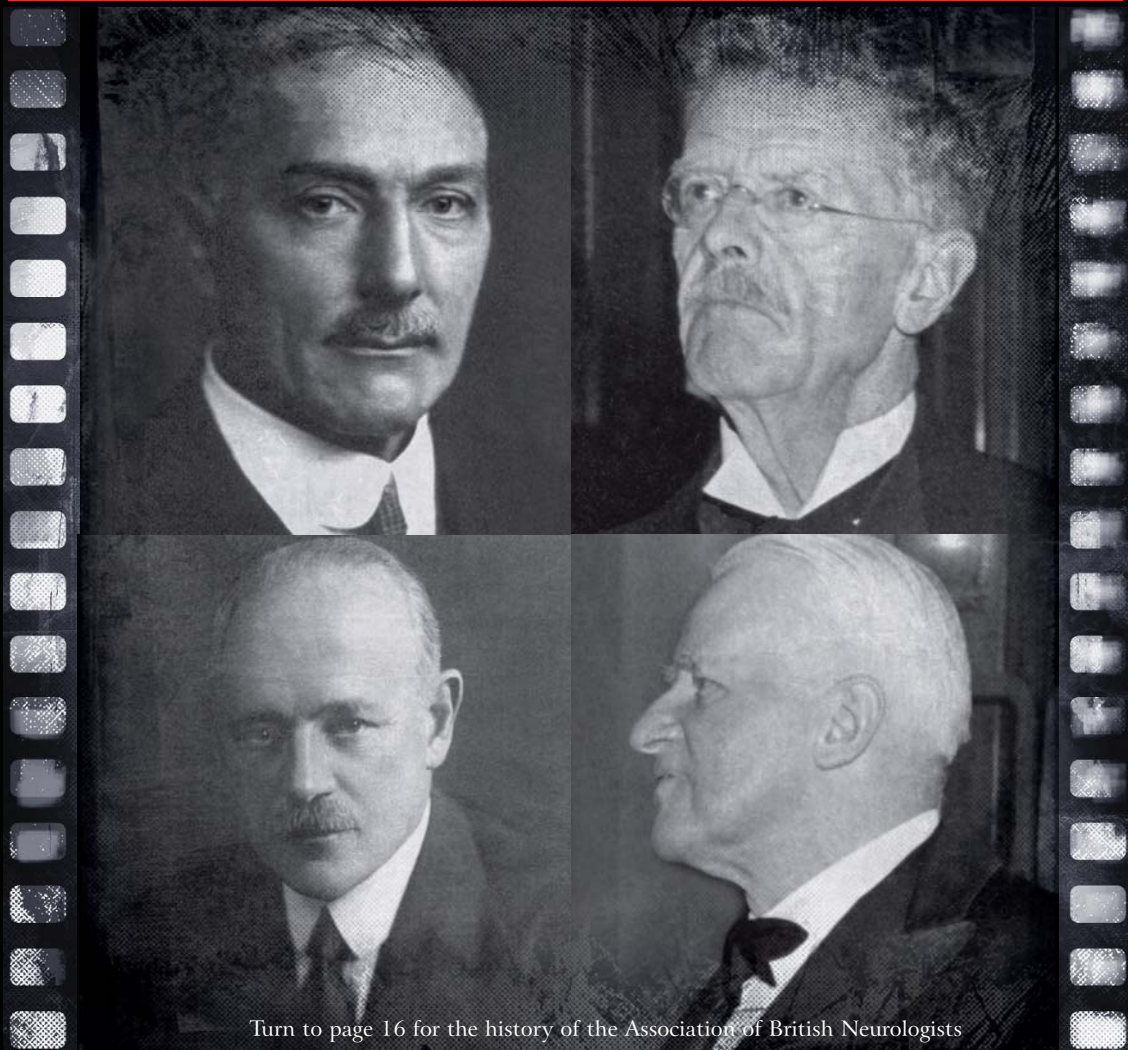


ACNR

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Advances in Clinical Neuroscience & Rehabilitation



Turn to page 16 for the history of the Association of British Neurologists

Tom Hayton, Julian Furby, Raj Kapoor

The Demyelinated Axon

Angela Vincent, Christian Bien

Paraneoplastic Neurological Diseases

Stephen Casper

“Then why not an Association of British Neurologists?”:
British Neurologists and the Founding of an Elite Medical Society

PARKINSON'S & ON & ON & ON & ON & ON & ON &

APO-go: treatment for both
PREDICTABLE and UNPREDICTABLE
symptoms of Parkinson's disease

Predictable symptoms: Use **APO-go Pen** early in treatment plan for rapid reversal of impending "off's". Simple, easy to use sc injection

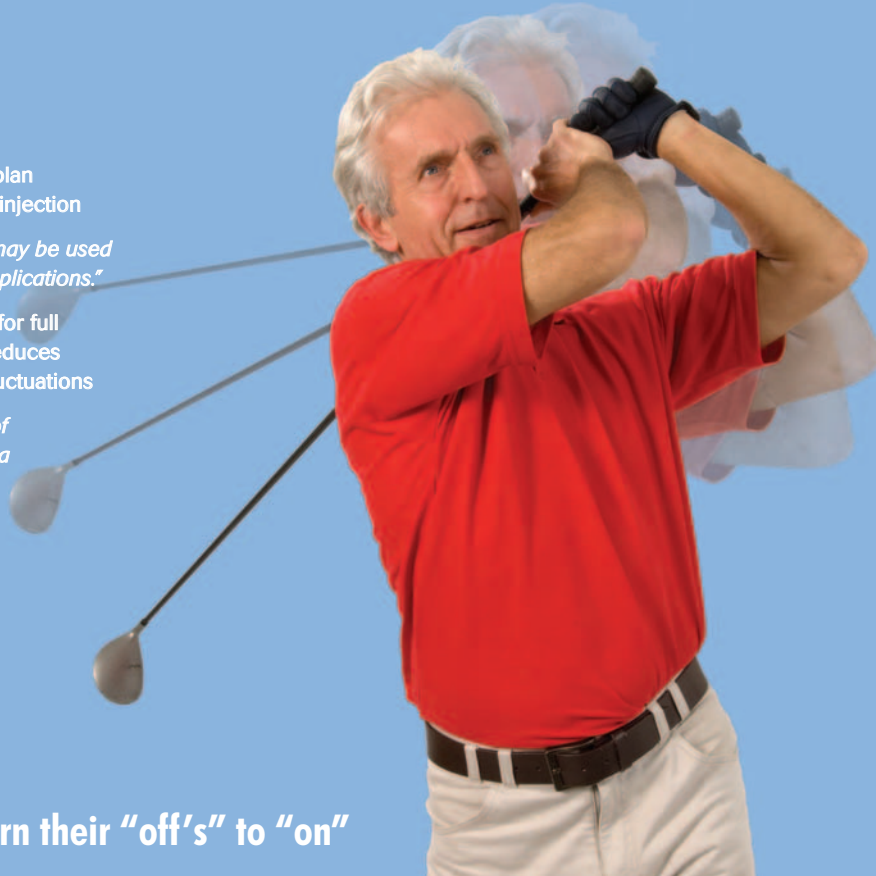
Positive NICE review: "Intermittent apomorphine injections may be used to reduce "off" time in people with PD with severe motor complications."

Unpredictable symptoms: Use continuous **APO-go infusion** for full waking-day cover. Continuous dopaminergic stimulation – reduces pulsatile treatment-related complications including "on-off" fluctuations

Positive NICE review: "Continuous subcutaneous infusions of apomorphine may be used to reduce "off" time and dyskinesia in people with PD with severe motor complications."



APO-go Make the switch and turn their "off's" to "on"



ABRIDGED PRESCRIBING INFORMATION

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. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation** Caution should be exercised if prescribing apomorphine to pregnant women and women of childbearing age. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. **Precautions** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea and vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive 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 while driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa when given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. **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 dyskinesias 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 transient. Transient 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-go 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 as exhibiting 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, 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 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 £123.91 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. **Marketing Authorisation Numbers:** APO-go Ampoules: 05928/0020 APO-go Pens: 05928/0021 APO-go Pre-filled Syringes: 05928/0025 **Legal Category:** POM. **Date of Last Revision:** August 2007. For further information please contact: Britannia Pharmaceuticals Limited 41-51 Brighton Road, Redhill, Surrey RH1 6YS Version Number: APG.API.V6

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Adverse events should also be reported to Medical Information at Britannia at the above
address or telephone: 01737 773741 or e-mail drugsafety@forumgroup.co.uk

“Recently a great deal has been learned about the response of the axon to demyelination particularly in response to an inflammatory insult and this knowledge has led not only to a deeper understanding of how symptoms can arise in demyelinated axons but also to the possibility of treatment to limit the disability resulting from demyelination and the associated change of the axon itself.” So writes Raj Kapoor and colleagues in their article on the demyelinated axon. This succinct account lays out a clear hypothesis on the sequence of events from demyelination to axonal loss and the relative role of ion fluxes and how this could be modulated by drugs such as lamotrigine.



Our second review article by Angela Vincent and Christian Bien concentrates on paraneoplastic diseases. Within this article are a large number of useful and practical insights, including some brief illustrative cases as well as some incredibly helpful tables. It is a particular pleasure to have this article, as Angela was on of the authors in our first ever issue of ACNR back in March-April 2001.

The repair of a cranial defect or deformation with cranioplasty is often regarded as a relatively straightforward process, but Heinke Pülhorn and Robert Redfern in their article in the Neurosurgery series take us through the history and practice of this procedure. They begin by relating the case of “The first reported cranioplasty... a Russian nobleman who, after receiving a sword blow to the head, had the resultant defect (and his health) restored with a piece of dog's cranium”, and end with a discussion on stem cell derived repair strategies. A real tour de force.

Stephen Casper gives a wonderful account of the origins of the Association of British Neurologists along with a potted biography of the first 5 presidents of this organisation. As he so eloquently writes, this organisation came into existence in 1932 and 75 years on is still thriving, although exactly what format the content of this meeting should take remains contentious (see ACNR 7.3). This highly enjoyable account by such a renowned medical historian is a delight to read.

Talking of the ABN, we have Chris Allen on behalf of the ABN MS panel responding to the recent critique by Neil Scolding on their guidelines in MS, which was the first in our new Controversies in Neurology series.

“Excitability testing involves measuring the threshold current required to stimulate an axon or population of axons, most commonly at a single accessible nerve point in the limb”. This technique with a

number of attractions and problems is discussed by Karl Ng and David Burke in their excellent contribution to our Neurophysiology series.

In our Neurogenetics series Paola Giunti and Nick Wood take us through the bewildering array of inherited ataxias. This article lays out the vast explosion of conditions that now live within this family of disorders with some helpful advice on what is common and what is not.

In our Neuropathology series, we have a wonderfully clear account of the pathology of raised intracranial pressure by Antonia Barlow and Willie Stewart. This article presents the pathology with great clarity and includes some extremely helpful tables and illustrative pictures.

In our series on Indian neurology, Dr Subhash Kaul in passing comments on some unusual causes of stroke in India (e.g. viper envenomation) as well as treatment (e.g. a massage with pigeon blood). However the main part of his review deals with the reality that “stroke burden in India is rising in the last few decades, in contrast to developed countries”. The reasons for this are discussed as well as the challenges that this presents for India and its limited health resources.

Following on from this theme, we have the first in what I hope will be a new series on medical electives which attempt to describe the practicalities of how one goes about organising such initiatives, as well as what one learns from these experiences. We are therefore grateful to Catherine Slattery for sharing with us her travels to the neurology departments of St Vincent's in Melbourne and Queen Square in London, and the contrast in neurological practice (as well as those who attend with patients) in these two countries.

Andrew Larner in his latest contribution to Neurological Literature leads us through a range of cases, from Livingstone and “his clergyman's throat” to Heidi and her sleep walking. This fascinating account once more highlights how superficially I read most books!

Sadly we have to report the loss of another great British neurologist and neuroscientist, Professor John Newsome-Davis. John sadly was killed in a road traffic accident in August this year, and his loss his huge and will be felt by many in the world of both neurology and neuroimmunology- areas to which he contributed so much.

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

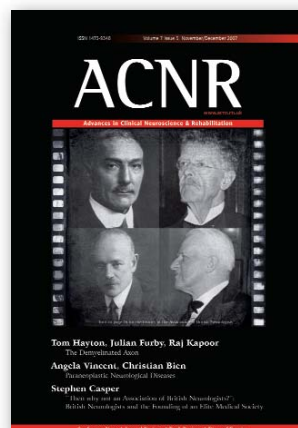
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This issue includes an account of the origins of the Association of British Neurologists, along with a potted biography of the first five Presidents of the organisation. The front cover image shows four of the five. See page 16 for a Who's Who.

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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.



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David J Burn 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.



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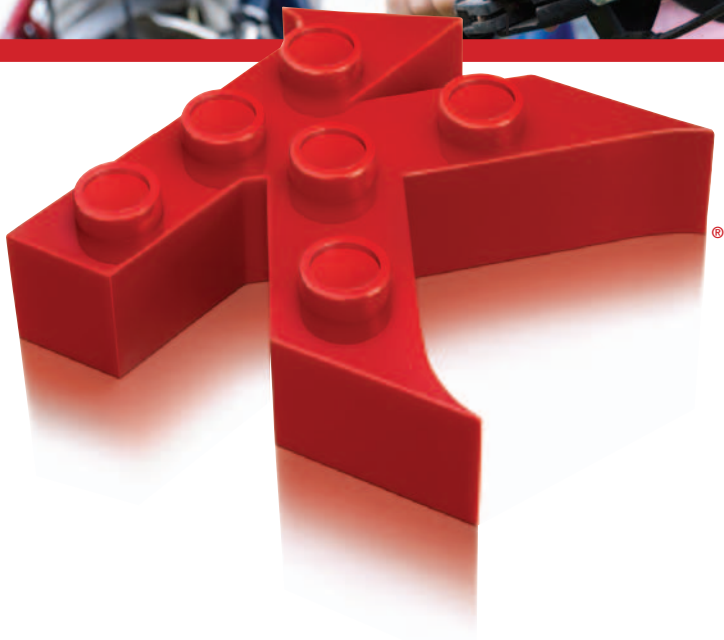
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contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. *Pregnancy and lactation:* Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. *Driving, etc:* Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Adverse Effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (≥10%): asthenia/fatigue, somnolence. *Common* (between 1%–10%): GI disturbances, anorexia, weight increase, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, balance disorder, disturbances in attention, memory impairment, emotional lability/mood swings, hostility, depression, insomnia, nervousness/irritability, agitation, personality disorders, thinking abnormal, vertigo, rash, eczema, pruritus, diplopia, vision blurred, myalgia, infection, nasopharyngitis, cough increased, thrombocytopenia. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** *Tablets:* None. *Oral solution:* Store in original container. After first opening use within 2 months. *Infusion:* Use immediately after dilution. **Legal Category:** POM. **Marketing Authorisation Numbers:** 250 mg x 60 tabs: EU/1/00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1,000 mg x 60 tabs: EU/1/00/146/024. *Solution x 300 ml:* EU/1/146/027, *Infusion (500 mg/5 ml) x 10 vials:* EU/1/00/146/030. **NHS Cost:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1,000 mg x 60 tabs: £101.10. *Solution x 300 ml:* £71.00, *Infusion (500 mg/ 5ml) x 10 vials:* £135.00. **Name and Address of PL Holder:** UCB S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd., 208 Bath Road, Slough, Berkshire, SL1 3WE. **Tel:** 01753 534655. **Fax:** 01753 536632. **Email:** medicalinformationuk@ucb-group.com
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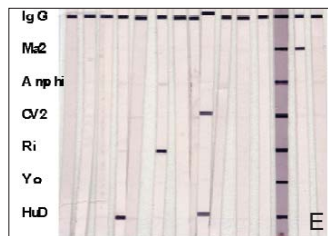
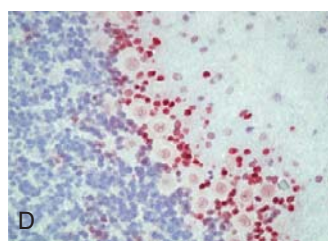
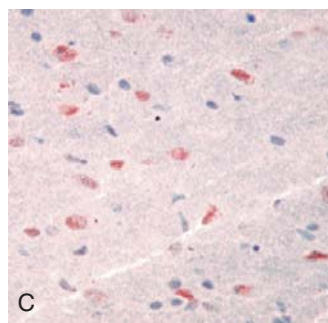
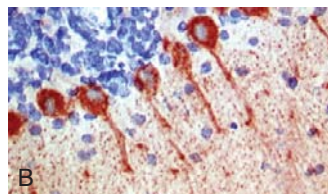
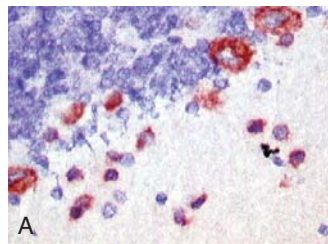
Paraneoplastic Neurological Diseases

Paraneoplastic neurological syndromes (PNS) are neurological disorders which are the indirect effect of a tumour, ie. in which there is no direct involvement of the tumour or its metastases or its treatment. Although some conditions can be caused by, for instance, alterations in the levels of circulating hormones or growth factors, the PNS are now generally thought of as immune-mediated conditions.

There are a number of classical syndromes in which a suspicion of PNS must always be considered (Table 1). The finding of an onconeural (paraneoplastic) antibody defines the neurological disease as being tumour-related and a search for the most likely tumour should be initiated. The PNS are not common diseases, affecting at most 5% of those with small cell lung cancer (SCLC) which is the most common PNS-associated tumour. In a recent survey conducted among UK physicians, around 50 PNS were reported in one year¹ which would give an approximate incidence of 1/million. However, there is likely to be under-recognition and under-reporting of these syndromes when the patients' symptoms may be inappropriately ascribed to tumour-associated morbidity or treatment effects. Criteria for classification of PNS as definite or possible have recently been proposed.²

The syndromes

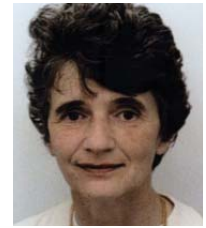
There are a number of classical PNS (Table 1). These can be rigorously defined by following clinical, MRI and other criteria which are summarised in several reviews.²⁻⁴ The typical PNS presents subacutely with progression over a period of around three months, after which it may stabilise or (if the patient survives) may take a progressive course.⁵ The clinical status can be assessed by a Rankin score.



Onconeural antibodies

The antibodies (Tables 1 and 2) were originally described by indirect immunohistochemistry on human or rodent brain sections (fixed in paraformaldehyde or acetone) by virtue of their very distinct patterns (e.g. Figure 1A-D). However, not all sera producing these patterns are specific for the paraneoplastic antigens and immunoblotting has to be performed to confirm the identity of any antibody. Fortunately, there are now commercial immunoblots which contain six characterised antigens so that serum testing can be performed in a more standardised manner (Figure 1E). Nevertheless, certain antigens (e.g. Tr, Figure 1B) are not available on the commercial immunoblots.

It is thought that the typical antineuronal antibodies, Hu, Yo, Ri, amphiphysin, CV2, Ma2 and Tr are extremely rare in patients without tumours, but it is possible that in some cases the tumour is occult throughout the life of the patient. On the other hand, some of the ion channel antibodies that can be associated with PNS are also found in non-paraneoplastic forms of the disorders (e.g. in Lambert Eaton myasthenic syndrome (LEMS), acquired neuromyotonia).⁶ The presence of Hu, CV2, or the recently described anti-glial nuclear antibody



Angela Vincent is Professor of Neuroimmunology at the University of Oxford and an honorary consultant in Immunology at the Oxford Radcliffe Trust. She heads the Neurosciences Group in the Weatherall Institute of Molecular Medicine, researching into antibody-mediated neurological diseases, and since 2005 has been Head of Department of Clinical Neurology.



Christian G Bien, MD, is a Senior Neurologist and Leading Assistant Medical Director at the Department of Epileptology at the University of Bonn, Germany. He is especially responsible for the presurgical assessment of pharmacoresistant epilepsy patients and has a special interest in immunologically mediated epilepsies.

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Figure 1: Examples of immunohistochemical detection of onconeural antibodies binding to (A) Yo in the Purkinje cells, (B) Tr in the Purkinje cells and molecular layer (C) Ma/Ma2 in the brain stem, and (D) nuclei in the Bergmann glia. (E) Examples of immunoblots showing strong bands representing binding of different sera to (reading from left) HuD, Ri, HuD and CV2, and Ma2. Positives represent a mixture of different sera. Courtesy of Dr E Amyes and Mr James Hoy.

Table 1

Classical paraneoplastic syndromes	Well-recognised onconeural antibodies	Most common tumours
<i>Panencephalomyelitis</i>	<i>Hu, CV2, amphiphysin</i>	<i>SCLC, NSCLC, breast, thymoma</i>
<i>Subacute cerebellar degeneration</i>	<i>Yo, Hu, Tr, CV2, Amphiphysin, Ma</i>	<i>Ovary, breast, SCLC, NSCLC</i>
<i>Limbic encephalitis</i>	<i>Hu, Ma2, CV2, amphiphysin, hippocampal neuropil, VGKC</i>	<i>SCLC, NSCLC, testicular non-seminoma, testicular seminoma, thymoma, ovary, breast, prostate</i>
<i>Subacute sensory neuropathy</i>	<i>Hu, CV2, amphiphysin, Ma2</i>	<i>SCLC, NSCLC, prostate</i>
<i>Lambert Eaton myasthenic syndrome</i>	<i>VGCC, also Hu, amphiphysin, Yo, Ri, CV2, Tr</i>	<i>SCLC, NSCLC</i>
<i>Dermatomyositis</i>	<i>None</i>	<i>SCLC, NSCLC, ovary, breast, prostate</i>
<i>Opsoclonus myoclonus</i>	<i>Hu, Ri</i>	<i>SCLC, NSCLC, breast</i>
<i>Chronic gastro-intestinal pseudoobstruction</i>	<i>Hu, CV2</i>	<i>SCLC, NSCLC, breast</i>

Classical syndromes according to Graus et al (2004). Others that are 'non-classical' but which may be paraneoplastic include brainstem encephalitis, optic neuritis, cancer-associated retinopathy, stiff person syndrome, necrotising myelopathy, motor neuron disease, Guillain-Barré-Syndrome, brachial neuritis, other neuropathies, myasthenia gravis, acquired neuromyotonia. The antibodies listed, apart from Tr, are principally those that are widely available and well characterised, and available on immunoblots (e.g. Figure 1). Tr is not yet defined at the molecular level. VGCC and VGKC antibodies are also present in non-paraneoplastic cases and not available as part of any paraneoplastic screen, in the UK. They should be requested separately if appropriate. SCLC = Small cell lung cancer and NSCLC = non-small cell lung cancer.

(AGNA^{7,8}, see Figure 1D), should help to indicate an associated SCLC even in these cases.

Because the immune response is made in the periphery against the tumour, the antibodies are found at highest levels in the serum rather than in the CSF. The only exception may be the neuropil antibodies which are said to be easier to detect in the CSF.⁹ The reason for this is not clear.

The tumours

The tumours that are most frequently associated with PNS (Tables 1 and 2) are those with neuroendocrine origins, such as SCLC, or concerned with the immune system, such as thymomas and lymphomas. Non-small cell lung cancers (NSCLC) are also quite commonly associated with PNS. Tumours of ovary and breast and many others may also induce PNS.

There are two PNS that are worth highlighting. Young men (<50 years) presenting with limbic encephalitis, often with additional brainstem and hypothalamic symptoms, may have a testicular tumour, and detection of Ma2 antibodies is critical in pointing to this association.¹⁰ These patients appear to do reasonably well with treatment of the tumour and immunosuppression for the neurological syndrome. Young women (below 45 years, so far) with a limbic encephalitis and often a more global encephalopathy with severe disturbance of cognitive function, often central hypoventilation and dyskinesias, may have an ovarian or other teratoma associated with antibodies to 'neuropil' of the hippocampus, in some cases defined as NMDA receptors.⁹ These patients also are reported to do well with the appropriate treatments for the tumours and immunosuppression for the neurological syndrome.

Mechanisms

In most cases the antibodies are markers for the immune response directed against the tumour and are not in themselves pathogenic. This applies

particularly to the well characterised antibodies. The reasons for believing this is that the patients do not respond well to immunotherapies alone, and passive transfer of antibodies to experimental animals does not induce disease. Concordantly, the titre of Hu antibodies does not correlate with disease severity on longitudinal studies.¹¹ On the other hand, the pathology of the brain (Figure 2D) suggests that infiltrating T cells may be involved in producing inflammation and in directly attacking neurons. This is particularly likely to be the case in paraneoplastic cerebellar degeneration where loss of Purkinje cells has been demonstrated in post-mortem tissue. Although T cell studies have not

Case vignette:

A 50-year-old lady with a longstanding history of cigarette smoking presented with the following complaints: Starting three years ago, she had been experiencing attacks typical of simple partial temporal lobe seizures, a disturbance of recent memory, and weight loss. Standard blood and CSF laboratory values including microbiological search for common neurotropic viruses were unremarkable. Brain MRI revealed a temporomedial high intensity FLAIR signal clearly greater on the right side (Figure 2A). Testing for onconeural antibodies by indirect immunohistochemistry on rat brain revealed a pattern typical for AGNA (Figure 2B). A tumour search revealed a left hilar pulmonary mass (Figure 2C) which was found to represent a SCLC with limited disease. The diagnosis was paraneoplastic limbic encephalitis with SCLC associated with AGNA. Following surgical, chemotherapeutic and radiation therapy, the patient has been relapse free for a follow-up of 2.5 years up to now. The neurological syndrome has remained unchanged.

