changes in MG-patients. In conclusion, no distinct features of the ECG can be assigned to MG alone, and the significance of ECG in evaluation of MG-related cardiac disease is uncertain.

Clinical cardiac function

Few studies have clinically investigated cardiac function other than ECG in MG-patients. Johanssen found a reduced peak diastolic filling rate in 25 MG-patients without any known cardiovascular disease, hypertension, diabetes mellitus or pulmonary disease. Ejection fraction was similar in patients and controls. Another study demonstrated a reduced global heart ejection fraction in 40% of MG patients without known cardiac disease after exercise, interpreted as a true association between MG and heart disease. We have recently studied cardiac function in MG-patients without known cardiovascular disease, and found a reduced cardiac tissue velocity and strain (Owe et al, in press). These findings indicate subclinical alterations in cardiac function of some MG-patients. No modality of examination has been proven to be of value in routine examination of MG patients without symptoms of heart disease, and MG-patients do not have an increased risk of heart-related deaths. There is a need for larger-scale clinical studies examining cardiac function in MG patients.

Post-mortem examinations and thymoma MG

The most convincing evidence for cardiac involvement in MG comes from autopsies. As early as 1901, Weigert demonstrated myocardial abnormalities in MG-patients. Later studies have confirmed the pathological findings in the hearts of MG-patients, focal inflammation and necrosis, and in the absence of atherosclerotic disease. The focal (spotty) appearance of the inflammation and necrosis bears resemblance to findings in skeletal muscles of MG-patients, and is believed to be due to lymphocytic infiltration of the myocardium. In a review from 1975, Gibson found myocarditic changes in 28 of 75 patients with MG, the majority being associated with thymomas. Hofstad reported focal myocarditis in all three examined thymoma-MG patients. Among non-thymoma MG-patients, focal myocarditis or non-specific myocardial changes were found in three of five autopsies. Thus, thymomas are usually associated with myocardial involvement, but this can also occur in non-thymoma MG-patients.

Thymoma MG-patients are in addition prone to local thymoma-infiltration and invasion of the pericardium, myocardium, large vessels and other neighbouring structures, with the possible result of altered cardiac function. The observed high frequency of myocardial pathology in thymoma MG-patients could mean that an immunological attack with resulting inflammation and myocardial necrosis represents a paraneoplastic phenomenon related to the thymoma. Furthermore, thymoma patients have a broad range of autoantibodies, providing a theoretical mechanism for altered cardiac function, whether it is due to altered contractile force or altered conduction.

Effect of acetylcholine esterase inhibitors

The effect of acetylcholine esterase inhibitors (ACh-I) on cardiac function has been highlighted in several studies. Ashok found that non-specific ECG abnormalities in MG-patients reverted towards normal following neostigmine. Johanssen found an increase in the peak diastolic filling rate in MG-patients following pyridostigmine. We have demonstrated a normalizing of cardiac tissue velocity and...
Conclusions
When evaluating cardiac involvement in MG, a distinction has to be made between laboratory findings and clinical cardiac function. There is good evidence for myocardial pathology in MG patients, including a diversity of heart-reactive autoantibodies and focal inflammation with cellular infiltrates and myocardial necrosis. On the other hand, any firm clinical correlates to these findings have yet to be established. Clinical studies indicating a functional alteration in cardiac function are either too small, have conflicting results or cannot reliably distinguish any altered cardiac function caused by MG from altered function of other causes such as atherosclerotic disease. The indirect effect of MG, due to respiratory impairment and low muscle tone, can reduce venous return, altering cardiac haemodynamics. Hypoxia, hypercapnia, acidosis and associated respiratory infections in a myasthenic crisis could give rise to persisting myocardial changes. Susppected MG-related cardiac disease often occurs late in life, at a time when there is an increased risk of atherosclerotic disease. This creates a dilemma: excluding from the studies MG-patients with the slightest symptoms of cardiac disease may produce false negative findings, whereas inclusion of all MG-patients may obscure results due to presence of coexisting cardiovascular disease.

From the present evidence, one should regard thymoma MG-patients as a group at special risk for myocardial pathology. Heart symptoms in thymoma MG-patients should always be suspected as being caused by myocardiitis (or pericarditis) and related to MG and autoimmunity. However, with available modalities of heart examination, there is, in our opinion, no need for MG-patients, regardless of any thymic pathology, to be examined routinely for heart disease unless cardiac symptoms arise.

References

Presenting Information – UK and ROI

PRESENTING INFORMATION – UK AND ROI

REBIF® 8 MICROGRAMS AND 22 MICROGRAMS SOLUTION FOR INJECTION
REBIF® 22 MICROGRAMS SOLUTION FOR INJECTION
REBIF® 44 MICROGRAMS SOLUTION FOR INJECTION

Interferon beta-1a

Presentation Rebif 8.8 and 22: Pre-filled glass syringe containing 8.8 μg or 22 μg of interferon beta-1a in respectively 0.2 or 0.5 ml. Rebif 22 and 44: Pre-filled glass syringe containing 22 μg or 44 μg interferon beta-1a in 0.5 ml. Indication Treatment of relapsing multiple sclerosis. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. Dosage and administration Initiate under supervision of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection Recommended dose: Weeks 1 and 2: 8.8 μg three times per week (TIW); weeks 3 and 4: 22 μg TIW; week 5 onwards: 44 μg TIW (22 μg TIW if patients cannot tolerate higher dose). Limitations published data suggest that the safety profile in adolescents aged 12-16 years receiving Rebif 22 TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection anaphylactic shock has been reported in 1 of 123,000 cases treated. Consideration for anaphylaxis is advised if there is a history of anaphylaxis. Contraindications History of allergy to natural or recombinant interferon beta, or to any of the excipients; treatment with another interferon; current severe depression and/or suicidal ideation. Precautions Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Close monitoring of patients experiencing depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Close monitoring patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aspecfic injection technique and rotate injection sites to minimize risk of injection site necrosis. If break in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy at months 1, 3 and 6 and periodically thereafter. Stop treatment if clinical symptoms or signs of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and at abnormal every 6 – 12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraceptive. Limitations published data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. If overdose occurs, hospitalise patient and give supportive treatment. Side effects In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. Very common: flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. Common: injection site pain, myalgia, arthralgia, fatigue, rigor, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia. Severe side effects include: injection site necrosis, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, suicide attempt. Consult the Summary of Product Characteristics for more information relating to side effects. Legal category POM

Legal category POM

Price
Rebif 8.8 and 22: 6 (0.2 ml) - 6 (0.5 ml) syringes - £586.19
Rebif 22: 12 syringes (0.5 ml) - £550.13
Rebif 44: 12 syringes (0.5 ml) - £386.28
For prices in Ireland, consult distributors Alphar Services Ltd.
Marketing Authorisation Holder and Numbers:
Serono Europe Ltd, 56 Marsh Wall, London, E14 9TP, EU/1/08/03/007; D03 & D06
For further information contact:
UK: Merck Serono, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX
Tel: 020 8018 7373
Republic of Ireland: Merck Serono, 3012 Lake Drive, Citywest Business Campus, Dublin 24
Tel: 01 466 1910
Date of Preparation: September 2007

Adverse events should be reported to Merck Serono - see contact details within PI. Information about adverse event reporting in the UK can be found at www.yellowcard.gov.uk.

Date of preparation: October 2007
REB07-0146
Rebif® New Formulation
Balancing Performance & Safety

Prescribing information is available on the adjacent page
Date of preparation: October 2007
REB07-0146
Management of Chronic Subdural Haematoma

Chronic subdural haematoma (CSDH) is one of the most common clinical entities encountered in daily neurosurgical practice. It generally occurs in the elderly population in whom age related reductions in brain volume with a corresponding increase in the size of the subdural space increase the vulnerability to this disease. Cerebral atrophy is also important in increasing the risk of CSDH in patients with epilepsy, alcoholism, Huntington's disease and those with overdrainage from a ventriculo-peritoneal shunt. Patients with a coagulopathy, including antiplatelet and antithrombotic therapy (e.g. aspirin, dipyridamole, warfarin and heparin) are also at an increased risk of CSDH.

Pathogenesis (Figure 1)
Two mechanisms, either alone or in combination, appear to play an aetiological role in the development of a CSDH.

1. An acute subdural haematoma that has not been evacuated may evolve into a CSDH. As the acute haematoma matures an inflammatory membrane forms and envelopes the clot. Repeated minor haemorrhages from neovascular structures in the membrane may contribute to haematoma expansion.3 In addition the acute haematoma liquefies within days of the initial bleed. Fluid ingress, driven by an osmotic gradient generated by fibrinolytic products within the haematoma has been postulated to cause expansion during the conversion of an acute to a chronic subdural haematoma.1,2

2. Subdural hygroma formation secondary to a traumatic tear of the cortical arachnoid membrane allowing egress of CSF into the subdural space. The further expansion of the hygroma with conversion to a CSDH is attributed to repeated minor haemorrhages into the subdural collection from the membrane that surrounds the collection.4 The demonstration of Beta--trace protein, a highly specific CSF marker, in the subdural fluid of the vast majority of patients with CSDH and all of the patients with a subdural hygroma offers support for this hypothesis.5

Presentation
Patients can present with one or more of the following clinical scenarios:
1. Symptoms and signs of raised intracranial pressure: headache, nausea, vomiting, impaired level of consciousness, papilloedema.
2. Focal neurological deficit secondary to compression of neuronal pathways: This depends on the location of the subdural haematoma (e.g hemiplegia with a posterior frontal haematoma, dysphasia with a dominant temporal haematoma, and sensory inattention with a parietal haematoma). In clinical practice deficits, including altered level of consciousness can fluctuate in severity leading to a delay in diagnosis.
3. Seizures: Focal or generalised.

Investigations
Computed tomography remains the preferred imaging modality and CSDH is classically described as a hypodense sickle-shaped extra axial fluid collection with evidence of surrounding mass effect. Where the haematoma evolves as a result of an acute bleed its density and appearance change with time in relation to the surrounding cortical surface. Three phases are described:
1. Hyperdense (0-7 days)
2. Isodense (1-3 weeks)
3. Hypodense (>3 weeks)

Figure 1: Diagram showing the pathogenesis of chronic subdural haematoma.
Azilect® 1mg tablets

Prescribing information (Please refer to the Summary of Product Characteristics (SmPC) before prescribing)

Presentation: Tablets containing 1mg rasagiline (as the mesilate).

Indication: Treatment of idiopathic Parkinson’s disease as monotherapy or as adjunct to levodopa in patients with end of dose fluctuations.

Dosage and administration:
Oral, 1mg once daily taken with or without food. 

Children and adolescents (<18 years): Not recommended.

Patients with renal impairment: No change in dosage required.

Patients with hepatic impairment: Predominant hepatic metabolism. Do not use in patients with severe impairment. Avoid use in patients with moderate impairment. Use with caution in patients with mild impairment and stop if progresses to moderate.

Contraindications:
Hypersensitivity to the active substance or to any of the excipients.

Do not use in patients with severe hepatic impairment. Avoid use in patients with moderate hepatic impairment. Use with caution in patients with mild hepatic impairment and stop if progresses to moderate.

Do not use in patients with severe hepatic insufficiency. Co-administration of other monoamine oxidase (MAO) inhibitors is contraindicated due to risk of hypertensive crisis. Concomitant pethidine treatment is contraindicated. Allow at least 14 days off rasagiline before using other MAO inhibitors or pethidine.

Special warnings and precautions:
Administer antidepressants with caution as serious adverse reactions have been reported with concomitant use of selective serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants, MAO inhibitors and a selective MAO-B inhibitor. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Avoid use in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson’s disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation.

Undesirable effects in clinical trials: Monotherapy: >1%: headache, flu syndrome, malaise, neck pain, dyspepsia, arthralgia, depression, conjunctivitis, allergic reaction, fever, arthralgia, anorexia, lumbago, arthritis, vertigo, rhinitis, contact dermatitis, vesiculobullous rash, skin carcinoma, hallucinations, urinary urgency. <1%: cerebrovascular accident, myocardial infarct. Adjunct therapy: >1%: abdominal pain, accidental injury, postural hypotension, constipation, vomiting, weight loss, dyskinesia, neck pain, anorexia, dry mouth, arthralgia, tarsorrhaphy, dystonia, abnormal dreams, ataxia, rash, hallucinations. <1%: angina pectoris, cerebrovascular accident, skin melanoma, confusion. Please refer to the SmPC for a full list of adverse events.

Basic NHS Price: Azilect® (tablets) 1mg x 28 £70.72

Legal category: POM

Marketing Authorisation Number: 1mg tablets (28 pack size) EU/1/04/304/003

Marketing Authorisation Holder: Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany

Date last revised: May 2008

Further information available from: Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.
In the majority of cases a CSDH is visualised as a mass comprising hypo and hyperdense signal characteristics. Bilateral isodense SDH’s may result in a misdiagnosis due to difficulties in identifying cerebral cortex and the absence of midline shift (Figure 2). A contrast CT scan will show any enhancing membranes and can delineate the haematoma more precisely. MRI is also a useful adjunct in some cases. For the most part, T1 and T2 images both show the haematoma to be hyperintense relative to brain and CSF. The change of signal intensity correlates with the length of time the haematoma has been present and the breakdown of blood in the haematoma capsule (Figure 3).

**Treatment**

Conservative and surgical approaches can be adopted when managing patients with a CSDH. A watch, wait and re-scan policy is usually recommended in asymptomatic or minimally symptomatic patients with a thin CSDH. Bed rest, osmotic diuretics and corticosteroids have been used although the evidence to support these measures is sparse. For a patient with a symptomatic CSDH, surgery is the treatment of choice.

**Preoperative workup**

When undertaking surgery for a CSDH the coagulation status of the patient is of paramount importance. Aspirin should be stopped. In some cases the clinical status of the patient will necessitate urgent surgery despite aspirin treatment. If the patient’s condition is stable, neurological deficits minor and the haematoma relatively small, surgery can be delayed for a few days to permit recovery of platelet function after cessation of antiplatelet therapy.

Another important factor in the treatment decision making process is the patient’s coagulation status especially with the widespread use of therapeutic blood thinning agents. Warfarin therapy poses specific problems. Historically, warfarin reversal comprised oral or i.v. Vitamin K administration supplemented with fresh frozen plasma. Such a process can lead to unacceptable delays in performing emergency surgery while FFP is obtained, thawed, administered and haematological parameters rechecked. Complete and rapid reversal of warfarin over-anticoagulation is better achieved with 5 or 10mg of intravenous vitamin K and II, VII, IX and X factor concentrate (Beriplex®). Surgical options

The surgical approaches to the management of patients with CSDH are mainly limited to burr hole drainage, twist drill drainage and craniotomy. A small craniectomy has also been advocated as an alternative approach. Combining each technique with the use of intraoperative irrigation and/or post-operative drainage provides a variety of treatment options.

**Surgical Techniques**

Chronic SDHs are most commonly treated by burr hole evacuation. The number and location of the burr holes depends upon the size and location of the haematoma as determined by CT scan. Two burr holes located along the same line as the incision of a trauma flap are commonly employed. Care must be taken to secure any dural bleeding. The distinctive grey encapsulating membrane is opened to permit drainage of the liquefied haematoma. This is often under considerable initial pressure. Occasional conversion to a craniotomy is required if a substantial solid component persists. Irrigation of the subdural space, facilitated by the use of a soft Jacques catheter, is commonly performed to facilitate evacuation.

Twist drill craniotomy has been advocated in search of a less invasive treatment option with a skull opening usually less than 5mm. However, irrigation through such a small aperture is difficult. A craniotomy permits fluid evacuation and partial removal of the haematoma membrane in patients with recurrent, persistent chronic subdural haematomas. A small craniectomy is an alternative that enables the significance of post-operative collections to be assessed by palpation and treated by percutaneous aspiration. A valveless subdural-peritoneal conduit fashioned from a peritoneal catheter with side holes cut for the subdural space and securely anchored to the galea can be useful in the treatment of patients with an atrophic brain where persistence of the subdural collection occurs despite recent drainage.

