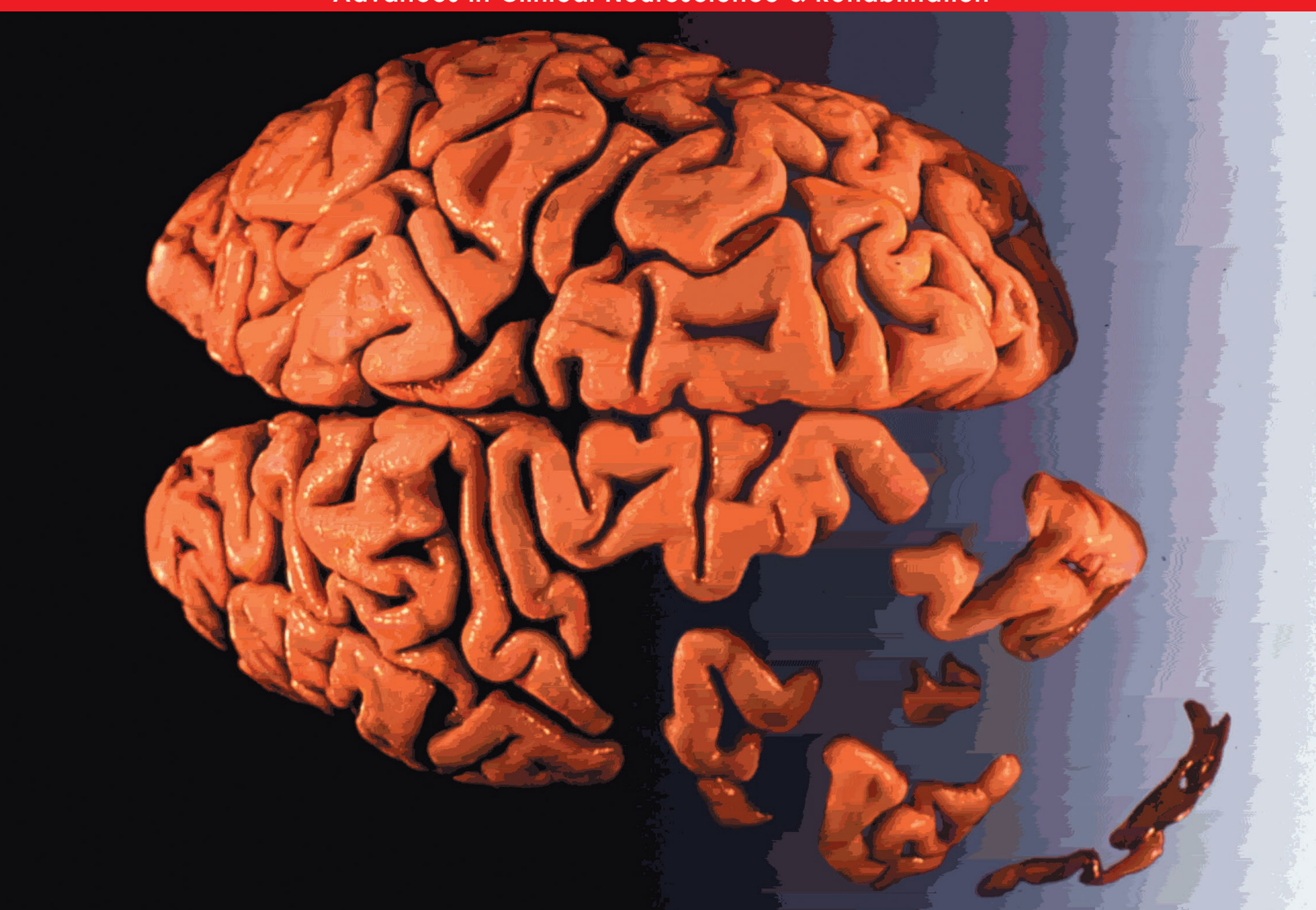
ISSN 1473-9348 Volume 2 Issue 2 May/June 2002