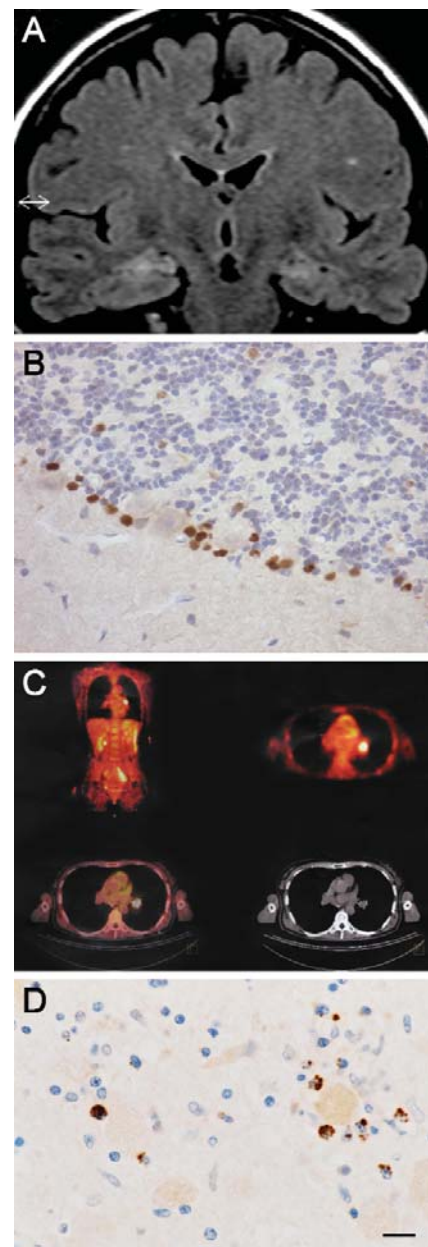


Figure 2: Case of a 50-year-old female patient with paraneoplastic limbic encephalitis with small cell lung cancer and serum antibodies against AGNA. (A) Coronal brain FLAIR MR image indicating increased hippocampal signal without atrophy. (B) [18F]-fluorodeoxyglucose positron emission tomography coregistered with CT reveals a left hilar hypermetabolic mass. Histological diagnosis: small cell lung cancer, limited disease (C) Indirect immunohistochemistry showing staining of patients serum on paraformaldehyde fixed rat brain. Note the nuclear staining of the Bergmann glia in the Purkinje cell layer of the cerebellum. (D) Brain stem section of a deceased patient with paraneoplastic encephalomyelitis associated with Ma2 antibodies and lung carcinoma, immunohistochemical staining for the cytotoxic protein granzyme B: Multiple granzyme B positive (i.e. cytotoxic) T lymphocytes attached to two neurons (bar:20µm).

Table 2: The onconeural antibodies and associated tumours

Table 2: The onconeural antibodies and associated tumours	
Well characterised antibodies	
<i>Hu</i>	<i>SCLC, other</i>
<i>Yo</i>	<i>Breast, gynaecological</i>
<i>Ri</i>	<i>Breast, gynaecological, SCLC</i>
<i>CV2</i>	<i>SCLC, thymoma, other</i>
<i>Amphiphysin</i>	<i>Breast, SCLC</i>
<i>Ma2/Ta</i>	<i>Testicular or other solid tumours</i>
<i>Tr*</i>	<i>Hodgkins lymphoma</i>
Not widely recognised yet but can be helpful	
<i>Zic4, ANNA3, PCA2, Sox1</i>	<i>SCLC</i>
<i>Hippocampal neuropil including NMDAR</i>	<i>Teratoma of the ovary</i>
<i>Retinal antigens eg. recoverin</i>	<i>SCLC or melanoma</i>
Antibodies associated with treatable syndromes	
<i>Ma2 antibodies, usually young males</i>	<i>Germ cell tumours of testis</i>
<i>Neuropil antibodies including NMDAR</i>	<i>Teratomas (ovarian)</i>
<i>Ganglionic AChR, autonomic neuropathies</i>	<i>SCLC, others</i>
<i>VGCC, LEMS</i>	<i>SCLC</i>
<i>VGKC, neuromyotonia, limbic encephalitis</i>	<i>Thymoma, others</i>
<i>AChR, myasthenia gravis</i>	<i>Thymoma</i>
*Tr is not a well characterised antibody but can be readily recognised by its distinctive staining pattern on cerebellum. SCLC = small cell lung cancer	

Table 3: Some points to remember

Look for subacute onset, expanding MRI lesions, early progressive course often with stabilisation after a few months

There may be more than one clinical syndrome

Tumour may not be found for up to five years (or even more sometimes)

Specific onconeural antibodies are not present in all cases

The tumour may be atypical

There may be more than one tumour

Detection of a well characterized onconeural antibody justifies a whole body CT-PET scan.

been extensive, they have shown some evidence of antigen specific T cells which could be directly pathogenic (reviewed in reference 12).

These concepts do not, however, apply to PNS with ion channel antibodies. In myasthenia gravis, Lambert Eaton myasthenic syndrome and acquired neuromyotonia, the diseases do respond well to immunotherapies even in those with aggressive SCLC or malignant thymoma. This is also the case with autonomic neuropathies associated with ganglionic AChR antibodies,¹³ and is likely to be the case with newly defined limbic encephalitis syndromes which are associated with VGKC antibodies (see reference 6). This condition is usually non-paraneoplastic but can be associated with thymomas or other tumours. In both cases the response to immunotherapy is very good, with substantial clinical improvement.

Treatment

The primary therapeutic efforts in cases of PNS should be directed against the underlying neoplasm, but immunological treatments should also be tried. Successful tumour treatment is associated with a halt in neurological disease progression in about two-thirds of the patients.¹⁴ Even in the absence of a large body of data (let alone high-grade trial evidence), some experience with immunotherapy directed against the immune reaction in the nervous system is available: In LEMS and myasthenia gravis, intravenous immunoglobulins and plasma exchange are effective therapeutic options for suppressing the immune response.¹⁵ In paraneoplastic encephalomyelitis including cerebellar degeneration, on the other hand, immunosuppressive or immunomodulatory therapies have in

general been rather disappointing with a majority of patients having progressive neurological disease.¹⁶ Ma2 antibody associated PNS seems to be an exception to the rule because about half of the patients stabilise or even improve on therapy.¹⁰ Fortunately, immunotherapy does not seem to be associated with a more rapid tumour progression. Therefore, immunotherapy (immunoglobulins, methylprednisolone, cyclophosphamide or a combination of those) from early on in conjunction with tumour treatment is recommended^{11,17} especially if the patient's neurological condition deteriorates rapidly. In cases of disease progression despite treatment, escalation of immunotherapy with increasing risks of side effects should be used with caution. Usually, patients deteriorate or are left with significant disability despite immunosuppressive or immunomodulatory treatment.

Conclusions

Detection of a specific antibody and recognition of a condition as paraneoplastic is important because the information has aetiological and prognostic relevance, and treatment of an underlying tumour often stabilises disease progression. However, it should be appreciated that despite the very important guidelines and associations between different syndromes, antibodies and tumours, there are often exceptions to these rules. Table 3 highlights some points to remember.

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NEU3887

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The Demyelinated Axon

The best known demyelinating diseases in clinical practice are multiple sclerosis (MS) and the demyelinating neuropathies, but axons can also be demyelinated by a variety of other immunological, viral, metabolic and traumatic insults. In recent years a great deal has been learned about the response of the axon to demyelination, particularly in response to an inflammatory insult, and this knowledge has led not only to a deeper understanding of how symptoms can arise in demyelinated axons, but also to the possibility of treatment to limit the disability resulting from demyelination and the associated damage to the axon itself. Thus, injury to myelin is followed by electrophysiological adaptation of the axonal membrane which can restore electrical conduction, but which may itself contribute to symptoms and make the axon vulnerable to degeneration.

Conduction block

The myelin sheath forms an insulating layer which decreases membrane capacitance and increases membrane resistance, allowing secure and rapid propagation of the action potential from one node of Ranvier to another. Acutely demyelinated internodes leak current, and conduction can be blocked because the nodal sodium current may be insufficient to depolarise the denuded axolemma. In clinically eloquent pathways this will lead to disability, for example during relapses of MS¹ or in demyelinating neuropathies. There is also evidence to suggest that products of inflammation interact adversely with axonal function and contribute to conduction block, and of particular importance may be nitric oxide, which has been shown to block conduction at concentrations comparable to those thought to occur in acute MS lesions² (see Figure 1).

Restoration of conduction

Conduction can recover as inflammation subsides, and inflammatory mediators such as nitric oxide are gradually depleted. Demyelination is also followed by a number of changes in the density and distribution of membrane channels which further help to restore conduction. In central axons the Na_v1.6 channels, normally aggregated at the nodes of Ranvier, are redistributed in a diffuse pattern along the axon,³ and this can enable the action potential to

propagate across the demyelinated internode. Many demyelinated axons also acquire a diffuse distribution of the Na_v1.2 channel subtype, which is usually seen in premyelinated axons during development³ (see Figure 2). Na_v1.2 populated axons seem to be resistant to injury, but may be more liable to conduction failure and ectopic activity. Finally, it is known that the N-type voltage-gated calcium channel can be expressed abnormally along the demyelinated axolemma in MS,⁴ and this may play a role in axonal injury.

Remyelination is another factor which aids the recovery of conduction. A nodal like clustering of sodium channels, along with other paranodal and juxtaparanodal proteins, is seen in a proportion of demyelinated axons and this may be a prerequisite for remyelination to occur.⁵ It is believed that oligodendrocyte contact could be responsible for triggering these changes in central axons. New central myelin internodes are shorter and thinner than normal, but conduction is restored nonetheless.⁶ Furthermore, remyelinated nodes have the normal Na_v1.6 aggregations, favouring the restoration of secure conduction.⁷ In MS, remyelination is seen particularly in younger patients early in the course of the illness, and the reasons why remyelination fails and is not a more ubiquitous process remain unclear.

Although these recovery mechanisms can restore conduction, it usually remains insecure, and leaves the demyelinated axon vulnerable to a temporary conduction block in certain circumstances, which include:

- Small rises in body temperature. These shorten the action potential by speeding the kinetics of sodium channels, hence reducing the current available to depolarise the axonal membrane to its firing threshold.
- Sustained electrical activity, which loads the axon with sodium and hyperpolarises its membrane away from the firing threshold through increased activity of the electrogenic Na/K ATPase pump.⁸
- Sodium channel blocking agents such as lidocaine can induce an iatrogenic conduction block by reducing the excitatory nodal current.⁹

The clinical consequence of these events is a temporary worsening of pre-existing disability with raised ambient temperatures or with activity, although silent lesions may also be unmasked.



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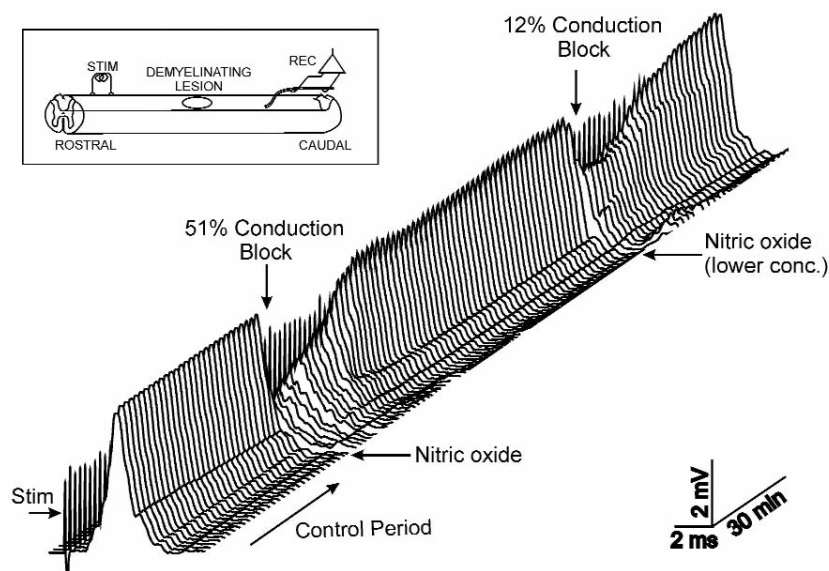


Figure 1: This figure shows a series of averaged compound action potentials propagating through an experimental demyelinating lesion in the spinal cord and recorded at two minute intervals. The injection of a nitric oxide donor into the lesion temporarily blocks conduction of a proportion of nerves, and this occurs in a dose dependent manner, with a second, lower dose of the donor producing a smaller degree of conduction block. Reprinted from reference 2.

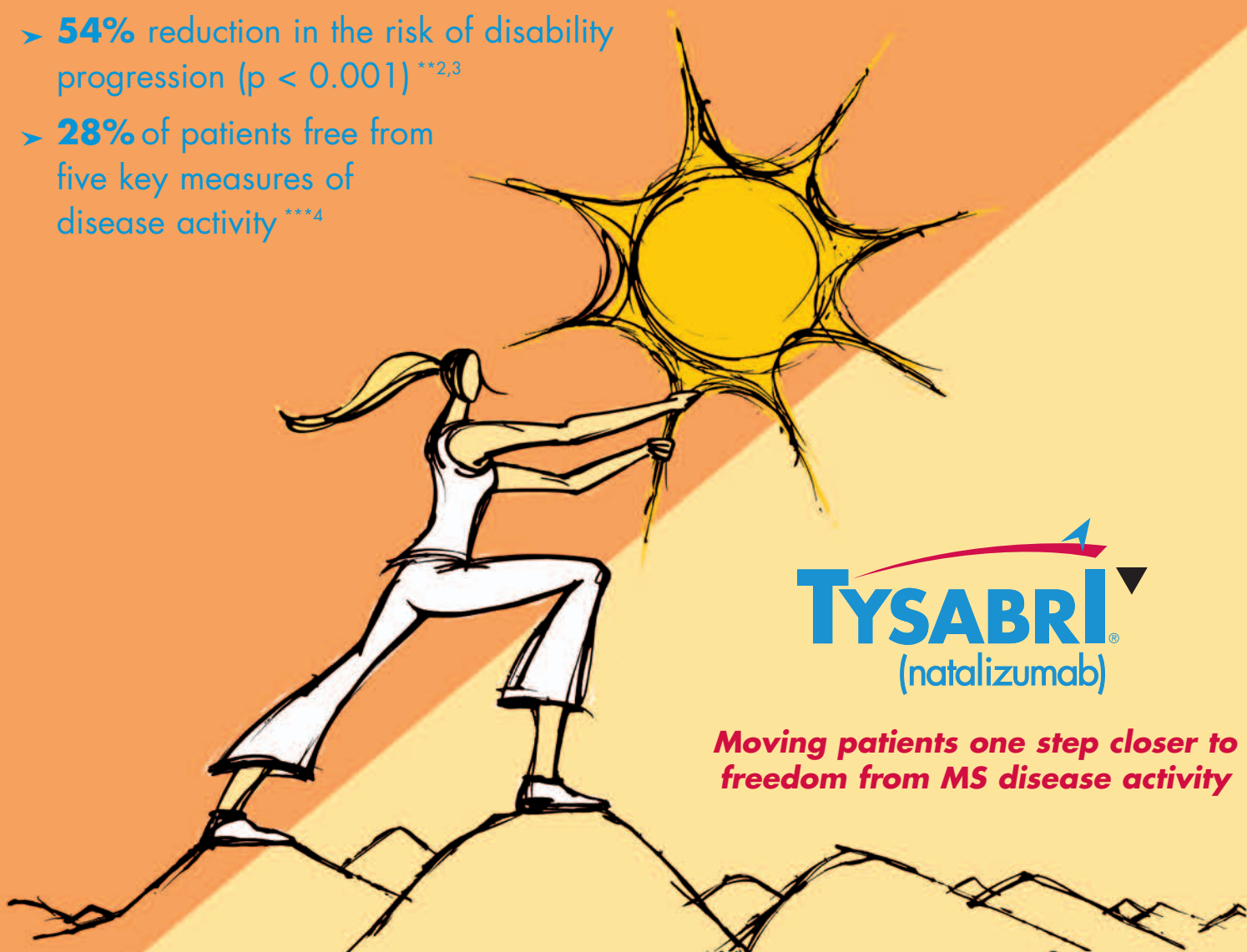
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** defined as disability progression, sustained for 24 weeks, as assessed over 2 years

*** defined as relapses, disability progression, gadolinium enhanced lesions, T1 weighted hypointense and T2 weighted hyperintense lesions over two years

References:

1. NICE TAG 127 - Natalizumab for adults with highly active relapsing remitting multiple sclerosis - August 2007.
2. Polman CH, et al. *NEJM* 2006; 354(9): 899-910.
3. TYSABRI SmPC, Biogen Idec Ltd.
4. Data on File Biogen Idec LTD TY00-004.

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Ectopic activity

Positive symptoms such as paraesthesiae, tonic spasms and paroxysmal ataxia or pain can sometimes occur because of ectopic impulse activity arising from demyelinated internodes.¹⁰ The depolarisations generating these discharges may sometimes be due to the slow inward sodium currents which arise from the adaptive changes to the demyelinated axonal membrane discussed earlier, or else to abnormal accumulation of extracellular potassium, which can lead to the axonal potassium currents reversing direction and becoming excitatory. Well over a hundred thousand extra action potentials can be generated from a single axon per hour.¹⁰ Mechanosensitive discharges may also occur in these axons, manifesting in MS most commonly as Lhermitte's phenomenon and visual phosphenes.

Axonal degeneration

In addition to acute and paroxysmal symptoms, demyelination leads to progressive disability. Disability may arise partly from a failure of the recovery mechanisms of remyelination and membrane adaptation, but there is a growing body of evidence that indicates that the inflammatory response can damage axons directly, and that chronically demyelinated axons are particularly vulnerable to degeneration.

In experimental models of inflammation, axons can degenerate when exposed to nitric oxide, particularly if they are electrically active.¹¹ Nitric oxide is known to be present in the plaques of MS, and may injure axons through a number of actions, among them an inhibition of mitochondrial respiration resulting in energy failure, a loss of ionic homeostasis, and a consequent intracellular accumulation of sodium ions. In models of ischaemia, axons loaded with sodium are at risk of degeneration because of the secondary influx of calcium ions through the reverse function of the membrane Na⁺/Ca²⁺ exchanger (NCX),^{12,13} and a similar mechanism may operate in the presence of nitric oxide, where axonal degeneration can be blocked by inhibition of sodium channels or of the NCX.¹⁴

Like the NCX, the sodium/glutamate transporter is also driven, in part, by the sodium gradient, though in this instance both sodium and glutamate are imported together in exchange for potassium. When the sodium gradient is reversed, so too is the direction of the exchange, resulting in a net release of glutamate and an increase in its extracellular concentration. In animal models glutamate-mediated white matter injury is thought to be mediated by 1) by α -amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) receptors¹⁵, and 2) via increased axonal expression of metabotropic glutamate receptors,¹⁶ both favouring intracellular calcium accumulation. AMPA antagonists have been shown to reduce axonal damage and disability in EAE.¹⁷

Neuroprotection with sodium channel blockers

Based on the possibility that intracellular sodium accumulation can damage axons, the neuroprotective potential of drugs which block voltage gated sodium channels has been examined in various animal models. In experimental allergic encephalitis (EAE), the rodent model of MS, several sodium channel blockers have been shown to prevent axonal loss and to reduce disability.¹⁸ This work has led to a phase II clinical trial of neuroprotection with lamotrigine in people with secondary progressive MS at the Institute of Neurology in London. The result of this trial should be available in early 2009.

Other possible neuroprotective agents

Cannabinoids have also been identified as possible neuroprotective agents. By acting on the CB1 receptor an endogenous cannabinoid

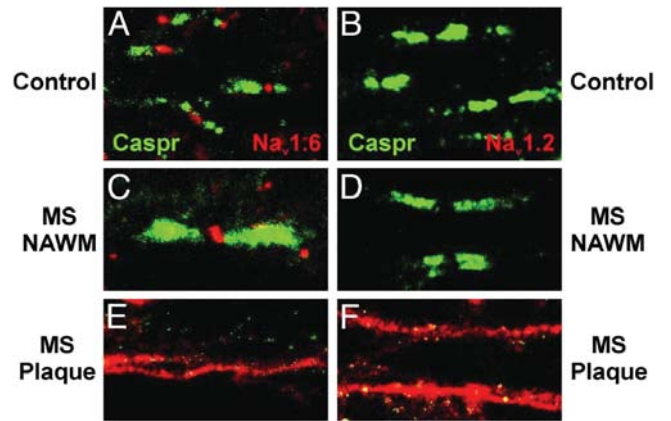


Figure 2: Immunostaining of post-mortem white matter from controls and MS patients. Nodes of Ranvier are indicated by immunostaining of paranodal contactin-associated protein (Caspr, green). Na_v1.6 (left, red) is aggregated at nodes in control CNS and MS normal appearing white matter (NAWM). In contrast a diffuse distribution along the demyelinated axon is seen within plaque tissue (E). Na_v1.2 (right, red) is found only in plaque tissue where it is distributed in a diffuse pattern (F). Reprinted from reference 3.

compound, 2 arachidonyl glycerol, is thought to modulate glutamate release and thereby reduce the impact of glutamate induced toxicity. Evidence from EAE and knockout mouse models supports this hypothesis¹⁹ and a clinical trial of neuroprotection with cannabinoids in progressive MS is currently under way in the UK.

Some calcium channel blockers, administered with or shortly after induction of EAE, improve clinical recovery after relapse and may also limit axonal degeneration.²⁰ It is possible that calcium channels may also be future targets for neuroprotection.

Imaging demyelination

Magnetic resonance imaging (MRI) is widely used in the diagnosis of MS. However, the T2-weighted high signal white matter lesion load correlates only modestly with disability.²¹ It is now thought that not all of these T2 high signal lesions represent areas of demyelination.²²

Newer, quantitative MRI techniques may be more specific for demyelination. Of note is the magnetization transfer ratio (MTR). This technique exploits the transfer of energy from protons bound to large molecules, such as those found in myelin or axons, to free protons in surrounding water. The higher the MTR, the greater the number of large molecules present in a tissue. Recent studies in MS²³ and EAE²⁴ have indicated that low MTR may be more specific for demyelination than other techniques, while studies in other central demyelinating disorders, such as adrenoleucodystrophy, suggest that it may also be more sensitive.²⁵

Conclusion

Acute inflammatory demyelination gives rise to disability from conduction block. As the inflammation resolves and recovery processes set in, the level of disability may improve. However, because conduction remains insecure, the axon is still vulnerable to temporary conduction block, giving rise to brief exacerbations of disability. Positive symptoms can also occur as a consequence of ectopic impulse

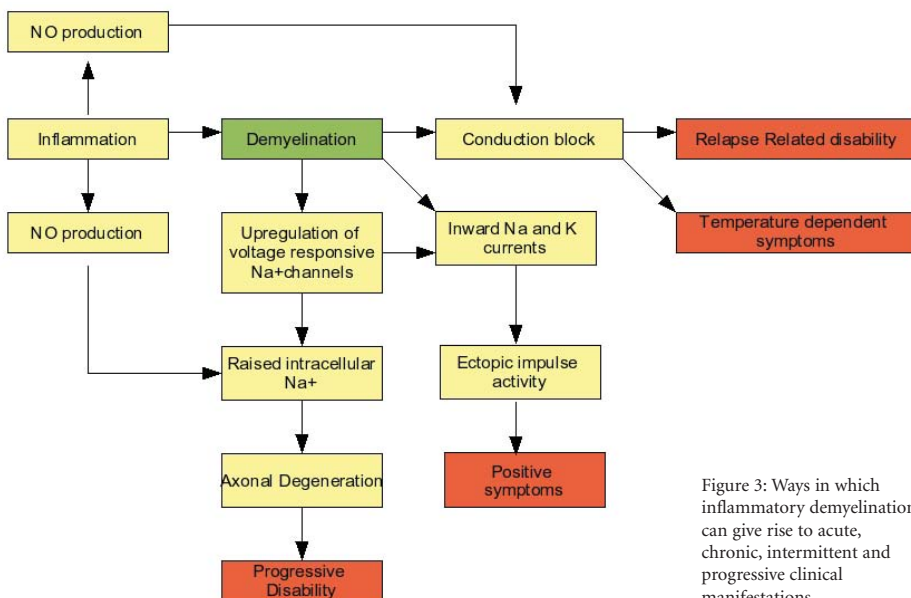


Figure 3: Ways in which inflammatory demyelination can give rise to acute, chronic, intermittent and progressive clinical manifestations.

activity due to changes in sodium and potassium currents.

With time a proportion of axons undergo remyelination, and this, together with adaptive changes in the expression and distribution of sodium and other membrane channels, may help to restore conduction. However these same adaptive changes may favour the accumulation of intracellular sodium and calcium ions and, as a consequence, promote gradual axonal degeneration and hence lead to progressive disability. It may be possible to slow down the progression of axonal degeneration using sodium channel blockers, and a phase II placebo-controlled trial of lamotrigine is currently under way to test this hypothesis.