Weigel et al. analysed 48 publications (1981-2001) in a comprehensive meta-analysis comparing the outcome of various surgical techniques. A wide range of cure, recurrence and mortality rates were found with each procedure. Overall, there was no significant difference in mortality between the three techniques. Mortality of up to 11% was noted. The morbidity from a craniotomy was reported to be higher than drainage procedures. Comparison between burrhole drainage and twist drill craniotomy revealed a higher recurrence rate with a twist drill approach.

**Irrigation and drainage**

The use of intraoperative irrigation with warm isotonic saline or artificial CSF until the effluents are clear is widespread. No significant differences were reported in the patients who received irrigation compared with those who did not in several series. In a twist drill series, irrigation was found to improve the recurrence rate from 29.2% to 6.7%. In contrast a lower recurrence rate has been reported in a more recent series in patients in whom intra-operative irrigation was not used.

The use of closed post-operative subdural space drainage has long been considered. Some prospective studies showed no beneficial effect, whereas other authors report lower recurrence rates with the use of post-operative drains. In patients undergoing twist drill craniotomy, post-operative drainage did appear to reduce the recurrence rate from 68% to 9% in a meta-analysis. The use of a closed subgaleal drainage system has also been reported. Whilst there are no reports of a proven increased risk of infection with drains, this concern must exist.

Peri-operative continuous inflow and outflow irrigation with Ringer’s lactate solution after evacuation of the haematoma has been reported to reduce the recurrence risk in a small prospective randomised study. However the differences did not reach statistical significance (1/19 vs 4/18). A retrospective comparison of post operative inflow and outflow drainage with burr hole evacuation +/- closed drainage and craniotomy showed significantly lower recurrence rate in patients with continuous inflow-outflow drainage. Despite these small studies such techniques have not been widely adopted.

**Complications**

Postoperative CT scans to follow the progress of patients have shown that residual haematoma is
and high levels of interleukin-6 signifying inflammation of membranes or enhanced expression of VEGF and bFGF in the outer membrane may result in a higher risk of a recurrence. 1,2,4

Other complications include seizures, pneumocephalus, subdural empyema and rarely intracranial haemorrhage. Extracranial complications such as post-operative pneumonia and pulmonary embolism may also occur in patients with a CSDH. Following surgery the risks and benefits of antipatelet and anti-coagulant therapy need careful consideration on a case by case basis before reintroduction.

Summary
The diagnosis of chronic subdural haematoma should be considered in any elderly patient presenting with focal neurological signs or with any suggestion of raised intracranial pressure. For the majority of patients surgical drainage of a symptomatic chronic subdural haematoma is readily performed with a relatively low risk of operative morbidity and mortality. Most patients make a satisfactory recovery. Recaccumulation is the most common sequelae and can be troublesome in a small minority of patients. A number of operative variations have been reported to try and minimise this risk, however the evidence to support any specific operative technique is not persuasive. The use of post-operative anti-coagulants and antiplatelet agents needs careful consideration particularly in patients with a history of haematoma recurrence.

References
Epilepsy and Hippocampal Sclerosis: Cause or Effect?

Hippocampal sclerosis (HS) is the most common pathological finding in mesial temporal lobe epilepsy,1 accounting for approximately 70% of cases in patients undergoing surgery for drug-resistant partial seizures.2 Other focal lesions associated with partial epilepsy are listed in Table 1. The broader term mesial temporal sclerosis (MTS) acknowledges the frequent involvement of neighbouring limbic structures including the amygdala and parahippocampal gyrus. Despite the strong association between hippocampal sclerosis and temporal lobe epilepsy, it remains unclear whether or not the relationship is causal – or if both conditions might reflect an underlying developmental abnormality of the hippocampus. In this article we will briefly review the pathological features of hippocampal sclerosis, before moving on to discuss some of the relevant experimental and clinical evidence.

Hippocampal sclerosis

The typical MRI features of hippocampal sclerosis, also known as Ammon’s horn sclerosis (AHS), are unilateral volume loss and increased signal intensity on T2-weighted images. There is no sex or side preference and a proportion of cases are bilateral. Macroscopically the hippocampus is firm and shrunken, sometimes with visible collapse of the CA1 subfield (Sommer’s sector). Microscopic findings include a characteristic pattern of neuronal loss and reactive gliosis (Figure 1) that varies in severity from case to case (Table 2).3 The mechanism of neuronal loss and selective vulnerability in MTS is likely to be excessive release of the excitatory neurotransmitters glutamate and aspartate, acting at calcium-permeable NMDA and AMPA receptors (‘excitotoxicity’).4 This leads to intense depolarisation and calcium overload which triggers multiple cell death pathways. In addition to neuronal loss and gliosis, two commonly associated findings are mossy fibre sprouting and granule cell dispersion (Table 3).

Aetiology and pathogenesis

Several animal models of limbic status epilepticus demonstrate that HS can be acquired – and the pathological features in many cases are similar to those seen in humans.5 MRI and post-mortem studies also confirm that acute hippocampal damage may follow status epilepticus.6 7 An influential hypothesis suggests that an initial precipitating insult (IPI) in childhood such as a febrile convulsion may injure the hippocampus and that this ‘first hit’ at a critical period of development may act as a template for progressive neuronal loss and gliosis.8 It has been known for many years that more than half of patients with HS and temporal lobe epilepsy have a history of febrile convulsion or status epilepticus in infancy.9 10 This is typically followed by a variable ‘latent interval’ of around 7–10 years before the onset of spontaneous seizures. MRI studies in children with prolonged febrile convulsions have demonstrated acute changes in the hippocampus consistent with neuronal injury and oedema. Some follow-up studies have shown subsequent hippocampal atrophy9 or hippocampal sclerosis2 although the presence of a pre-existing abnormality cannot be excluded. It is important to note that most of these children do not develop epilepsy10 and that at least a third of patients with hippocampal sclerosis have no documented IPI.

Do seizures damage the brain?

It is often said that ‘seizures beget seizures’, but it has been difficult to demonstrate conclusively that patients with pharmacoresistant temporal lobe epilepsy suffer ongoing hippocampal damage. Some studies have shown a gradual deterioration in hippocampal volume, metabolism or memory performance over time11 or evidence of progressive neuronal loss and gliosis.8 It is often said that seizures beget seizures, but it has been difficult to demonstrate conclusively that patients with pharmacoresistant temporal lobe epilepsy suffer ongoing hippocampal damage. Some studies have shown a gradual deterioration in hippocampal volume, metabolism or memory performance over time11 or evidence of progres-

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
<th>Possible significance</th>
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<tr>
<td>Mossy fibre sprouting (MFS)</td>
<td>New axons arising from granule cells extend upwards into the molecular layer of the dentate gyrus. This can be demonstrated by immunostaining for the neuropeptide dynorphin (see Figure 1F).</td>
<td>May contribute to epileptogenesis by forming potentially self-excitatory connections within the dentate gyrus. However, inhibition of MFS in experimental models does not prevent spontaneous seizures.</td>
</tr>
<tr>
<td>Granule cell dispersion (GCD)</td>
<td>Increased width of granule cell layer, which is normally 4–5 cells thick, but is more than 10 cells deep in at least 40% of HS cases. Cells often have a spindle-cell appearance, reminiscent of migrating neurons (see Figure 1G).</td>
<td>Also occurs in the opposite side, therefore may be a response to generalised seizure activity rather than signifying damage. Some animal models show increased neurogenesis in the subgranular layer, with upward migration of new neurons along radial glia.</td>
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| Table 1: Common pathological findings in epilepsy surgical specimens |
|-------------------|------------------|
| Hippocampal sclerosis (HS) |
| Malformations of cortical development (MCD) |
| – focal cortical dysplasia (FCD) |
| – mild malformations of cortical development (formerly ‘microdysgenesis’) |
| Low grade glioneuronal tumours |
| – ganglioglioma |
| – dysembryoplastic neuroepithelial tumour (DNT) |
| Vascular / traumatic lesions |
| Dual pathology |
| – usually mild HS in combination with a second pro-epileptogenic lesion |

<p>| Table 2: Simple classification of hippocampal sclerosis |</p>
<table>
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<tr>
<th>Subtype</th>
<th>Main pathological features</th>
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<tr>
<td>Classical</td>
<td>Neuronal loss and gliosis mainly in CA1, CA3 and end-folium</td>
</tr>
<tr>
<td>Total</td>
<td>Severe neuronal loss in all hippocampal subfields and the dentate gyrus</td>
</tr>
<tr>
<td>End-folium</td>
<td>Neuronal loss and gliosis restricted to the hilum of the dentate gyrus</td>
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Table 3: Features commonly associated with hippocampal sclerosis

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<tr>
<th>Feature</th>
<th>Description</th>
<th>Possible significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mossy fibre sprouting (MFS)</td>
<td>New axons arising from granule cells extend upwards into the molecular layer of the dentate gyrus. This can be demonstrated by immunostaining for the neuropeptide dynorphin (see Figure 1F).</td>
<td>May contribute to epileptogenesis by forming potentially self-excitatory connections within the dentate gyrus. However, inhibition of MFS in experimental models does not prevent spontaneous seizures.</td>
</tr>
<tr>
<td>Granule cell dispersion (GCD)</td>
<td>Increased width of granule cell layer, which is normally 4–5 cells thick, but is more than 10 cells deep in at least 40% of HS cases. Cells often have a spindle-cell appearance, reminiscent of migrating neurons (see Figure 1G).</td>
<td>Also occurs in the opposite side, therefore may be a response to generalised seizure activity rather than signifying damage. Some animal models show increased neurogenesis in the subgranular layer, with upward migration of new neurons along radial glia.</td>
</tr>
</tbody>
</table>
Impairment:

Adult: Zonegran must be added to existing therapy. Initial daily dose is 50 mg in two divided doses. After one week, increase to 100 mg daily and then at one weekly intervals, in 100 mg increments. Consider two weekly intervals in renal or hepatic impairment and patients not receiving CYP3A4-inducing agents. Zonegran can be administered once or twice daily after the titration phase. Withdraw gradually. Elderly and patients with renal or hepatic impairment: Caution (see SPC). Not recommended in severe hepatic impairment.

Children and adolescents under 18 years: Not recommended.

Contra-Indications: Hypersensitivity to zonisamide, sulphonamide or any excipient. Pregnancy: Zonegran must not be used during pregnancy unless clearly necessary in the opinion of the physician, and only if potential benefits justify risk to the foetus. Specialist advice should be given to women who are or plan to become pregnant. Women of childbearing potential must use contraception during pregnancy and for one month after discontinuation.

Lactation: Zonisamide is secreted into breast milk. A decision must be made to either discontinue Zonegran or stop breast-feeding. Breast-feeding should not be resumed until one month after stopping Zonegran. Warfarin and Proton: Serious rash es occurs in association with Zonegran therapy; including cases of Stevens-Johnson syndrome. Zonegran contains a sulphonamide group. Serious immune mediated adverse reactions are associated with the sulphonamide group e.g. rash, allergic reaction, major haematological disturbances including aplastic anaemia, which very rarely can be fatal. Closely supervise and consider discontinuation in patients with unexplained fever, assess markers of muscle damage, e.g. serum creatine phosphokinase and alanine aminotransferase and consider discontinuation. Zonegran 100 mg hard capsules contain 84.10, which may cause allergic reactions. Caution in patients less than 60 kg. In patients with weight loss consider dietary supplement increased food intake or discontinuation.

Drug Interactions: No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone) insufficient data with carbonic anhydrase inhibitors e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing uric acid, therefore caution with substances that can induce or inhibit these enzymes. Side effects: The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and nausea. Adverse reactions associated with Zonegran in clinical studies and post-marketing surveillance 'Very common effects (>1/10):' anorexia, agitation, irritability, confusion, state depression, anxiety, dizziness, memory impairment, somnolence, diplopia, decreased libido. Common effects (<1/10):' coryza, hypotension, affect liability, anxiety, insomnia, psychotic disorder, bradypnoea, disturbance in attention, erythromelalgia, parasthesia, speech disorder, disorder, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, urticaria, lymphadenopathia, leucocytosis, leucopenia, lymphadenopathy, panhypopituitarism, defaecation, behaviour in attention, angina, pancreatitis, myopathy, hyperkalaemia, hyperglycaemia, hypertension, affect liability, anxiety, insomnia, psychiatric disorder, bradypnoea, disturbance in attention, erythromelalgia, parasthesia, speech disorder, disorder, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, urticaria, lymphadenopathy, leucocytosis, leucopenia, lymphadenopathy, panhypopituitarism, defaecation, behaviour in attention, angina, pancreatitis, myopathy, hyperkalaemia, hyperglycaemia, hypertension, affect liability, anxiety, insomnia, psychiatric disorder, bradypnoea, disturbance in attention, 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The granule cell layer is focally bilaminar in up to 10% of cases, illustrated here by immunostaining for the neuronal marker granule cell dispersion is seen in at least 40% of HS cases. The normal dentate gyrus contains a compact and sharply-defined layer of granule cells. Reactive gliosis/astrocytosis generally parallels the degree of neuronal loss, demonstrated here (dark brown staining) by immunohistochemistry for the astrocytic marker glial fibrillary acidic protein (GFAP). Mosy fibre sprouting is identified in diagnostic practice as a band of dysphosphin-immunoreactive (light brown) in the supragranular layer of the dentate gyrus. The normal dentate gyrus contains a compact and sharply-defined layer of granule cells.

Concluding remarks: chicken or egg? The association between temporal lobe epilepsy and hippocampal sclerosis has been recognised for over a century, but despite many decades of basic and clinical research it is still not possible to assign an arrow of causality. One explanation is that hippocampal sclerosis may represent a phenotypically-similar manifestation of a heterogeneous group of pathologies with diverse pathogenesis, derived from a complex interplay of numerous factors (including genetic, developmental and environmental components). These same factors may also explain why some people are susceptible to seizure-associated hippocampal damage and others appear to be resistant. It is hoped that more light may be shed on this intriguing issue over the coming decades, perhaps facilitated by large-scale prospective neuroimaging studies which can be used to follow its evolution during the early years of life.

References
14. Thom M, Zhou J, Martinian L, et al. Quantitative post-mortem study of the hippocampus in chronic epilepsy: seizures do not inevitably cause hippocampal damage and others appear to be resistant. It is hoped that more light may be shed on this intriguing issue over the coming decades, perhaps facilitated by large-scale prospective neuroimaging studies which can be used to follow its evolution during the early years of life.
Charles Bonnet’s Syndrome

The Charles Bonnet syndrome is a visual phenomenon characterized by the presence of vivid, complex visual hallucinations among elderly individuals without mental deficiency. It is a syndrome named after Charles Bonnet (1720-93), a Swiss physician and philosopher, who first described it in his Essai analytique sur des facultés de l’âme, in 1760. Bonnet noted that elderly people without mental deficits could experience recurrent visual hallucinations, often of men, women, birds, cars, and buildings, which he explained as 'fictions' of their brain. This syndrome is often referred to as the ‘Charles Bonnet syndrome’ (CBS). The term is used to describe complex visual hallucinations associated with age-related visual impairment, without delusions or loss of insight.

The CBS is thought to arise from a cortical reorganization in the primary visual cortex, leading to the activation of subcortical areas that are normally involved in visual processing. This can result in the perception of complex visual hallucinations. The condition is most commonly seen in older adults, with a peak incidence in the 80s and 90s.


References
Fitness to Ride – Horse Racing in Great Britain

Horse racing is an immensely popular global sport with television audiences of over 100 million for major events such as the Melbourne Cup and Kentucky Derby. Racing takes place on 60 racecourses in England, Scotland and Wales and there are approximately 1475 race meetings annually with total attendance figures of over 5 million spectators.

Racing is broadly divided into flat and jump racing and involves both amateur and professional riders. All riders are over 16 and all types of racing take place over a full 12 month season, apart from Point to Point (PtoP) racing. PtoP is jump racing that is restricted to amateurs and has a limited season (November to June).