ACNR

Advances in Clinical Neuroscience & Rehabilitation



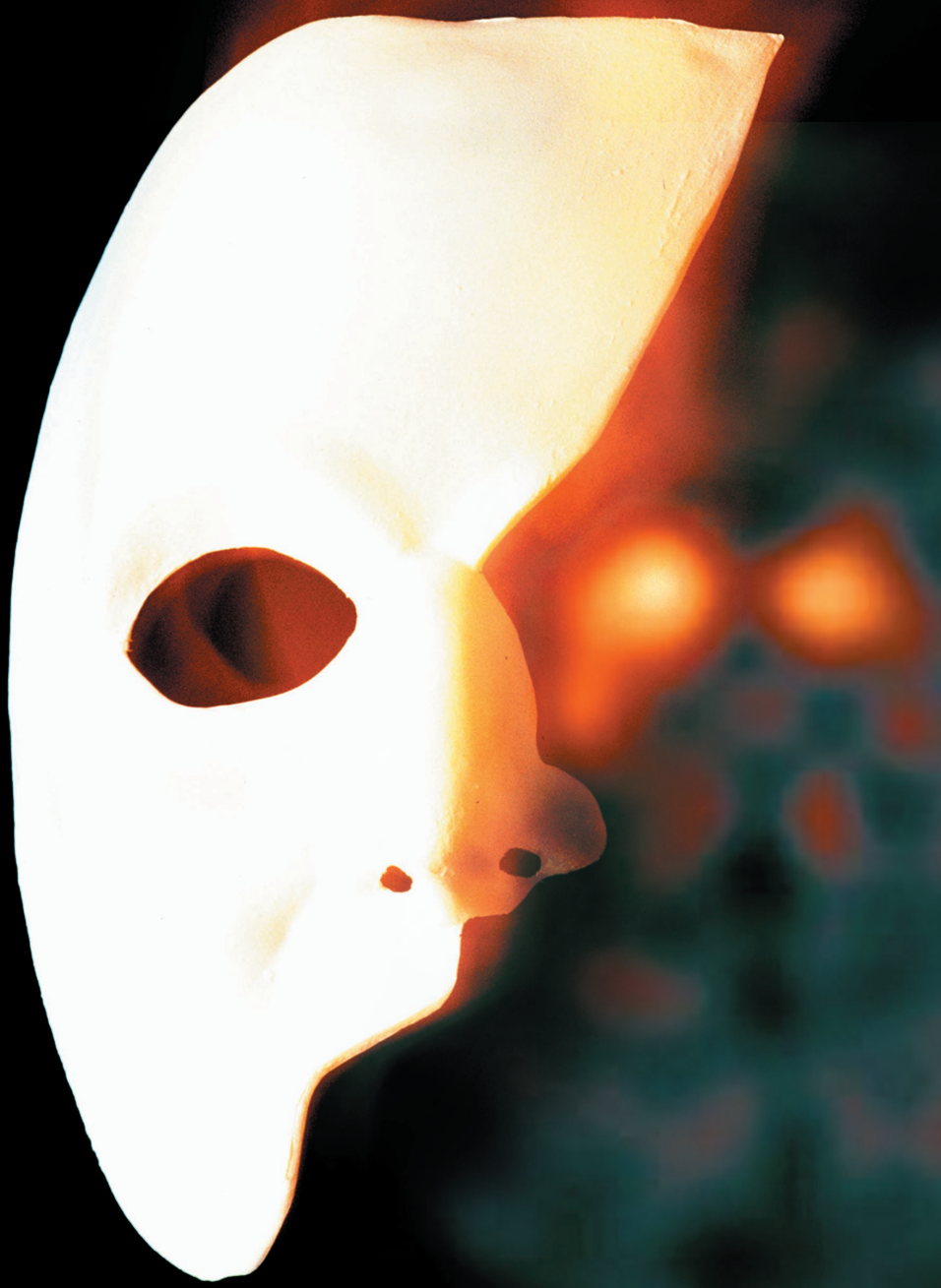
journal reviews • events • management topic • industry news • rehabilitation topic

Review Articles: Clinical features of Varicella Zoster Virus infection of the nervous system; Glioma therapy

Rehabilitation Article: Randomisation in single-case experimental designs

Management Topic: Inflammatory Muscle Disease

THE TRUTH BEHIND THE MASK



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Marketing Authorisation numbers: EU/1/00/135/001 & EU/1/00/135/002
Date of preparation: February 2001

[1] Benamer H et al. Accurate differentiation of Parkinsonism and Essential Tremor using visual assessment of ^{123}I-FP-CIT SPECT imaging: the ^{123}I-FP-CIT Study Group. Movement Disorders 2000;15:503-510.

Date: October 2001, DaT/459/OS

Amersham Health

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contents

may/june 2002

Welcome to another edition of the ACNR, which this month boasts its first transatlantic author. Don Gilden and colleagues from Denver have provided a beautiful up-to-date account of varicella zoster virus (VZV) infection and the nervous system, the senior author himself having personally described 4 new neurological entities associated with VZV. These complications of VZV are important to recognise, not least because they can occur some time after the initial reactivation and the article presents a good account of therapies, even though proper controlled trials do not exist for many of these complications. This difficulty of trying to make substantiated generalised statements in the absence of large data sets and properly controlled trials is becoming more problematic in medicine and aspects of this are discussed by Professor John Todman in his article on randomisation in single-case experimental designs. In particular the article explores how one can extract the most useful data from single case studies or studies where n is very small.