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Presented by: the Encephalitis Society

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Time: 13.00 – 18.00

Venue: The Resource Centre, 356 Holloway Road, London N7 6PA

Type of event: Seminar with Evening Wine Reception

Speaker(s): Professor Tom Solomon, Dr Ian Hart, Professor Gavin Giovannoni, Dr Sarosh R Irani

Admission: £50 normal rate, £35 student rate

Contact: Elaine Dowell • 01653 604366 • elaine@encephalitis.info

CPD applied for

Seminar Programme

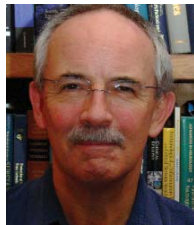
13.00 Welcome Professor Clive Hawkins, Chair of the Encephalitis Society Advisory Panel • **13.10** Keynote Address: Global Infectious Encephalitis Professor Tom Solomon, Chair of Neurological Science, University of Liverpool • **13.50** Voltage Gated Potassium Channel Antibody Encephalitis. Dr Sarosh R Irani, Clinical Research Fellow Neurosciences Group, John Radcliffe Hospital, Oxford • **14.20** Fungal encephalitis: diagnostic and therapeutic challenges Dr William Hope, Infectious Diseases Physician and Senior Research Fellow, The University of Manchester • **14.50** Refreshments • **15.20** Keynote Address: Autoimmune Encephalitis Dr Ian Hart, Consultant in Neurology and Neuroimmunology, The Walton Centre for Neurology and Neurosurgery • **16.00** Encephalitis Lethargica Professor Gavin Giovannoni, Head of Neurology The Royal London Hospital • **16.30** Discussion • **17.00** Wine Reception

ABN Guidelines for Treatment of Multiple Sclerosis with β -Interferon and Glatiramer Acetate

As the new chairman of the ABN Multiple Sclerosis panel I am responding, on behalf of the Council, to the criticism of the ABN's latest guidelines for the use of disease modifying treatments in MS by Neil Scolding and his colleagues in Bristol. The first point to make is that all ABN guidelines are expressions of consensus and are formulated, as were these, after extensive consultation with ABN members. The MS panel is made up of a combination of ABN members expert in the disease and 'ordinary' clinical neurologists (expert only in talking to patients about these difficult issues); the present chairman is in the latter group. Guidelines are for guidance; they are not operating instructions, and the Appendix to the ABN guidelines makes clear that the informed patient should be involved in decisions so that, after a Clinically Isolated Syndrome (CIS), further MRI imaging may be performed even in the absence of a second event to discover if that person meets revised criteria for the diagnosis of MS, i.e. 'has MS'. Such a patient, in the opinion of the majority of MS experts in the UK, would in principle benefit from an effective disease modifying treatment. As Alasdair Coles has pointed out in these columns, this majority feels vindicated by the BENEFIT study's recently published latest report.

I suspect that what has provoked this 'controversy' is the knowledge that better disease modifying treatments are around the corner and likely, in the view of many, to supplant the two agents which are currently accepted as having some effect. However, for the moment, β -interferon and Glatiramer Acetate are the only ones that are available (outside trials) for 'ordinary', as opposed to 'aggressive', MS (Natalizumab has just been accepted by NICE as a cost effective treatment of the latter). The MS panel feel they have identified from the available evidence, by applying the modified McDonald criteria, those patients with CIS who may benefit from the early use of disease modifying treatments and the latest from the BENEFIT study tends to support this assessment. Of course we and Professor Scolding hope and expect that therapies of less ambiguous efficacy will soon be available for this group of patients. Clinical Guidelines are based upon evidence, but in dealing with patients it is also wise to interpret that evidence in the patients' favour. So far, it looks as if the MS panel has been right in its advice.

The facts that more information from future trials will inform this debate and better disease modifying treatments are needed are acknowledged. However clinicians in the field need to manage their patients now and must often extend decisions beyond the hard, academically uncontroversial, evidence in their interests. In view of the relative speed with which advances are being made in the treatment of MS it is very likely that the ABN will be issuing new guidelines before too long but I would be surprised if these do not advocate early treatment in patients with identified active disease (even after only one clinical event), but whilst nevertheless offering more effective (and we can hope cheaper) treatments.



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“Then why not an Association of British Neurologists?”: British Neurologists and the Founding of an Elite Medical Society

On the evening of 28 July 1932, a group of British physicians and scientists gathered at 9 Wimpole Street, the private London-residence of the neurologist Gordon Morgan Holmes (1876-1966).¹ Most of those attending were from London, but others had come from Bath, Edinburgh, Liverpool, Manchester, Newcastle, and Oxford (see Table 1). All present held prestigious positions as teaching hospital consultants and some were University Professors of Medicine; most numbered among the influential doctors of the interwar period. By the close of the meeting, they had decided to form an Association of British Neurologists (ABN), an organisation of which the ‘membership’ was to be ‘limited to those actively engaged in any branch of neurology’.²

The idea for such an association was first suggested in the summer of 1931.³ Noting that a national-level society for neurology had not existed in Britain since 1907, an essayist writing in the *Journal of Neurology and Psychopathology* thought that such a body would be a welcomed complement to other national organisations, such as *The Ophthalmological Society of the United Kingdom* or the *Association of Physicians*. Admitting that the members of the *Neurological Society of the United Kingdom* had disbanded in preference for the London-based Section of Neurology of the Royal Society of Medicine, which in 1932 was acting as the national body for neurology, the author argued that the RSM was nonetheless mainly of benefit to consultants living in the Capital.⁴ A new medical society would correct this imbalance, by bringing neurologists from across the country together to discuss basic and clinical research and practice.

Despite these ambitions, in its early years the ABN functioned as an elite club. Although many of its members served on prominent professional committees or as advisors to the government, the Association rarely took positions that advanced a political agenda for neurology. As the number of its members grew, however, the ABN was increasingly able to influence the development of neurology in the health service.⁵ Meetings of the Association

furthermore allowed important guests – hospital and government administrators and representatives of philanthropies – to attend and judge the vitality of individuals and their research.⁶ This often had the valuable consequence of increasing the international prestige of the community and its resources. In addition, scientific reports at the general meetings disseminated therapeutic and technological innovations, and sometimes even spurred further scientific and clinical investigations (see Figure 1). Thus, in time the ABN became British neurology’s most significant social, scientific, and political body.⁷

In many respects, the biographies of early Presidents of the ABN illustrate the social and political status most members of this organisation enjoyed in both British medicine and wider society, while also illustrating their similar backgrounds and dispositions. The Association’s first President was Wilfred Harris, who was born in Madras, India, the son of William Henry Harris, the Surgeon General of the India Medical Service.⁸ Educated at Cambridge and St Mary’s Hospital, Harris qualified in 1894. Between 1901 and 1902, he was Resident at the *National Hospital for Paralysis and Epilepsy*, where he worked under such founders of British neurology as John Hughlings Jackson (1835-1911) and William Gowers (1845-1915). In 1905, Harris was elected Assistant Physician in St Mary’s Electricity Department, which in 1907 became the first Department of Neurology in the United Kingdom. In 1909, Harris became Full Physician, and by then he also held a comparable position at the *Maida Vale Hospital for Nervous Diseases*, where he was known as a specialist in diseases of the nerves with interests in neuritis, facial neuralgia, and epilepsy.

Wilfred Harris’s successor was Edwin Bramwell (1873-1952).⁹ Bramwell was born in North Shields, the son of Sir Byrom Bramwell (1847-1931), a physician with interests

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Table 1: Founders of the Association of British Neurologists

Bath	Ronald Grey Gordon (1889-1950)
Edinburgh	Edwin Bramwell (1873-1952)
Liverpool	Henry Cohen (1900-1977)
London	William John Adie (1886-1935)
London	Anthony Feiling (1885-1975)
London	Charles Worster-Drought (1888-1971)
London	Gordon Morgan Holmes (1876-1966)
London	James Godwin Greenfield (1884-1958)
London	James Stansfield Collier (1870-1935)
London	Samuel Alexander Kinnier Wilson (1874-1937)
London	Wilfred John Harris (1869-1960)
London	William Johnson (1885-1949)
Manchester	Donald Elms Core (1882-1934)
Newcastle	Frederick John Nattrass (1891-1979)
Newcastle	George Hall (1879-1955)
Oxford	Edward Farquhar Buzzard (1871-1945)

Most Active Participants in the First Ten Meetings

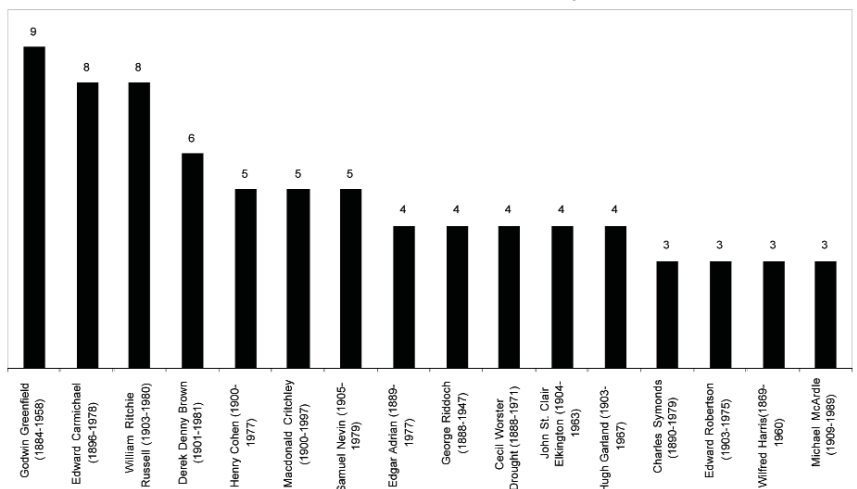


Figure 1: Between 1933 and 1947, there were ten general meetings of the Association of British Neurologists, with 141 papers given. Most members of the Association gave a paper at least once during this period, but some contributed more often. James Godwin Greenfield (1884-1958), Edward Carmichael (1896-1978), and William Ritchie Russell (1903-1980), for example, were the most active members of the society. Greenfield’s papers were often collaborative projects with more than one author, and they invariably focused on subjects relating to neuropathology. Edward Carmichael, by contrast, presented his own research, which he conducted as Director of the MRC-supported Neurological Research Unit at Queen Square. William Ritchie Russell, who would become the first Professor of Neurology at Oxford, worked in Edinburgh. His communications focused mainly on physiological matters.

Arthur Stanley Barnes



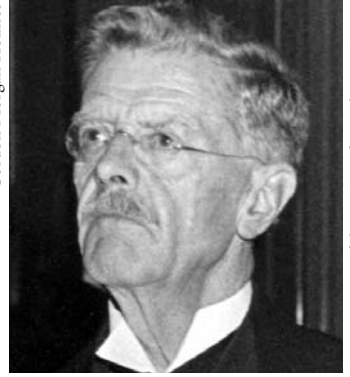
Edward Farquhar Buzzard



Wilfred Harris



Gordon Morgan Holmes



Pictures courtesy of the Institute of Neurology, UCL.

in the diseases of the nervous system and a Professor of Medicine in Edinburgh.¹⁰ Educated at Edinburgh University, Edwin Bramwell qualified in 1896, and then studied at La Salpêtrière (1899) under Joseph Jules Dejerine (1849-1917). Later he held a House appointment at the *National Hospital for Paralysis and Epilepsy*, where he too worked under Hughlings Jackson and Gowers. In 1907, he was appointed Assistant Physician at the Royal Infirmary of Edinburgh, becoming Full Physician there in 1919, and Moncrieff-Arnott Professor of Clinical Medicine at the University in 1922. A clinician in the old-patrician style, Bramwell speculated on the nature of the nervous system in his private diary, but he less commonly engaged in laboratory research.¹¹

Edward Farquhar Buzzard (1871-1945), the third president, was born in London, the son of Sir Thomas Buzzard (1831-1919), renowned as a founder of British neurology.¹² Initially more acclaimed for his athleticism than his academics, Buzzard was educated at Oxford and St. Thomas's Hospital, qualifying in 1894. Training under Hughlings Jackson, whom he had known from a young age as a personal friend of his father's, Buzzard became Physician to Out-Patients in 1905 at the *National Hospital*.¹³ From 1910 until 1926, he was Physician at St Thomas's, a position he held until his appointment as Regius Professor of Medicine at Oxford. A shooter and fisherman, the unusually silent Buzzard was created Baronet in 1929. He was an excellent clinician but was regarded as a ponderous lecturer.

The Association's fourth President, Arthur Stanley Barnes, was born in Birmingham, the son of Starkie Barnes, Headmaster.¹⁴ Stanley, as he was called, was educated at Mason Science College and Birmingham University, qualifying in 1899. Trained under Hughlings Jackson, Gowers, and Victor Horsley (1857-1916), Barnes was Resident Medical Officer from 1901 until 1903 at the *National Hospital* before being appointed Assistant Physician at Birmingham General Hospital in 1907. Later he was made Full Physician (1913), and he eventually became Dean of the Faculty of Medicine at the University of Birmingham. Barnes was remembered as a passionate advocate for his University and an outstanding lecturer, who 'mimicked' his past Queen Square teachers with startling accuracy.

Gordon Morgan Holmes, the son of Gordon Holmes, a gentleman farmer, was born near Castlebellingham, Ireland.¹⁵ He was the Association's fifth President. Educated at

Trinity College Dublin and qualifying in 1898, Holmes won a scholarship to study in Germany, where he worked under Carl Weigert (1845-1904) and Ludwig Edinger (1855-1918). A Resident Medical Officer at the *National Hospital* in 1903, he eventually became Full Physician there in 1909. He also worked at Charing Cross Hospital.¹⁶ A Fellow of the Royal Society, Holmes was a short-tempered teacher and practitioner, yet he was a marvelous diagnostician and an international figure in neurology, made famous especially by his studies during World War I of traumatic brain and nerve injury.

As these biographies illustrate, members of the ABN in the interwar and early post-war periods were distinguished figures, and accordingly, many neurologists, when asked even today, can readily recall the terror they experienced in presenting their first paper before the Association's members; the quality of delivery was generally regarded to be decisive for election to the membership.¹⁷ Communications were presented informally,¹⁸ but the audience was solemn and sometimes prickly. When John David Spillane (1909-1985) was elected President of the Association in 1974, it was recalled that his first paper had been greeted by Francis Martin Rouse Walshe's (1885-1973) barbed comment that "clearly *someone* [other than Spillane] will have to look into all this".¹⁹

In many ways, meetings in the early years were like those of today, although fewer physicians attended and the banquets were black-tie affairs. From the beginning, the Association alternated its meetings between London and provincial centres. Various institutions such as the *National Hospital* and the *Royal College of Physicians* hosted the Association's general meetings in London, while extra-metropolitan meetings tended to take place in cities with universities. In 1937, the Association held its first joint meeting with a foreign body, the *Amsterdam Neurological Society*. That year the Association also began recognising overseas Members, although initially these could only be former members taking up appointments abroad. The Association did not convene throughout the whole of the Second World War. An administrative meeting to discuss the government's plans for a nationalised health service was held in 1944, but 1945 marked the year when the Association's annual proceedings resumed. In 1950, the Association began meeting twice yearly, once in London and once in an extra-metropolitan centre. This pattern continues to the present day.

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The Inherited Ataxias

Introduction

The inherited ataxias are a complex group of neurodegenerative disorders. The clinical phenotype is characterised by a progressive cerebellar ataxia variably associated with neuropathy, ocular abnormalities, pyramidal and extrapyramidal signs, cognitive dysfunction and seizures. In some recessive inherited ataxias there is more widespread multisystem involvement. Over the last two decades a tremendous collaborative effort has resulted in the identification of many causative genes for these rare disorders. These genes have led to the implication of a large variety of processes such as polyglutamine neurotoxicity, mitochondrial DNA impairment, RNA processing dysfunction, DNA repair and cellular metabolism failure. Hereditary ataxias can be divided into autosomal dominant, recessive, X-linked and mitochondrial on the basis of the respective inheritance.

Autosomal dominant cerebellar ataxias

The autosomal dominant cerebellar ataxias (ADCA) or spinocerebellar ataxias (SCA) are a group of conditions for which twenty eight loci have been identified to date (Table 1). Disease onset is usually between 30 and 50 years of age, although early onset in childhood and onset after 60 years have been reported. The prognosis is variable depending on the underlying cause of the spinocerebellar ataxia subtype. The most common among these conditions SCA1, 2, 3 and 6, together with 7, 17 and DRPLA are caused by the expansion of a CAG repeat sequence within the coding region of specific genes. The CAG sequence encodes an abnormal polyglutamine (polyQ) tract in the encoded proteins named ataxins 1, 2, and 3 (SCA1,2,3), alpha 1A-voltage-dependent calcium channel (SCA6), ataxin 7 (SCA7), TATA box binding protein (SCA17), and atrophin 1 (DRPLA) respectively. These SCAs have several common clinical-pathological features. The second group of SCAs, including SCAs 8, 10, and 12, are caused by a repeat expansion located outside of the coding region of the disease genes leading to dysregulation of gene expression. While the molecular mechanisms underlying SCAs 8 and 10 are unclear, SCA12 appears to be caused by dysregulation of the activity of the crucial enzyme protein phosphatase 2 (PP2) in cerebellar Purkinje cells. Cerebellar ataxia and neurodegeneration in SCAs 5, 13, 14, and 27, are caused by alterations in amino acid composition in beta-III spectrin (SPTBN2), potassium channel KCNC3, protein kinase C (PRKCG) and fibroblast growth factor 14 (FGF14) respectively. The genes and, therefore, the mutations that cause the remaining SCAs have yet to be identified and characterised.

In the pre-genomic era, ADCAs have been particularly controversial in terms of nomenclature and classification. Harding first proposed a classification based on the clinical symptoms. She grouped them in three main categories (Table 2).¹ So far Harding's classification has not

been overridden by the genetic classification and is still valuable as a guideline in clinical practice and to prioritise genetic tests for diagnosis. ADCA type I is characterised by ataxia of the gait variably associated with ophthalmoplegia, pyramidal and extra pyramidal signs, cognitive impairment, optic atrophy, or peripheral neuropathy. The clinical features in this group of ataxias are caused by a combination of degeneration of the cerebellum, basal ganglia, cerebral cortex, optic nerve, pontomedullary systems, spinal tracts, or peripheral nerves. ADCA type II is distinct from ADCA type I by the presence of pigmentary retinopathy. A third group, ADCA type III includes relatively pure cerebellar ataxias where the degenerative process is limited to the cerebellum. ADCAs I and III are clearly genetically heterogeneous, whereas at least two different genes are associated with ADCA II. The vast majority of ADCA II families seem to be caused by SCA7 (Table 2).²

Spinocerebellar ataxias are rare disorders. Epidemiological studies have found prevalence rates between 0.9-3.0:100.00.^{3,4} In some geographically isolated regions, the frequency is much higher due to a "founder effect"⁵ for example in Cuba, the Azorean island Flores and in the south of Italy for SCA 2, 3 and 1 respectively (⁵ Giunti unpublished data). The most common types worldwide among the SCAs are SCA1, 2, 3 and 6. These four conditions account for at least 57% of all SCA families.⁶⁻⁷ The following section focuses on the clinical and genetic features of the SCAs due to CAG expansion.

SCAs due to expanded CAG repeats

SCA1, SCA2, SCA3, SCA6, SCA7 and DRPLA have common clinical and genetic features. Longer expansions are associated with an earlier onset and more severe progression of disease. CAG repeats are unstable and tend to expand further mainly through paternal transmission. This leads to a more severe phenotype and an earlier age at onset in successive generations (a phenomenon called anticipation). Anticipation is rarely observed in SCA6 where the CAG tends to be smaller and more stable.

Another common feature among these disorders is the progressive neurodegeneration of specific neuronal subsets with the formation of polyQ-containing protein aggregates leading to characteristic nuclear or cytoplasmic inclusions.⁸

In SCA1 the cerebellar ataxia is associated with pyramidal sign, ophthalmoplegia, and, in later stages, with sensorimotor peripheral neuropathy and extrapyramidal features. In SCA2, slow saccades and the absence of tendon reflexes characterise the clinical picture. There are reported families with parkinsonism and other extrapyramidal disorders such a dystonia. SCA3 has the most variable presentation. The most common phenotype is characterised by cerebellar ataxia and pyramidal signs although it may present with parkinsonism associated



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The inherited ataxias are a complex group of neurodegenerative disorders

Table 1: Genes/loci and molecular defects accounting for the SCAs.

*SCAs 19 and 22 are likely allelic forms of the same gene. ** The gene encoding puratrophin 1 lies on the same chromosomal region of SCA4 gene. D, deletions; MM, missense mutations; SNS, single nucleotide substitutions; U, unknown. (modified from reference 2).

SCA subtype	Chromosomal location	Gene/Locus	Protein	Mutation	Main clinical features
SCA1	6p22.3	ATXN1	Ataxin 1	CAG repeat	Ataxia, pyramidal signs, neuropathy, ophthalmoplegia
SCA2	12q24.13	ATXN2	Ataxin 2	CAG repeat	Ataxia, slow saccades, neuropathy
SCA3	14q32.12	ATXN3	Ataxin 3	CAG repeat	Ataxia, pyramidal signs, ophthalmoplegia, neuropathy, dystonia
SCA4	16q24-qter	SCA4	U	U	Ataxia, sensory neuropathy
SCA5	11q13.2	SPTBN2	Beta-III spectrin	D, MM	Almost pure cerebellar ataxia
SCA6	19p13.13	CACNA1A	CACNA1A	CAG repeat	Almost pure cerebellar ataxia
SCA7	3p14.1	ATXN7	Ataxin 7	CAG repeat	Cerebellar ataxia, pyramidal signs, pigmentary maculopathy
SCA8	13q21	KLHL1AS	Kelch-like 1	CTG repeat	Ataxia, sensory neuropathy
SCA9	Reserved	U	U	U	
SCA10	22q13.31	ATXN10	Ataxin 10	ATTCT repeat	Ataxia and epilepsy
SCA11	15q14-q21.3	SCA11	U	U	Almost pure cerebellar ataxia
SCA12	5q32	PPP2R2B	PPP2R2B	CAG repeat	Ataxia, tremor
SCA13	19q13.33	KCNC3	KCNC3	MM	Ataxia, mental retardation
SCA14	19q13.42	PRKCG	PRKCG	MM	Ataxia, myoclonus dystonia
SCA15	3p24.2-pter	ITRP1	ITRP1	D	Almost pure cerebellar ataxia
SCA16	8q23-q24.1	U	U	U	Almost pure cerebellar ataxia
SCA17	6q27	TBP	TBP	CAG repeat	Ataxia, chorea, psychiatric manifestations, dementia, epilepsy
SCA18	7q31-q32	U	U	U	Ataxia, sensory neuropathy
SCA19*	1p21-q21	U	U	U	Ataxia, myoclonus, cognitive impairment
SCA20	11	U	U	U	Ataxia, disphonia
SCA21	7p21.3-p15.1	U	U	U	Ataxia, parkinsonism
SCA22*	1p21-q23	U	U	U	Ataxia
SCA23	20p13-p12.2	U	U	U	Ataxia, sensory neuropathy
SCA24	1p36	U	U	U	Almost pure cerebellar ataxia
SCA25	2p21-p15	U	U	U	Ataxia, sensory neuropathy
SCA26	19p13.3	U	U	U	Almost pure cerebellar ataxia
SCA27	13q33.1	FGF14	FGF14	MM	Ataxia tremor mental retardation
SCA28	18p11.22-q11.2	U	U	U	Ataxia, ophthalmoplegia
DRPLA	12p13.31	ATN1	Atrophin 1	CAG repeat	Ataxia, myoclonus, seizures, psychiatric manifestation, dementia
Undefined**	16q22.1	PLEKHG4	Puratrophin 1	5' SNS	Ataxia, sensory neuropathy

with sensory motor peripheral neuropathy even a spastic paraparesis with minimal cerebellar ataxia. SCA6 typically has a pure phenotype but dystonia or parkinsonism have been described. SCA7 is characterised by maculopathy, cerebellar degeneration and pyramidal signs. The maculopathy can precede the appearance of the cerebellar ataxia by up to 20 years. SCA17 is distinguished by pronounced cognitive impairment/psychosis and behavioural changes plus parkinsonism, chorea and seizures in addition to cerebellar ataxia. DRPLA is very rare and the phenotype is variable, with dementia, psychosis, seizures, chorea and myoclonus and can mimic Huntington's disease.

The autosomal recessive ataxias

The autosomal recessive ataxias are a group of neurodegenerative disorders with early onset (<20 years).¹ However, since genetic tests have been introduced in clinical practice, it has become apparent that the age at onset can be variable (e.g. presentation of Friedreich's

ataxia or AOA2 in adulthood).

Pathogenetically they can be divided into two main categories:

1. Lack of energy control and oxidative stress are the main underlying mechanisms that lead to neurodegeneration. This group includes Friedreich's ataxia (FRDA), ataxia with isolated vitamin E deficiency (AVED), abetalipoproteinaemia and Cayman ataxia.
2. Defects in DNA repair and processing. This group includes ataxia telangiectasia (AT) and AT-like disease, Nijmegen breakage syndrome, AOA1, AOA2 and spinocerebellar ataxia with peripheral neuropathy (SCAN) (Table 3).

Friedreich's ataxia

FRDA is the most common inherited spinocerebellar ataxia with estimated prevalence of one in 30,000-50,000 in the Caucasian population and carrier frequency of 1 in 85.⁹⁻¹⁰

FRDA is rare in American Indian, African and Asian populations.¹¹

In more than 95% of the patients it is caused by a homozygous GAA repeat expansion in the first intron of the FRDA gene.¹² The remaining 2-5% are compound heterozygotes for one GAA expansion and a micro deletion or point mutation on the other allele. Therefore genetic testing is widely available and to date there have been no reported cases of two point mutations. Age at onset is between 5-25 years of age. There are two main phenotypes. Early onset FRDA is characterised by ataxia, deep sensory loss, hyporeflexia, nystagmus, extensor plantars, optic atrophy and deafness which is variably associated with scoliosis, cardiomyopathy and diabetes. MRI in these cases shows cervical spinal cord atrophy with normal cerebellum. The second phenotype, which has onset of ataxia after 25 years of age, is associated with pyramidal features and retained tendon reflexes. The MRI shows mild midline cerebellar atrophy.