There are approximately 110,000 rides a year (60,000 flat, 35,000 jump and 12,000 Point to Point) and 1800 jockeys are licensed annually by the BHA (250 flat, 200 jump, 450 amateurs and 900 PtoP amateurs).

Over the period 1993-2007, there have been over 20,000 fixtures, 1.3 million rides, 53,000 falls, 10,250 injuries and 1,275 concussions in Great Britain, details of which are already in the published literature.1,2,3

Horses travel at 20-40mph, the jockey is seated in a saddle perched two metres above the ground and a ride may last anything from 40 seconds (flat) to 6 minutes (jump).

Incidence and type of injury

Amateur jockeys fall every 7.9 rides, Jump jockeys fall every 15.8 rides and Flat jockeys fall every 211 rides on turf (every 258 rides on All-Weather tracks). It is therefore not surprising that horse racing has some of the highest rates of injury seen in any sport, including the highest rates of concussion and fatal accidents in the published literature. Concussion rates are in fact six times greater than in Australian Rules Football – the sport with the closest incidence of concussion.

Soft tissue injuries account for 75-80% of all injuries, fractures 10-18%, dislocations 1-4% and concussion 8% (professional racing) - 18% (amateur racing).

Horse racing has detailed regulations covering all aspects of a jockeys’ fitness to hold a license, clearance to return to race riding following an accident, and the minimum medical provisions required on every racecourse on every raceday. These are published on the BHA website -

Standards of Medical Fitness to Ride
http://www.britishhorseracing.com/inside_horseracing/about/whatwedo/medical/medical.asp

Provision of medical services on racecourses – BHA General Instruction 11

Prohibited substances and testing of jockeys
http://www.britishhorseracing.com/inside_horseracing/about/whatwedo/medical/testing-banned-bkt.pdf

Fitness to Ride regulations

When applying for an initial licence, every rider must reach the minimum medical standard of fitness to ride. The same standard applies to all amateur and professional jockeys and some specified conditions warrant exclusion – epilepsy, anti-coagulant therapy, deafness, monocular vision, insulin-dependent diabetes etc.

Jockeys are required to notify the BHA Medical Department immediately if they suffer any illness or injury during the 12 months that the licence is valid. All jockeys are required to renew their licences annually and are required to complete a Health Declaration with details of all injuries and illnesses suffered since the last application. In addition, all jockeys are required to have a full medical examination carried out by their own GP every five years.
When riders reach a designated age threshold (over 37 jump, over 45 flat, over 55 amateur), they are also required to have an annual medical examination by the BHA CMA (to include blood profile, ECG and Exercise Stress Test if warranted).

Protection equipment
The Rules of Racing require all riders to wear helmets and body protectors when race riding and all protective equipment must meet the current European Standard – EN 1384:1996 (helmets) and EN 13158:2000 (body protectors). Helmets cost around £120 each and are designed as ‘single impact protectors’ - so should be discarded after every head injury or concussion. Body protectors are only designed to mitigate rib fracture (not injuries to the spine) and cost around £150.

Injury monitoring and recording
On every raceday, a minimum of two trauma trained doctors are required to be on duty (Racecourse Medical Officers – RMOs). When a jockey falls, a doctor or paramedic must attend the fallen rider within 60 seconds. Before riding again, the jockey must be examined by an RMO and a decision made as to his/her fitness to continue riding that day. All injuries must be recorded on a standardised form (MRB3) and reported to the BHA Medical Department at the end of racing. These are referred to as “Red Entries” and these data are currently stored on a central computer database within racing (Weatherbys). This system will shortly be replaced by a customised injury management system (Presagia Sports – Injury Zone). In addition, amateur riders carry a “Medical Record Book” (MRB) with details of all injuries incurred during racing – a medical passport. For amateurs, the RMO will record the Red Entry in the MRB as well as recording it on the MRB3 Form.

All jockeys who are unable to ride, for whatever reason, are recorded on a “Red Entry List”. This list is updated each evening and is available on every racecourse before racing starts. Any jockey whose name appears on the Red Entry List must be medically cleared by the BHA CMA and examined by an RMO before they are allowed to return to race riding.

For example, a jockey who suffers a fracture-dislocation of the shoulder will be sent directly to hospital in an ambulance and his name entered on the Red Entry List. When he has completed treatment, his specialist will be required to send a detailed report to the BHA CMA confirming that the condition is resolved and that the jockey can return to race riding. The BHA CMA may request additional information or examine the jockey himself but, more usually, the BHA CMA will accept the specialist recommendation and allow the jockey to return to a racecourse for examination by an RMO. Before racing starts, the RMO is required to examine the injured jockey and decide if the rider is in fact fit to race ride. At that stage, the RMO will either clear the Red Entry (allowing the jockey to ride) or, refer the jockey back to the BHA CMA for further evaluation.

Jockeys who are subject to a medical suspension (Red Entry) are uninsured and cannot ride in GB or any other country until cleared by the BHA CMA. Medical standards of fitness to ride apply across all racing authorities (Article 27 of the International Agreement) and some injuries are inevitably career ending.

Concussion management
Prior to 2004, the Jockey Club operated a fixed period of suspension (related to loss of consciousness – LOC) for any jockey who suffered concussion:

Mild – no LOC – jockey suspended for 2 clear days
Moderate – LOC of less than 60 seconds – jockey suspended for 6 clear days
Severe – LOC of over 60 seconds – jockey suspended for 20 clear days

In 2004, the Jockey Club/BHA introduced a standardised concussion management system and analysis of some 350 concussions that occurred in the 4.5 year period, 1st Jan 2004 – 30th June 2008, will be published shortly. The total budget for the BHA Concussion program is approximately £80,000 pa.

The current BHA Concussion protocol has three elements -

1. Neuro-Psychological (NP) testing
This takes place at one of 12 regional centres established by the BHA. These centres are located in private (independent) hospitals or GP surgeries and a trained nurse at each location will carry out the NP testing on behalf of the BHA. The jockey is required to complete a computised test (CogSport) and a series of pen and paper tests (Colour trails, STROOP, Symbol-digit, SCIOLP, digit span) – the whole process takes about 60 minutes to complete. The various tests are then evaluated by one of 4 Clinical Neuro-Psychologists retained by the BHA.

2. Standard Assessment of Concussion (BHA AC)
Whenever a jockey suffers a concussion, the doctor in attendance at the racecourse will carry out a standardised concussion assessment as mandated by the BHA. This involves a set of screening questions and a more detailed neurological evaluation for those riders who fail to answer the screening questions correctly. In every case, the doctor will be required to make a definitive diagnosis in regard to concussion. Is this rider suffering from concussion – YES/NO?

3. Post-concussion evaluation (fitness to return to race riding)
Any rider who is diagnosed as having concussion (as per 2/ above) will be required to undergo a two part evaluation before being allowed to return to race riding. This evaluation will normally take place no earlier than six clear days after the concussive incident:

a) Repeat NP testing (as for 1/ above) with report from Neuro-Psychologist.
b) Examination by a Consultant Neurologist (or Neurosurgeon). This consultation takes place at the same Regional Centre as the NP testing.

The reports from both these examinations are sent to the BHA CMA who is then responsible for deciding if the rider can safely be allowed back to race riding, or if a further period of rest is required. If the NP tests have not returned to baseline levels, the rider will normally be suspended for a further 14 days after which repeat post-concussion evaluation will take place (NP testing +/- consultant review). This process will be repeated until it is deemed safe for the rider to return to race riding.

The arrangements for baseline screening vary for the different types of jockey but the BHA AC and post-concussion review are identical for all jockeys (see Stages 1 and 2 above).

Professional jockeys
Neuro-Psychological testing - annual baseline
Amateur jockeys
Neuro-Psychological testing - baseline before first license is issued and repeat baseline every 5 years (or at the start of the season after any concussion).

Point-to-Point Riders (who do not hold an Amateur Licence – see above)
Neuro-Psychological testing – no baseline required but NP testing is available to riders on a voluntary basis (cost to be paid by the rider).

Head height for a jockey is approximately three metres above the ground and a fall from over two metres warrants specific medical management under the NICE Guidelines on Head injuries (June 2007).

References
Computed Tomography in Neurology

Computed tomography (CT) of the head was first used in clinical practice at the Atkinson Morley’s Hospital, London in 1972. On the earliest equipment, images were low resolution and tediously slow to acquire involving several hours of acquisition and processing time. Now, high resolution images of the brain can be obtained in a few seconds. Speed is a great strength of modern CT making it ideal for ill and poorly co-operative patients. Rapid data acquisition is exploited in contrast enhanced angiography and perfusion techniques, although these will not be discussed in detail in this article. CT is still the best method available to detect bony abnormalities and acute blood products. For these reasons, CT remains at the forefront of neuroradiology despite the remarkable advances in other imaging technologies.

Basic physics

X-ray images are formed by interactions of X-ray photons with matter. As photons pass through objects, they interact primarily with electrons. The photon may be completely absorbed releasing an electron from an atom (photoelectric effect). More usually, the photon is not fully absorbed but part of its energy is used to move an electron into a higher energy orbital (Compton effect). The photon emerges from this interaction with reduced energy and is slightly deflected from its original course. These effects on photons generate image contrast because tissues attenuate photons to differing extents depending on their electron density. The electron density of tissue components is quantified using CT and thus reliably differentiated.

CT uses data from a bank of detectors which are irradiated by a tube rotated around the patient. In the first generations of CT equipment, data was acquired slice by slice. A significant advance came with the development of slip ring technology which allows continuous gantry rotation around the patient and thus data acquisition from a volume of tissue (so called helical or spiral CT). This increases the speed of imaging and provides the information required for 3D reconstructions with no gaps between slices. The latest technology has taken this idea a step further, using a large bank of detectors capable of acquiring up to 320 slices in a single gantry rotation lasting less than a second (so called multislice, multidetector or volume CT).

Processing the data from detectors is a complicated process requiring powerful computers. Images are constructed using algorithms which not only localise anatomical structures but minimise artefacts. There are different algorithms available which demonstrate bone, brain and soft tissues optimally.

Approach to neurological CT

1. Anatomical localisation of lesions

One of the most difficult and important steps in trying to work out the nature of a lesion is to decide whether a mass arises inside the brain parenchyma or outside, usually from the meningeal coverings. A lesion within the brain parenchyma is termed intra-axial and one outside is extra-axial. The shape of a mass and its effect on neighbouring structures (such as displacement of brain and bone remodelling) are helpful in making this distinction. Parenchymal lesions can be usefully divided into those involving grey or white matter. For example, many tumours arise in white matter, whereas ischaemia typically affects grey matter, causing loss of grey-white differentiation.

Table 1: CT terminology (see Figure 1)

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Description</th>
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<tbody>
<tr>
<td>Helical/spiral/volumetric CT</td>
<td>Data acquisition occurs as the patient moves through the gantry generating a volume dataset. This can be post-processed into images of different slice thickness in any plane.</td>
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<tr>
<td>Multislice/multidetector/multilow CT</td>
<td>Multiple rows of detectors (typically 16, 64 or 128 rows of 0.5mm thickness) are installed in the gantry so that many imaging slices can be obtained with one rotation.</td>
</tr>
<tr>
<td>Post-processing</td>
<td>Image manipulation performed after data has been acquired.</td>
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<tr>
<td>High resolution CT</td>
<td>Thin section images viewed after processing with an edge-enhancing algorithm. This allows detection of very small structures (eg bone in the middle ear down to 0.5 mm or less in thickness). This technique only works in tissues where there is high intrinsic contrast (eg bone or lung). When applied to soft tissues the algorithm provides a very grainy appearance.</td>
</tr>
<tr>
<td>Image contrast/Contrast resolution</td>
<td>The difference in density between tissues determines how easily they can be distinguished using imaging. The areas of the body where there is greatest contrast between pathology and normal tissue on CT are the lungs and bones. In brain, white matter and grey matter can be differentiated with Hounsfield Unit (HU) of 20 and 30 respectively (see Figure 10).</td>
</tr>
<tr>
<td>Algorithm/Kernel</td>
<td>Computerised reconstruction of data which optimises images. This ranges from image smoothing (for soft tissue) to edge enhancement (for bone and lung). Algorithms are used to suppress artefacts caused for example by beam hardening.</td>
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Lytic or sclerotic metastatic bone lesions may be seen on CT. Fractures are often better seen on plain films than CT.

b. Dura mater (Figure 4)
Most normal dura mater (apart from the falx and tentorium) is not seen on CT as it is applied to the skull.

c. Arachnoid mater/subarachnoid space (Figure 5)
CSF spaces are easily compressed by space occupying lesions or by brain swelling. In hydrocephalus, the ventricles are typically large with effacement of cerebral sulci. In young people the sulci are normally small and this can be misinterpreted as brain swelling. Enlargement of the sulci usually indicates volume loss, either focal (eg related to an infarct) or diffuse (usually related to atrophy/neurodegeneration). Increased density in the sulci typically indicates subarachnoid haemorrhage.

d. Grey matter (Figure 6)
Infarcts typically involve grey matter but contusions and low grade tumours may be seen here.

e. White matter (Figure 7)
This is a typical site for high grade gliomas. Metastases and abscesses are often seen near the grey-white junction because of the high blood flow here, and the size of the vessels in which tumour cells and bacteria can lodge. Oedema also involves white matter (Figure 11).

Table 2: Physics/techniques (see Figure 2)

| Compton and photoelectric effects | These describe the interaction of X-ray photons with physical matter. In the photoelectric effect, a photon of suitable energy is completely absorbed, releasing an electron from its orbit around the nucleus. In this process, positively charged ions are produced. In Compton interactions, the X-ray photon is not completely absorbed, but deposits some of its energy, displacing but not removing an electron from an atom. The X-ray photon’s course is deflected and its energy is reduced. The deflection of the photon is a source for the loss of sharpness in the CT image. |

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Figure 2: X-ray photons of suitable energy interact with electrons, either releasing them from the atom (ionisation) or pushing them into a higher energy orbital. In the process, the photon may be completely absorbed, or reduced in energy. The interaction may also cause deflection of the photon (see Table 2).

Figure 3: Scalp/skull lesions. A. Skull lesions from Langerhan’s cell histiocytosis. B and C. Skull fracture. Note the full extent of the fracture is often better appreciated on plain film (arrowheads indicate fracture).

Figure 4: Dura mater. A. Images with and without contrast medium. Meningioma with a wide base on the convexity dura. B. Subdural haematoma. C. Post contrast CT image with a subdural empyema indicated by arrowheads. Note compression of the subarachnoid spaces.

Figure 5: Arachnoid mater/subarachnoid space. A. Prominent subarachnoid spaces due to atrophy. B. Subarachnoid haemorrhage. C. Arachnoid cyst.

Figure 6: Grey matter. A. Established cortical infarct in the anterior cerebral artery territory. B. Calcified low grade oligodendroglioma.

Figure 7: White matter. A and B. High grade glioma with vasogenic oedema (A before and B after contrast medium). See Figure 11 for description of patterns of oedema.
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Life with epilepsy can be much more than just a gap between seizures.
Figure 8: Vessels. Dense middle cerebral artery following recent occlusion (arrowhead).

Figure 9: Blindspots. A. The sella is enlarged by a pituitary adenoma (arrowheads). B. Orbital mass (arrowheads). C. Lymphoma involving nasopharynx and infratemporal fossa (arrowheads).

Figure 10: Density of lesions. A. Hounsfield Units (HU). Each tissue type has a specific electron density which can be quantified into attenuation coefficients or Hounsfield Units. B. Coil inserted in an intracranial aneurysm is of very high density and causes artefact (HU>1000) because of the attenuation of the x-ray beam. C. Calcification in a low grade glioma (HU=500). D. Recent haemorrhage in a subdural collection (HU=200). E. Dermoid containing fat (HU=-200).