Our other major review article this month is from Jeremy Rees who takes us on a tour of the rather depressing aspect of glioma therapy (see also journal reviews). This is a timely account given the recent developments in chemotherapy and the possible use of targeted therapy, using such vehicles as stem cells (Aboody KS et al. Proc Natl Acad Sci U S A 200097:12846-51). One of the striking points that I took away from this article was the fact that the anaplastic oligodendrogliomas with loss of chromosome 1p and 19p are very chemosensitive. This is not only a useful clinical point, but raises hopes that understanding the molecular genetics of tumours may help explain their behaviour and the development of more specific and effective therapies.

There are also our usual articles and of special note this issue is the magnificently colourful anatomy primer of Justin Cross and Alasdair Coles on the lumbar spine. It is good to know that such creativity still exists with the ranks of neurology in the 21st century! We also have another excellent article in our series on muscle disease by Gillian Hall and a collection of reviews and conferences.

Once more we want to thank you all for the feedback we are receiving and do keep us informed on how we can improve, and what else you would like to see within the journal - within reason of course!

Roger Barker
AdvancesCNR@aol.com

Erratum: In Prof Confavreux's article on page 7 of the March/April issue, the chapter entitled "The interplay : a dissociation between relapses and progression ?", paragraph 4 devoted to the natural history of MS should read: "Progression of irreversible disability from the assignment of a score of 4 on the DSS Kurtzke scale27 to the assignment of a score of 6 or 7 is unaffected by the presence or the absence of a relapsing-remitting phase before the progressive phase of MS..." we apologise for this error.

Features

Regulars

ACNR is published by Whitehouse Publishing,
7 Alderbank Terrace, Edinburgh EH11 1SX.
Tel. 0131 477 2335/0777 969 7677, **Fax.** 0131 313 1110
E-Mail. AdvancesinCNR@aol.com
Publisher: Rachael Hansford
Design & Production: Barbara Newton
Printed by: Stephens & George Magazines, Tel. 01685 388888.

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Date of Review: December 2000.

Date of Preparation: December 2001.

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Roger Barker is co-editor in chief of Advances in Clinical Neuroscience & Rehabilitation (ACNR), and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. He trained in neurology at Cambridge and at the National Hospital in London. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

Alasdair Coles is co-editor of ACNR and contributes our Anatomy Primer. He is a Wellcome Advanced Fellow working on experimental immunological therapies in multiple sclerosis, based at the Dunn School of Pathology in Oxford and Department of Neurology in Cambridge.

Stephen Kirker is the editor of the Rehabilitation section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He graduated from Trinity College, Dublin in 1985 and trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.

David J Burn is the editor of our conference news section and Consultant and Senior Lecturer in Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He qualified from Oxford University and Newcastle upon Tyne Medical School in 1985. His MD was in the functional imaging of parkinsonism. He runs Movement Disorders clinics in Newcastle upon Tyne and Sunderland. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

Andrew Larner is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

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Justin Cross is a Consultant Neuroradiologist at Addenbrooke's Hospital, Cambridge. He trained in neuroradiology in Cambridge and Toronto. Current research interests include the imaging of paediatric brain tumours and the use of web-based media for neuroanatomy teaching. He is a supervisor in neuroanatomy at Peterhouse, Cambridge.

Gillian Hall contributes our Muscle Management Feature. She is a Consultant Neurologist working between The Western General Hospital, Edinburgh and Forth Valley. She trained in Glasgow, Oxford and Cambridge and has a particular interest in diseases of muscle.

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Clinical features of Varicella Zoster Virus infection of the nervous system

Varicella zoster virus (VZV) is an exclusively human neurotropic herpesvirus that causes approximately four million cases of chickenpox annually. After chickenpox, VZV becomes latent in cranial nerve, dorsal root and autonomic nervous system ganglia along the entire neuraxis. The neurological complications of VZV reactivation are shown in Fig. 1.