Table 2: Modified Harding's classification of ADCAs. **A British ADCAII family negative for the SCA7 mutation has been reported.²

ADCA Type	ADCA I	ADCA II	ADCA III
Clinical Presentation	Cerebellar syndrome with ophthalmoplegia / pyramidal / extrapyramidal signs / cognitive impairment / peripheral neuropathy	Cerebellar syndrome with pigmentary retinopathy	Pure cerebellar syndrome
Neuropathology	Degeneration of the cerebellum, with basal ganglia / cerebral cortex / optic nerve / ponto-medullary systems / spinal tracts / peripheral nerves	Cerebellar and pigmentary retinal degeneration	Cerebellar degeneration
Genetic loci	SCAs 1, 2, 3, 4, 8, 10, 12, 13, 17, 18, 19/22, 20, 21, 23, 24, 25, 27, 28, DRPLA	SCA7**	SCAs 5, 6, 11, 14, 15, 16, 26

Table 3: Genes/loci and molecular defects accounting for autosomal recessive ataxias.

AR = autosomal recessive; D = deletions; I = insertions; MM = missense mutations; NM = nonsense mutations; FM = frameshift mutations.

AR ataxias	Genomic Location	Gene/Locus	Protein	Mutation	Main clinical features
Friedreich's ataxia	9q13	FRDA	Frataxin	GAA repeat (intronic)	Ataxia sensory loss, Hyporeflexia, cardiomyopathy, diabetes
Ataxia with vitamin E deficiency	8q13.1-13.3	TTPA	Alpha tocopherole transfer	FM/MM	Friedreich like phenotype but with head tremor and retinopathy
Abetalipoproteinaemia	4q24	MTP	Microsomal triglyceride transfer	MM	Friedreich like phenotype but with retinopathy, acanthocytosis Steatorrhea
Cayman ataxia	19p13.3	ATCAY	Caytaxin	MM	Ataxia mental retardation
Ataxia telangiectasia	11q22-23	ATM	Ataxia telangiectasia mutated	D, MM	Telangiectasias, immune deficiency predisposition to cancer increase alpha fetoprotein
Ataxia telangiectasia-like disorder	11q21	MRE11	Meiotic recombination 11	MM/NS	Milder course than AT
Ataxia with oculomotor apraxia (AOA1)	9p13	APTX	Aprataxin	I,D,MM	Ataxia choreoathetosis, oculomotor apraxia, hypolabuminaemia
Ataxia with oculomotor apraxia (AOA2)	9p34	SCAR1	Senataxin	MM/NSM	Ataxia choreoathetosis, neuropathy increased alphafetoprotein/CK
Spinocerebellar ataxia with axonal neuropathy	14q31	TDP1	Tyrosyl-DNA phosphodiesterase1	MM	Ataxia ,neuropathy, hypolabuminaemia, hypercholesterolaemia

The age at onset and severity of disease are inversely correlated with expansion size, and there is a direct correlation with the systemic symptoms.¹³⁻¹⁴ The expansion interferes with the FRDA gene transcript. The size of the smaller allele has a closer relationship to the phenotype because it is the major determinant of the amount of the encoded protein, frataxin.

Frataxin is a mitochondrial protein that appears to be involved in iron handling (storage and transport), biosynthesis of iron-sulphur (Fe-S) centres, oxidative phosphorylation and antioxidant function.¹⁵⁻¹⁸

Treatment trials have focused on antioxidants. An open label trial using CoQ10 and Vitamin E in FRDA patients for four years reported an improvement in cardiac function.¹⁹ Idebenone, a derivative of CoQ10, seems to have an effect on cardiac hypertrophy but not on cardiac function.²⁰ However, it is unclear if antioxidants affect neurological symptoms.

Ataxia with isolated vitamin E deficiency

AVED is caused by a mutation in the alpha-tocopherol transfer protein responsible for transport of the vitamin E into very-low density lipoproteins. Vitamin E in the plasma is reduced to less than 10%.²¹

This condition is more prevalent in North Africa and in the Mediterranean population.²² The phenotype is similar to FRDA with early onset. Frequently a head tremor with less prominent sensory peripheral neuropathy

and pigmentary retinopathy help distinguish AVED from FRDA.

Different mutations are responsible for the severity of the phenotype. Truncating mutations lead to a very early onset and severe progression of the disease. Conversely, missense mutations result in a less severe phenotype.²¹

Vitamin E is an antioxidant; its deficiency causes neurodegeneration through lipid peroxidation of the membranes and oxidative stress.²³ Vitamin E supplementation can modify disease progression and, if the therapy starts early, the occurrence of cerebellar ataxia.

Abetalipoproteinaemia

The disease is due to mutations in the gene that codes for a subunit of the microsomal triglyceride transfer protein (MTP).²⁴ These mutations seem to prevent formation of VLDL, thereby reducing vitamin E level. Vitamins A and K are also reduced due to fat malabsorption. In addition to the neurological signs seen in AVED, acanthocytosis and retinopathy are also present.

Cayman ataxia

Cayman ataxia is a rare form of cerebellar ataxia identified in an inbred population of the Gran Cayman Island.²⁵ Affected individuals are homozygous for mutations in the ATCAY gene encoding caytaxin. The protein is similar to the alpha-tocopherol binding protein. Patients with this condition present early onset hypotonia, cerebellar ataxia and psy-

chomotor retardation. Neuroimaging shows atrophy of the cerebellum.

Ataxia telangiectasia

AT is a common recessive ataxia with prevalence of 1 per 100,000 live births in the USA.²⁶ Typically the age at onset is before five years and progression is rapid with significant deterioration within a few years. The clinical features are oculocutaneous telangiectasias, cerebellar ataxia, immune defects and an increase risk of malignancy, especially leukaemia. A high serum alpha fetoprotein is present. In AT, cells are hypersensitive to ionising radiation which can be a useful diagnostic test.

AT is caused by mutations in the ATM gene.²⁷ The protein encoded by this gene is involved in transduction, in mitogenic signals and meiotic recombination cell-cycle control regulating responses through other tumour suppression proteins P53, CHK1 and CHK2.²⁸

The ataxia telangiectasia-like disorder (ATLD) is clinically very similar to AT. Age of onset is later and the progression less severe. It is distinct from AT by the absence of telangiectasia and high alpha fetoprotein. Another similar condition to AT is the Nijmegen syndrome(NBS)²⁹ characterised by microcephaly and psychomotor delay development. ATLD and NBS are due to mutations in the MRE11 and NBS1 genes respectively. Both of these proteins are involved in DNA repair. There is only symptomatic treatment for all these conditions.

Ataxia with oculomotor apraxia (AOA)

This syndrome has two distinct conditions, AOA type 1 and 2. Both AOA1 and AOA2 have onset later than AT, usually above 7 in AOA1 and 10 in AOA2, although adult onset has been reported.³⁰ AOA1 and AOA2 are caused by mutations in aprataxin (APTX) and in senataxin (SETX) respectively. Cerebellar ataxia and sensory motor peripheral neuropathy are common findings. Oculomotor apraxia is common in AOA1 and occurs in nearly half of patients with AOA2. Extrapyramidal signs, such as chorea and dystonia are present, in addition to mild cognitive impairment. In contrast to AT, neither AOA1 or 2 have immune disorders nor the tendency to develop cancer. AOA1 has hypoalbuminemia and hypercholesterolemia in AOA1 and increased alpha-fetoprotein and in some cases an increase of CK in AOA2. An allelic variant of AOA2 is a rare form of autosomal dominant juvenile lateral sclerosis (ALSA4).

Genetic counselling

In autosomal dominant ataxia, 50% of the offspring, independent of sex, will inherit the

mutant allele. However, genetic counselling is complex. In SCA families there is a large inter and intra-familial phenotypic variability, largely, but not entirely due to the CAG repeat instability.

It is particularly challenging when the CAG repeat is highly unstable, for example in SCA7. In this condition, it is not uncommon for an affected individual to have no family history or in some cases the presence of a late onset visual failure without cerebellar ataxia in one of the grandparents.

Genetic counselling is also problematic for subjects with intermediate alleles that have the potential to expand in future generations. Pre-symptomatic and pre-natal testing are also more difficult when the disorder is inherited from an affected father. SCA8 represents a particular problem for genetic counselling as neither the size nor penetrance of pathogenic alleles is known with any certainty. Several ADCA families have been reported in which a SCA8 expansion does not segregate with the affected phenotype. Subjects with the expansion remain unaffected in old age.³¹ Until further clarification on the pathogenesis of this mutation

becomes available, in the authors opinion, SCA8 genetic testing for diagnostic and pre-symptomatic purposes is inappropriate.

Genetic counselling for the recessive ataxias is more straightforward. In a family with one affected child, the risk to subsequent pregnancies is 1 in 4. Two thirds of unaffected siblings will be carriers. Where a genetic test is available, prenatal diagnosis and carrier screening can be carried out.

Conclusion

The inherited ataxias are a relatively common heterogeneous group of neurodegenerative disorders. In the last two decades a collaborative effort has been successful in identifying the genetic defects that underlie several of these conditions, which have made genetic testing possible. However, a disease modifying treatment is available only for AVED.

Establishing a precise diagnosis is important for clarifying the condition and its prognosis. For the great complexity of these conditions, the multidisciplinary approach is of great value in the management for both patients and their carers.

Establishing a precise diagnosis is important for clarifying the condition and its prognosis. For the great complexity of these conditions, the multidisciplinary approach is of great value in the management for both patients and their carers

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Sleep-Related Disorders

Sleep-related disorders have progressively achieved a higher profile in neurological practice in recent years, with the inception of more subspecialty clinics, although the UK still lags behind other countries in such provision. As with other neurological conditions, possible accounts of sleep-related disorders are to be found in stories and novels, which may predate clinical recognition.

As is well-known,¹ one sleep-related disorder takes its name from a literary description, viz. the Pickwickian syndrome. In Charles Dickens's *Posthumous Papers of the Pickwick Club* (1837), Joe the fat boy is reported to be obese, with a ruddy complexion, hypersomnolence, and dropsy, features which subsequently prompted use of the term "Pickwickian syndrome" to describe similar cases, a term more recently superseded by obstructive sleep apnoea-hypopnoea syndrome (OSAHS). However, Cosnett, reviewing this case and other possible instances of sleep-related disorders in the works of Dickens,² suggests that Joe may in fact have had a diencephalic tumour or possibly suffered the consequences of a head injury. He also identifies Mr Willet in Dickens's *Barnaby Rudge* (1841) as a possible case of OSAHS.

Although only described as such in recent years, OSAHS has in all likelihood been around for centuries, possibly millennia. Dionysius, the obese tyrant of Heracleia on the south coast of the Black Sea in the fourth century BC, was in danger of choking if he fell deeply asleep, and thus had to be woken with fine needles pricked into his skin.³

Another possible account occurs in Anton Chekhov's play *The Cherry Orchard* (1903): Boris Borisovich Simeonov-Pishchik, a landowner, "drops asleep and snores" in the midst of speaking, only to wake again "at once" and continue what he was saying. Later, he reports that he has high blood pressure and has had a stroke twice already, which makes dancing difficult, before again falling asleep, snoring, and waking almost at once.⁴ OSAHS may present in the neurological clinic in various guises, including headache, blackout, seizure, stroke, or memory impairment,⁵ and may be associated with high blood pressure and be a risk factor for stroke.

Before he undertook his major expeditions in Africa, Dr David Livingstone had his uvula excised in 1852, ostensibly because he suffered from "clergyman's sore throat", a disorder which affected his ability to preach to large numbers of people.⁶ However, he comments of the uvula that:

It sometimes fell down on the opening of the wind-pipe in sleep & made me start up as if suffocating.⁷

One wonders if perhaps these were episodes of sleep apnoea, although certainly one nowhere has the impression that Livingstone suffered from excessive daytime somnolence. Another possibility is the "sleeping-choking syndrome", a little-described parasomnia.

Of the many recognised parasomnias, sleepwalking is perhaps the most dramatic, and one which artists have been willing to make use of: Bellini devotes an opera to the subject (*La Sonnambula*). In Johanna Spyri's *Heidi* (1880), strange things come to pass when the little girl is residing in the Frankfurt city home of Clara Sessman: each morning the doors are found wide open, despite being closed at night, leading the servants to believe that there is a ghost in the house. Herr Sessman summons his old friend the doctor to sit up with him all night to solve the mystery: Heidi is a sleepwalker. The doctor elicits the

history that during her somnambulation Heidi is dreaming of her natal home with her grandfather in the mountains. The diagnosis is that Heidi is consumed with home-sickness and must be sent back to her native mountain air. "This illness is not one to be cured with pills and powders" the doctor shrewdly advises. Interestingly, it had been previously mentioned that Heidi's deceased mother, Adelheid, was "a sleep-walker, and had fits".⁸

Excessive daytime somnolence often provokes a provisional diagnosis of narcolepsy, but the full syndrome of daytime somnolence, impaired nocturnal sleep, cataplexy, sleep paralysis, and hypnogogic or hypnopompic hallucinations is rather seldom encountered in clinical practice. One possible literary example of a character with sleep paralysis is to be found in *The Subtle Knife*, the second book in Philip Pullman's trilogy *His Dark Materials*: the aeronaut Lee Scoresby finds himself pursued by airborne enemies, who are counter-attacked by the thought commands of his passenger, the shaman Stanislaus Grumman:

"Pinned in his dream, Lee could neither move nor cry out, and he suffered the terror of the pilot as the man became aware of what was happening to him."⁹

Possible sleep-related disorders have also been identified in another Oxford based classic, the Alice books: the excessively somnolent dormouse at the mad tea party (*Alice's Adventures in Wonderland*, chapter 7), and the snoring The Red King and the White and Red Queens (*Through the looking-glass*, chapters 4 and 9).¹⁰

Sleep and its addenda were clearly subjects which fascinated William Shakespeare. Everyone knows "To sleep, perchance to dream" from the famous "To be or not to be" soliloquy in *Hamlet* (Act III, scene i, line 65). In *The Tempest*, Sebastian is clearly ahead of the medical thinking of his time when he remarks to Antonio "Thou dost snore distinctly. There's meaning in thy snores" (II;i:220-221). The many references to sleep in *Macbeth* include "wicked dreams abuse the curtain'd sleep" (II;i:50-51) and "sleep in the affliction of these terrible dreams, that shake us nightly" (III;ii:17-19). Might these possibly be early references to dream enactment in REM sleep behaviour disorder?

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Stroke in India

Incidence and prevalence

Stroke is a major health problem in India.¹ A recent community survey² in the eastern Indian city of Kolkata showed the prevalence rate of stroke to be 545 per 100 000 population. The average annual incidence rate of stroke in the same study was 145 per 100 000 persons per year.² These rates, age standardised to world standard population, are similar to or higher than many Western nations.³ These rates are also much higher than those reported previously from other parts of India.^{4,5} Stroke burden in India has been rising in the last few decades, in contrast to developed countries, where stroke prevalence has decreased or plateaued.^{6,7}

Reasons for the rise of stroke burden in India

The reasons for a rise in stroke burden in India include smoking, increasing longevity, and changes in lifestyle accompanying urbanisation. In India, the average life expectancy rose from 41.2 years in 1951-1961 to 61.4 years in 1991-1996.⁸ Indians may also be genetically prone to stroke due to a high prevalence of the metabolic syndrome consisting of central obesity, high levels of triglycerides, and low levels of HDL cholesterol with or without glucose intolerance.⁸

Studies of stroke risk factors in India

The Indian Council of Medical Research (ICMR), in 1989, found hypertension, diabetes mellitus, tobacco use and low concentration of normal haemoglobin, as the most important risk factors for ischaemic strokes.⁹ The World Health Organisation (WHO) Task Force Report on Stroke (1989), found hypertension, smoking, elevated blood lipid levels and diabetes as important modifiable risk factors for ischaemic stroke in India.¹⁰

sis was the most common mechanism in the prospective, hospital based Hyderabad Stroke Registry. This was followed by lacunar, cardio-embolic and extracranial carotid disease respectively.²¹ While intracranial disease is very uncommon in the West (<5%) and extracranial carotid artery disease is uncommon in far eastern countries like China and Japan (<5%), both vascular patterns are common in Indian stroke patients and this may be called 'the Indian pattern'. Common risk factors for the development of large and small artery disease are similar and constitute hypertension, diabetes and smoking.^{21,22} For cardio-embolic stroke, rheumatic heart disease, and ischaemic heart disease are dominant risk factors in India.²³

Stroke mortality

The World Health Organisation estimated that in 1990, out of 9.4 million deaths in India, 619,000 deaths were due to stroke, giving a mortality rate of 73 per 100,000 population. In the same year, the number of deaths due to stroke were 22 times that due to malaria, 1.4 times that due to tuberculosis, 4 times that due to rheumatic heart disease and almost equal to that due to ischaemic heart disease.²⁴ Stroke mortality rates among Indians have been found to be two to three times higher than the in Caucasians.²⁵

Stroke outcome studies in India

Limited data suggests that recurrence may be higher in India due to poor compliance with treatment and control of risk factors.²⁶ Of the stroke survivors, only about one third are fully independent in their daily activities of living while more than one fourth cases are bed ridden. The poor outcome in functional recovery may be due to lack of rehabilitation and treatment facilities.²⁶



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Due to the increasing life span, urbanisation and changing life style, stroke is already a major public health problem in India

What is specific to stroke in India?

Indian studies have shown that about 10% to 15% of strokes occur in people below the age of 40 years, which is high compared to other countries.^{11,12} Cerebral venous thrombosis and rheumatic heart disease are important causes of stroke in the young.¹² Subacute tubercular meningitis leading to arteritis or autoimmune angiitis are also important stroke risk factors.¹³ Reported risk factors among the young include coagulopathy, elevated lipoprotein(a) and elevated anticardiolipin antibodies.¹⁴⁻¹⁶ Some Indian studies have reported interesting causes of stroke, like viper envenomation and also suggested mechanisms like squatting whilst on the toilet as an important triggering factor for stroke in Indians, by raising the blood pressure.^{17,18}

Stroke subtypes in India

The Indian Collaborative Acute Stroke Study (ICASS), a prospective study on consecutive and CT-confirmed cases of acute stroke from the major university hospitals in India, reported that up to 80% of stroke patients were ischaemic in nature.¹⁹ In a population based study, done in Kolkata, CT scan proved infarction occurred in 68% of cases.²⁰

Among the ischaemic strokes, intracranial atherosclero-

Stroke services in India

There are no organised stroke services in many parts of India. The government health planners have so far focused their attention mainly on diseases related to infection and malnutrition. Secondly, low educational levels adversely affect the risk identification process and the taking of appropriate steps for stroke prevention. In the last decade, about fifty stroke units have sprung up in various cities of India. However, the majority of Indians live in villages, who cannot afford even a CT scan of the brain. General practitioners provide most of the stroke-related care in India. Home and traditional treatment of stroke is also an accepted practice in the rural areas of India. Many strange culture-specific beliefs about stroke treatment are in existence, one of which is that a massage with pigeon's blood can cure the paralysis.²⁷

Stroke thrombolysis in India

Tissue plasminogen activator (tPA) was only approved in 2006 for use in acute ischaemic stroke in India. At present approximately 15 stroke units in India use tPA. Thus far, approximately 400 patients have received intravenous tPA in different centres across the country. Intra-arterial thrombolysis therapy is being used in

approximately 10 centres in India with good results.²⁷ Most centres are in the private sector, although some government university hospitals have been running successful thrombolysis programs. The barriers towards stroke thrombolysis are due to a lack of infrastructure, lack of awareness and poor affordability. However, it is clear that hyperactive thrombolysis in acute ischaemic stroke is feasible in urban private and public sector tertiary hospitals and can be widely used if a greater number of dedicated stroke teams/stroke units become available, and the cost of drugs is reduced.

Conclusion

Due to the increasing life span, urbanisation and changing life style, stroke is already a major public health problem in India. It is likely to assume epidemic proportion in the coming years and cause enormous strain on India's limited health care resources. The thrombolytic therapy is available to very few people. The main national health planning strategy should be the primary prevention of stroke by controlling the major risk factors of hypertension, diabetes and smoking. Stroke registries need to be set up at community and hospital level to understand not only the risk factors but also various stroke subtypes and their short and long-term outcomes. Such efforts will go a long way in evolving health care policies for appropriate and cost effective preventive and treatment strategies for stroke in India.

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The Pathology of Raised Intracranial Pressure

Under normal circumstances intracranial pressure (ICP) is maintained in the range 5-15mmHg with continuous, small fluctuations reflecting physiological variations in arterial or venous pressure such as arterial pulsation, coughing and straining. Maintenance of intracranial pressure at these levels is critical to safeguarding adequate cerebral perfusion. Inside the unyielding box that is the skull, expansion of intracranial contents may precipitate a rise in ICP with potentially serious consequences. In this article a brief review of the historical concepts contributing to our understanding of raised ICP is provided followed by detail on the neuropathological findings in circumstances where ICP has been elevated in life.

Historical background

Initial observations on the consequences of raised ICP were influenced by the doctrine of Monro¹ (1783) and Kellie² (1824) which holds that, once the fontanelles have closed, the incompressible intracranial contents, comprising brain and blood, are contained within the rigid skull. Omitted from their description, but subsequently added by Burrows³ was the contribution of cerebrospinal fluid (CSF). The interaction of these components in the context of an expanding, intracranial tumour subsequently formed the basis for the description of the clinical stages of raised intracranial pressure by Theodor Kocher⁴ (Table 1). In stage 1, the increase in tumour volume is compensated for by a reduction in volume of blood and CSF resulting in no increase in ICP. However, as these compensatory mechanisms become exhausted ICP starts to rise slowly with clinical symptoms beginning to manifest (stage 2). In stage 3, the compensatory mechanisms are overwhelmed such that relatively small rises in tumour volume result in a large rise in ICP. Eventually, unchecked, intracranial pressure may rise to equal arterial blood pressure with resultant failure of cerebral perfusion, vasomotor paralysis, coma and, ultimately, death.

A number of intracranial pathologies may precipitate a rise in intracranial pressure which may be summarised in the 'four lump' concept comprising the mass, accumulation of CSF, vascular congestion and cerebral oedema (Table 2). In the majority of cases the pathology is

localised and, together with surrounding brain swelling, produces distortion of the brain with eventual herniation and pressure gradients between CSF spaces. For example a supratentorial mass lesion may lead to a pressure gradient between supratentorial and infratentorial compartments by occlusion of the subarachnoid space as the medial temporal lobe impinges on the tentorium. Coincident with this shift, the blood supply to the brain may be compromised by direct compression of cerebral blood vessels. This compounds vascular compromise as a consequence of rising ICP and falling cerebral perfusion pressure.⁵ A further consequence, therefore, of raised ICP is hypoxic/ ischaemic damage, both localised and diffuse.

Neuropathology findings in raised intracranial pressure

To the Neuropathologist the pathology of raised ICP is a function of the causative pathology, any associated, localised deformation of the brain, a reduction in CSF volume, shift of the brain and herniation with the associated vascular consequences (Figure 1). To these features can be added the consequences of any intervention to alleviate raised ICP.

Figure 1: Autopsy findings in raised intracranial pressure

- Tight dura
- Flattened gyri
- Compressed sulci
- Asymmetry of cerebral hemispheres
- Midline shift
- Internal herniation
 - subfalcine/supracallosal
 - tentorial
 - tonsillar
- External herniation
- Posterior cerebral artery infarction
- Posterior inferior cerebellar artery infarction
- Diffuse hypoxic/ischaemic injury
- Brainstem haemorrhage/ infarction



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Table 1: Clinical stages of raised intracranial pressure

	Intracranial response	Clinical symptoms/ signs
Stage 1	increase in tumour volume; compensatory reduction in CSF and blood volume; no rise in ICP	none
Stage 2	compensatory mechanisms exhausted; slow rise in ICP	drowsy, headache
Stage 3	rapid rise ICP; falling cerebral perfusion pressure	deteriorating conscious level; intermittent elevations in blood pressure and bradycardia
Stage 4	cerebral vasomotor paralysis; ICP equals mean arterial blood pressure; cerebral perfusion ceases	coma; fixed dilated pupils; death

Table 2: Causes of raised intracranial pressure

Mechanism	Example
Mass effect	tumour, haemorrhage, infarction, contusions, abscess
Brain swelling	diffuse traumatic brain injury, metabolic/ hypertensive encephalopathy, meningitis
Increased venous pressure	venous sinus thrombosis, heart failure, depression fractures over major venous sinuses causing obstruction
Obstructed CSF circulation and/or absorption	hydrocephalus, meningeal infiltration
Increased CSF production	meningitis, choroid plexus tumour



Figure 2: View of the head following removal of the calvarium. The dura is taut reflecting raised intracranial pressure as a consequence of diffuse brain swelling.



Supratentorial expanding lesions

A consequence of an expanding mass lesion in a cerebral hemisphere is compression and distortion of adjacent structures resulting in swelling of the brain. With this, the vertex may become compressed against the dura with obliteration of the subarachnoid space, flattening of the gyri and compression of the sulci. This can be demonstrated at autopsy by careful reflection of the calvarium, leaving the dura intact. Where brain swelling is present the dura are taut with the brain compressed against the inner surface such that reflecting the dura without damaging the underlying brain can be difficult (Figure 2). On removal of the brain the extent of distortion and displacement is often most evident on inspection of the base where tentorial herniation, brainstem ischaemia, third nerve compression and the consequences of vascular compromise may be present (Figure 3).

The extent of displacement and any secondary vascular complications are optimally demonstrated on sectioning the brain. Ipsilateral to an expanding mass lesion the lateral ventricle may become compressed whilst the contralateral ventricle may be enlarged as a result of obliteration of the foramen of Monro (Figure 4). Further expansion of the mass lesion then produces shift in the brain with associated internal herniation.

Supracallosal/ subfalicine herniation – lateral displacement of the cingulate gyrus under the free edge of the falx cerebri (Figure 4). With this there may be associated pressure necrosis of the cingulate gyrus in addition to ischaemia of the parasagittal cortex as a consequence of compression of the pericallosal arteries. Estimation of the degree of displacement of the herniated cingulate gyrus may serve as an indicator of the degree of midline shift.