Figure 11: Outline/patterns of oedema. A and B. Pre- and post-contrast imaging. Meningioma showing a well defined margin. C and D. Pre- and post-contrast imaging. Glioma showing ill defined margins. E. Vasogenic oedema involving white matter only, in a case of olfactory groove meningioma (tumour not shown).

f. Vessels (Figure 8) Focal increased density in a vessel may indicate recent thrombosis. Aneurysms are rarely identified on unenhanced CT but may be seen following contrast enhancement.

g. Blindspots (Figure 9) Extracranial soft tissues may show pathology which is incidental to the symptoms for which imaging was performed. The sella, skull base and orbits are frequent blind spots.

2. Characterising lesions

a. Density (Figure 10) The CT density of different tissue types can be predicted (Fig 10a-e). In practice, tumour types cannot be precisely differentiated from density alone, but certain tumours (meningioma, lymphoma, medulloblastoma) tend to be higher density than others (glioma). Detection of calcium and blood is often easier on CT than MRI.
b. Outline/ patterns of oedema (Figure 11)
Many benign tumours have well defined margins whereas aggressive tumours and inflammatory processes tend to be ill-defined. This does not apply universally and some rapidly growing tumours may appear well-defined.

Vasogenic oedema is caused by disruption of the blood brain barrier around inflammatory, neoplastic or ischaemic lesions. This is usually confined to white matter. Cytotoxic oedema is caused by ischaemia and involves grey and white matter.

c. Contrast enhancement (Figure 12)
Contrast enhancement is caused by a combination of increased vascularity and disruption of the blood brain barrier. Patterns of enhancement clarify the extent of abnormality and can help differentiate disease processes.

d. Mass effect (Figure 13)
Recognising the consequences of mass effect is important as shift between intracranial compartments can result in rapid clinical deterioration because of pressure on vital structures.

3. Recognising artefacts (Figure 14)
The appearance of artefacts is learned through experience but a few examples are provided in Figure 14.

Conclusion
Neurological CT continues to develop rapidly with new technology becoming available almost every year. CT is not only the first line neurological imaging investigation, but also provides excellent diagnostic information which is complementary to other techniques such as MRI. More advanced applications of CT such as angiographic imaging and quantification of perfusion have not been covered in this article, but are becoming more widely used in clinical practice.

References
Encephalitis, a guide

‘Encephalitis, a guide’ comes in an interesting format. Slightly reduced A4 size, turned lengthways to open on strong spiral rings and holding a DVD in a pocket inside the end cover immediately says that this is a book production out of the ordinary. The pages open up easily, displaying two pages at a time and the dividers, well known to all with bulging ring folders, invite further exploration. Certainly a lot of time and trouble has been taken with the design. There are 6 sections. The style is clear, headings and paragraphs, highlights and encapsulated ‘pearls of wisdom’ appear with the same even editorial style. No obvious multi-author text here!

Section 1 – ‘Encephalitis the Illness’
Section 2 – ‘The Effects of Encephalitis’
Section 3 – ‘Specialists and Services’
Section 4 – ‘Returning to Normal Life’
Section 5 – ‘Further Reading’

The factual presentation of the book is softened by the very personal approach of the DVD starring Martin Kemp, Patron to the Encephalitis Society, patients and families whilst not holding back on medical detail good or bad. The DVD ends with the place and purpose of the Encephalitis Society.

The book itself will find a place in every medical library. Professionals will be able to read it quickly. Patients and their families will read and re-read the book. So who is the real target audience? There is a timely reminder for the professionals in Section 6 – ‘paths through a Medico-Legal Investigation’ in other words ‘how to start a medico-legal investigation in the rare cases where recovery is compromised by poor medical care there is a legal entitlement to financial compensation’.

So the book is for families of Encephalitis sufferers from the Encephalitis Society who clearly mean business! If it makes us, the professionals, more aware of encephalitis in terms of early diagnosis, treatment and rehabilitation process then the book has succeeded. It will be improved upon one day but certainly it will serve its purpose for a long time to come. Incidentally, I like the design and layout and as DVD’s go, it is well produced.

Reviewed by: Dr Rudy Capildeo, Brentwood Hospital, Brentwood, Essex, UK.

Cognitive Neurology: A Clinical Textbook

Neurology in the UK sits within the group of physicianly specialties. Most UK neurologists, in order to get MRCP, will have been on medical rotations comprising cardiology, gastroenterology etc. While this can be helpful when managing a sick neurological in-patient with multi-system disease, it must be admitted that a knowledge of some medical subspecialties is of little value to the neurologist most of the time. Due to the quite separate training structures for neurology and psychiatry, most neurologists will not, however, have done any psychiatry, not even a six month SHO post. This is regrettable given that a knowledge of psychiatry is so helpful and indeed necessary to practise good neurology. It is particularly unfortunate, however, for those who practise in the borderland between neurology and psychiatry, namely cognitive neurology.

Due to the traditional lack of neurologists in Britain, many neurological diseases are managed by non-neurologists. As neurology has expanded, this has led to some jostling with other specialties for conditions such as stroke and Parkinson’s. Most dementia is assessed and treated by old age psychiatry, who have multi-disciplinary teams well set up to manage the overall requirements of dementia patients and their families. This raises the question of what role, if any, does neurology have in the dementia. Traditionally, it is younger patients and those with atypical presentations who are seen in neurology. This is mainly due to neurology having better access to investigation in order to refine the diagnosis, but services for the ongoing management of dementia patients tend to be in old age psychiatry settings.

Focal cognitive deficits, whether due to stroke or tumour, or cognitive deficits due to disease, such as multiple sclerosis or epilepsy, are managed by the relevant neurological subspecialist.

Memory and cognitive disorders clinics have sprung up in a few of the larger neurology centres, and are mainly concerned with investigating memory complaints, the bread and butter being differentiating early dementia, mild cognitive impairment and psychological causes of impaired memory. A few of the more esoteric focal cognitive disturbances also present in such clinics.

This multi-author text has been written to provide an introduction to the field. After an introductory section on investigation (neuropsychology, imaging and neurophysiology), there is a useful section with chapters on the various focal deficits. In addition to covering the usual suspects (memory, language, etc.) there is a helpful chapter on neurobehavioural disorders after stroke.

The dementias section has a helpful chapter on differential diagnosis, followed by descriptions of the four commonest causes of dementia. These chapters achieve a useful balance between the clinical features and underlying pathology.

There then follows a section covering areas sometimes neglected in other cognitive texts, namely trauma, MS, epilepsy, schizophrenia and depression. Lastly, to illustrate that diagnosing cognitive disturbances is not an academic exercise, there follows a useful section on drug treatment and rehabilitation of cognitive disorders.

The book is excellently referenced. While bigger tomes covering this area exist (e.g. Rizzo & Eslinger), this book nevertheless provides a very useful introduction to cognitive neurology. It will be of use to neurologists, psychiatrists, psychologists and others interested in this field.

Reviewed by: John Greene, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK.
Greenfield’s Neuropathology 8th Edition

Greenfield’s needs no introduction within the field of neuropathology. It is the primary reference text referred to by training and practising neuropathologists alike. This edition co-incidentally marks the 50th anniversary of the first edition of the book. The editors, from both sides of the Atlantic, have drawn upon the expertise of over seventy contributors from across the globe. More than half of these contributors are new. The result is a dramatic refinement and re-working of the previous edition, which itself stood out as a remarkable text.

The stated aims of this book are “to provide an authoritative, comprehensive account of the pathological findings in neurological disease, their biological basis and clinical manifestations…underpinned by a clear description of molecular and cellular processes…” The editors have clearly achieved these aims with flourish. Much of the historical data has been removed, and replaced by recent research data, providing a modern and up-to-date stance. A reference text is usually used to provide an answer to a specific question, or to help the reader understand a single disease entity. This book is distinct in its digestability. It is possible to read a chapter in one sitting and retain much of it, and that is a real achievement in writing.

This new edition contains more illustrations and tables, many of the former are new and all are good quality. The images are also available on the dvd, and, usefully, the publishers state that they can be used for non-web-based teaching as long as the copyright label is visible. This makes the dvd incredibly useful for personal use, and also a fantastic resource for lectures.

This new edition has a different focus. The introductory chapters from previous editions have been sacrificed for more detail elsewhere. The ophthalmic chapter has also been withdrawn. These changes are an understandable evolution. While the value of the lost chapters is undeniable, they are well represented in other books. The result is a collection of approachable chapters that stand alone as complete authorities and are arranged in a logical order.

This edition has an altered layout. The book still feels pleasant to handle, and has maintained its “quality feel”. Page numbering is now continuous between the two volumes, preventing the frustration of picking up the wrong volume that I personally suffered with in the last edition. The new edition is a similar length to its predecessor. The index, however, is shorter and only present at the back of volume II. This, and the lack of the page-keeper ribbons are two oversights that are minor compared to the book’s many strengths.

This new-and-improved Greenfield’s has exceeded my expectations and is likely to take up a much-used place on many Neuropathologists’ bookshelves. It is also invaluable to other clinicians within the field, enhanced by the closer links with clinical data that this edition enjoys. I imagine the shift in emphasis towards genetic and research data, often from animal models of disease, will increase the readership of this book to include more from the non-clinical research community. There is simply nothing in paper-form that compares with it.

Reviewed by: Nicki Cohen, SpR Neuropathology, Southampton, UK.

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Future directions of the Association of British Neurologists

As Neurologists, we face many pressures and changes in our working practices. Guidelines, recommendations, reports, new models of inpatient and outpatient care, re-appraisal and revalidation, inundate us. At the same time, the daily work remains. This is the heart of what we do and love: in our clinics, in the laboratory, and on the wards. It is easy to feel swamped by external guidelines and protocols.

Reflecting our daily lives, the Association of British Neurologists (ABN) must also juggle many activities to pro-actively influence the direction of our work. If we are passive, we have no voice in shaping our future, or the future care of our patients.

The ABN must provide and facilitate education, communication, research, and guidelines for Neurologists, both in their clinical and scientific work.

Education is central to the function of the ABN. Its focus is to organise stimulating and inspiring meetings. These gatherings bring together basic science, clinical practice and new developments with national and international speakers, scientific presentations, teaching sessions, along with platform presentations and posters from members at all stages of their careers. The structured components of meetings need to be complemented by informal discussions amongst academic and clinical neurologists at both consultant and training stages of their careers.

To further this aim, and with support of most members, the ABN is planning an exciting new development. From 2009, we will hold a single five-day meeting instead of the former bi-annual three-day meetings. We are providing a forum for greater depth of teaching and scientific sessions, along with more time for informal discussions and exchange of ideas.

The first of these new-look meetings will be in Liverpool from 22-26 June, 2009, at the Arena and Convention Centre. This Joint meeting with the Spanish Society of Neurology (original meeting held 1-2 June 1990, Valencia) will hold a single five-day meeting instead of the former bi-annual three-day meetings. We are providing a forum for greater depth of teaching and scientific sessions, along with more time for informal discussions and exchange of ideas.

The ABN will also continue to facilitate education through regular news in ACNR, and distribution of the JNNP quarterly supplement ‘Neurology in Practice’ and Practical Neurology to members. The Association supports neurologists with travel expenses for research projects and educational visits to economically less-developed countries. As a result, the ABN Africa Neurology Interest Group has produced a CD entitled ‘Neurology Teaching Resource for African students’.

At this turbulent time, future consultants continue to have an active representation on Council, and the Association provides administrative support to ABN Trainees. The need for ABN input into sound training programmes cannot be overestimated: this is our future. The Training and Education Committee (TEC) advises the Association on matters relating to undergraduate education, postgraduate training, continuing professional development and relevant issues in Europe. The Association is pro-active in Knowledge-based assessment, and provision of student bursaries and annual prizes.

2008 sees a face-lift for the ABN website. It will be more attractive, and easier to use. New features will include an improved online forum for members and useful information for the general public and other medical societies. The monthly electronic newsletter updates members on developments.

The Association administers and funds the British Neurological Surveillance Unit, assisting researchers investigating rare neurological conditions on a national scale. The electronic system has been upgraded in 2008, greatly enhancing its use. The Clinical Research and Academic Committee (CRAC) will now link this to their work, building on this potential for research in a number of other neurological conditions. The ABN is part of the Joint Neurosciences Council. It plays an active and important role in practice guidelines, working with the Royal College of Physicians and NICE to do so, and with the Department of Health, for example in the implementation of the National Service Framework for Long Term Conditions.

The Services and Standards Committee looks at standards of neurological care, organisation and distribution of neurological services in the United Kingdom, including manpower monitoring, standards development and advice regarding commissioning. We have great opportunities for taking a lead in acute neurological care, such as stroke. The Committee’s function is also vital in protection of consultant time for professional development and research.

The ABN is an important facility for us, and a unified focus. Things are changing and we have a choice between shaping our future and our patient care, or having its shape imposed on us. Your participation is vital. The ABN is taking a pro-active role in a new format for revitalised annual meetings, an improved website and enhancement of research potential. These changes are essential to stimulating excitement about being a neurologist, in keeping abreast with the enormous changes in both the science and practice of neurology and in facilitating communication between members and our community.
Key symposia:

- Management of stroke: from bench to guidelines
- The molecular era of neuromuscular disorders
- From pathophysiology to new treatments in epilepsy
- Parkinson’s disease: advances in diagnosis and treatment
- Critical issues on MS diagnosis and treatment

The congress programme includes interactive case presentations, 23 teaching courses, 16 workshops organised by the ENS subcommittees, practical breakfast sessions in clinical neurophysiology and selected scientific sessions in the form of oral sessions, poster sessions (guided poster walks) and satellite symposia.

Abstract Submission Deadline: February 11, 2009
Early Registration Deadline: April 22, 2009

For further information please contact:
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The Institute of Child Health, Guilford St, London
◆ All you need to know about the limbic system
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110th Meeting of the
British Neuropathological Society

January 7-9th 2009
Venue: Institute of Child Health,
Guilford Street, London WC1N 1EH

Symposium: “New perspectives in Parkinson’s Disease”.
Organiser: Professor Tamas Revesz,
UCL Institute of Neurology, London, UK
Speakers: Professor Andrew Lees, London, UK
         Professor David Brooks, London, UK
         Professor Maria Spillantini, Cambridge, UK
         Professor Nicholas Wood, London, UK
         Professor Patrik Brandin, Lund, Sweden

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◆ Full programme of talks and posters
◆ The Society Dinner to be held at The Honourable
  Society of Gray’s Inn

We welcome Neuropathologists, Neurologists and Neuroscientists to a
meeting attracting a wide range of speakers from the UK and abroad.
Trainees in Neuropathology and Neurology are particularly encouraged
to attend. Join us for a full academic programme with an excellent
opportunity to meet and discuss professional and academic matters.

Full details: http://www.bns.org.uk/
The annual conference of the British Association for Cognitive Neuroscience (BACN) was held from September 1st-3rd at the University of Swansea (picture). The association is home to UK cognitive neuroscientists from a variety of backgrounds, ranging from psychophysiologists (BACN emerged from the British Psychophysiology Society) to those with a background in neuroimaging. The Association prides itself on the friendly and supportive atmosphere of its annual meetings and is particularly welcoming to scientists at the start of their career. International visitors this year travelled as far as from Taiwan and Kenya.

The first symposium was devoted to the auditory basis of language learning impairments, especially those associated with specific reading disability (SRD) and specific language impairment (SLI). Dr. Halliday (UCL, Oxford) showed impaired auditory processing in SRD but preserved ERP evidence for auditory cortical maturation. Dr. Baker (UCL) reported that ERP indices of delayed auditory processing in SLI were correlated with reduced basal ganglia grey matter density. Dr. Hamalainen (Cambridge) reviewed behavioural and ERP studies of sound processing in SRD and concluded that deficits in sound onset perception were the most consistent deficit. A keynote from Prof Scott (UCL) reviewed recent progress in mapping brain networks for speech comprehension and their link to speech production. Of interest was the sensitivity of the left anterior temporal cortex to speech intelligibility and the involvement of a posterior superior temporal region to sensorimotor integration, which supports the notion of a dual stream model of speech perception.

They reported altered brain function (EEG) and slower speed of cognition but normal neurological functions in those children living above 3500m.

The second symposium was dedicated to recent advances in cognitive neurophysiology (ERP and EEG). Representatives from major ERP system manufacturers demonstrated their newest developments, ranging from automated artefact correction methods (Gutberlet, Brain Products), low resolution electromagnetic tomography (van de Velde, ANT) to multimodal image registration and volume conductor models for EEG source localisation (Fuchs, Compumedics Neuroscan). The developers of Statistical Parametric Mapping (SPM) gave an introduction to Dynamic Causal Modelling (DCM), a novel SPM extension for hypothesis-driven exploration of electrophysiological and neuroimaging data (Kilner, UCL). The plenary talk by Prof Stam (Amsterdam) was dedicated to the emerging application of modern network theory to disruption of functional brain networks in human brain diseases such as Alzheimer’s disease, schizophrenia and epilepsy.

Among the numerous high quality open-platform presentations, the study by Dr Hogan and colleagues (Southampton, UCL, Universities of Granada and Western Australia, Univalle and UPSA Bolivia) deserves a mention. They used modern cognitive neuroscience methods (psychometrics, ERP and EEG) in a large-scale field study in Bolivia to evaluate the adaptation of cognition to high-altitude living in infants and children. They reported altered brain function (EEG) and slower speed of cognition but normal neurological functions in those children living above 3500m.

This year’s BACN conference was jointly organised with the Welsh Institute for Cognitive Neuroscience, which held its inaugural meeting in Swansea. Its symposia included advances in the cognitive neuroscience of memory. The plenary lecture was given by Dr Wilding (Cardiff) on ERP studies of memory retrieval. Of particular interest was also the report by Vann and colleagues (Cardiff, Bristol, Manchester) on a large cohort of patients with colloid cysts and variable degree of fornix and mammillary body damage which resulted in selective loss of memory recall with preservation of recognition abilities.

Torsten Baldeweg,
UCL Institute of Child Health,
University College London (UCL), UK.

The next Annual meeting will be held from 21st-23rd September 2009 in London, at the UCL Institute of Child Health. Symposia will cover topics such as neural plasticity in cognition and advances in multimodal neuroimaging. Those interested in hosting a symposium at this meeting should contact T.Baldeweg@ich.ucl.ac.uk.
Falling asleep on the outskirts of London and waking in the Scottish highlands on board the Caledonian Sleeper was a perfect start to the last ‘old-style’ ABN conference, held in the beautiful setting of Aviemore.

A stroke symposium reflected the current political importance of this area, and the increasing engagement of neurologists in stroke medicine. Dr Malcolm Macleod discussed the reasons for the failure of translation from successful treatments in animal models of stroke into clinical benefits in patients. He dramatically illustrated the impact of low power, lack of randomisation and blinding and failure to model co-morbidity in animal models. These problems, equally significant in animal models of neurodegeneration, suggest the need for radical changes in the approach to pre-clinical therapeutic studies. Dr Ed Littleton presented the results of an audit of the introduction of a 24 hour thrombolysis service. The audit found that paramedics and A&E triage nurses find it difficult to use the ‘FAST’ assessment system appropriately, and suggests that models of thrombolysis delivery need to be carefully designed to avoid negative impacts on neurology training.

The short scientific papers given by members were of consistently high quality. Dr J Jones presented three-year follow-up data from the trial of altezumab (Campath) in early active multiple sclerosis. A clear reduction in progression of disability in the treated group may herald an important breakthrough in MS treatment from the ongoing Phase III trials. Dr Sarosh Irani described the clinical features and natural history of sub-acute encephalopathy associated with NMDA receptor antibodies in a cohort of 31 patients. This syndrome appears to have a very distinctive phenotype. Presentation with psychiatric symptoms is followed by seizures, reduced conscious level, autonomic instability and movement disorder. Further studies of antibody levels in disease control groups will establish the specificity of the diagnostic assay.

The ABN medal was presented to Dr John Morgan-Hughes. He provided an inspiring overview of his scientific legacy, which is particularly remarkable for having been achieved whilst working as an NHS clinician in a small research group.

A highland banquet and ceilidh, as well as a mini-triathlon, allowed delegates to make the most of their time in Scotland. Despite looking forward to the new format of a five day annual conference, many will look back fondly on our last small and traditional ABN meeting.

Biba Stanton, ABN Trainees Committee Secretary, Royal Free Hampstead NHS Trust.

The Association of British Neurologists’ 2008 autumn meeting in Aviemore was followed by a unique sporting event. Some 23 members of the Association took part in the first ever ‘ABN mini-triathlon’, which benefitted from glorious sunshine, spectacular scenery and the stunning backdrop of the Cairngorm Mountains.

Competing over a ‘modified super-sprint’ distance, the entrants swam sixteen lengths of the hotel pool, before exiting the hotel past startled onlookers, to pick up their pre-hired mountain bikes from the car park. They then cycled over a 6.5 km course which included a fairly punishing uphill component, a short rocky technical section – which clearly favoured experienced mountain bikers - and a fast forest track back to the hotel for the cycle-run transition. A final 2.5km run through the woods of the Rothiemurchus estate returned the competitors to the finish line at the Hilton Coylumbridge.

The event was won by Dr Richard Davey, consultant neurologist in Wakefield with a time of 30 minutes 30 seconds. Dr Ursula Schultz from Oxford was a close second, arriving at the finish line some 58 seconds later. Entrants included a past President of the ABN, Professor Charles Warlow, who completed the entire course in a commendable 61 minutes. All the finishers were awarded a medal and a commemorative T-shirt.
With the profusion of neurological congresses around the world, many dedicated to specialist and subspecialist interests, it is perhaps inevitable that a general neurological congress will not be the forum at which investigators will wish to announce startling new findings. It may be said that the emphasis is more on encouraging us, the foot soldiers of neurology, to retain the information which is already in the public domain, with any gain of new information being a bonus. Hence, the arena of focused workshops and satellite symposia, amongst which the following proved helpful to my wanting cognitive powers of factual retention. The limitations of functional imaging in the trigemino-autonomic cephalalgias, showing activation of the neural pain matrix, were emphasized, prior to a stimulating account of the possible place for neurostimulation in these conditions. One literature review has suggested >60% efficacy in chronic drug-resistant patients, but the drawbacks are many: weeks to months before improvement occurs, the risk of adverse effects from surgery, the generator or the electrodes, and the current absence of any double-blind studies (1 apparently ongoing in France). The latter will require homogeneous patient selection criteria, agreed assessment methods and long-term follow-up.

A lecture on advances in genetics in movement disorders demonstrated how these findings have increased understanding of disease pathogenesis, for example in Parkinson’s disease, specifically in terms of mitochondrial dysfunction and misfolded protein toxicity. Parkin, PINK1, and DJ1 all encode proteins which normally protect neurones from oxidative stress and regulate mitochondrial morphology, whilst α-synuclein and LRRK2 proteins become misfolded and aggregate. The possible importance of autophagy, a constitutive lysosomal mechanism to protect neurones, was introduced: knockout of this process in animal models leads to neurodegeneration, which may be relevant in the rare Kufor-Rakeb disease.

Some conditions which are only occasionally seen in the general neurology clinic, and hence in congress symposia, made welcome appearances. A focused workshop on myotonic dystrophy covered the genetics of DM1, wherein the correlation between increased trinucleotide repeat size in the DMPK gene and disease severity does not necessarily permit accurate prognosis, with some families showing a variable phenotype despite the same number of repeats. Missed diagnosis of both DM1 and DM2 seems common because the presentation is often to other, non-neurological, specialties, in DM1 including ophthalmology, cardiology, OB&G, and paediatrics, although neurologists are not immune from error, the differential diagnosis of DM2 encompassing inflammatory myopathies, mitochondrial myopathies, acid-maltase deficiency, FSH dystrophy, fibromyalgia and iatrogenic myopathy. In view of the systemic nature of DM1, a plea was made to rename the disorder as ‘Batten-Gibb syndrome’ since these individuals described the systemic features in 1909, the same year that Steinert emphasised the muscular problem which has formed the basis for disease nomenclature ever since.

Treatment of Friedrich’s ataxia, hitherto entirely symptomatic, was the focus of a drug-company sponsored symposium. Idebenone may have effects on the cardiomyopathy and possibly also the neurological features. The increased understanding of disease pathogenesis, stemming from the identification of the underlying genetic mutations and the functional roles of frataxin, has prompted the possibility of disease-modifying treatment, for example with iron chelation.

As a medical student in the last century, I got interested in the possible viral pathogenesis of multiple sclerosis. The subject still lives, with a symposium on herpes viruses looking at their potential causative roles in MS (EBV, HHV6, VZV), Behcet’s disease (HSV1), and Bell’s palsy (HSV1). Furthermore, it has been noted that similar brain areas are injured in herpes simplex encephalitis and Alzheimer’s disease, with anecdotal reports of HSV1 infection in dementia brains, and in vitro and in vivo evidence of increased Aβ production associated with HSV1. CSF PCR remains the gold standard for diagnosis of herpes simplex encephalitis, although may be negative if testing is very early or late in the disease course. The role of steroids remains uncertain, no randomised study having yet been performed, although a retrospective study (JNNP 2005;76:1544-9) found poor outcome in patients who did not receive steroids.

Amongst the more than 1500 scheduled poster presentations, I noted two describing parkinsonism of late onset in type 1 Gaucher’s disease: this may apparently look identical to idiopathic Parkinson’s disease. In a French national prospective study, nearly a quarter of the patients developed parkinsonism. For those seeking advances in the treatment of neurological disease, three posters looked at the use of prolonged-release ropinirole (PREPARED study) which seems to produce better symptom control and levodopa sparing in advanced PD than standard ropinirole (I have already had enquiries from a patient).

A careful study (double-blind, placebo-controlled, crossover) from Newcastle suggested a possible role for levetiracetam in the treatment of MS intention tremor, but I was less convinced by a report from elsewhere of transcranial magnetic stimulation for MS ataxia. A trial from Iran of rivastigmine for memory disorder in MS found equal improvement in both treatment and placebo-control arms of the study, perhaps inevitable in a brief (12-week) study; the severity of the pre-treatment impairments in the MS patients did not appear to be mentioned. In a case study from Greece, rituximab was reported to be useful in neuromyelitis optica, in agreement with a larger study from the Mayo Clinic now being published (Arch Neurol).

For those for whom all this activity was too much, and a brief snooze required at the back of one of the lectures rooms, solace was at hand in the form of a poster documenting ‘Inspiration from dreams in neuroscience research’, relevant to two Nobel Prize Winners, Otto Loewi and John Eccles. As a Nature paper from 2004 stated, sleep inspires insight!

The History of Medicine session focused on the work of Santiago Ramon y Cajal, describing how his painstaking studies using the Golgi stain allowed him to develop the neurone theory, in succession to the reticular theory of Golgi, wherein the neurone was viewed as an autonomous unit in contact but not in continuity with other neurones, an infinitely fragmented system. The history tour visited the old Hospital de San Carlos, where there are several atmospheric lecture theatres including the Aula Ramon y Cajal where he used to teach; there is also a garden dedicated to him and a statue, the latter somewhat solemn and linear. Another Spaniard, lesser known outside his own country, Pedro Lain Entralgo (1908-2001), formed the subject of Ivan Iniesta’s lecture which reviewed many of the works of this medical historian, and to whom the final words of this review may be given: ‘the history of medicine is memory at the service of hope’.

AJ Larner, Walton Centre for Neurology and Neurosurgery, Liverpool, UK.
As the biggest demyelination show in the world rolled into Quebec this September, Montreal struggled a little with the infrastructure required to support the hoards but her charm just about won through in the end. Despite its size, the meeting itself was a surprisingly modest affair. There were no scientific fireworks declared here, but WCTRIMS offered a nice review of the progress that has been made on several fronts over the past 12 months.

The teaching courses were popular and successful. It’s a reflection of how far things have come in the past year that the advances in our understanding of aetiology; both in determining relevant environmental exposures, and even more strikingly the genetic contributors to susceptibility, are now part of “teaching” sessions rather than being trumpeted from on high as “key breakthroughs”. It is also to the great credit of the investigators involved that the important lessons learned during the long struggle to reach this point have led to a sober and realistic view of how far we still have to go, and our ability to take those next steps.

In descriptive pathology, Esther Breij received a frosty reception from the audience in response to her inability to replicate the heterogeneity of the Luccinetti lesional classification system. ‘Different selection criteria’ was the uneasy but diplomatic conclusion. Perhaps MS is yet one disease! The great pathogenic debate of our times remains as an uneasy stand-off between the primary inflammationists and the primary degenerates. However the debate as presented here meekly conceded the premise that inflammation drives the disease and resolved to a question of whether it primarily targets glia versus simultaneously targeting glia and neurons. Regardless, the more fundamental inflammationists declaring MS to be a self-limiting disease may have overstepped the mark and were met by a gloriously Gallic non plussed response from the gathered audience. Happily, this response was also given to the other lot when their case was put forward. The Quebec charm may have contributed, or perhaps a communal sense was evidenced that descriptive pathology may still have the upper hand in declaring lesions that the MRI doctors miss, and the final say in taxonomy, but is fundamentally limited by its cross sectional approach. The natural historians can help, as can the therapists, but there was little news from either to further illuminate. The therapists tell us that Copaxone has now mirrored the BENEFIT, CHAMPS and ETOMS trial results in delaying time to second event; and that the quest for oral DMTs is nearing a position of having something to say for itself, but the repair doctors still have nothing meaningful to offer to patients. For them (and I am one), achieving a more fundamental understanding of how remyelination occurs (and why it fails) remains the issue – there were no breakthroughs to be found in Montreal but steady progress in the roles of OPC guidance molecules, axo-glial interactions that contribute to axonal injury, and the metabolic microenvironment determinants of injury response.

The natural historians were not completely silent, telling us that while prognostication for the individual patient remains challenging, being non-white and young predicts a more severe early disease course. Interestingly, it seems that disease course is relatively stereotyped in both site and severity during the initial attacks; perhaps reflecting undiscovered genetic disease course modifiers. The Ebers group presented their evidence that the HLA DRB1*01 allele may have a beneficial effect on disease course through examination of allelic discordance in sib-pairs. This (admittedly limited) progress was briefly encouraging, however the mighty MSBase team were subsequently to confirm our worst suspicions that early disease is indeed the hardest for which to prognosticate, and that EDSS in the mid-ranges remains a lottery for the long-term outcome even at advanced disease duration time points. At least they were able to console us with news that (as we intuitively always suspected) patients who remain relatively free of disability, or who are heavily disabled at advanced disease durations, tend to remain as they are.

But with statements such as the last, one cannot get away from the limitations of our assessment measures. Poor responsiveness to real change at the ends of the ruler used to measure change might account for predictability in a fundamentally unpredictable disease. So are we any better, or will we be any better in the future at measuring our patients’ disease burden? Not really is the conclusion from the evidence presented here. There are no new clinical trials, and our MRI surrogates still present problems. Maria Pia Sormani tackled the problem by using clever statistics to bridge the clinical-radiological chasm; establishing ‘ecological correlation’ between accumulation of new T2 lesions and annualised relapse rates in the published trials, but concluding that we haven’t yet reached the stage where ‘causal correlation’ can be established at an individual patient level. This leaves us in an interesting position where measuring T2 lesion load isn’t pointless, but neither is it yet validated as clinically meaningful! The speaker’s frustration was clear about the difficulties in advancing this work due to the possessiveness of investigators and companies over outcome data. Our intellectual isolationism means that replicating these promising initial efforts for atrophy measures is presently beyond even what the redoubtable Dr Sormani and her team can face. As an imaging footnote, the MR modalities embarrassingly still labelled as ‘new’ (MRS, MTR etc.) continue to search for their role as useful and interpretable endpoints. We will see.