Tentorial/ uncal herniation (Figure 4) – displacement of the medial temporal lobe structures downwards through the tentorial incisura. With this the midbrain may become distorted and displaced, compressing the contralateral cerebral peduncle against the free edge of the tentorium and the ipsilateral third nerve against the adjacent posterior cerebral artery. Clinically these manifest as dilatation of the pupil and hemiparesis ipsilateral to the expanding mass lesion. A further complication of tentorial herniation is necrosis of the inferomedial temporal cortex, which may be compressed over the tentorial edge. Similarly the posterior cerebral arteries are at risk of being compressed with associated vascular compromise of the medial and inferior occipital lobe (Figure 5).

Tonsillar herniation (cerebellar cone) – downward displacement of the cerebellar tonsil through the foramen magnum. This is recognised at autopsy as grooving of the inferomedial surface of the cerebellum associated with haemorrhagic necrosis of the tonsils and flattening of the medulla. This distortion of the caudal brainstem may be associated clinically with apnoea. Occasionally the posterior inferior cerebellar arteries may become compressed resulting in infarction of the inferior cerebellar hemispheres.

Brainstem haemorrhage (Duret haemorrhages) and infarction – representing the terminal events as a consequence of raised ICP. At autopsy these are recognised as small foci of haemorrhage and/ or infarction in the paramedian parenchyma of the rostral brainstem (pons and midbrain) towards the anterior aspect⁶ (Figure 3). Originally described by Duret, their pathogenesis remains unclear with compromise of the perforating branches of the basilar artery through downward displacement of the brainstem favoured.^{7,8}

Infratentorial (posterior fossa) expanding mass lesions

Mass lesions in the posterior fossa may lead to obstruction of CSF flow resulting in lateral and third ventriculomegaly as a consequence of displacement of the aqueduct and fourth ventricle. As with a supratentorial mass lesion, tonsillar herniation may occur with the associated vascular complications. Upwards displacement of the superior cerebellar hemispheres and vermis through the tentorial incisura may also occur

Figure 3: Base of the brain. As a consequence of an expanding supratentorial mass lesion, in this case a large, right-sided subdural haematoma, there is ipsilateral tentorial herniation (arrows) with haemorrhagic necrosis of the involved medial temporal cortex. Shift in the brainstem has also resulted in compression of the contralateral cerebral peduncle against the free edge of the tentorium (arrowhead). Finally, haemorrhagic necrosis is present in the midline of the midbrain (Duret haemorrhages).

resulting in reverse tentorial herniation, recognised at autopsy as upwards displacement of the superior vermis with associated distortion of the medial temporal lobes. This may be exacerbated by supratentorial decompression in the presence of a pressure gradient across the tentorium from infra- to supratentorial spaces. Clinically the result is rapid onset, bilateral extensor rigidity and loss of pupillary light reflexes.

External cerebral herniation

As noted above, as a rigid, closed box the skull, though ideally constructed for the protection of the delicate intracranial contents, is 'flawed' when the volume of those contents rises resulting in a rise in intracranial pressure. To address this in circumstances such as diffuse traumatic brain injury or malignant middle cerebral artery infarction, where medical interventions may have met with limited success, decompressive craniectomy has been utilised as a means to permit the intracranial contents to expand and so reduce ICP.^{9,10} Where there is a defect in the calvarium, either by such surgical intervention or through trauma, segments of cortex may herniate resulting in external herniation. Pressure necrosis of the cortex at the margins of the hernia may then ensue with further ischaemic damage of the herniated cortex following.

Conclusion

To the Neuropathologist the consequences of an expanding mass lesion within the rigid, closed skull are readily evident at autopsy as a constellation of findings revealing the degree of distortion of the intracranial contents in an attempt to accommodate the added volume of the mass lesion and the subsequent rise in ICP which follows as these compensatory adjustments fail. An awareness, therefore, of the range of abnormalities and their often inconspicuous appearance serves to inform the neuropathology autopsy examination where raised ICP is suspected from removal of the calvarium to review of the histology for the subtleties of early, acute hypoxic/ ischaemic damage.

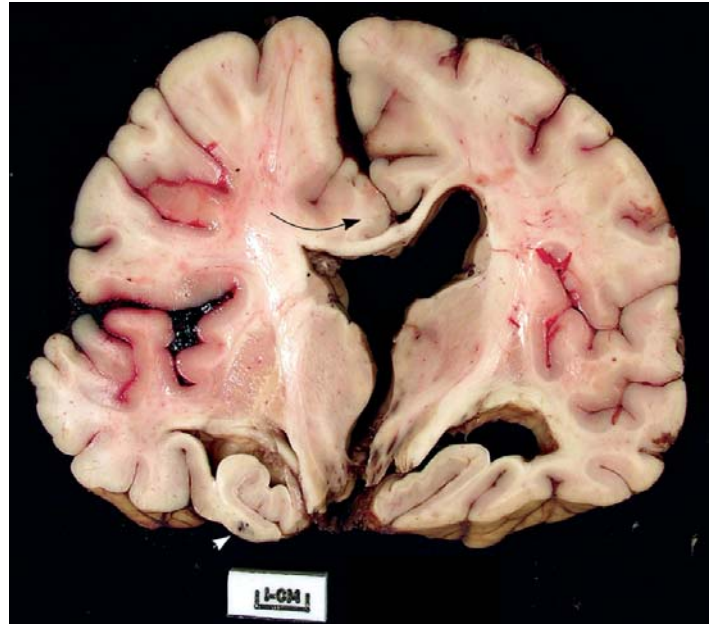


Figure 4: Coronal section of cerebral hemispheres. As a consequence of a subdural haemorrhage on the left hand side there has been midline shift, demarcated by supracallosal herniation from left to right (arrow), tentorial herniation with pressure necrosis of the inferomedial temporal lobe (arrowhead) and contralateral ventriculomegaly arising from obstruction of the foramen of Monro.

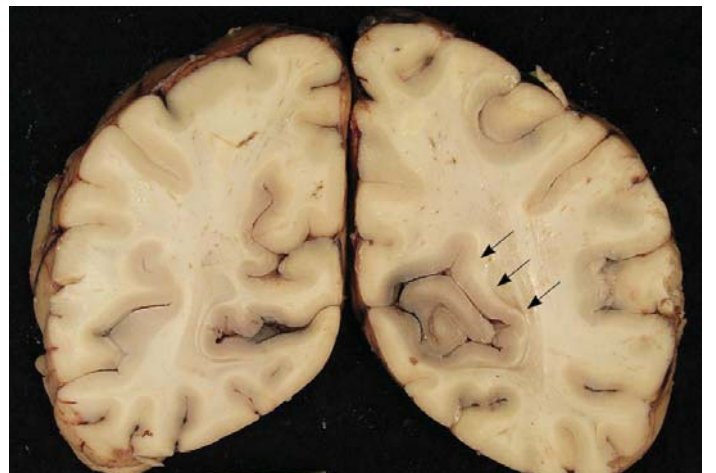


Figure 5: Coronal slices of the occipital lobes. Compression of the posterior cerebral arteries with tentorial herniation may lead to ischemia of the medial occipital lobes (arrows).

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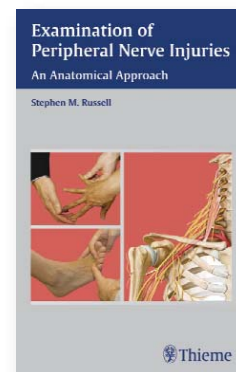
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Examination of Peripheral Nerve Injuries

I think the author, Stephen Russell, and the publisher, Thieme, have produced a little gem in this book. Although written by a surgeon, and therefore tilting for a surgical market (hence the 'injuries' of the title), nonetheless there is much in this book for neurologists, trainee or otherwise. Since peripheral nerve problems are relatively uncommon in the general neurology clinic, many neurologists will perhaps retain only sketchy recollections of peripheral nerve pathways, motor and sensory innervation, clinical findings and syndromes; indeed it is taken as read by the authors (Staal et al.) of the excellent *Mononeuropathies: examination, diagnosis and treatment* (London: Saunders, 1999) that most neurologists will not have this information at their fingertips and will need to have recourse to a textbook. In eight chapters Russell systematically tackles anatomical course, motor innervation and testing, sensory innervation and (briefly) clinical findings

and syndromes of median, ulnar, radial and sciatic nerves, brachial and lumbosacral plexus, all admirably concise and well-illustrated. Clearly the author writes from an experiential perspective (witness, "Mentioning the phrase 'brachial plexus anatomy' is likely to clear a medical school classroom faster than a fire drill"), and is particularly good on differential diagnosis (radiculopathy vs. plexopathy vs. mononeuropathy) although these sections might have been highlighted to better advantage. There are a few typos (e.g. is the muscle piriformis or pyriformis?), a thorough index, and no references (where this book does lose out to Staal et al.). Personal experience indicates that the book can reside unobtrusively in the briefcase until required. Recommended for those wishing to brush up on peripheral neurology.

AJ Larner, WCNN, Liverpool, UK.



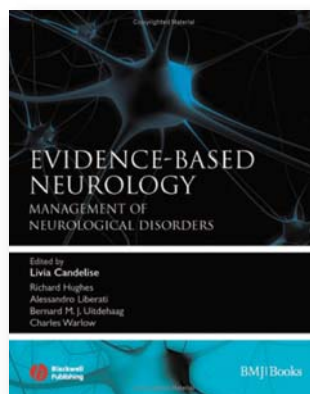
Russell SM
 Published by: New York - Thieme, 2006
 ISBN: 9783131430717
 Price: Euros 39.95

Evidence-Based Neurology

What is it about EBM that so polarises opinion? Try googling 'cult' and 'EBM' to feel the heat. Maybe it comes down to how you like evidence. Glossy brochures, coloured bar charts (with minutely-typed references in obscure journals) and a big headline (ideally delivered by an opinion-leader in an exotic location), or worthy lists and tables of less-than-perfect studies illustrated with forest plots. This book is unashamed in its hyphenated title. Can it tempt the non-believer? Is it the best place to look if you are already a follower? And if you don't give a stuff for the argument can it just help you to do the job better?

Part one is a four chapter introduction to the world of EBM, and parts two and three present the evidence for intervention with neurological symptoms and then neurological diseases. The spectre of EBM-pathergy (Warlow has claimed EBMitis for those who can't function without it) hangs over the introductory chapters which are enjoyable, educational and thought-provoking though not terribly useful in a clinic. Chapter one is defensive (one paragraph identifies the enemies of EBM – you're either with 'em or against 'em) and demanding: 'traditional clinical research is too narrow... health care systems should promote research into areas that are not likely to attract resources'. Chapter two (what to do when there is no evidence) is witty and wise, defends clinical wisdom over EBMitis (a big hurrah from the non-believers) and promotes the position of 'well-informed uncertainty'. Chapter three considers outcomes on which evidence is based. The bias is towards the 'patient-centred', with QoL getting a particularly soft reception. The claim that 'the overall objective of any intervention in epilepsy is to improve the patients' QoL' might be disputed by the families of SUDEP sufferers. Chapter four highlights the lack of research into diagnostics and illustrates how the evidence-based approach might be applied here too (is there no hiding place?). Some scepticism about symptoms and disease might have fitted in here too. Is it the existence of a pathology or a patient support group, a headline in the tabloids or an expensive wonder cure that counts?

The rest of the book is divided between EBM in neurological symptoms and in neurological disease. Here authors take symptoms or diagnoses and apply the method. The list of symptoms/diseases covered is comprehensive though there are notable omissions in both categories (for example fatigue, Huntington's disease). Clinical questions are framed e.g. 'what are the consequences of sleep disordered breathing on the severity and outcome of stroke', and the evidence presented, as text, table or plot. Some chapters also add a clinical scenario to illustrate the clinical dilemma. The difficulty this approach faces is that for any one neurological symptom or diagnosis there may be hundreds of clinical questions, but a book can really only allow the consideration of four or five. The other inevitable is that a book dates. In Parkinson's disease the NICE guidance, freely available on the web, covers



Edited by: Candelise L, Liberati A, Uitdehaag B, Hughes R, Warlow C.
 Published by: BMJ Books
 ISBN: 9780727918116
 Price: £75

more and is more up to date. In epilepsy the book was written before the publication of SANAD, which answers three of the set questions. Sometimes questions are considered that truly feel done to death (stroke units). These pages have numerous authors (there are 55 in total) and lack a unity of style. It works best where the evidence is presented then weighed and placed in context by a neurological greybeard. It works least well where the questions are asked, the studies listed, and the conclusion made that the available evidence is not good enough and, groan, that more and better studies are needed. The editing and language could have been better. One chapter refers to a patient with a left field cut smoking one package of cigarettes, another repeatedly asks 'which is the risk' when 'what is the risk' is intended. I searched for the unreferenced 'Prentiss criteria', before deciding the authors meant Prentice. For a book that takes a dim view of commercial involvement it was disappointing not to read of conflicts of interest.

A multi-authored medical book is unlikely to be entirely free of drug company influence, but a buyer is entitled to know which author's opinions and which evidence might be sponsored. The otherwise excellent chapter on Migraine doesn't note that the cited US Evidence-based guidelines (which don't, incidentally, look at cost-effectiveness) were sponsored by, amongst others, Abbott, AstraZeneca, BristolMyersSquibb, and Glaxo Wellcome. Occasionally it reads as if the authors haven't distanced themselves sufficiently from the sponsored merry-go-round to be completely objective. How else could the conclusion to the Parkinson's chapter mention every other drug available yet omit the evidence-based conclusion that L-dopa, certainly in the short term and maybe even in the long, gives the best motor control with the least adverse effects?

Will this book convert the sceptic? I doubt it; if neurological professionalism involves stating weak evidence with great confidence it might just get in the way. Can it help the jobber do the job? Yes if they believe in practice supported but not dictated by whatever good evidence is available. Is it the best place for them to look? It might be quicker to look here than Cochrane or NICE, but you may not find the answer to your question and if you do it may be out of date. Any doubts about an author's independence or authority will also undermine its value.

So I approve wholeheartedly of the concept, and applaud the effort put into the book, but I couldn't recommend individuals to buy it for their daily use; at £75, it's also way too expensive to buy for a browse. On the other hand, putting it in a prominent position on your bookshelf is a sure way to let everyone else know where you stand.

Paul Morrish, Royal Sussex County Hospital, UK.

Nerve Excitability Studies in the Present Era

Most clinicians with more than a passing interest in peripheral nerve diseases may have come across recent research in the area of axonal excitability. Excitability testing is not, in fact, a particularly new technique but its historical vogue was short-lived because of the development of accurate methods of measuring nerve conduction velocities in the last half century. More recently, it has experienced a renewed interest in specialised laboratories in the UK, Germany, Australia and Japan, because of highly refined software that has enabled rapid and reproducible *in vivo* testing of subjects.

Excitability testing involves measuring the threshold current required to stimulate an axon or population of axons, most commonly at a single accessible nerve point in the limb. It measures the relative ease with which an axon or axons in a nerve bundle can be depolarised past the threshold for excitation. In this regard, it differs from nerve conduction which is primarily concerned with the speed and security of impulse conduction between two points on the largest and fastest axons. The latter has been particularly useful for the study of demyelinating neuropathies, but even so, conduction velocity can be altered by changes in membrane potential and Na⁺ channel permeability, as well as disorders of myelination, not to mention cooling.

The method of excitability testing most commonly employed now uses threshold tracking.^{1,2} When determining the threshold of a nerve bundle, one measures the response obtained either from the compound motor action potential amplitude over muscle when stimulating the motor fibres, or the sensory action potential when stimulating cutaneous afferent fibres. The stimulus current is varied to produce a target potential of fixed size. Then, membrane potential is disturbed by subthreshold conditioning currents or by suprathreshold stimuli that cause axons to discharge. The proportional change in current required to elicit the target potential in response to these conditioning stimuli is measured. Such relative changes in threshold are more useful than absolute changes which can be influenced by current access to the nerve.

A battery of excitability tests is most efficiently performed now with software ('QTracs') developed by Professor Hugh Bostock at the Institute of Neurology, London. Multiple measures can be obtained in a short and convenient protocol ('Trond') which is usually more tolerable to the subject than standard nerve conduction studies.³ The study usually takes 10 minutes for motor, and 15-20 minutes for sensory studies. Most published studies have been performed on the median nerve at the wrist. There are four main domains in the most commonly employed protocol:

- (i) strength-duration properties – this is the study of rheobase (the minimum charge required to just cause excitation with a current of infinitely long duration) and chronaxie (the current duration corresponding to twice the rheobase) estimated by different pulse widths and their corresponding intensities required to elicit the target potential;
- (ii) threshold electrotonus – often used synonymously with excitability tests. Threshold electrotonus provides insight into how axons accommodate (adapt to) long-lasting changes in membrane potential. In it, we measure the changes in threshold that occur during and after subthreshold depolarising and hyperpolarising currents of set intensity but of varying length;
- (iii) current-voltage relationship – here, the threshold change is measured immediately after the injection of subthreshold currents of set length but of varying

intensity, in the depolarising and hyperpolarising directions;

- (iv) recovery cycle – this documents the threshold changes following a suprathreshold conditioning stimulus that causes the axons to discharge. The recovery cycle consists of three phases: absolute and relative refractory periods, the early superexcitable period and late subexcitable period.

From earlier experimental work on the myelinated rat axon and human studies, the patterns of changes can give an indication of channel permeabilities. The patterns of threshold alterations and their interpretation are too complex for the scope of this article, but some fundamental processes can be deduced with this method. These include a change in the resting membrane potential. The properties of various voltage-gated ion conductances at the node and internode can also be determined, such as the behaviour of transient and persistent Na⁺ channels which are responsible for depolarisation during activation, fast and slow K⁺ channels which limit depolarisation, and inwardly rectifying currents which permit ingress of Na⁺ and K⁺ ions and limit activity-dependent hyperpolarisation. The interpretation of the changes is now greatly aided by a computer model developed by Professor Bostock, which can alter conductances and weightings of different parameters both at the node and internode, to see if the changes observed in testing can be simulated in the model.⁴ A noteworthy example is the faithful reproduction of the test results in a group of patients suffering acute tetrodotoxin poisoning by reducing Na⁺ channel permeability in the model by a factor of 2.⁵ Tetrodotoxin is the poison of puffer fish and blocks Na⁺ channels.

The table lists the findings of burgeoning clinical research that has now been performed in various neuropathic disorders over the years. The method is also proving of worth in assessing plastic changes seen in peripheral nerves following central nervous lesions and disorders.⁶ It can be modified to assess the effect of a physiological experiment such as limb ischaemia (see Figure) on a single excitability parameter. No doubt, the list will expand with the increasing availability of commercial software and hardware systems developed for the method above. There are though, limitations to this elegant method for studying nerve pathophysiology. First of all, there has to be a sufficiently large target response to study, and this can be a problem with moderate to severe neuropathies. Testing is restricted to sites of nerve accessibility, which may explain the lack of evidence for hyperexcitability in some conditions such as neuromyotonia, where the ectopic motor discharge may arise from nerve terminals.⁷

What relevance does this have presently for the clinician at the coalface not involved in studying nerve physiology? To date, the technique has not proved a useful diagnostic tool. Even where very significant differences have been observed between patient and control groups in a certain disorder, the variability of the results has prevented unambiguous categorisation of a single test result in a patient. Further, there has not been shown to be sufficient specificity in the various disorders, with sometimes different conditions producing similar alterations in their excitability profiles. For example, the changes observed in end-stage liver disease are quite similar to those of Fabry disease, showing perhaps the result of a common final pathway of ischaemic deactivation of the Na⁺/K⁺ ATPase pump.^{8,9} However, there could be a role for monitoring nerve function. Another problem is that the properties assessed belong to nerves that are still able to generate



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David Burke, MD, DSc, FRACP, is a consultant neurologist and clinical neurophysiologist at Royal Prince Alfred Hospital, and is Professor and Dean, Research & Development (Health) at the University of Sydney. He has published extensively on axonal excitability in human subjects, as well as on human motor control.

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Figure

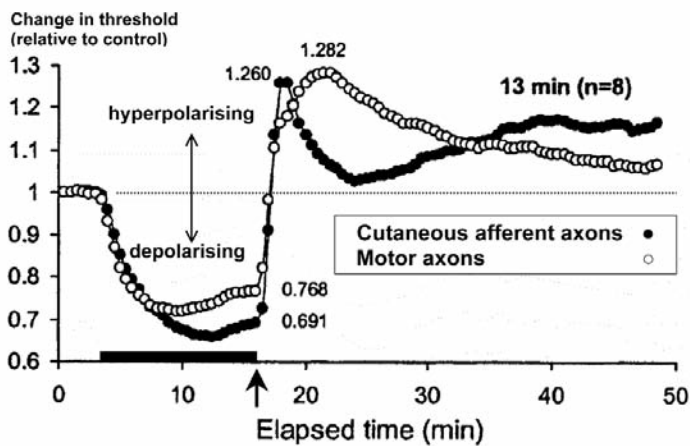


Figure legend:
Median cutaneous afferent and motor axons stimulated at the wrist. Mean excitability data for 8 subjects, before, during (heavy bar) and after ischaemia for 13 min with a cuff around the upper arm. During ischaemia, there is a decrease in threshold (depolarisation) and, following release of ischaemia at the vertical arrow, there is an increase in threshold (hyperpolarisation) relative to the control level. Note that the changes for sensory and motor axons differ. The subjects all experienced post-ischaemic paraesthesiae following release of the ischaemia, and they occurred during the falling phase of the notch on the threshold trace for cutaneous afferent axons. None developed post-ischaemic fasciculation.

impulses. Paradoxically, if the nerves with the most disordered thresholds for excitation drop out, excitability studies might normalise. However, nerve excitability studies can provide unique information about the state of the axon and, as such, they complement other neurophysiological tests: standard nerve conduction, EMG and motor unit estimation. Excitability studies have not only advanced our understanding of nerve dysfunction but also led to new approaches to management. For example, one study in Machado-Joseph disease (SCA-3) detected increased strength-duration time constant, probably due to an excessive persistent Na⁺ current. The authors were prompted to try mexiletine to reduce these currents, and this resulted in a partial normalisation of the abnormality and a dramatic reduction in disabling muscle cramp in their cohort.¹⁰

For a more comprehensive review of the topic, the reader is referred to The Handbook of Clinical Neurophysiology, Elsevier, with the chapter "Assessment of Nerve Excitability Properties in Peripheral Nerve Disease" by Lin, Kiernan, Burke and Bostock.

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Table: Clinical peripheral nerve excitability studies to date	
Disorder	Reference (first author)
Metabolic and medical conditions	
Diabetic neuropathy	Weigl 1989, Strupp 1990, Horn 1996, Kuwabara 2002, Kiernan 2002, Kitano 2004, Krishnan 2005, Misawa 2005/6, Yerdelen 2007
Uraemic neuropathy	Kiernan 2002, Krishnan 2005/6
Hepatic neuropathy	Ng 2007
Critical illness neuropathy	Z'Graggen 2006
Fabry disease	Tan 2005
Acquired hypokalaemic paralysis	Kuwabara 2002
Mononeuropathies	
Carpal tunnel syndrome	Mogyoros 1997, Kiernan 1999, Cappelen-Smith 2003
Hemifacial spasm	Kiernan 2007
Motor neuropathies	
Amyotrophic lateral sclerosis	Bostock 1995, Horn 1996, Mogyoros 1998, Priori 2002, Nakata 2006, Kanai 2006, Vucic 2006/7
Multifocal motor neuropathy	Kaji 2000, Kiernan 2002, Cappelen-Smith 2000/2
Acquired neuromyotonia	Maddison 1999, Kiernan 2002
Acquired and hereditary demyelinating neuropathies	
CIDP	Cappelen-Smith 2000/1/2
AIDP	Kuwabara 2002, Sung 2003
Charcot-Marie-Tooth 1a	Nodera 2003
Chemotherapy and toxins	
Taxol-cisplatin-oxaliplatin	Quasthoff 1995, Hanauske 1995, Schilling 1997, Krishnan 2006
Tetrodotoxin poisoning	Kiernan 2005
Central nervous system disorders	
Cerebral stroke	Jankelowitz 2007
GEFS	Kiernan 2005
Spinal cord injury	Lin 2007
Other	
Machado-Joseph disease	Kanai 2003
Myotonic dystrophy	Krishnan 2006
GEFS = Generalised epilepsy with febrile seizures plus	

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From Melbourne to Bloomsbury

Having enjoyed my undergraduate neuroscience lectures and clinical neurology placement I decided to use my elective period to gain further insight into a career in this field. I organised two neurology placements, each lasting four weeks; the first at St Vincent's Hospital, Melbourne, Australia, and the second at the National Hospital for Neurology and Neurosurgery (NHNN), Queen Square, London.

Australia is somewhere I have always wanted to visit and appealed to me as an elective destination as it is English speaking, not somewhere I'd be likely to catch a horrible diarrhoeal infection, and there is plenty to do; everything from scuba diving on the Great Barrier Reef to watching the sunrise at Uluru. As a general rule, Australia gets booked up for electives about a year in advance, so it can be difficult to get a place doing the specialty of your choice. It is also necessary to apply for a visa from the Australia High Commission and insurance cover with the Medical Indemnity Protection Society (MIPS). I wanted to spend my second placement at the NHNN because it a world famous pioneering hospital. Students are advised to organise electives here 18 months in advance as it is a very popular centre and there are limited spaces for visiting undergraduates.

St Vincent's is a large tertiary referral centre and home to one of the four Clinical Schools at the University of Melbourne. There are fifteen consultants in the neurology department who rotate through looking after inpatients, spending the rest of their time doing research and 'consults' (clinics). There are two registrars and one resident (equivalent to a FY2 doctor), with whom I attended morning ward rounds. We usually had between six and ten inpatients, split between the neurology ward and the 'MediHotel'. The 'MediHotel' caters for patients who are not acutely unwell, but need several investigations, all of which are booked for the same week. The nursing care is minimal and patients are responsible for taking their own medications. This system worked really well as given the vastness of the country some people in Australia have to travel for several hours to reach a specialist centre. My responsibilities included clerking new admissions, taking bloods and performing supervised lumbar punctures; very useful experience. I also attended general public clinics and various private specialist clinics, including epilepsy, multiple sclerosis, movement disorders, headaches and

neuropsychiatry. I was surprised one day when a lady came in with a small dog which growled viciously if either myself or the doctor tried to examine her. Apparently it is not unheard of for patients to turn up with animals, I was told that one lady attended with a joey that she was fostering! The staff were all very friendly, I enjoyed the laid back 'no worries' Aussie attitude and learning some of the Australian colloquialisms.