In the absence of anything exciting to report, the therapists offered a fascinating meta-perspective on why there is nothing exciting to report – it seems that all the relapses have gone! The annualised relapse rate in placebo arms of DMT trials has fallen from around 0.8 in the pivotal studies to current levels of around 0.3. As a result, it has become hard in these difficult times to prove that our wonderful new treatments work, further compounded by the fact that those pesky ethicists won’t let us use placebo arms anymore. So what is an MS researcher to do? The development of new ‘platform’ based study designs (where lengthy trials are performed to test the addition of novel vs placebo treatments onto existing best practice) seemed too sensible to ever catch on. The audience quietly reflected on the prospects of big Pharma accepting this vision for a brave new
February, 2009; London, UK.

The 11th national conference for all those working with patients suffering from dementia will be taking place in London in February next year. The 2-day conference, organised in association with the British Journal of Hospital Medicine, will give delegates a review and update on current developments in the dementias; in the fields of research, investigations, clinical care and service and policy issues.

The conference is aimed at all professionals involved with dementia, including old age psychiatrists, neurologists, geriatricians and physicians with an interest in the elderly; mental health service workers and team members, community nurses, hospital nurses and practice nurses.

Programme advisors Professor Tom Arie, CBE, Professor Emeritus of Health Care of the Elderly, University of Nottingham and Professor Alistair Burns Head of School of Psychiatry & Behavioural Sciences, Professor of Old Age Psychiatry, University of Manchester, have put together a programme of speakers from all over the country. Professor Arie and Professor Burns have worked together producing the programme for this national conference since the first conference took place in 1999.

The first day will begin with a key-note speech from Professor Ray Tallis, University of Manchester, looking at the philosophical aspects of dementia and consciousness. Following a range of talks on clinical topics, the day will conclude with a discussion on ‘The best paper on dementias that I have read in the past year’, with contributions from all speakers on day 1.

Professor Sube Banerjee, Professor of Mental Health and Ageing at the Institute of Psychiatry, London, will open the second day of the conference with a talk on the National Dementia Strategy: where are we now? Following talks on Psychotherapy and dementia and An overview of nursing care of people with dementia, Professor Roy Jones, Director of the Research Institute for the Care of Older People in Bath, will outline drugs which are currently in clinical trials, and look at the potential these may offer for future treatments.

In the afternoon of day 2, Professor Edzard Ernst, Laing Chair of Complementary Medicine from Peninsula Medical School, Exeter, will outline the place of complementary medicine in the treatment of patients with dementia, and then Professor Elaine Perry, Professor of Neurochemical Pathology, Institute for Ageing and Health, Newcastle University will talk about Plant power: the potential of phytotherapeutics. These will be followed by a discussion of case histories and opinions on alternative treatments, which should make for an interesting debate.

The conference will provide participants with an update on ongoing clinical, research, organisational and policy developments that are taking place in the field of dementia, a forum to share and exchange views with eminent faculty speakers, a chance to look at progress in old age psychiatry and its service provision, and an update on the management of clinical conditions and practices associated with dementia, e.g. agitation and depression, as well as the chance to debate and discuss ‘alternative therapies’ for dementia.

For further information, or to book a place, go to www.mahealthcareevents.co.uk or phone 020 6501 6762
Recent Advances in the Treatment of Focal Dystonia: Update from the Dystonia Europe 2008 conference

The Dystonia Europe 2008 conference (October 17–19 in Hamburg, Germany) was the first major meeting to achieve an exclusive focus on dystonia. It brought together experts from Europe and North America to discuss the latest developments in clinical practice and research.

The conference included a number of posters reviewing the latest findings from an extensive clinical development programme for Xeomin® in the treatment of focal dystonia. Xeomin® is a new formulation of botulinum neurotoxin type A that has recently been launched in the UK. Unlike existing therapies, Xeomin® is free from complexing proteins and can be stored at room temperature (≤25°C) prior to reconstitution.

The posters presented data demonstrating that Xeomin® is effective and well tolerated in the treatment of cervical dystonia and blepharospasm and challenged the concept that complexing proteins may play a positive role in the stability and diffusion of botulinum toxin once injected.

Comparable outcomes of Xeomin® (Botulinum neurotoxin type A) and Botox® in the treatment of focal dystonia

The results from two key studies were combined in a pooled analysis by Professor Jost from the Deutsche Klinik für Diagnostik in Wiesbaden, Germany. The studies represented the two largest, randomised, double-blind, active-controlled clinical trials of botulinum neurotoxin conducted in patients with spasmodic torticollis or blepharospasm.

In both studies, patients with a stable therapeutic response to Botox® were randomised to either maintain their existing Botox® dose or be switched to a matched dose of Xeomin®. Due to the differences in LD50 assays used by different manufacturers, unit doses are specific to individual products and are not interchangeable. In these studies a conversion factor of 1:1 was used, such that if a patient was stable on 100 (Allergan) units of Botox® they were switched to 100 (Merz) units of Xeomin®. In the two studies a total of 384 patients received Botox® and 379 patients received Xeomin®.

In this combined analysis, Xeomin® was found to be equally as efficacious as Botox® across a number of physician and patient assessed parameters.

- 72.8% of the investigators rated Xeomin® as ‘good’ or ‘very good’ (compared with 68.4% for Botox®) (Figure 1).
- 76.6% of patients indicated a moderate or marked improvement – including the complete abolition of symptoms – with Xeomin® treatment (compared with 72.0% with Botox® treatment) (Figure 2).
- 89.5% of patients indicated they had improved with Xeomin® treatment (compared with 85.8% with Botox® treatment) (Figure 2).
- The duration of treatment effect was almost identical in each treatment group (110 days with Xeomin® and 111 days with Botox®).
- The efficacy of Xeomin® and Botox® were shown to be statistically comparable.

Contra-indications:

Known hypersensitivity to Botulinum neurotoxin type A or to any of the excipients, generalised disorders of muscle activity (e.g. amyotrophic lateral sclerosis or dystonia) or other serious diseases which result in peripheral neuromuscular dysfunction and in targeted muscles which display pronounced weakness or atrophy. Reduced blinking following injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration. Careful testing of corneal sensation should be performed in patients with previous eye operations.

Undesirable effects: The following adverse reactions were reported with Xeomin®:

- Frequency by indication defined as: Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100).
- Injections into the orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. The initial dose should not exceed 25 U per eye but this can be subsequently increased. The total dose should not exceed 100 U every 12 weeks. Spasmodic torticollis: Inject using a 25-30 gauge needle in superficial muscles or 22 gauge into deeper musculature. Xeomin® may only be used if swallowing, speech or respiratory disorders arise. Xeomin® should be used with caution if bleeding disorders occur, in patients receiving anticoagulant therapy, patients suffering from amyotrophic lateral sclerosis or other diseases which result in peripheral neuromuscular dysfunction and in targeted muscles which display pronounced weakness or atrophy. Reduced blinking following injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration. Careful testing of corneal sensation should be performed in patients with previous eye operations.

Marketing Authorisation Holder: Merz Pharmaceuticals GmbH, 60048 Frankfurt Main, Germany. Further information available from: Merz Pharma UK Ltd., 260 Centennial Park, Elstree Hill South, Elstree, Hertfordshire WD6 2SR. Date of revision of test: January 2008. Xeomin® is a registered trademark of Merz GmbH.

Article publication sponsored by Merz Pharma UK Ltd.
In a further poster, Professor Roggenkämper et al from the University Eye Clinic in Bonn, Germany presented a sub-analysis of his original paper comparing outcomes of blepharospasm patients switched from Botox® to Xeomin®.6

In this prospective, multicentre, randomised, double-blind, active-comparator study, 300 patients with blepharospasm were randomised to receive either Xeomin® or Botox® at a maximum respective dose of 50 units per eye.

Within the study protocol, patients with a stable therapeutic response to Botox® were randomised to either maintain their existing Botox® dose or be switched to a matched dose of Xeomin®. As previously stated due to the differences in LD50 assays used by different manufactures, unit doses or be switched to a matched dose of Xeomin®. As previously stated due to Botox® were randomised to either maintain their existing Botox® dose

units per eye.

When the pH increased towards one of physiological value, releasing the

dissociation of the 900kDa neurotoxin complex at various pH values was

leading to clinical failure.6 The authors conceded that complexing proteins may be required to stabilise first generation neurotoxin formulations. However, they argued that based on these data, the concept that complexing proteins may stabilise the neurotoxin once injected into the muscle or inhibit its diffusion one minute.5 Others point out that complexing proteins have no proven therapeutic benefits, and may actually play a role in the formation of antibodies that neutralise botulinum neurotoxin, thereby potentially leading to clinical failure.7

In a poster at Dystonia Europe 2008, by Eisele et al, an analysis of the dissociation of the 900kDa neurotoxin complex at various pH values was presented. The researchers found that the 900kDa neurotoxin complex, which was stable at a pH of 6, rapidly separated into several fractions when the pH increased towards one of physiological value, releasing the 150kDa neurotoxin from the protein complex with a half-life of less than one minute.3 The authors compared the efficient release of the 150kDa neurotoxin following injection in physiological conditions with the extended time to onset of therapeutic effect, which is typically measured in days.9 The authors conceded that complexing proteins may be required to stabilise first generation neurotoxin formulations. However, they argued that based on these data, the concept that complexing proteins may stabilise the neurotoxin once injected into the muscle or inhibit its diffusion must now be questioned.

The authors concluded that the rapid release of the 150kDa neurotoxin from the 900kDa complex under physiological conditions aids in the understanding of comparable clinical efficacy and safety demonstrated between Xeomin® and a botulinum complex containing complexing proteins.7

Clinical safety of Xeomin®: a meta-analysis

Xeomin® is indicated for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults. Data presented in a poster by Dr Benecke from the Neurology Clinic in Rostock, Germany, presented the results of a meta-analysis of safety data from six controlled clinical trials (in patients with blepharospasm, cervical dystonia, post-stroke upper limb spasticity and healthy volunteers) involving 539 Xeomin®-treated subjects, 442 Botox®-treated subjects and 75 placebo-treated subjects.4

The meta-analysis demonstrated that (Table 2):1

• The incidence, type, and severity of adverse events (AEs) were similar in the Xeomin®-treated patients and the Botox®-treated patients.
• The incidence of serious AEs was low across all studies and all treatment groups.
• Most AEs reported with either Xeomin® or Botox® were mild or moderate in severity.
• The most common AEs (with an incidence ≥1%) in patients with cervical dystonia were dysphagia (a well-known injection site reaction), back and skeletal pain, and muscle weakness. The most common AEs in patients with blepharospasm were ptosis (another well-known injection site reaction), abnormal vision and back pain.
• Clinical laboratory evaluations showed no clinically-relevant safety signals.

The poster also included an analysis of the post-marketing surveillance from an estimated 62,000 patients treated with Xeomin® in clinical practice worldwide since the launch of Xeomin® in 2005. The authors reported that no new safety concerns had been identified, and that the spontaneous reports identified from the surveillance either related to already well-known safety concerns and/or were considered unlikely to be related to Xeomin® by the treating physician. The authors concluded that Xeomin® has a positive risk:benefit ratio, with a tolerability and safety profile comparable to Botox®.4

Complexing proteins and BTX-A preparations: therapeutic benefit?

The role and clinical significance of complexing proteins in first-generation neurotoxin products has been the subject of ongoing debate, with some researchers suggesting that they may be required for product stability, to prolong neurotoxin persistence, and inhibit neurotoxin diffusion into adjacent tissues. Others point out that complexing proteins have no proven therapeutic benefits, and may actually play a role in the formation of antibodies that neutralise botulinum neurotoxin, thereby potentially leading to clinical failure.4

Table 1: Mean change from baseline in BSDI scores three weeks after injection

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number of patients</th>
<th>BSDI Score</th>
<th>Number of patients</th>
<th>BSDI Score</th>
<th>Number of patients</th>
<th>BSDI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>45</td>
<td>-0.84</td>
<td>29</td>
<td>-1.00</td>
<td>100</td>
<td>-0.83</td>
</tr>
<tr>
<td>Female</td>
<td>90</td>
<td>-0.86</td>
<td>66</td>
<td>-0.67</td>
<td>75</td>
<td>-0.97</td>
</tr>
<tr>
<td>≤65 years</td>
<td>73</td>
<td>-0.27</td>
<td>66</td>
<td>-0.67</td>
<td>75</td>
<td>-0.97</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>52</td>
<td>-0.86</td>
<td>66</td>
<td>-0.67</td>
<td>75</td>
<td>-0.97</td>
</tr>
</tbody>
</table>

Table 2: Summary of adverse events reported with XEOMIN® (NT 201) and Botox® (BTXCo) in a pooled analysis of all studies.

<table>
<thead>
<tr>
<th>AEs (%)</th>
<th>BTXCo (n = 442)</th>
<th>XEOMIN® (NT 201)</th>
<th>Placebo (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with AEs (%) of intensity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>98 (18.2)</td>
<td>81 (18.3)</td>
<td>13 (17.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>63 (13.7)</td>
<td>43 (9.7)</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>9 (1.7)</td>
<td>5 (1.1)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Subjects with AEs (%) leading to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Values are n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE: Adverse events; SAE: Serious adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Product stability analysis

Unlike first generation neurotoxin complexes which require an effective cold-chain for storage and distribution, Xeomin® does not need to be refrigerated. An unopened vial can be safely transported and stored at room temperature conditions, of up to 25°C, for up to 3 years. To validate these storage conditions Grein et al. performed a series of tests as defined in the ICH Q1A(R2) guideline on stability testing of drug products. Samples were stored at a range of temperatures including 5°C and 25°C and underwent a series of temperature stress tests. Samples were tested in real time and under accelerated conditions using qualified incubators with narrow temperature tolerances. The authors confirmed that there were no detrimental effects on the quality of Xeomin® across a range of temperature stress tests and that storage of Xeomin® at ambient conditions (25°C) for up to three years will not negatively affect its activity. The authors concluded that, in the case of Xeomin®, complexing proteins are not required to achieve product stability.12

References


Xeomin® prescribing information can be found on page 39.

KEY POINTS SUMMARY

Studies presented at Dystonia Europe 2008 (17–19 October 2008, Hamburg, Germany) have confirmed that:11,12
• Xeomin® is an effective treatment for the symptoms of spasmodic torticollis and blepharospasm
• Patients switched from their existing Botulinum toxin therapy to Xeomin® experienced comparable efficacy and tolerability
• Post-marketing surveillance of an estimated 62,000 patients worldwide has not identified any new safety concerns for Xeomin®
• Prior to reconstitution Xeomin® can be stored without refrigeration (±25°C) for up to three years

Side-effects of anticonvulsants

In this study the authors take a fairly rigorous view of the studies they are assessing and in the tradition of meta-analyses many less rigorous studies are excluded. They identified adverse effects which occurred more frequently (+) or significantly more frequently (+++) in the treatment arm than in the placebo arm. I have added weight change and my impression of some older drugs in purple. The study supports the view that most drugs have a similar range of toxic effects but that lamotrigine is cleaner than the others with regard to cognitive effects. Sodium channel blocking drugs all seem to cause ataxia and diplopia – as is commonly recognised in clinical practice. Topiramate only caused a trend towards depression; it is more of a problem in my clinical experience. This is representative of the problem with this study, which is that the less common but severe side effects such as major depression and psychosis are not common enough to reach clinical significance in the studies used, so that the differences between drugs are under-emphasised. It is nevertheless interesting to see that the similarities are greater than the differences; perhaps we should just toss a coin. – MRAM
Zaccara G, Gangemi PF and Cinocotta M.
Central nervous system adverse effects of new anti-epileptic drugs. A meta-analysis of placebo-controlled studies.
SEIZURE 2008;17:405–21.

DEPRESSION: prevention of perinatal depression

If you identify depression in the last trimester of pregnancy, is there anything you can do to promote remission.. and avoid all the harmful consequences of poor bonding with the child? Well, intervention X reduces the prevalence of depression at 6 months after birth from 53% to 23%, and this effect is sustained for 12 months. Not bad. But what is remarkable is that agent X is not a drug, but cognitive behavioral therapy; more surprising still it is administered not to the affluent eloquent but to unselected mothers in rural Pakistan. People charmingly referred to as “Lady Health Workers” had a brief training and then administered one session of CBT every week for 4 weeks in the last month of pregnancy; three sessions in the first postnatal month, and nine 1-monthly sessions thereafter. The cost of this is not laid out. Sadly for the investigators, none of the infant-related outcomes differed significantly. Good on the Wellcome for funding work on an unglamorous condition, with negative pharmaceutical value, amongst overlooked peoples. – AJC
Rahman A, Malik A, Sikander S, Roberts C, Creed F.
Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial.