The NHNN is a teaching hospital in the University College London Hospital Trust and is closely linked with the Institute of Neurology (ION), a leading neurological research institute. I was attached to the movement disorders firm under the supervision of Professor Lees. My responsibilities included clerking in patients arriving as elective admissions at the beginning of the week, and presenting them on the weekly ward round. This was challenging as some patients were being investigated for, or had been diagnosed with, conditions I had not even heard of! Over the weeks I saw patients with fragile X tremor ataxia syndrome, orthostatic tremor, corticobasal degeneration, myoclonus, dystonia, and the more familiar Parkinson's Disease. I also tried to see patients on other firms, and clerked people with multiple sclerosis, peripheral neuropathies, and epilepsy. In addition I arranged to spend some time in theatres and was able to observe a variety of operations including microvascular decompression for trigeminal neuralgia, deep brain stimulation surgery for Parkinson's Disease, and an awake craniotomy with cortical stimulation and tumour resection. It was a most surreal experience talking to patients during the awake procedures. There were many clinics to attend and the clinical teaching was excellent, despite my placement being in the summer months when there are fewer sessions organised.

My elective has enabled me to visit a new part of the world and experience working in both a different health care system and a specialist neurology centre. I have improved my history taking and examination skills and seen lots of interesting cases. It has been thoroughly enjoyable and I would recommend it to anyone thinking of doing something similar.

Many thanks to St John's College, Cambridge, for their generous grant from the Rollerston Fund, without which I would not have been able to undertake these placements.



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Cranioplasty

Introduction

Cranioplasty involves the repair of a cranial defect or deformation. The commoner causes of skull defects include trauma, neurosurgical procedures and infections. The main indications for cranioplasty are protection of the cranial contents and, in children, the provision of an intact cranial vault for normal growth and development of the brain. Aesthetic and psychosocial implications also need to be considered.

History

There is evidence of cranioplasty having been performed by several early cultures, including pre-Columbian Incans using gold or silver plates, and neolithic Celts using bone 'rondelles'.^{1,2} However, the first reported cranioplasty was probably that of a Russian nobleman who, after receiving a sword blow to the head, had the resultant defect (and his health) restored with a piece of dog's cranium (Van Meekeren, 1668). Subsequently, after he had been excommunicated from the Russian church (which could not accept the presence of animal bone on a human skull), removal of the graft was impossible due to bony union.^{1,2}

Bone graft integration

During the 19th century, when the dynamic nature of living bone was first realised, many more descriptions of cranioplasties using bone pieces and plugs appeared in the medical literature. In 1893 the histological sequence of bone replacement, termed 'creeping substitution',¹ was discovered. Survival of a bone implantation graft depends on the reaction of the surrounding tissue and on functional contact between cancellous bone and adjacent resident bone.

During the first week after grafting, capillaries from surrounding bone diploe, dura and scalp infiltrate the transplant bed. During the second week fibrous granulation tissue proliferates and osteoplastic activity occurs. Primitive mesenchymal cells differentiate into osteoprogenitor cells, a process nowadays termed osteoinduction, and subsequently these osteoprogenitor cells differentiate into osteoblasts that are capable of forming new bone to replace the necrotic bone which is gradually absorbed.³

Osteoconduction is the process whereby osteoprogenitor cells from the surrounding tissue migrate into the three-dimensional structure of bony and protein matrix. It is now understood that auto- and allo-grafts have relied on osteoconduction as the main principle of cranioplasty. It is also understood that, by contrast, in osteoinduction cells do not have to migrate from the surrounding tissues but, probably with the help of bone morphogenetic proteins, can be produced in situ.¹

Materials

The ideal material for undertaking cranioplasty should be malleable to fit precisely even complicated cranial defects; strong but lightweight; easily securable to the cranium; biocompatible and chemically inert; radiolucent; non-ferromagnetic; readily available; and inexpensive. No such material currently exists.

Natural bone is the obvious choice of cranioplasty material. Bone sources are diverse, ranging from the membranous bone of the cranium itself to endochondral bone from various other sites. Bone substitutes exist in the form of metals and non-metals.

Autologous bone has the obvious advantage of lack of immune reaction and absent risk of disease transmission. Furthermore, it is readily available and has potential to grow. On the other hand the available tissue may not readily fit the defect and usually necessitates a second operative field with associated morbidity.

The simplest form of cranioplasty is the replacement of the actual bone flap that has been removed since this provides the perfect fit. If closure of the craniotomy has to be delayed (see above) the bone flap can be stored either within the patient, for example within the abdominal wall or thigh,⁴ or extracorporeally by freezing or freeze-drying.

Intracorporeal storage maintains the viability of superficial cells and of some bone matrix, and cosmetic results and low infection rates have been encouraging.⁵ The bone may, however, be absorbed over time or may become contaminated during storage. Also, an often unsightly scar results and storage may be uncomfortable. Autoclaving or boiling of bone flaps prior to extracorporeal storage can result in destruction of bone proteins; in these circumstances the bone flap will not revitalise but will be reabsorbed. All methods of removing and storing bone are covered by the Human Tissue Act (2007) which prohibits removal and storage of human cells without appropriate consent and also specifies the need for a scheduled, qualifying purpose for all removed tissue.

The inner table of the cranium may be used as a split-graft (first described in 1890,⁶ but increasingly more popular during the 20th century⁷). For this technique the section of donor skull to be used is split and the outer table is applied to cover the craniotomy defect leaving the inner table to cover the donor site. Split calvarial grafts result in an aesthetically pleasing contour. However, they are not usually available to cover large defects and both the donor and recipient sites are less biomechanically stable than adjacent skull.¹ Allogeneic bone may be obtained as a live or cadaveric graft. Although it has the advantage of being in good supply there is the risk of disease transmission and cadaveric bone in particular carries ethical issues. Since the 1980s



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Survival of a bone implantation graft depends on the reaction of the surrounding tissue and on functional contact between cancellous bone and adjacent resident bone

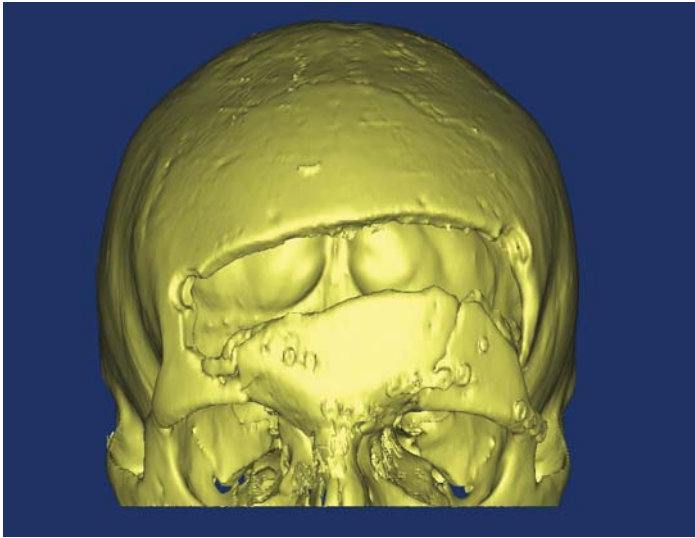


Figure 1: 3D CT reconstruction showing a bilateral frontal bone skull defect.



Figure 2: Resin model constructed from the CT data.



Figure 3: Pre-fabricated titanium plate moulded using the resin model to provide an aesthetically pleasing forehead contour. This plate is now suitable for sterilisation and implantation.

demineralised allogeneic bone matrix has become commercially available and has been used with encouraging results.⁸ Chaulking the demineralised bone powder with autologous bone paste (obtained by mixing blood and bone dust from the operative site) results in the formation of new bone throughout the cranioplasty.⁹ Furthermore, this bone paste can easily be applied to the cranial defect resulting in good cosmesis.¹⁰ Although bone donors are routinely screened for syphilis, hepatitis B and C, HIV and HTLV, the risk of disease transmission with allogeneic bone graft remains.⁹ The use of xenografts obtained from dog, goose, ape, rabbit, calf and eagle has been reported but their use has now been abandoned.

Natural bone substitutes such as temporalis fascia, fat and cartilage have also been used to cover cranial defects. However, their use is limited by a relative lack of size to cover large defects together with poor structural support. Furthermore, a tendency to reabsorption results in undesirable cosmetic results.¹

Various foreign materials have been used in cranioplasties. Metals have been widely employed but each has its shortcomings. Gold and silver are rather soft and expensive;¹¹ aluminium is epileptogenic and disintegrates over time; lead is toxic; and platinum, though very biocompatible, is prohibitively expensive. Alloys such as ticonium (first used during the 1930s) are generally cheaper than pure metals, lightweight, strong and often chemically inert.

Tantalum, a chemically inert, non-absorbable and non-corrosive material, was first successfully employed as a cranioplasty material during WW II. Unfortunately, tantalum is an excellent thermoconductor, leading to patients' complaints of headaches in extreme temperatures, and its radioopacity interferes with diagnostic radiological studies. Thus, when stainless steel (which is considerably cheaper) and acrylic compounds (which are radiolucent) were introduced, it was soon replaced.

Titanium was first used for cranioplasty in the 1940s. It is more radiolucent and less expensive than tantalum, biocompatible, non-magnetic, non-corrosive and strong. However, it is also difficult to mold intraoperatively.

Non-metals that have been used for cranioplasty include celluloid, hard rubber, plaster of Paris, gum cork and sheet mica. Due to various undesirable handling qualities and side effects none of these have gained popularity.¹²

Acrylic resins were used even before WW II as dental prostheses and since the 1940s have been employed for cranioplasty because of their good biocompatibility. Methylmethacrylate is chemically inert and, being malleable before it sets, allows for good cosmetic results. It is also lightweight, non-magnetic, non-thermoconductive and similar to bone in strength.¹³ It needs a totally dry, bloodless operative field to set, but its main drawback is the exothermic reaction produced during setting of the polymer, which can reach temperatures in excess of 100°C, with the potential for damage to underlying brain tissue - the surgeon can counteract this rise in temperature by irrigating the implant with cold saline while it sets. It is also very brittle and therefore breaks or shatters easily¹³ so that, to reduce the risk of plate breakage, it is nowadays often used with a stainless steel or titanium mesh core. Methylmethacrylate cranioplasties can be preformed, thus saving on operative time and also avoiding the hazard of intraoperative exothermic reaction during setting.

Hydroxyapatite is a calcium phosphate compound that is found naturally in human bone and teeth but which, since the 1970s, can be produced synthetically by sintering, a process in which the powder is heated until its particles adhere to each other thus producing densification. It is manufactured as a paste providing ease of application and a good fit to the defect, but is now also available as granules and preformed buttons and plates. Most importantly, hydroxyapatite sets without the exothermic reaction of methylmethacrylate.¹⁴ The porosity of the compound encourages the ingrowth of fibrovascular tissue which can subsequently ossify.¹⁵ Again, however, it does not set when exposed to fluids and, compared to methylmethacrylate, is relatively expensive.¹⁶

Ceramics are relatively new materials in cranioplasties having first emerged in the 1980s. They are chemically stable and tissue compatible. They are also very strong but somewhat prone to shat-

ter. Ceramic cranioplasty plates have to be pre-formed.

Complications occurring from cranioplasty can be broadly divided into those related to the operative procedure in general and those specifically related to the particular material used (see above).

In general, mortality from cranioplasty is low at approximately 0.2%.⁷ The commonest significant complication is infection (meningitis, abscess and sinus formation) since most cranioplasty materials are foreign bodies. An infected cranioplasty generally has to be removed and prolonged treatment with antibiotics may be necessary. The infection rate is approximately 5% for methylmethacrylate but less for bone cranioplasties.⁷ Inflammatory tissue reaction, loosening of the graft and exposure of the graft through the skin may also occur (sometimes many years after implantation) but such complications are more common with bone substitutes, especially acrylic resins, than bone itself.¹⁶ Alloplastic materials can also result in erosion of the underlying bone which in turn results in a larger cranial defect.¹⁰

Unpredictable resorption of cranioplasty material is a complication when using bone, especially autoclaved bone, and can be as high as 25-40%.^{3,17} Other complications specific to bone relate to its harvest: split calvarial grafts carry the risk of intracerebral haematoma, sub-

arachnoid haemorrhage, dural tears and CSF leaks, while other sources of bone may lead to donor-site morbidities, such as pain, infection, unsightly scarring, nerve injury, hernias, fractures, bowel perforation and pneumothorax.

Future developments

The search for the ideal cranioplasty material and technique continues. Novel natural as well as synthetic materials have been used. These include natural corals which have a porous structure similar to human bone and can undergo ossification;¹² and the Norian bone cement system, a synthetic carbonated calcium phosphate compound which can be reabsorbed and replaced by human bone.¹⁸ Likewise, new techniques are being developed. Known materials are mixed, e.g. acrylic resins with titanium struts,¹¹ and their qualities improved, e.g. antibiotic coating of pre-formed plates.¹⁹ Techniques are being transferred from other surgical specialties, e.g. distraction osteogenesis with contractile polymers, or even bioresorbable dynamic implants that could be applied without transcutaneous pins.²⁰ Preforming of implants has advanced due to 3D-CT scanning, computer-assisted design^{12,21} and stereolithography.^{19,22}

In our unit we routinely use the MIMICS® (Materialise's Interactive Medical Image Control System) to prefabricate defect-specific titanium membranes for cranioplasty. A 3D-CT image of the region of interest is formatted and

a resin model is then created by fused deposition modelling. This model then acts as a template for the actual cranioplasty membrane which is fashioned preoperatively by specialised maxillo-facial prosthetic consultants.

There have also been exciting developments in 'tissue engineering' using molecular biology techniques, such as harvesting osteoblasts or bone marrow-derived mesenchymal stem cells, to seed onto the scaffold for the cranioplasty.¹² Bone morphogenetic proteins of the transforming-growth factor- β family, and various polypeptide growth factors, play a central role in fracture healing. These factors can now be manufactured by recombinant DNA techniques and potentially incorporated into implants to evoke osteoinduction.^{12,23} Furthermore, absorption of circulating endogenous or exogenous bone morphogenetic protein leads to secondary induction of bone growth²⁴ and retroviral transfection of bone morphogenetic protein-7 into periosteal cells which are then seeded onto cranioplasty matrices is now possible. This results in increased bone regeneration.²⁵ Thus, 'smart biomaterials' are the latest addition to the experimental armamentarium of cranioplasty surgery. In future, biodegradable implants could be used to provide immediate cover of the cranial defect whilst over time releasing bioactive molecules to transform the perfectly fitted implant into living bone.

In future, biodegradable implants could be used to provide immediate cover of the cranial defect whilst over time releasing bioactive molecules to transform the perfectly fitted implant into living bone

References

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To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 7 December, 2007

2007

November

Northern Neuroimmunology Interest Group 8th Annual Meeting

2 November, 2007; Nottingham, UK
E. lisa.hunt@srfhs.nhs.uk

Society for Neuroscience - Neuroscience 2007

3-7 November, 2007; San Diego, US
E. info@sfn.org, www.sfn.org

Multiple Sclerosis Trust 11th Annual Conference

4-6 November, 2007; Leeds, UK
T. 01462 476704,
E. Education@mstrust.org.uk,
www.mstrust.org.uk

Corso di epilettologia clinica, 7th EUREPA Course

4-11 November, 2007; Gargnano, Italy
Prof. Raffaele Canger
E. raffaele.canger@ao.sanpaolo.it

Launch of South West Brain Injury Social Work Regional Group

6 November, 2007; Cullompton, UK
T. 01752 272504,
E. jackie.burt@plymouth.gov.uk

BSRM Winter Meeting & AGM

7-9 November, 2007; Newcastle, UK
T. Sandy Weatherhead on 01992 638865

BISWG-West Midlands Regional Meeting

8 November, 2007; Birmingham, UK
T. 01384 2144654,
E. lucy.devlin@dgoh.nhs.uk

5th International Congress on Vascular Dementia

8-11 November, 2007; Budapest, Hungary
www.kenes.com/vascular

Clinical Update: Epilepsy in Adults and Adolescents

9 November, 2007; London, UK
T. 020 72903856,
E. tori.bennett@rsm.ac.uk

Deep Brain Stimulation: Shared Care

13 November, 2007; London, UK
E. jethro.hutchinson@medtronic.com

East Kent Motor Neurone Disease Conference: MND a Proactive Approach

19 November, 2007; Canterbury, UK
E. Mohamed.sakel@ekht.nhs.uk

ABN Joint Meeting with Norwegian Neurological Society

14-16 November, 2007; London, UK
E. info@theabn.org

MR Spectroscopy Study Day

15 November, 2007; Manchester, UK
T. 01276 696474,
E. sara.cowan@siemens.com

International Conference on the Dietary Treatments for Epilepsy

15-16 November, 2007; Sussex, UK
E. Julie@mathewsfriends.org

1st Congress of the International Society for Intraoperative Neurophysiology (ISIN)

15-17 November, 2007; Lucerne, Switzerland
T. 0-612-713-551,
F. 0-612-713-338,
E. mail@imk.ch

BMJ Masterclass for Physicians: Neurology

20 November, Manchester, UK
T. 020 7383 6985,
E. masterclasses@bmjgroup.com

2nd European Federation of Neuropsychiatry Congress

21-24 November, 2007; Florence, Italy
E. info@efnp.org,
T. 0115 969 20 16,
F. 0115 969 2017, www.efnp.org

Supporting People with Acquired Brain Injury: Law and Good Practice

22 November, 2007; London, UK
E. ukabif@btconnect.com

Working with Families Following Acquired Brain Injury

23 November, 2007; Ely, UK
T. 01353 652176

2nd Congress of the European Federation of Neuropsychiatry: The Neuropsychiatry of the Emotional Brain

22-24 November, 2007; Florence, Italy
www.efnp.org

Working with Couples after Acquired Brain Injury

23 November, 2007; Ely, UK
E. janet.beveridge@ozc.nhs.uk,
T. 01353 652176.

Ion Channels and Cancer

25-28 November, 2007; Bavaria, Germany
E. m.djamgoz@imperial.ac.uk

Clinical Trials in CNS

26-27 November, 2007; London, United Kingdom
T. 020 7827 6000,
www.smi-online.co.uk

Dizziness – A Multidisciplinary Approach

26-29 November, 2007; London, UK
T. 0845 155 5000 x 723275,
E. Karen.cox@uclh.co.uk

Neurology Symposium

27 November-5 December, 2007
Dr. Martin Gerretsen,
T. 1-888-647-7327,
E. cruises@seacourses.com

Focus on Acquired Brain Injury - ABI Information and Education Conference

27 and 28 November, 2007; Dublin, Ireland
E. Karen.kcahill@peterbradleyfoundation.ie,
T. 01-2804164 or 086-3868851.

3rd International Congress on Brain & Behaviour

28 November – 2 December, 2007; Thessaloniki, Greece
www.psychiatry.gr/congress/

Measuring Chronic Disease Outcomes in the Modern NHS

28 November, 2007; Leeds, UK
T. 0113 3055086,
E. adele.archer@nhs.net

Nature and Nurture in Brain Function: Clues from Synesthesia and Phantom Limbs

28 November, 2007; London, UK
E. events@roysoc.ac.uk,
T. 020 7451 2500.

European Charcot Foundation University Classes in MS IV Focused on Progressive MS

28 November, 2007; Fuggi, Italy
www.charcot-ms.eu

European Charcot Foundation Symposium 2007: Treatment Targets in MS

29 November- 1 December, 2007; Fiuggi, Italy
www.charcot-ms.eu

West of England Seminars in Advanced Neurology

29-30 November, 2007; Exeter, UK
E. N.J.Gutowski@exeter.ac.uk or
cgardnerthorpe@doctors.org.uk

61st Annual Meeting of the American Epilepsy Society

30 November-4 December, 2007; Philadelphia, USA
E. csluboski@aesnet.org

6th Meeting of the British Society of Neuro-Otology

30 November, 2007; London, UK
Janet Mills, T. 0208 846 7285,
E. neuro-otology@imperial.ac.uk

Peripheral Neuropathy Symposium – Festschrift for Professor Richard Hughes

30 November, 2007; London UK
T. 020 7848 6122,
E. lynette.clover-simpson@kcl.ac.uk

December

BISWG 'Insight into Injury'

3 December, 2007; Edinburgh, UK
Fen Parry T. 0131 5 37 6857,
E. fen.parry@edinburgh.gov.uk or
mhairi.mckay@lpct.scot.nhs.uk

What Do We Want to See in Brain Imaging?

3-4 December, 2007; London, UK
T. 020 7409 2992,
E. events@ri.ac.uk
www.nyas.org/IMGconf

Molecular Mechanisms of Neurodegeneration 2007

3-6 December, 2007; St. Mary's Parish, Antigua
www.abcam.com/index.html...=pagetrap

Multiple Sclerosis Trust Specialist Masterclass in MS

4 December, 2007; UK
T. 01462 476704,
E. Education@mstrust.org.uk
www.mstrust.org.uk

UK Stroke Forum Conference

4-6 December, 2007; Harrogate, UK
Daniela Queen,
E. ukstrokeforum@stroke.org.uk,
T. 0115 969 1169

Understanding and Treating Attention and Information Processing Deficits after Brain Injury

7-8 December, 2007; London, UK
E. enquiries@braintretraining.co.uk,
www.braintretraining.co.uk

Advances in Clinical Neuroimmunology

7-8 December, 2007; Poznan, Poland
Prof. Jacek Losy,
T. + 48 61 869 15 83,
E. jlosy@amp.edu.pl,
www.neuroim2007.poznan.pl

17th International Congress on Parkinson's Disease and Related Disorders

9-13 December, 2007; Amsterdam, The Netherlands
E. berlin@cpo-hanser.de,
www.parkinson2007.de

Restoring Mobility: Theories, Technologies and Effective Treatments

10 December, 2007; London, UK
E. conferences@rplondon.ac.uk,
T. 020 7935 1174

BNA Christmas Symposium: The Ageing Brain

12 December, 2007; London, UK
T. 0151 794 4943, E. events@bna.org.uk

Cambridge Dementia Course 4

13-14 December, 2007; Cambridge, UK
E. penny.pearl@addenbrookes.nhs.uk

New Ways of Managing Stroke Disability

17 December, 2007; London, UK
E. carolecross@ukconnect.org.uk,
www.ukconnect.org/connectcourses_19_102.aspx,

2008

January

SRR Winter Meeting

15 January, 2008; Oxford, UK
Patricia Dziunka,
E. patricia.dziunka@srr.org.uk,
T. 0115 8230244.

EuroNeuro 2008

17-19 January, 2008; Maastricht, The Netherlands
www.euroneuro.eu/
T. 011-31-411-611-199,
E. info@euroneuro.eu

Cognitive Rehabilitation Workshop

18-19 January, 2008; London, UK
E. enquiries@braintretraining.co.uk,
www.braintretraining.co.uk

Encephalitis – The Broader Spectrum

22 January, 2008; London, UK
T. 01653 692583,
E. Elaine@encephalitis.info

Understanding Brain Injury

25 January, 2008; Ely, UK
E. carolyne.threadgold@ozc.nhs.uk

February

2nd International Congress on Gait & Mental Function

1-3 February, 2008; Amsterdam, The Netherlands
www.kenes.com/gait/

36th Annual INS Meeting

6-9 February, 2008; Waikoloa, Hawaii, USA
International Neuropsychological Society
T. + (614) 263-4200,
F. + (614) 263-4366,
E. ins@osu.edu

MR Paediatric Study Day

11 February, 2008; Manchester, UK
T. 01276 696474,
E. sara.cowan@siemens.com

Learning, Memory and Cognitive Function. Mechanisms, Pathology and Therapeutics

10-12 February, 2008; Valencia, Spain
T. +34 96 197 4670,
E. catedrasg@cac.es,
www.fundacioncac.es/catedrasg

Rehabilitation: How do we know it is effective?

15-16 February, 2008; London, UK
T. 020 7647 3538,
E. rehabilitation@rcn.org.uk

4th Annual Update Symposium Series on Clinical Neurology and Neurophysiology

18-19 February, 2008; Tel Aviv, Israel
ISAS International Seminars, POB 574,
Jerusalem 91004, Israel
T. 972-2-6520574,
F. 972-2-6520558,
E. register@isas.co.il,
www.neurophysiology-symposium.com/

Insight Workshop

22-23 February, 2008; London, UK
E. enquiries@braintretraining.co.uk,
www.braintretraining.co.uk

Neurobiology of Addiction: New vistas

25-26 February, 2008; London, UK
E. discussion.meetings@royalsoc.ac.uk

March

2nd International Conference on Hypertension, Lipids, Diabetes and Stroke Prevention

6-8 March, 2008; Prague, Czech Republic
www.kenes.com/strokeprevention2008

3rd Meeting of the UK Parkinson's Disease Non Motor Group

8 March, 2008; London, UK
E. yogini.naidu@uhl.nhs.uk, www.pdnmg.com

Birmingham Movement Disorders Course

12-14 March, 2008; Birmingham, UK
T. 0121 507 4073, E. susan.pope@swbh.nhs.uk

International Neuroimmunology Symposium

14 March, 2008; Dublin, Ireland
T. +353 1 716 6700, E. mniest@ucd.ie,
www.ucd.ie/mniest/Neuroimm_workshop.html

8th Advanced Prosthetic & Amputee Rehabilitation Course

17-19 March, 2008; London, UK
T. Sandy Weatherhead on 01992 638865

ABN Spring Meeting

26-28 March, 2008; Dublin, Ireland
E. info@theabn.org

The Science, Culture and Art of Neurorehabilitation, Tripartite Regional Meeting of Neurological Rehabilitation

27-29 March, 2008, Cebu City, Philippines
E. NeuroRehab@yahoogroups.com

MS Life

29-30 March, 2008; Manchester, UK
www.msconvention.org.uk

April

60th Annual Meeting of the American Academy of Neurology

5-12 April, 2008; Chicago, USA
T. +1 651 6952171,
E. memberservice@aan.com

The Psychosocial Burden of Epilepsy: Ameliorating the impact

6-8 April, 2008; Oxford, UK
E. Isabella@eruk.org.uk,
www.epilepsyresearch.org.uk

The International Brain Injury Association's 7th World Congress on Brain Injury

9-12 April, 2008; Lisbon, Portugal
E. mjoberts@aol.com, or
T. 001 703 960-6500

European Federation of Neurological Societies (11th Congress)

25-28 August, 2007; Brussels, Belgium.