HEADACHE: transformed migraine and analgesia

Two point five percent of those with episodic migraine converted to chronic (transformed) migraine over a one year period. This report, which won the Harold G Wolff Lecture award for 2008, comes from the massive 120,000 population study (the American Migraine Prevalence and Prevention Study),

Xeomin® prescribing information can be found on page 39.
which followed 8219 (6.8%) migraineurs over five years. Of those migraineurs identified in 2005, 209 (2.5%) developed chronic migraine by 2006. This figure seems low, but the follow up was only one year, and this is likely to be at least one explanation. Unsurprisingly, higher baseline headache frequency was a risk factor for transforming to chronic migraine. Use of barbiturates and opiates were associated with increased risk of chronic migraine, even after adjusting for co-variates including baseline headache frequency and severity. Triptans were not associated with increased risk of transition from episodic to chronic migraine. Non-steroidal anti-inflammatory drugs (NSAIDs) had a variable effect, with a protective effect at low to moderate headache frequency, but an increased risk of transition to chronic migraine at high levels of monthly headaches. It is important that chronic migraine is now a recognised entity, as some previous classifications excluded those with daily headache from migraine; leaving them in a diagnostic and treatment limbo. What are the implications for us in the United Kingdom? Codeine use in headache patients is common, although barbiturate use is not. Other workers, particularly Diener, recognise opiate users as a refractory group of chronic migraineurs. It is often difficult to persuade these patients that the uncomfortable period of opiate withdrawal is worth it. Preventing this situation is important. The association between opiate use and chronic migraine is a strong argument for adequate and early prophylaxis to reduce the transformation from episodic to daily headache. There is still much work to be done on this, starting in primary care and emergency departments. – HAL

Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB.
Acute Migraine Medications and Evolution From Episodic to Chronic Migraine: A Longitudinal Population-Based Study.
HEADACHE
2008;48:1157-68.

PARKINSON’S DISEASE: deciphering the dyskinesias

The development of levodopa induced dyskinesias (LIDs) is inevitable in patients with Parkinson’s disease as they advance with their condition. The basis of these drug induced movement disorders has been debated for many years and has become a topic of even further interest since the description of graft induced dyskinesias in patients transplanted with fetal ventral mesencephalic tissue. One of the most popular hypotheses relates LIDs to a failure of dopamine storage in the remaining nigral dopaminergic terminals such that levodopa cannot be buffered and dopamine is released synchronously with each levodopa dose. Of late a second major theory has been evolving that relates LID to the mishandling of levodopa in 5HT nerve terminals in the striatum which then releases dopamine as a false transmitter again in an unregulated way. In other words the released dopamine cannot be taken up and thus there will be a pulsatile delivery of dopamine in time with the oral administration of the drug. This in turn will act via the postsynaptic dopamine receptors to effect downstream changes with the induction of long term LIDs. Lee et al have now added another part to the story using 6 hydroxydopamine lesioned rats. They show that once there is a greater than 60% denervation of the striatum, LIDs can be induced and this can be attributed to terminal sprouting from the intact nigrostriatal dopaminergic neurons. These sprouted terminals are capable of releasing dopamine but lack the necessary apparatus to transport and store it and thus contribute to LIDs. Thus once a threshold is passed when terminal sprouting with dopamine release is the dominant mode of synaptic dopamine delivery to the striatum, LIDs ensue. This paper contains an interesting series of experiments designed to confirm this observation and whilst not proven as the mode by which these dyskinesias occur in patients, does nevertheless help explain why LID’s may occur. However the reality is, as the authors themselves acknowledge, that this is probably only one of several different mechanisms, all of which contribute to LID’s and which in theory are all amenable to treatment.

STROKE: Functional Electrical Stimulation can reduce unilateral spatial neglect after stroke

Spatial inattention or ‘neglect’ to the contralesional side is common in acute stroke. This deficit resolves in many cases but there are a small proportion of patients in whom the problem persists. Since severe and persistent spatial neglect prevents this sub-group of patients from regaining independence after stroke there is much interest in finding rehabilitation strategies to treat it. Unilateral spatial inattention is considered to be a syndrome because a variety of symptoms have been identified. This makes development of effective treatments that can be applied to very severely affected patients a challenging task and to date long-lasting treatments have been lacking. A proof of principle study reported recently in Neuropsychological Rehabilitation may be the start of a new lead in resolving this important clinical problem. Functional electrical stimulation (FES), a treatment that is normally applied to people with hemiparesis to activate muscles and bring about movement, was applied in this case to see if proprioceptive information on the contralesional side would improve patients’ spatial awareness. The treatment was tested on four severely affected right hemisphere stroke patients and in three of them the treatment effects were remarkable. An A-B-A treatment-withdrawal design was used. Each patient was assessed weekly on a number of clinical tests over the baseline period of 4 weeks. A treatment phase immediately followed by a phase in which the stimulation was applied to the wrist/finger flexors and extensors of the forearm on the ipsilesional side (4 weeks). After that a second treatment phase stimulating the contralesional forearm (4 weeks) was delivered followed by a withdrawal phase (4 weeks) and a final follow up assessment 16 weeks after that. Thus the design allowed the effects of stimulation on spatial neglect to be separated from its effect on arousal by applying the electrical stimulation first to the arm on the ipsilesional side, before it was applied to the arm contralateral to the lesioned hemisphere. In three of the four patients the time series plots of performance remained consistently poor until the stimulation was applied to the contralesional side, then performance was greatly improved and was maintained through to the follow up assessment. The fourth patient did not change in performance throughout. The authors suggest that FES activates a proprioceptive map within the right parietal lobe. The level of activation is otherwise diminished by the lesion and that this both increases awareness of the contralesional side and stimulates functional interactions with the environment. This is a very simple treatment to apply in clinical practice and deserves further investigation to see if clinically meaningful results can be found in a larger study. – AJT

Harding P, Riddoch MJ.
Functional Electrical Stimulation (FES) of the upper limb alleviates unilateral neglect: A case series analysis.
NEUROPSYCHOLOGICAL REHABILITATION
2008, DOI: 10.1080/09602010701852610

HEADACHE: olfactory hypersensitivity and migraine

This report gives another fascinating example of changes in the brain of patients with migraine. Visual hypersensitivity in migraine, and related physiological and blood flow changes, are well documented. Although less common, olfactory hypersensitivity both during and between migraine is established, and odours may trigger migraine. This study examined regional cerebral blood flow, in headache-free periods, in migraineurs with documented olfactory hypersensitivity. Regional cerebral blood flow in the left piriform cortex and antero-superior temporal gyrus was increased in 12 subjects in periods without odour stimulation, compared to 11 controls. During odour stimulation, migraineurs showed increased activation of frontal (left inferior and right middle frontal gyri), temporo-parietal regions, posterior cingulate gyrus and right locus coeruleus. These studies show a change in cerebral blood flow in these odour-sensitive migraineurs “at rest” and during activation. The authors point out that the study doesn’t tell us the physiological mechanism of the changes. We don’t know whether this represents a chronic change in cerebral flow consequent on migraine, or a primary change in the regulation of olfactory responses. It also doesn’t tell us the mechanism of olfactory hallucinations as a migrainous aura, which must be distinguished from ictal olfactory aura by the clinical setting, in particular their duration. It does add to the evidence that there is something different both about how people with migraine process sensory input, and how their brain is between headaches. – HAL

Demanquy G, Royet JP, Mick G, Ryvlin P.
Olfactory hypersensitivity in migraineurs: a H2150-PET study.
CEPHALALGIA
PARKINSON’S DISEASE: dopamine and the sleeping brain

Proper sleep is important for the well being of us all and problems with inappropriate sleepiness during the day can be a feature of many neurological conditions, perhaps best described in Parkinson’s disease (PD). In a recent issue of the Journal of Neuroscience two papers touch on the role of dopamine in this whole process. In the first of these papers Volkow et al study the effect of sleep deprivation on the dopaminergic systems in the striatum and thalamus using PET. These workers took healthy subjects and studied them after a night of normal restful sleep and again after a night of sleep deprivation. They looked at the dopaminergic system with two PET ligands-11C-Cocaine which labels dopamine transporters and 11C raclopride (RAC) which labels mainly D2 receptors. They found that RAC (but not 11C-Cocaine) binding in the striatum and thalamus was decreased after sleep deprivation and that this reduction correlated with the level of tiredness, fatigue and cognitive dysfunction. The decrease in RAC signal implies that sleep deprivation increases dopamine release as this PET ligand competes with endogenously released dopamine (or alternatively that sleep deprivation alters dopamine receptors directly). This suggests that in an attempt to maintain arousal, in the face of lost sleep the dopaminergic system at these sites upregulates anyway, although proving that this is truly the case will require further work. However, Qu et al show that, in mice, modafinil induced wakefulness is dependent on dopamine receptors- D1 and D2 in particular. This is demonstrated using standard pharmacological studies as well as the D2 receptor deficient mice. These studies therefore tell us that dopaminergic stimulation underlies wakefulness, or at least contributes to it in the face of either sleep deprivation or the administration of modafinil. However, how this exactly plays out with other systems involved with sleep and wakefulness is not clear, nor why some diseases with dopaminergic loss, such as PD, cause problems with somnolence. Nevertheless it does show that this most basic of processes is complex and that dopamine is integral to its regulation. — RAB Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Wong C, Ma J, Pradhan K, Tomasi D, Thanos PK, Ferré S, Jayne M.


Qu WM, Huang ZX, Xu XH, Matsumoto N, Urade Y.

Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil.


STROKE: thrombolysis after 3 hours…?

*** RECOMMENDED

Just when we had just got our heads around thrombolysis for those lucky 4% of patients who get to an appropriate place within three hours of their stroke, the goalposts may be moving. There have been several previous suggestions that intravenous tPA might be effective beyond the 3 hour window established by the NINDs study. But this is the most convincing evidence to date. The Safe Implementation of Treatments in Stroke (SITS) study is not a trial that intravenous tPA might be effective beyond the 3 hour window established by the NINDs study. But this is the most convincing evidence to date. The Safe Implementation of Treatments in Stroke (SITS) study is not a trial. Nevertheless it does show that this most basic of processes is complex and that dopamine is integral to its regulation. — RAB Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Wong C, Ma J, Pradhan K, Tomasi D, Thanos PK, Ferré S, Jayne M.


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Changes in the Editorial Board of Journal of Neurology

At the end of the year, there will be a change of Chief Editors in the Editorial Board of the Journal of Neurology. The long-time Board Member David Miller, London, will step down as Joint Chief Editor and will be succeeded by two new Chief-Editors, Dr Roger Barker, Cambridge, and Gérard Said, Paris. Prof Thomas Brandt, Munich, will continue to serve as Joint Chief-Editor of the Journal.

Roger Barker is Reader in Clinical Neuroscience at the University of Cambridge, UK, Honorary Consultant in Neurology at the Cambridge Centre for Brain Repair, and founding Editor of ACNR. He trained in neurology at Cambridge and at the National Hospital in London. His main area of research is in neurodegenerative and movement disorders, in particular Parkinson’s and Huntington’s diseases.

The Journal of Neurology is an international peer-reviewed journal which officially represents the European Neurological Society (ENS) and provides a source for publishing original communications on clinical neurology and related basic research. For more details visit www.jn.org
Contact: Springer, Uschi Kidane, T. +49 6221 487-8166, E. uschi.kidane@springer.com

MRC grant successes for UCL

Professor Ken Smith who works in the Department of Neuroinflammation is one of the recipients of recently announced Medical Research Council awards, totalling £10.6 million.

UCL has been awarded eight out of the 20 available grants made by the MRC to fund research to develop better models of human disease – worth an estimated £4.2 million to the university.

The awards are one component of a strategic initiative to target bottlenecks in translational research, as part of the MRC’s Translational Research Strategy, and Professor Smith’s award of £761,372 is to develop therapies, and a strategy for their translation to treat early lesions in multiple sclerosis.

For more information contact: www.ion.ucl.ac.uk

ABN Case Presentation Competition

Congratulations to Kate El Bouzidi who won the case presentation competition at the recent ABN Autumn meeting in Aviemore. Kate won the £100 prize from ACNR for her case presentation ‘A case of reflex epilepsy associated with food-related stimuli.’ Kate trained in Edinburgh and came across the case when she was a neurology house officer at the Department of Clinical Neurosciences at the Western General Hospital. She is now a core medical trainee and hopes to specialise in Infectious Diseases. The case will be reported in a future issue of ACNR.

Dr Sean O’Sullivan wins the Charles Symonds Prize

Dr Sean O’Sullivan from the Reta Lila Weston Institute of Neurological Studies has been awarded the Charles Symonds Prize by the Association of British Neurologists (ABN). This prize was awarded for the best platform presentation at the ABN Spring Meeting 2008. This prestigious and highly competitive award was based on research investigating clinical outcomes of progressive supranuclear palsy (PSP) and multiple system atrophy (MSA).

The study, using clinical data from pathologically-proven cases of PSP and MSA from the Queen Square Brain Bank, has been published in the journal ‘Brain’ in May 2008. Dr O’Sullivan said “This perspective of the whole disease course should help clinicians to anticipate patterns of disease progression in their management of people with PSP and MSA. Our findings may also furnish historical control data for future interventional studies”.

For more information contact: www.ion.ucl.ac.uk

Winners at the BMA Book Awards

Champagne corks have been popping at Cambridge University Press, following a string of successes at the 2008 BMA Book Awards. In the Neurology category, two titles garnered praise: Dizziness (Bronstein) was Highly Commended by the judges, whilst Frontotemporal Dementia Syndromes (Hodges) was also Commended.

The Press also scooped first prizes in Cardiology (Cardiac Arrest: The Science and Practice of Resuscitation Medicine, Paradis et al) and Mental Health (Handbook of Liaison Psychiatry, Lloyd and Guthrie).

Richard Marley, publishing director for Life Sciences, Earth Sciences and Medicine, said, “I’m delighted by our success this year. These awards are a welcome and public endorsement of the quality of our content, as well as recognition of the dedication and effort that the authors and Press staff put into making these books happen.”

For more information visit www.cambridge.org/medicine

Manson Publishing is honoured and pleased to announce that Understanding Neurology by John Greene and Ian Bone has won the Neurology prize in the BMA Medical Book Competition 2008. Richard Dawkins (right) is pictured presenting the award to Michael Manson.

The Judge commented, “Well-written with excellent diagrams and illustrating case studies. I particularly liked the visual field testing photos. Excellent - I would buy this and will recommend it …… a practical neurology textbook.”

To order please contact Manson Publishing Ltd, 73 Corringham Road, London NW11 7DL. T. 020 8905 5150, F. 020 8201 9233, W. www.mansonpublishing.com

We have two copies of the book to give away to ACNR readers. Simply email your details to editorial@acnr.co.uk or write to ACNR, 1 The Lynch, Mere, Wiltshire BA12 6DQ by 12th December and the first two names out of the hat will win.
VIMPAT (lacosamide), a new epilepsy treatment for adults with partial onset seizures

Vimpat (lacosamide), a new adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older, has been launched in the UK. The efficacy of VIMPAT® as adjunctive therapy at recommended doses (200mg/day, 400mg/day) was established in three multicentre, randomised, placebo-controlled clinical trials with a 12-week maintenance period. Overall, the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200mg/day and lacosamide 400mg/day, respectively. In addition, results from an open-label extension study demonstrate long-term retention on Vimpat.

Lacosamide was generally well tolerated when added to a broad range of AEDs, with no clinically relevant drug-to-drug interactions seen with the most commonly used AEDs. For further information T. 01753 447 950, E. ian.weatherhead@ucb-group.com

High-speed spectral acquisition with a single scan

Nikon Instruments’ A1 series of confocal laser scanner systems has now been further enhanced by the launch of the A1Si spectral detector option which provides fast 32-channel spectral imaging with speeds of up to 16 fps at 512 x 64 pixels and real time spectral unmixing. This cell-friendly system offers the ultimate solution for reducing light exposure during multiprobe studies, capturing full spectral data in just one fast scan.

Fast fluorescence unmixing during image acquisition is possible, with a 512 x 512 pixel, 32-channel image unmixed in less than one second. Coupled with high-speed spectral imaging, a clearly resolved image with no crosstalk between closely overlapping fluorophore emissions can be created in real time.

In addition, a new virtual filter function freely utilises the 32 channels, providing the flexibility to handle any new fluorescence probes. Desired spectral ranges can be selected and the total intensity of each range adjusted individually. Broader band spectral imaging is achieved on the A1Si, which requires only one pass of the laser to capture all the spectral data in the sample. For further information contact Nikon Instruments Europe, T. 0208 247 1718, E. info@nikoninstruments.eu W. www.nikoninstruments.eu

MRI imaging leads pioneering neurological research

The MRC Cognition and Brain Sciences Unit (CBU) in Cambridge is an internationally renowned centre for research in the field of cognitive neurosciences. Its ground breaking studies into the brain function of vegetative state patients has provided invaluable insight into diagnosis pathways and the consequent care of the ‘locked-in’ patient.

The CBU is renowned for its clinical studies of vegetative state patients conducted in collaboration with colleagues at the Wolfson Brain Imaging Centre at Addenbrooke’s Hospital which houses an identical MAGNETOM Trio MRI scanner from Siemens. Led by Dr Adrian Owen, the team recently looked into the brain activity during vegetative state, a condition where patients who emerge from a coma appear to be awake, but show no signs of conscious awareness. Traditionally, diagnosis for vegetative state is based on patient reaction to external stimuli i.e. noise or smell, but approximately 40% of patients are misdiagnosed as vegetative when in fact they may retain some degree of conscious awareness.

Using functional MRI (fMRI), a neuroimaging technique to study activity in the brain, researchers were able to test the neural responses of patients diagnosed as vegetative. The findings suggested that residual cognitive capabilities were apparent in some cases and these allowed such patients to communicate their thoughts simply by modulating brain activity. When asked to process and respond to specific commands, the scanned images of apparent vegetative state patient’s brains were indistinguishable from those of a healthy volunteer. The clinical studies took place at the Wolfson Brain Imaging Centre where patients with brain injuries are examined for evidence of preserved cognitive function.

For more information visit W. www.siemens.co.uk/healthcare

MicroMaxx® ultrasound system helps injured Manchester City players back to fitness

Manchester City Football Club’s doctor has chosen the SonoSite MicroMaxx® point-of-care ultrasound system to assess players’ muscle injuries regularly and ensure that they are back on the field as quickly as possible.

“I liked the SonoSite MicroMaxx system because it is compact and portable,” said Dr Mark Whitaker, the club doctor. “I thought it would be ideal in an environment like our treatment room. We use it mainly to help modify our rehabilitation programme; the pressure is on to keep the player fit and trained, and the MicroMaxx gives us the confidence to push players on if we can see that there is no significant injury. Ultrasound imaging has allowed us to play some of our footballers in senior games that we would not have played before. The fact that we’re looking at it in a scientific way gives the footballers huge reassurance too.”

Dr Whitaker is involved in Manchester PCT’s tier two musculoskeletal service and feels the potential for quick, early diagnosis of community patients using the MicroMaxx will ensure patients are treated in the most appropriate manner.

For more information T. 01462 444 800, E. europe@sonosite.com W. www.sonosite.com
**Donation of Brain Surgery System to ‘Ukraine 3000’**

Elektta recently announced a donation of Leksell Stereotactic System® for minimally invasive brain surgery to the International Charitable Foundation ‘Ukraine 3000’ for which Mrs Kateryna Yuschenko, wife of the President of Ukraine is the prime guardian. This donation was presented in the presence of Her Majesty Queen Silvia of Sweden, founder of the World Childhood Foundation. The system will be used for treating a wide range of brain disorders at one of the leading neurosurgery hospitals in Ukraine.

Elektta is a human care company pioneering significant innovations and clinical solutions for treating cancer and brain disorders. The Leksell Stereotactic System is a system for advanced stereotactic neurosurgery, a minimally invasive form of surgery which allows the surgeon to take biopsies and treat brain disorders with the highest precision and minimal trauma to the patient. It has become the system of choice in the whole world for treating functional diseases, for example Parkinson’s disease. The total value of the donated system, which also includes training at one of Elektta’s renowned European reference sites, is around EUR 70,000. 

For more information T. +46 8 587 254 27, E. lena.hoglund@elektta.com

**Elektta extends its line of Stereotactic Treatment Solutions at 2008 Congress of Neurological Surgeons Annual Meeting**

Elektta recently introduced Extend™*, a new stereotactic treatment programme that lets neurosurgeons and radiation oncologists apply the power and precision of Gamma Knife® surgery to an even broader class of targets in the head and neck.

For more than twenty years, Leksell Gamma Knife® surgery has been the gold standard in intracranial radiosurgery. With its new relocatable frame and support for fractionated treatments, the Extend program now provides the ability to treat large or critically located targets in the head and neck that were previously untreatable with Gamma Knife surgery.

The result is an exciting crossover solution for neuro-oncology that combines Elektta’s recognised excellence in stereotaxy with its proven expertise in radiation medicine.

“When faced with lesions that are too large or too critically located to be safely treated in a single session, Extend enables clinicians to divide the radiation dose over multiple treatments,” says Mark Symons, Senior Vice President, Stereotactic Business Unit. “It also includes the most precise non-invasive fixation option available, allowing both neurosurgeons and radiation oncologists to treat more patients with greater confidence.”

For further information E. Joanne.Latimer@elektta.com

**Carl Zeiss introduces Axio Scope.A1**

Life science research and routine applications will benefit from the flexibility and adaptability of the Axio Scope.A1 microscope from Carl Zeiss. The modular design allows users to configure a microscope to their precise needs, safe in the knowledge that changes and upgrades can be implemented easily and quickly if demands change.

The Axio Scope.A1 is ideal for pathology, histology, cytology, microbiology, environmental research, molecular biology, plant physiology, developmental biology or genetics laboratories. Users have a choice of 23 stands, LED or halogen illumination, a retro-fittable fluorescence system, phase contrast, differential interference contrast (DIC) and the PlasDIC technique developed by Carl Zeiss, available in an upright routine microscope for the first time.

The LEDs for fluorescence applications are fully integrated into the stand and offer a long service life with reduced running costs, excellent image contrast and ease of use. The newly-developed Ergo-stage can be locked along the y axis in exactly the position that a user finds most comfortable and convenient and an extended specimen area is adjustable for specimen heights of up to 110 mm. If one of the optional Vario stands is chosen, larger specimens of up to 380mm may be examined.

For further information E. micro@zeiss.co.uk

**Image capture at two wavelengths simultaneously**

Faster, simpler imaging of cellular events is now possible as Nikon’s Eclipse Ti Series inverted microscopes can capture images at two different wavelengths simultaneously, using dual cameras. Accelerating image acquisition while maintaining full frame resolution, the system is ideal for FRET and the capture of rapid dynamic cellular events using calcium or other ion-targeted probes, ratio probes, dual emission ratio-metric dyes etc.

The two cameras are positioned on the Eclipse Ti’s back and side ports. Perfect registration between the two cameras is assured on installation to ensure that no information is lost during imaging. No further realignment or specialised alignment software is required. Even when the intensity difference between wavelengths is large, high-quality images can be captured by adjusting camera sensitivity for each wavelength.

Nikon has partnered with Andor to offer their full range of high-performance iXon+ and Luca EMCCD cameras. The iXonEM+ 897 back-illuminated EMCCD camera offers high sensitivity, low noise and rapid frame rates giving distinct speed advantages in FRET applications. The cameras are optimised for use with Nikon’s dedicated NIS-Elements software for image capture, processing and analysis. Unified integrated control of microscope and cameras offers significant benefits for cutting-edge live cell research. NIS-Elements C for confocal microscope applications includes FRET analysis software as standard.

For further information contact Nikon Instruments Europe, T. 0208 247 1718, E. info@nikoninstruments.eu W. www.nikoninstruments.eu/a1/
NanoSight speeds Leeds University’s characterisation of wear debris in orthopaedic implants

NanoSight Limited, the nanoparticle characterisation company, has announced that the University of Leeds is committed to the use of their Nanoparticle Tracking Analysis system for the study of wear debris generated in orthopaedic implants.

Dr Joanne Tipper of the Institute of Molecular and Cellular Biology studies nanoparticle sized polymer debris, specifically polyethylene generated first in vitro (to prove its presence) and then in vivo (from tissue around failed hip replacements). The objective was first to characterise the particles and then to consider their bioactivity and effect on cell responses.

New software from Carl Zeiss automatically extracts biologically relevant data from micrographs by combining high-resolution fluorescence imaging and complex image analysis. Developed with the high content screening specialist, Cellomics®, the AxioVision ASSAYbuilder module inherits 15 years of expertise in the field of High-Content Analysis (HCA) to offer the most reliable method of high content analysis and screening.

ASSAYbuilder supports the examination of processes in cells, between cells or in small organisms and will be especially useful in studies such as apoptosis, cytotoxicity, molecule localisation and translocation, cell differentiation and proliferation, GFP expression, and GPCR signal pathways. For example, users can analyse the position of the cytoskeleton or determine the proportion of living and dead cells in a sample. Furthermore, it allows the characterisation of cell cultures, the identification of new cellular starting points for the development of future medication, and the identification of lead substances in small or medium screenings in pharmaceutical research.

The ease-of-use means that researchers can concentrate on efficiently planning further experiments and publishing their results rather than having to become expert at the fundamentals of image analysis. However, the software module is sufficiently powerful to cope with even highly sophisticated requirements, such as subpopulation analyses.

For more information visit W. www.zeiss.co.uk

Anaesthetic team evaluation reveals the Lightman® detects inaccurate Pulse Oximeter probes

The Electrode Company Ltd, inventors of the world’s first patient in adaptive noise cancellation in pulse oximetry produce the Lightman®. This market-leading pulse oximeter sensor tester was the subject of a successful presentation at the summer scientific meeting of the Anaesthetic Research Society in June.

The presentation was made by Dr C Dunstan, on behalf of the team from The Anaesthetic Departments of the University Hospital Wales and the Clinical School of the Royal Gwent Hospital, Newport. In it they concluded that “the Lightman® can detect the faulty probes” and ‘facilitate the removal of faulty probes from the clinical environment.’

Siemens, high performance partner of GB Rowing, and The Stroke Association have launched the Stroke for Stroke campaign 2008 aiming to highlight the positive benefits of regular exercise and help educate and inform the public about strokes and stroke prevention. In 2007 the initiative raised £40,000.

“Each year an estimated 150,000 people in the UK will have a stroke. This puts a big pressure on the NHS in terms of identifying symptoms quickly so that an accurate course of treatment can be prescribed. Prevention has to go hand in hand with expanding the provision of diagnostic and treatment facilities available to patients. Access to rapid CT scanning upon admission to hospital is essential to diagnosis and determination of treatment. This is especially important as some patients may benefit from a reperfusion therapy that is only currently administered within a three hour window from the onset of symptoms. This treatment not only helps to save lives, it can also dramatically improve the quality of life to survivors of this condition,” states Peter Harrison, Director of Imaging & Oncology Systems at Siemens Healthcare.

Four time Olympic gold medallist, Sir Matthew Pinsent CBE is backing the campaign.

For more information visit W. www.siemens.co.uk/healthcare

Automatic High-Content Image Analysis Simplifies Cell Research

Dr Tipper has made measurements on different materials used for implants (metal-metal, ceramic-ceramic and polymer-polymer). She has had good results on model metal and ceramic particle systems. The metal nanoparticle debris are typically in the range of 20-80nm which is particularly suited to NTA when compared to light scattering methods. The NTA results compare extremely well with high resolution FEG-SEM, and these particles compare well with clinically generated wear debris. NTA has proven to be much easier to use, requiring minimal sample preparation time compared to SEM and then providing results in minutes. When studying polymers, NTA produced excellent results for polyethylene particles in the 100-800nm range, again when compared to FEG-SEM.

For more information visit W. www.nanosight.co.uk

‘Oar’ inspiring stroke campaign launched

NanoSight® found 11% of the probes to be significantly inaccurate leading to ‘possibly serious consequences’ or ‘unnecessary and perhaps harmful intervention’.

For more information T. 01291 650279, W. www.electro.co.uk

The presentation which also featured lively Q&A session showed that in a previous hospital survey at Newport, the Lightman® found 11% of the probes to be significantly inaccurate leading to ‘possibly serious consequences’ or ‘unnecessary and perhaps harmful intervention’.

Cell Research

The Lightman® is designed to detect pulse oximeter sensor accuracy. The Anaesthetic Team decided to evaluate its predictions against a blood gas analyser. The evaluation showed that sensor errors are larger at lower saturation levels. Blood gas analysis confirmed errors of up to 9%. A lively Q&A session followed the presentation which also showed that in a previous hospital survey at Newport, the Lightman® found 11% of the faulty probes’ and ‘facilitate the removal of faulty probes from the clinical environment.’

New software from Carl Zeiss automatically extracts biologically relevant data from micrographs by combining high-resolution fluorescence imaging and complex image analysis. Developed with the high content screening specialist, Cellomics®, the AxioVision ASSAYbuilder module inherits 15 years of expertise in the field of High-Content Analysis (HCA) to offer the most reliable method of high content analysis and screening.

ASSAYbuilder supports the examination of processes in cells, between cells or in small organisms and will be especially useful in studies such as apoptosis, cytotoxicity, molecule localisation and translocation, cell differentiation and proliferation, GFP expression, and GPCR signal pathways. For example, users can analyse the position of the cytoskeleton or determine the proportion of living and dead cells in a sample. Furthermore, it allows the characterisation of cell cultures, the identification of new cellular starting points for the development of future medication, and the identification of lead substances in small or medium screenings in pharmaceutical research.

The ease-of-use means that researchers can concentrate on efficiently planning further experiments and publishing their results rather than having to become expert at the fundamentals of image analysis. However, the software module is sufficiently powerful to cope with even highly sophisticated requirements, such as subpopulation analyses.

For further information E. micro@zeiss.co.uk
COPAXONE® (glatiramer acetate)
PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. Indication – Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients who have had at least two relapses in the preceding two years before initiation of therapy. Dosage and administration – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. Children (<18 years) Not recommended. Elderly No specific data. Impaired renal function No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. Contra-indications – Known allergy to glatiramer acetate or mannitol (excipient). Pregnancy Special warnings and precautions – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dypnea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and re-inject such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchoospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. Interactions – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. Pregnancy and lactation – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. Undesirable effects – Injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, lipatrophy). An immediate post-injection reaction (one or more of vasodilatation, chest pain, dypnea, palpitation, tachycardia) may occur within minutes, reported at least once by 41% of patients receiving Copaxone compared to 20% of patients receiving placebo. >1%: Nausea, anxiety, rash, sweating, chills, face oedema, syncope, vomiting, lymphadenopathy, oedema, nervousness, tremor, herpes simplex, skin benign neoplasm, eye disorder, vaginal moniliasis. Rarely: Anaphylactoid reactions, convulsions, shifts in white blood cell counts, elevated liver enzymes (with no evidence of clinical significance) and skin necrosis at injection sites. Please refer to the SPC for a full list of adverse events. Overdose – Monitor, treat symptomatically. Pharmaceutical Precautions – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Legal Category – POM. Package Quantity and Basic NHS Cost – 28 pre-filled syringes of Copaxone: £545.59. Product Licence Number – 10921/0023. Further Information – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. Date of Preparation – May 2008.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.


Date of preparation: June 2008. Code: C0807428e