Is migraine a cardiac disorder? This startling question was posed at about nine o'clock on Sunday morning (my UK body clock was still at 0800) in a lecture on headache, stroke and patent foramen ovale (PFO), prompted by the high incidence of PFO, as defined by various imaging techniques, in migraine with aura (MA) but not migraine without aura. Might MA and PFO reflect common, genetically determined, endothelial and endocardial dysfunction? Whilst acknowledging that Belgium is the birthplace of Magritte, and



all in this world is not as it seems or is represented, nonetheless I cannot persuade myself that our cardiologists will be willing to take on the burden of headache. On the vexed question of PFO closure in MA, which has proven positive in some small series, the lecturer endorsed the statement of the European Headache Federation that there is "no reason to intervene"¹ although 2 RCTs (MIST, ESCAPE) are in progress. Professor Jean Schoenen, the chairperson of the Local Organising Committee, reviewed the mechanism of action of migraine drugs, pointing out the poor ("lousy") efficacy of drugs given during the aura, and hence the likelihood of non-efficacy in variants such as basilar migraine and migrainous vertigo. Questioned from the floor, he gave his first choice for migraine prophylaxis as riboflavine, on the grounds of excellent side effect profile, followed by propranolol and lamotrigine, choices which might raise eyebrows elsewhere and which, happily, contradict official EFNS guidelines on the subject.²

Continuing the theme of revised nosology, is progressive supranuclear palsy (PSP) a cognitive disorder? (It may be recalled that corticobasal degeneration, first defined as a movement disorder, has increasingly been recognised to present with cognitive deficits.) A study from Greece compared cognitive and behavioural function in patients with frontotemporal dementia (FTD) and PSP and found marked overlap, but with greater impairment in social/interpersonal interaction in FTD, presumably reflecting the greater orbitofrontal circuit disruption early in the disease course. Great interest was stimulated by Professor Ian Bone's report on the UK experience with pentosan polyphosphate (PPS) given to a small number of patients (n = 8) with prion diseases (vCJD,³ GSS, human growth hormone-related iatrogenic CJD). These observational, uncontrolled data emphasised the frequency of complications with intraventricular catheters, and the variability of drug dose and follow up investigation. Although all patients progressed, many too far for clinical assessment, nonetheless survival exceeded the mean of other, historical, cohorts, especially for vCJD. Nonetheless,

reservations must remain as to the place of PPS therapy (for full results see www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d)

A series of CJD patients reported from Madrid (21 sCJD, 2 fCJD) noted psychiatric presentation in 13%, indicating that this presentation is not exclusive to vCJD.

The genetic heterogeneity and complexity of restless legs syndrome (RLS), in which up to 60% of patients have a positive family history, was emphasised in a paper from Germany. Six loci have been defined (chromosomes 12q, 14q, 9, 2, 20, 6) to which a possible 7th was added (19p13). Several presentations, sponsored and otherwise, related to a RCT of efficacy and tolerability of the rotigotine patch in RLS. Continuous dopaminergic stimulation seems desirable despite the nocturnal exacerbation of symptoms. However, since application site reactions were much more frequent in the active group (42.5% vs. 1.7% in placebo) one might argue that the trial was partially unblinded.

The 1990s were described as a "magnificent decade" for stroke by Professor Bo Norrving. Now the emphasis is on the implementation of thrombolysis, the earlier the better, but delay in seeking care is a major problem with up to 75% of patients presenting after the three-hour window. The main cause is patient delay, due to social factors (living alone, consulting with a physician, relatives) and cognitive/emotional factors (appraising symptoms as not serious). Community stroke education via the mass media may help, but only transiently, information campaigns having little carry-over on patient behaviour. Those who thought heparin as a treatment for stroke was effectively killed off by trials such as IST, in part due to the haemorrhagic adverse effects, were obliged to think again following an excellent lecture by Angel Chamorro from Barcelona who presented various reasons for believing that heparin was not adequately tested previously and could be useful if given within three hours. However, the RAPID (Rapid Anticoagulation in Patients with Ischaemic Damage) trial recruited only 67 patients in three years.⁴ His plea was for an academia-driven study.

Drug of the conference, as judged by ubiqui-

ty, lay between rotigotine (patches), and lacosamide (1 presentation and 13 posters, according to my calculation). The latter seems to be good as an add-on for seizures of partial origin and for neuropathic pain, as in diabetic neuropathy.

Two topics dominated the history sessions at EFNS: Belgium, and the World Federation of Neurology (WFN), the latter celebrating its 50th anniversary. It was at the International Congress of Neurological Sciences in Brussels in July 1957 that the WFN was founded. An eye wit-

ness account, and details of the subsequent development of the WFN, were given by Lord Walton, sometime president, including his personal reminiscences of Ludo van Bogaert, the first WFN president (1957-1965). Van Bogaert's life and work were discussed in the session devoted to the Belgian contribution to neurology: apparently his driver doubled as a technician performing some of the post mortem work! WFN has recently collaborated with the World Health Organisation, producing an atlas of neurological resources.⁵ A striking graphic of neurologists per head of population showed a forlorn British Isles sticking out at the northwest corner of Europe with a ratio lower than virtually every other European country, and on a par with north Africa. Perhaps Belgium's greatest neurologist, Arthur van Gehuchten (1861-1914), was the subject of the Clifford Rose Memorial Lecture by Professor Aubert. Van Gehuchten was the first to use the term "Babinski sign", previously known as the "toe phenomenon", and also to film it, as shown in the lecture. Van Gehuchten was also commemorated in the 1957 meeting at which WFN was founded, as were three other neuroscience greats, the 100th anniversary of whose births fell in that year: Sherrington, Babinski, and Horsley.

AJ Larner,

Walton Centre for Neurology and Neurosurgery,
Liverpool, UK.

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Joint 4th European and 3rd World Congress on Huntington's Disease

7-11 September, 2007; Dresden, Germany.

I felt like one of Raphael's cherubs from 'The Sistine Madonna' (housed in Dresden's Gemäldegalerie Alte Meister (Old Masters Picture Gallery), which can be seen on-line at http://www.skd-dresden.de/media/400_pressebild_sixtina.jpg), as I listened to the latest developments at the joint European and World Congress on Huntington's Disease (HD) held in Dresden. Both meetings were intended for all interested groups in HD including laboratory researchers, clinicians, professions allied to medicine, carers and importantly patients themselves, with specialist interest groups open to all delegates.

The European meeting's opening talks were intended to reflect 'hot' topics in HD, such as Gillian Bates' clear summary of RNA as a target for potential therapy, using RNA interference to reduce mutant huntingtin protein expression and thereby aim to prevent the subsequent abnormal cascade of events resulting in neurodegeneration. While promising basic research is emerging from this field, the limitations of such a technique were addressed, including mode of delivery, currently intra-ventricular injections; potential to stimulate a presumed unwanted immune response; and also whether reduction of normal huntingtin protein in the adult which would occur alongside mutant protein reduction would in fact be deleterious as it is for the developing embryo. The other opening talks about weight loss, apathy versus depression, and curiously a talk on self-medication, did not match their 'hot' position and failed to engage the diverse backgrounds of the delegates, which was always going to be difficult to achieve.

Sarah Tabrizi introduced a development

from the biomarker working group, Track-HD. This is a three-year observational study to examine the sensitivity of single and multiple tests to track the subtle change in clinical phenotype between gene-positive asymptomatic HD and clinically evident HD, with the aim of finding evidence based biomarkers for eventual use in randomised clinical trials. Their net is wide including peripheral biomarkers such as saccadic eye movements, blood sampling for DNA, RNA and cytokines, a battery of cognitive tasks, and imaging with 3-T MRI using voxel-based and cortical thickness analysis. I wish them luck, as presumably a significant number of patients will need to clinically change sufficiently, over a relatively short time, to be certain that any changes seen are sensitive to disease progression.

The World Congress opened with a moving tribute by Alice Wexler about her father, Milton Wexler, who died earlier this year. He was a psychoanalyst that founded an organisation in 1968 that has become the Hereditary Disease Foundation. This was his reaction to discovering that his then ex-wife had HD, and therefore had the potential to affect both of his daughters. This was followed by his other daughter, Nancy Wexler, speaking about her work with a group of villagers living on Lake Maracaibo in Venezuela who are thought to have a common ancestor who had HD. This included a video of a couple who both had HD, and their 10 children, with some children as young as 5 already clearly symptomatic.

The rest of the congress was followed by a mixture of talks broadly divided into scientific, clinical, and those aimed at the International Huntington Association support group.

Highlights included:

- Anne Young's description of basal ganglia dysfunction, describing differences with both the internal circuitry, and also in the flow of transmission or 'oscillations' down the neural networks still present.
- Jean-Paul Vonsattel, who created the 'Vonsattel' grading of HD pathological specimens, gave an entertaining account of his work (see ACNR 7:3) and details of HD mimics that he is still attempting to diagnose!
- Paul Muchowski's work on targeting microglial activation, and the importance of pursuing ideas to the extent that he asked his father, a retired biochemist, to re-create a compound that a drug company was unwilling to donate, and then proceeded in improving its bioavailability.

The neuro-inflammation session in general was contentious. Early human and animal data suggests up-regulation of the acute phase reaction with increases in IL-6, IL-8 and TNF- α , but it remains unclear whether this is centrally or peripherally mediated, and, like microglia activation, whether this is due to tissue pathology or as result of mutant huntingtin protein expression, and its significance. The potential to use such information as a reliable biomarker will be explored further courtesy of Track-HD, and it will be interesting to see whether this will back-up the data presented thus far.

I left Dresden more enlightened and enthused than when I arrived. On that basis it was a successful conference, but I am also certain that while HD research has come far in the past 40 years, it still has a long way to go.

Ben Wright, Cambridge, UK.

APO-go Reborn

6 September, 2007; London, UK.

Dr Patrick Trend chaired the 'APO-go Reborn' meeting in September at Southwark Cathedral in London, which was attended by around 70 PD professionals. The meeting agenda covered talks on APO-go, CDS and Non-motor symptoms by Prof. Ray Chaudhuri, Infusion effects on motor fluctuations and dyskinesia by Prof. Per Odin from Germany, and Injection techniques "State of the Art" by Dr Marion from St Georges Hospital. The afternoon debate was chaired by Alison Forbes, PDNS at Kings College Hospital, and discussed various induction techniques to minimise hospital administration.

For more information contact Britannia Pharmaceuticals, T. 01737 773741.



Winter Meeting
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Symposia:

"Brain Plasticity as a Target of Therapy"

Prof Paul Matthews (Vice-President for Imaging, Genetics and Neurology;
Head, GlaxoSmithKline Clinical Imaging Centre, Imperial College London)

"Does Rehabilitation Prolong Illness"

Prof Derick Wade (Oxford Centre for Enablement, Oxford)

"Experimental Modulation as a Basis for Rehabilitation"

Dr Tom Manly (MRC Cognition and Brain Sciences Unit, Cambridge)

The 10th national conference

Dementias 2008

A review and update on the current developments in the dementias; in the fields of research, investigations, clinical care and service and policy issues

Savoy Place, London 14th & 15th February 2008

Day 1 – Thursday, 14th February

08.00 – 09.05	Registration and refreshments
09.05 – 09.10	Welcome and introduction: Professor Tom Arie C.B.E & Professor Alistair Burns Chair: Professor Alistair Burns
09.10 – 09.50	KEYNOTE ADDRESS: Detection and management of early dementia: new tools, new developments Professor Kenneth I Shulman
09.50 – 10.00	Discussion
10.00 – 10.40	Systemic inflammation and its importance in AD Professor Clive Holmes
10.40 – 10.50	Discussion
10.50 – 11.20	Refreshments and exhibition viewing
11.20 – 12.10	Economics of dementia Dr Paul McCrone
12.10 – 12.20	Discussion
12.20 – 12.40	An update on the Dementias and Neurodegenerative Diseases Research Network (DeNDRoN) Professor Ian McKeith
12.40 – 12.50	Discussion
12.50 – 13.50	Lunch and exhibition viewing Chair: Professor Tom Arie C.B.E
13.50 – 15.05	OPEN SESSION I Topic followed by panel discussion – case histories and challenges ETHICAL ISSUES (13.50 – 14.20) Dr Julian C Hughes Open forum – case histories and challenges (14.20–15.05) The Experts Dr David Jolley Professor Alistair Burns
15.05 – 15.30	Refreshments and exhibition viewing Chair: Dr David Jolley
15.30 – 16.00	Other dementias Dr Anoop Varma
16.00 – 16.30	Imaging Professor John O'Brien
16.30 – 16.40	Discussion
16.40 – 17.05	Teaching about dementia in a new medical school Dr Andrew Tarbuck
17.05 – 17.15	Discussion
17.15 – 19.30	Celebration – 10th Anniversary drinks reception with live music by The Jazz Dynamos

Day 2 – Friday, 15th February

09.00 – 09.30	Registration & refreshments Chair: Professor Sube Banerjee
09.30 – 10.05	Agitation Dr Peter Bentham
10.05 – 10.40	Depression in dementia Professor Sube Banerjee
10.40 – 10.50	Discussion
10.50 – 11.20	Refreshments and exhibition viewing
11.20 – 11.55	The first quarter century of psychogeriatric services Dr Claire Hilton
11.55 – 12.30	A NICE experience? Reflections on the 2006 dementias guidelines and drug guidance Professor Roy Jones
12.30 – 12.40	Discussion
12.40 – 13.40	Lunch and exhibition viewing Chair: Professor Tom Arie
13.40 – 14.15	Prevention of dementia Dr Nitin Purandare
14.15 – 14.50	Lewy body dementia Dr Jane Byrne
14.50 – 15.00	Discussion
15.00 – 16.15	OPEN SESSION II Topic followed by panel discussion – case histories and challenges Dealing with complaints (15.00 – 15.25) Mr Michael Pyrah Dr David Jolley Open forum – case histories and challenges (15.25 – 16.15) The Experts Dr Claire Hilton Dr Jane Byrne
16.15 – 16.20	Summing up and close of conference
16.20	Refreshments

PROGRAMME ADVISORS

- Professor Tom Arie, CBE, Professor Emeritus of Health Care of the Elderly, University of Nottingham
- Professor Alistair Burns, Head of School of Psychiatry & Behavioural Sciences, Professor of Old Age Psychiatry, University of Manchester

The views of the speakers are not necessarily those of the sponsoring companies

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CPD APPROVED



MS Society Professional Network Conference

21 September, 2007; London, UK



The British Library conference centre was full to bursting on 21 September when the MS Society's professional network considered the topical theme of self management, self care and MS at its annual conference. The professional network is a virtual grouping of more than 2,500 health and social care professionals who have a shared interest in improving services for people affected by MS. Membership is free and services to members include a magazine and opportunities for learning and information exchange – of which the annual conference is one.

This year, more than 220 people from all specialties came to listen to speakers from the Department of Health, the Expert Patient Programme Community Interest Company and the Foundation for Assistive Technology, among others.

Vicky Harker, who has MS, described the positive impact the expert patient programme had had on her life and how she had managed to limit the impact of many of her symptoms. Gavin Croft and Karen Saville spoke of how they use Gavin's individual budget to minimise the impact of MS on their lives. They do this by designing a support plan that fits with their lifestyle and makes sense to them. This enables Gavin to continue to live independently despite increasing disability.

Karen Walker from Skills for Care reminded us that the White Paper *Our Health, our care, our say* commits the government to developing a self care competence framework for the whole health and social care workforce. Over the past year, Skills for Health has been working with Skills for Care and the Department of Health to develop a set of core principles for self care. The six principles are:

- Ensure individuals are able to make informed choices to manage their self care needs;

- Communicate effectively to enable individuals to assess their needs and gain confidence to self care;
- Support and enable individuals to access appropriate information to manage their self care needs;
- Support and enable individuals to develop skills in self care;
- Support and enable individuals to use technology to support self care
- Advise individuals how to access support networks and participate in the planning, development & evaluation of services.

The Department of Health and Skills for Health and Care are now in discussion about how to implement and disseminate this work across the whole workforce.

Complementing this was Keren Down, chief executive of the Foundation for Assistive Technology who presented the self care approach to assistive technology. Helena Jordan talked about the Working in Partnership Programme, set up to create capacity in primary care through improved workload management. The conference also contrasted MS services in the UK with those in India.

A key area of the conference – and a growing area of interest for MS professionals – is mental health. The day before the conference, the MS Society launched a new interest group as part of its professional network – for professionals with a specific interest in mental health and wellbeing aspects of MS.

For more information about this or any other aspect of the MS Society's professional activities, email msnetwork@mssociety.org.uk

Epilepsy, Behaviour and Neurology: An Integrated Approach to Childhood Epilepsy

4 September, 2007; London, UK.

The National Centre for Young People with Epilepsy (NCYPE), the UK's leading provider of specialist services for young people with epilepsy, hosted an international meeting of epilepsy experts in association with the UCL Institute of Child Health in September.

The event was held at the UCL Institute of Child Health in London and featured presentations from Professors Christopher Gillberg, David Taylor and Eric Taylor, also Dr Philippa Russell CBE the Disability Rights Commissioner, and Dr Isobel Heyman.

The meeting was chaired by Brian Neville, Europe's first Professor of Childhood Epilepsy, who holds the position of The Prince of Wales's Chair of Childhood Epilepsy.

The programme focused on a practical approach to the common cognitive, psychological and psychiatric problems of children with epilepsy with the aim of producing comprehensive guidelines. The speakers covered different aspects of this topic and a discussion took place as to how such a programme could be put in place. It is hoped that some significant changes in services might be seen as a result of this event attended by around 140 delegates from all parts of UK.

Following the event, Professors Brian Neville, Christopher Gillberg and David Taylor held a workshop with staff from The NCYPE to further discuss the behavioural issues raised at the symposium and how they relate specifically to The NCYPE.

Speaking about the symposium, Brian Neville said, "In this symposium we have taken a practical approach to the common cognitive, psychological and psychiatric problems of children with epilepsy in the hope that



Pictured: Professors David Taylor (back row, on the right), Christopher Gillberg (front row, on the right and in black) and Brian Neville (front right) with staff from The NCYPE during the workshop at the charity's Lingfield campus.

we can produce comprehensive guidelines.

"From my perspective the integration of psychiatry and paediatric neurology can work brilliantly but frequently doesn't work at all. A major problem for educational integration is the lack of recognition of the major special educational needs of children with epilepsy."

For further information on future events please contact Felicity Pool, Meeting Co-ordinator at The NCYPE on T. 01342 831202, E. fpool@ncype.org.uk

Eighteenth Meeting of the European Neurological Society



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Separately to this offer, young colleagues who have an abstract accepted for presentation at the ENS meeting may also apply for a travel grant. Please see further details on the congress website.

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EDITOR'S CHOICE

ALZHEIMER'S DISEASE: New research diagnostic criteria for Alzheimer's Disease

The current NINCDS-ADRDA diagnostic criteria for Alzheimer's disease (AD) date back almost a quarter of a century (Neurology 1984;34:939-44), a time when the molecular nature of amyloid was only just being characterised, the molecular structure of neurofibrillary tangles was unknown, MRI was still in its infancy, and deterministic genetic mutations were yet to be defined. All these factors have prompted this (self-appointed) group to suggest new diagnostic criteria for AD. The old criteria required a 2-step process: 1. Is there dementia? 2. Is it AD? Possible, probable and definite categories of AD were defined. The recognition of mild cognitive impairment (MCI) as a possible prodrome of AD implies that disease may be present without the clinical correlate of dementia (as may also be true in other 'dementias' such as DLB, FTD, prion disease). The new criteria, although still probabilistic, aim to bypass this 'binary outcome' by taking a biological approach to disease definition, eliminating the categories of MCI and possible AD.

Core and supportive criteria are proposed. Core (criterion A) relates to cognition: gradual and progressive memory change, with objective impairment of episodic memory which may or may not be an isolated finding. Contrary to DSM-IV-TR, dementia diagnosis does not require presence of a functional disability (in agreement with studies which do not find ADL scales useful as a diagnostic test). Supportive criteria relate to imaging (B: presence of medial temporal lobe atrophy on MRI; D: specific pattern on functional imaging with PET, not SPECT), CSF (C: abnormal CSF biomarker), and genetics (E: proven autosomal dominant mutation within the immediate family). Diagnosis requires A + 1 or more of B-E. There are also exclusion criteria, similar to those of NINCDS-ADRDA.

Although still to be validated, undoubtedly some such revision of AD diagnostic criteria will be of value in the research and clinical trials settings. But what are their implications for day-to-day practice outside major research centres, particularly in light of UK NICE/SCIE guidance which envisages all dementia care as led by old age psychiatrists? Access to quality imaging (MRI, PET), specialised CSF markers, and neurogenetics is restricted or non-existent in much of the UK. Here presumably the old criteria will prevail: certainly the authors foresee "technically less demanding criteria for clinical settings". Some of the exclusion criteria may also be objected to, sometimes being transgressed in AD cases (e.g. sudden onset, early seizures). The proof of the pudding will be whether the criteria permit earlier AD diagnosis and, hopefully, meaningful disease-modifying interventions. – *AJL*

Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P.

Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria.

LANCET NEUROLOGY

2007;6(8):734-46.

EPILEPSY: Valproate and phenytoin for status epilepticus

*** RECOMMENDED

The use of antiepileptic drugs in status epilepticus is limited by logistical factors such as availability as an IV preparation and ability to give a large initial dose without gradual dose titration. Valproate has been available for a long time and has been looked at in a number of small and uncontrolled studies and this to my knowledge is the largest study to assess it. The authors used a definition of status as seizures lasting more than five minutes, which has been previously suggested but not universally adopted. Also their definition of ongoing status, in which patients had ceased to seize but had not yet woken up after 30 minutes, will have meant the inclusion of some patients with a milder problem than in other studies. Forty per cent had an associated illness, most commonly infective, especially septicaemia (14%) and 'viral fever' (8%). The commonest reason for status was drug withdrawal, whether accidental or through non-compliance. The study appears to have been only of patients with tonic-clonic status, but it is not entirely clear. They split 100

patients, who had not responded to an initial benzodiazepine into two groups, one receiving phenytoin and the other valproate. About half in each group had seizures which had lasted more than two hours. Overall response rates were 88% to IV valproate and 84% to IV phenytoin. When these were broken down according to duration of status, the response to valproate was 100% for those under two hour's duration and 70% for those over two hours. Comparable figures for phenytoin were 96% and 71%. One patient in each group left the study early, because of the cost of treatment. I assume, that unless their relatives withdrew them, that they had recovered. Mortality was 8% in either group and adverse events were similar. So this study gives further support to the use of valproate in status, although there are some differences in the patients being treated, both in terms of causes of status and severity from other studies and from common clinical practice in Western countries. – *MRAM*

Agarwal P, Kumar N, Chandra R, Gupta G, Arun R, Garg N.

Randomized study of intravenous valproate and phenytoin in status epilepticus.

SEIZURE

2007;16:527-12.

BRAIN INJURY Two neurons to rub together? – Applicability of neural reserve theory in mild traumatic brain injury

*** RECOMMENDED

One of the great challenges in predicting the longer term consequences of mild brain injury is that there is often little correlation between the severity of the injury and the eventual outcome. Two individuals may be unfortunate enough to have very similar accidents, producing identical physical brain damage and yet make completely different progress in recovery. The authors of this study suggest that a possible reason for the different outcomes lies in an individual's neural reserve. Put simply, the more brain you've got, the more you can lose before adverse effects kick in. While this theory has been used in models of different neurodegenerative diseases, there have only been two studies, to date, applying this model to brain injury. There is, apparently, a very good correlation between levels of education, IQ, and neural reserve (measured by brain volume, neuronal size and level of branching). This somewhat contentious proposal was used by the authors as a basis for assessing the effects of moderate brain injury, in terms of the duration of post traumatic amnesia, in people with different "neural reserves". Apart from educational attainment and IQ, alcohol use, marijuana consumption, age and previous neurological damage were also assessed as were levels of depression, anxiety and stress. A total cohort of 59 patients were identified and screened retrospectively for the measures in question. Unfortunately, post traumatic amnesia, which was being used as a marker of severity of injury, was assessed by asking patients to describe the point at which they developed continuous memories following the initial accident. This seems like rather a flawed process, but has been utilised in other research. Somewhat surprisingly, no correlation was found between duration of post traumatic amnesia and previous neurological injury, alcohol or marijuana use. There were, however, significant relationships between IQ, duration of education and the duration of post traumatic amnesia indicating that greater neural reserves may have a protective effect. While this is an interesting study, which addresses an important area in the field of brain injury, some of the methodological problems (retrospective data analysis, the use of subjective quantification of post traumatic amnesia and the assumption that IQ correlates with "neural reserve") mean that it is difficult to draw conclusions from it that would be helpful in the clinical context. – *LB*

Dawson KS, Batchelor J, Mears S, Chapman J, Marosszeky JE.

Applicability of neural reserve theory in mild traumatic brain injury.

BRAIN INJURY

2007;21(9):943-9.

PARKINSON'S DISEASE: adrenal transplants 16 years on

*** RECOMMENDED

In the 1980s following the paper by Madrazo et al in the New England Journal of Medicine, adrenal medullary transplants became an attractive experimental treatment for Parkinson's disease. The rationale was simple, the adrenal medulla produces catecholamines including dopamine albeit at low levels, and thus transplanting it from its normal site to the head of the caudate nucleus should produce clinical improvement from local dopamine release within this structure. However, with time the results proved equivo-

cal, and may have been as much due to the release of neurotrophic factors from the transplant and host sprouting as well as breaching of the blood brain barrier by the non fenestrated endothelium and better delivery of L-dopa to the brain, as to dopamine replacement by the transplant itself. Furthermore significant morbidity and mortality was attached to the procedure and so by the early 1990's the procedure fell out of favour. In this short report, Kompoliti et al report on the post mortem findings of an adrenal medullary transplant 16 years after it was performed in a patient who died after a 38 year-history of Parkinson's disease. The patient had significant benefit from the transplant for 4 years but subsequently declined and developed dementia and drug related psychosis. At post mortem some surviving chromaffin cells were found although none stained positive for tyrosine hydroxylase, the rate limiting enzyme that is used as a marker of catecholamine including dopaminergic cells. Thus the transplant failed to survive in a functionally useful state as the clinical course indicated. This is an important paper, because often the long term consequences and outcome of these experimental procedures are forgotten, as the initial enthusiasm for the therapy wanes to be replaced by uninterested scepticism. It is therefore good to see that follow up of the patient was continued in this case to the point of death and pathological examination of the brain. – RAB

Kompoliti K, Chu Y, Shannon KM and Kordower JH.

Neuropathological study 16 years after autologous adrenal medullary transplantation in a Parkinson's disease patient.

MOVEMENT DISORDERS

2007;22(11):1630-3.

SCHIZOPHRENIA: What is the problem?

Schizophrenia is a common disorder that affects a significant proportion of the population and the causes and treatment of it have been argued about for years. For many years now schizophrenia has been considered a neurodevelopmental disorder involving dopaminergic systems and in part this relates to the efficacy of dopamine receptor blockers as treatment for this condition and the non progressive changes that can be seen on imaging studies. However new ideas are always emerging in this field and more recently issues relating to neurogenesis and glutamatergic systems have been raised. Two recent papers provide further evidence in support of this. In the first of these, Patil et al have shown that metabotropic glutamate receptor 2 and 3 agonists are effective in schizophrenia possibly by reducing glutamate release without any effect directly on dopaminergic networks. This implies that manipulation of glutamate release could be important in the treatment of schizophrenia although this does not exclude some downstream action of such transmitter changes on dopamine networks. In another study Duan et al report that abnormalities in DISC 1 (Disrupted-In-Schizophrenia) alters neurogenesis during development and adulthood especially in the hippocampus in the latter case. How such alterations relate to the clinical features of schizophrenia are as yet unclear but again point the focus away from the dopaminergic synapse. Thus both of these new findings are interesting and may even be linked given the recent interest in neuro transmitter modulation of neurogenesis. Whatever the ultimate significance of this work both studies have suggested new ideas in the genesis of this devastating neuropsychiatric disorder. – RAB

Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, Avedisova AS, Bardenstein LM, Gurovich IY, Morozova MA, Mosolov SN, Nezmanov NG, Reznik AM, Smulevich AB, Tochilov VA, Johnson BG, Monn JA, Schoepp DD.

Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial.

NATURE MEDICINE

2007;13(9):1102-7.

Duan X, Chang JH, Ge S, Faulkner RL, Kim JY, Kitabatake Y, Liu XB, Yang CH, Jordan JD, Ma DK, Liu CY, Ganesan S, Cheng HJ, Ming GL, Lu B, Song H.

Disrupted-In-Schizophrenia 1 Regulates Integration of Newly Generated Neurons in the Adult Brain.

CELL

2007;130(6):1146-58.

HEADACHE: Topiramate treatment for chronic headache

*** RECOMMENDED

This randomised, double-blind, placebo-controlled trial of topiramate in chronic headache found a significant reduction in monthly migraine days on topiramate compared to placebo. Adults with more than 15 monthly days

were called chronic headache and of those, 78% met the criteria for acute medicine overuse at baseline. During the study, other migraine prophylactics, apart from antiepileptic drugs, were continued. Study completion rates were 75% in the topiramate group, and only 52% in the control group. The mean reduction in monthly migraine days was 3.5 compared to -0.2 in controls, and this was significant statistically. Data from quality of life questionnaires was conflicting, with improvement in the MIDAS rating (a migraine disability scale), but no change in the HIT-6 (Headache impact scale). Adverse events were high in both groups, with 73% in the topiramate group and 37% in the control group (who were taking a variety of medicines). In the topiramate group, the most common side effect was paraesthesiae (53%). Disturbance in attention in this trial was 6%, similar to other studies, and does not appear dose related so if it occurs, usually means the medication needs to be stopped. This study shows efficacy of topiramate in this headache group, who are often resistant to treatment. It is important that the treatment worked in patients overusing analgesics, as we need more good treatment options in this group in particular. – HAL

Diener H-C, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ, on behalf of the TOPMAT-MIG-201 (TOP-CHROME) Study Group.

Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study.

CEPHALALGIA

2007;27:814-23.

STROKE: Training stroke patients' arm movements

Task specific practice is recommended for improving motor function after stroke, but the best way to provide feedback in training is not known. Many therapists use manual guidance, using their hands to focus on the pattern of movement produced. Others focus on the achievement of goals and set up the position of targets to encourage the desired movements, for example to reach further or higher. Most give encouragement during the movement, after it or both. There is a lack of evidence to inform the most effective information to give as feedback and when to give it. The motor learning literature, which has been driven by sports science, distinguishes between two types of feedback: 1. Knowledge of Performance (KP) - on line feedback about performance as it occurs. 2. Knowledge of Results (KR) - information about the result of the movement when it is completed. In practice then KR may allow the person to know whether they were successful in picking up an object or placing it in the desired position, while KP could inform the person about the trajectory of the movement and the temporal relationships of joint motion as it happens. Cirstea and Levin have reported an interesting experiment to compare the effectiveness of KP and KR in stroke patients learning a pointing task. Twenty-eight stroke patients, who were at least three months post stroke, were randomly allocated to two groups. Both groups practiced reaching, with the affected arm, to a target for 75 pointing trials a day, for ten days. The target was positioned just out of reach, but the participants were asked to point to the target as quickly and accurately as possible in a single uncorrected movement. After a few initial trials with the eyes open, the participants were asked to practice with eyes closed to allow greater distinction between feedback regimes. One group was given concurrent verbal information about arm joint movements while they performed the pointing movements (KP), the other group were allowed to open the eyes at the end of the movements and correct their terminal position (KR). Statistically significant increases in joint range, better inter-joint coordination and generalisation of these gains to pointing to a target positioned in a different place were observed only in the group who received KP. In sports training for individuals without impairments the use of KP has been questioned. It has been argued that because motor planning is most likely to be done in terms of hand or foot space, it is better not to focus attention onto the performance of joints through the movement. It seems that this advice should not apply to training patients with stroke. These results go a little way to helping the therapist to direct feedback effectively. Many questions remain though. Would the difference in arm movement have been apparent if the patients had been allowed to use vision as well? Is it helpful to use manual guidance as feedback or is it better to use verbal feedback? Answers to these questions will help not only therapists in clinical practice but also the development of robots and virtual reality games for rehabilitation in the future. – AJT

Cirstea MC, Levin MF.

Improvement of arm movements patterns and endpoint control depends on type of feedback during practice in stroke survivors.

NEUROREHABILITATION AND NEURAL REPAIR

2007;21:398-411.



Sir Martin Evans wins Nobel Prize 2007

Sir Martin Evans has been awarded the 2007 Nobel Prize for Medicine, along with US scientists Mario Capecchi and Oliver Smithies, for their groundbreaking discoveries concerning embryonic stem cells and DNA recombination in mammals.

They developed the gene targeting technique which enabled them to replicate human diseases in mice by introducing genetic changes into the animal's stem cells. The Nobel Committee praised the technique as "an immensely powerful technology" that is now being used in virtually every area of biomedical research.

The technique, commonly described as gene 'knockout', also enables scientists to disable specific genes, and alter their expression in more subtle ways to create 'knock out' mice carrying the specific genetic alterations that underlie human diseases. More than 10,000 mice genes, around half of the total, have been knocked out to date, with the rest predicted to follow soon. As a result, more than 500 different mouse models of human disorders have been developed, including neuro-degenerative diseases.

Sir Martin Evans is a professor of mammalian genetics at Cardiff University.

Zeiss wins Microscopy Award

Carl Zeiss has won the Cell Biology Microscopy Instruments category at the Life Science Industry Awards 2007 The Scientist's Choice. "The Scientist's Choice is the ultimate accolade for any instrument manufacturer", says Aubrey Lambert, Marketing Manager at Carl Zeiss UK. "This is not an award for a single instrument but recognition of the whole company's attributes across the board. It demonstrates our commitment to innovation and excellence and our leadership in creating solutions optimally tailored to the needs of modern biomedical research that provide scientists with tools that increase the speed, efficiency and success of their work."

The 2007 Life Science Industry Awards was based on over 3,000 responses to an online survey from readers of The Scientist and registered

members of the Science Advisory Board, the world's largest online community of scientists and healthcare professionals. Consideration was given not only to practical aspects and outstanding properties of the product or complete solution, but also to the cost/benefit ratio.

Carl Zeiss has won Life Science Industry Awards in each of the last four competitions. Explaining the company's continuing success, Lambert says, "In other microscope companies it's still the physicists and engineers in the development team who decide what goes into the product. At Zeiss we have a multi-discipline approach. Our biologists, the people with the application edge, determine feature sets from the market-leading options given to them by the engineering team."



Rehabilitation research study awarded £2.3 million

Virtual therapists will help patients with chronic conditions take control of their home rehabilitation in a major new research project awarded £2.3 million by the Engineering and Physical Sciences Research Council. The four year SMART2 project, lead by Sheffield Hallam University's Centre for Health and Social Care Research, will look at how technologies can be used to help individuals and their families to manage long term conditions. Patients will be supported not only by home visits but also from remote contact with their therapists via high tech sensors and computers in their homes. This new study will look at ways in which the computer can work directly with the patient, changing and altering the programme in accordance with the information it receives about the person's movements both inside and beyond the home and informing their therapist when it does so.

Sheffield Hallam will lead a consortium of universities and institutions comprising University of Ulster, University of Bath and The University of Sheffield. The researchers will fit each of the 60 subjects' homes with a touch screen computer and a range of movement sensors and measurement equipment and study whether these systems improve the lives of the subjects.

British Geriatrics Society/Dunhill Medical Trust Research Fellowships

Through the generosity of The Dunhill Medical Trust, the British Geriatrics Society has announced two Fellowships, each for up to three years duration, for research related to older people.

Applications are invited to undertake research where the condition and/or interventions to be studied predominantly affect older people (i.e. more than 75% of the subjects are over 70 years of age) or the issue to be studied is specific to the old and/or the very old (i.e. those over 70 or 85 years of age). The Fellowships are open to registered health professionals working as nurses, occupational therapists, physiotherapists, and speech and language therapists or similar, and will cover salary, on costs and some running expenses. Successful applicants are expected to undertake an appropriate higher degree (e.g. MSc, MPhil, PhD).

The closing date for applications is 1 December 2007. It is not necessary for applicants to be members of the British Geriatrics Society. See www.bgs.org.uk/Grants/dunhill.htm

MS nurse becomes Queen's nurse

MS Nurse Kathy Franklin has been awarded the title Queen's Nurse. After a 40-year absence, the Queen's Nursing Institute (QNI) has relaunched the award to recognise and encourage excellence in practice, innovation and improvements in patient care.

"Going for this award was my way of thinking outside the box," Kathy says. "It's a differ-

ent way to show commissioners the value of our role as specialist nurses." Kathy's application was backed by testimony from colleagues and patients as well as examples of her innovative work, such as a project to improve palliative care in East Northamptonshire which brings together health services, voluntary organisations and service users.

Kathy has been an MS nurse for four years and before that worked as a lecturer/practitioner health visitor. She will join the other 18 Queen's Nurses to form learning sets to protect, improve and develop standards of care in nursing.

Details of QNI's awards can be found at www.qni.org.uk

Philips wins Pioneer in Technology Award

Philips Medical Systems was recently recognised by the International Society of Brain Mapping and Intraoperative Surgical Planning Society (IBMISPS) at their annual meeting in Washington, DC. Philips received the organisation's 'Pioneer in Technology' award for the company's leading role in the development and commercialisation of image guided procedures. This recognition was largely based on Philips' early development and long history of innovations in interactive magnetic resonance imaging (MRI), as well as interventional and intraoperative MRI. Philips

was also recognised for its involvement in developing the 'Operating Room of the Future,' suites that include multiple imaging systems to help physicians simplify diagnosis and improve patient care. Working closely with customers to drive innovation, Philips teamed with the University of California San Francisco (UCSF) to develop the XMR suite, combining MRI and cardio/vascular X-ray, and with Tokai University Japan to develop a MRXO suite, combining MRI, catheterisation (cath) lab, computed tomography (CT) and operating room.



Dr Helen F Routh, Vice President Philips Research, pictured with Mr Babak Kateb, founder and executive director of International Brain mapping & Intra-operative Surgical Planning Society.

David Marsden Award 2007



The David Marsden Award was presented for the first time in 2003 by the European Dystonia Federation. Professor David Marsden was one of the leading neurologists in Europe, and the Federation wishes to honour the enormous part he played in developing knowledge of an interest in Dystonia.

The Award is intended to encourage research into Dystonia in all European countries, especially by young scientists. The

Medical Advisory Board and the Board of the EDF evaluated 8 papers submitted for the David Marsden Award 2007, and the winner was Mirta Fiorio, from the University of Verona. Her paper was entitled "Defective temporal processing of sensory stimuli in DYT1 mutation carriers: a new endophenotype of dystonia?" The award of 2,500 Euros was made at the EFNS congress in Brussels at the Basal Ganglia Club meeting.

Peter Bradley Foundation Commendation

The Peter Bradley Foundation, in partnership with BRÍ, were delighted to receive funding for 2006/2007 through the Department of Justice, Equality and Law Reform's Enhancing Disability Services Programme, enabling them to deliver a project comprising of 12 Education and Information Events on Acquired Brain Injury (ABI) for people with ABI, their families and carers, healthcare and /allied professions; and the design and production of an ABI support manual.

This project received a commendation for Best Patient Education Project Non Pharmaceutical in the Irish 2007 Healthcare Awards and is one of just two projects shortlisted for this category. The final results were announced on Wednesday 24th October as ACNR went to press.



MS Partnership Awards

Each year the MS Society recognises high quality collaboration between volunteers and health and social care professionals through its Partnership Award scheme. By combining their expertise, resources and financial funds, volunteers and professionals working together can produce greatly enhanced services.

There were three winners this year: North Yorkshire & York PCT with the Hambleton &

Richmondshire MS Society adapted their physiotherapy to the needs of people in a rural area. Services are offered to groups or individuals in various locations depending on need; The West Midlands MS Strategy Group is a multi-faceted partnership of the acute sector, the MS Society's respite service, the PCT, the local authority and volunteers to coordinate services; The Douglas Grant

Rehabilitation Centre worked with MS Society Scotland to offer a six-week user-led education course for people living with MS combining information for newly diagnosed people with expert patient courses.

A vigorous assessment process ensures the winning services are valued, sustainable and innovative. See www.mssociety.org.uk/partnership

New formulation of Rebif offers improved injection tolerability

Merck Serono, a division of Merck KGaA, has announced results of a two year Phase IIIb study in 260 patients which has shown that the new formulation of Rebif (interferon beta-1a) offers a near three-fold improvement in injection tolerability for patients with relapsing remitting multiple sclerosis (RRMS). These results are compared with historical data for the previous formulation of Rebif (30.8% versus 85.8%).

The results were presented at a satellite sym-

posium and poster session at the recent Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). "Rebif is an established first-line disease modifying treatment for relapsing types of MS" said Professor Gavin Giovannoni from The Royal London Hospital. "Injection site reactions can lead to withdrawal from treatment. The reduction in these reactions with the new formulation should improve treatment benefit to patients."

The new study results have confirmed consistent efficacy of the new formulation of Rebif compared with previous experience. At 96 weeks, 53.3% of patients remained relapse-free and overall the expanded disability status scale (EDSS) score remained stable throughout the study. The new formulation of Rebif is due to be launched in the UK in early 2008.

For more information contact Merck on T. 020 8818 7200.

APO-go® ampoule service improvement

Following the success of the APO-go Pre-Filled Syringe (PFS) delivery pack, where plastic pump-dedicated syringes are supplied alongside the PFS order at no additional cost, Britannia Pharmaceuticals will shortly be providing a delivery pack for APO-go ampoule orders. This product improvement follows customer feedback, and is aimed at: Providing tailored numbers of plastic pump-dedicated syringes

rather than bulk deliveries; Reducing waste and releasing storage space; Providing less burden for the pharmacists and for patients.

Initially, the delivery packs will consist of boxes of APO-go ampoules (2ml x 5, 5ml x 5) plus a suitable number of plastic pump-dedicated syringes for that quantity of APO-go.

For more information T. 01737 773741.



Siemens relocates UK headquarters

After 16 years based in Bracknell, Siemens plc has relocated the majority of its headquarters-based employees to a new office which has been officially named 'Sir William Siemens Square' to mark the occasion.

1,400 Siemens employees moved from Bracknell and Staines to Frimley. 250 information technology services specialists continue to be based at Hyde House, a Siemens building adjacent to the site in Bracknell. A park and ride scheme also operates from Hyde House for employees who wish to commute to Bracknell and continue their journey to Frimley by shuttle bus. The park and ride scheme was introduced to help reduce traffic and alleviate the need for additional parking spaces at the new headquarters.

Built four years ago, Sir William Siemens Square, close to junction four of the M3 motorway, is a stand-alone site with four office buildings totalling 183,000ft² (17,000m²) of floor space. The offices have been refurbished with the latest state-of-the-art technology infrastructure.

Andrew Beshaw, managing director of Siemens Real Estates, who led the relocation project, said, "The relocation of our UK headquarters has been an ideal opportunity to rethink the way we work and massively reduce our impact on the environment," said Beshaw. "We have set ourselves the target of recycling 75% of all our waste at the new HQ. We will start by putting in mechanisms to measure what we are doing so we can report on what is recycled, how much waste goes to landfill and how much energy we use."

Globally, Siemens' own carbon footprint is estimated to be 4.5 million tonnes of CO₂, with the majority of that caused by electricity consumption. Lighting throughout Siemens' new headquarters in Frimley has been installed using Siemens' own intelligent technology ensuring minimal energy consumption. Siemens estimates it will make an annual saving of 122.6 tonnes of CO₂, and save more than £34,000 a year from the new lighting alone.

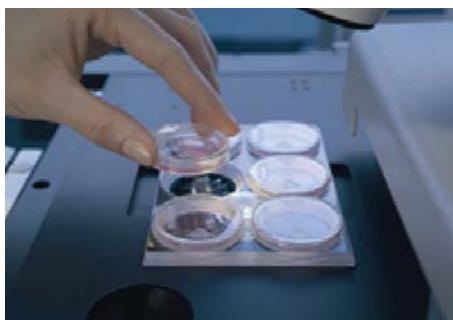
For more information
T. +44 (0)1344 396317.

PALM MicroBeam system enhancements

Carl Zeiss is introducing a range of new accessories for its PALM MicroBeam laser microdissection system to advance research into living cells. The PALM DuplexDish 35 culture dishes, PALM DishHolder 35 with CapCheck and PALM DishHolder 6/35 are specially tailored to the needs of laser microdissection and pressure catapulting technology (LMPC) and open up new experimental possibilities for the isolation and micromanipulation of cellular and sub-cellular systems. The enhanced system will be especially useful to life scientists working with PALM MicroBeam instruments in research institutes, universities and in the pharmaceutical industry.

DuplexDish 35 is a 35 mm diameter culture dish optimised for cell growth and micro-dissection. Cells can be isolated, collected and cultivated in the dish without an additional trypsinisation step. The small dish diameter cuts down on reagent volumes to reduce costs. Despite an additional membrane, the base offers optimal gas exchange and exhibits low autofluorescence. The main fields of application are living and stem cell applications with an emphasis on downstream applications such as transfection assays.

Zeiss also released two dish holders in which the DuplexDish is inserted before being placed



on the microscope stage for observation. The DishHolder 35 incorporates an aperture that allows the user to check for successful specimen isolation. The aperture also allows microdissected specimens to be ejected into the cap of a microtube where they may be examined without requiring the dish to be removed from the holder.

The DishHolder 6/35 will accommodate up to six of the 35mm culture dishes at a time. It can also be inserted in the stage for microscopic examination but also allows for convenient preparation under laminar airflow. The holder has a cover for all six dishes or each dish may be individually closed.

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

OXYSWING® Medical Oxygen Generators Manufactured to ISO 13485



The quality management system of IGS' manufacturing site in Italy has been certified to ISO 13485:2003 by Det Norske Veritas. IGS Italia is IGS' major manufacturer of the NITROSWING® and OXYSWING® PSA nitrogen and oxygen generators.

Tom Jeffers, President of Innovative Gas Systems, said: "The certification to ISO13485:2003 is the first step of our future strategy for medical oxygen and will further enhance the already strong market position of our current OXYSWING® PSA oxygen generators for healthcare applications. We will introduce our new OXYSWING® medical oxygen line during the Medica 2007 fair in Düsseldorf in November 2007. Besides a very innovative design, the new OXYSWING® medical oxygen product line will be certified to the 93/42/CE directive for medical devices as well."

Innovative Gas Systems is one of the world's major suppliers of on-site air separation plants for the production of nitrogen and oxygen. IGS' technologies for the production of nitrogen and air drying by Hollow Fiber Membranes (GENERON®) and for the production of nitrogen and oxygen by optimized Pressure Swing Adsorption processes (NITROSWING® & OXYSWING®) set new market standards in terms of performance and efficiency. IGS has production facilities and numerous sales and service centers in North America, Europe, Russia, Middle East, Asia and the People's Republic of China.

For more information
E. d.evangelista@igs-italia.com, or see
www.igs-global.com



3D fruit fly images to benefit brain research



A 3D image of a fruit fly generated after first bleaching the fly's exoskeleton. Different organs can be clearly seen.

MRC scientists have generated 3D images of the inside of a fruit fly using optical projection tomography (OPT), images which could help to speed up genetic research into Alzheimer's and other diseases affecting brain cells. A 3D image of a fruit fly generated after first bleaching the fly's exoskeleton. Different organs can

be clearly seen. Dr Mary O'Connell of the MRC Human Genetics Unit who led the research explained, "Neurodegeneration isn't a strictly human phenomenon. Insects are affected by it too."

Because the fruit fly and human share many genes with similar functions, the fly is widely used by genetic

researchers to study how genes influence human disease. OPT could help researchers to look at how the fly brain changes in response to alterations in the normal activity of a specific gene without the risk of damaging tissue through dissection.

For more information
T. +44 (0)20 7637 6011.

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, dyspnoea, 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 review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, 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, lipoatrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, 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** - September 2007.

Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.

Reference: Ford C. et al. Multiple Sclerosis 2006; 12: 309-320.

Your decision today can make a difference tomorrow



COPAXONE®
(glatiramer acetate)

Long-term active

TEVA


sanofi aventis

Because health matters

Date of preparation: October 2007 Code: C0807/428a



Because every day is precious

we don't waste a day

With Aricept Evess
the first dose is a therapeutic dose¹⁻⁷

 **Aricept® Evess**
donepezil hydrochloride

Continuing Commitment
To Alzheimer's

ARICEPT® EVESS® IS INDICATED FOR THE SYMPTOMATIC TREATMENT OF MILD TO MODERATELY SEVERE ALZHEIMER'S DEMENTIA.

ABBREVIATED PRESCRIBING INFORMATION

ARICEPT® EVESS® (donepezil hydrochloride orodispersible tablet)

Please refer to the SmPC before prescribing ARICEPT EVESS 5 mg or ARICEPT EVESS 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** **Adults/elderly;** 5 mg daily which may be increased to 10 mg once daily after at least one month. Orodispersible tablet which should be placed on the tongue and allowed to disintegrate before swallowing with or without water. Treatment should be initiated and supervised by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Monitor regularly to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. **Children;** Not recommended. **Contra-Indications:** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Pregnancy:** Aricept should not be used unless clearly necessary. **Lactation:** Excretion into human breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinus pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. As with all Alzheimer's patients, ability to drive/operate machinery should be routinely evaluated. No data available for patients with severe

hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. May interfere with anticholinergic agents. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT EVESS 5 mg; white, embossed, orodispersible tablets, packs of 28 £63.54. ARICEPT EVESS 10 mg; yellow, embossed, orodispersible tablets, packs of 28 £89.06. **Marketing authorisation numbers:** ARICEPT EVESS 5 mg; PL 10555/0019 ARICEPT EVESS 10 mg; PL 10555/0020. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** December 2006

Information about adverse event reporting can be found at www.yellowcard.gov.uk
Adverse events should also be reported to Eisai Ltd on 0208 600 1400 or Lmedinfo@eisai.net

References: 1. Aricept SmPC 2. Aricept Evess SmPC 3. Rivastigmine SmPC 4. Galantamine SmPC 5. Galantamine XL SmPC 6. Memantine SmPC 7. Data on File Studies 015, 016 and 017 (Eisai Ltd, Pfizer Ltd)
Date of preparation: January 2007
AR1016-ARI984 12-06