Zoster. Virus reactivation, mostly in elderly and immunocompromised individuals, produces zoster (shingles), characterised by severe sharp, lancinating, radicular pain and rash restricted to 1-3 dermatomes. In affected dermatomes, sensation is decreased, yet the skin is exquisitely sensitive to touch (allodynia). In the US, more than 500,000 cases occur annually. Although varicella occurs mostly in Spring, zoster develops any time of year. The incidence of recurrent zoster in immunocompetent individuals is less than 5%. Thoracic zoster is most common, followed by facial lesions, usually in the ophthalmic division of the trigeminal nerve and frequently accompanied by zoster keratitis, a potential cause of blindness if not recognised and treated promptly. Patients with ophthalmic zoster need immediate slit-lamp examination by an ophthalmologist, particularly if skin lesions extend to the medial side of the nose (Hutchinson's sign). Zoster in the maxillary and mandibular divisions of the trigeminal nerve may be associated with osteonecrosis and spontaneous tooth exfoliation. Facial nerve involvement, characterised by weakness of all facial muscles on one side, usually develops with rash in the ipsilateral external ear (zoster oticus) or hard palate. Zoster oticus with peripheral facial weakness constitutes the Ramsay Hunt syndrome (Sweeney and Gilden, 2001) from which recovery of facial paralysis is often less complete than in idiopathic Bell's palsy. Zoster may also be accompanied by ophthalmoplegia, most commonly affecting the third cranial nerve, or by optic neuritis, or both. Lower cranial nerve palsies are less frequent. Cranial neuropathy often occurs weeks after acute zoster. Since all cranial nerves receive their blood supply from the carotid circulation via small branches supplying groups of two or three cranial nerves (Lapresle and Lasjaunias, 1986), the occurrence of concurrent contiguous cranial neuropathies suggests small vessel-mediated infarction. VZV may spread transaxonally along trigeminal and other ganglionic afferent fibers from the carotid arteries (Mayberg *et al.*, 1984) to the vasa vasorum of small nerves. Cervical zoster is occasionally associated with arm weakness (zoster paresis) and less often with diaphragmatic paralysis. Lumbosacral zoster can be accompanied by leg weakness as well as bladder and bowel dysfunction. Zoster has developed within days-weeks after injury by lightning or injection of foreign material, and one time five hours after spinal anesthesia (Arnold, 1941).

Treatment. No protocol is universally accepted. Analgesia includes extra-strength acetaminophen and codeine 30-60 mg every 6 hours when necessary. Oral acyclovir (800 mg 5 times daily) or famciclovir (500 mg 3 times daily) decreases new lesion formation and reduces acute pain (Tyring *et al.*, 1993; Wood *et al.*, 1994).

We prescribe oral acyclovir or famciclovir for 7 days if new skin lesions have developed within the past week. Patients with ophthalmic distribution zoster should receive antivirals for at least 7 days.

Authors

Dr Gilden is Professor of Neurology and Microbiology and Chairman of the Dept of Neurology at the University of Colorado School of Medicine. Dr Gilden was the first to demonstrate VZV latency in normal human ganglia and concluded that most of 700,000 shingles cases in America annually are due to VZV reactivation, not new infection. He discovered four neurologic diseases caused by VZV: vasculopathy, recurrent myelopathy, zoster sine herpete and preherpetic neuralgia. He has published more than 180 papers, reviews and chapters.

Ms Lisa Williams is a graduate student in the Department of Microbiology at the University of Colorado School of Medicine and is currently working in the laboratory of Dr Cohrs on varicella zoster virus (VZV) latency.

Dr Cohrs is Associate Professor of Neurology at the University of Colorado School of Medicine. Dr Cohrs has been studying VZV latency for more than a decade. He's the first to clone and sequence transcripts mapping to 4 VZV genes in latently infected human ganglia. His critical work has laid the foundation for the molecular analysis of VZV latency.

Postherpetic Neuralgia (PHN). Pain that persists for months and sometimes years (PHN) develops in >40% zoster patients over age 60. Because the elderly and immunocompromised patient population is increasing, VZV can be seen as an important infection of the twenty-first century.

Prevention. We give acyclovir (800 mg 5 times daily) or famciclovir (500 mg 3 times daily) to zoster patients over age 60 for 7-10 days. No optimum therapy to prevent PHN exists. Various trials used antivirals, steroids, or both, as well as amantadine hydrochloride (a dopamine agonist); parenteral adenosine monophosphate; and a double-blind study with either oral levodopa and benserazide or placebo demonstrated some efficacy in preventing PHN. However, studies were hampered by potential toxic side effects (as with interferon), a small sample size, and an abnormally high incidence of PHN in control groups (reviewed in Gilden *et al.*, 2000).

Treatment of PHN. Like zoster, no universally accepted treatment exists. Tricyclic antidepressants, such as amitriptyline or nortriptyline (25-75 mg at night), and anticonvulsants carbamazepine (600-1200 mg daily), phenytoin (300-400 mg daily) and gabapentin (neurontin), 900-3600 mg daily relieve pain in some patients along with slow release oxycodone 10-30 mg twice daily. A short course of steroids, e.g. prednisone (40-60 mg daily for 3-5 days and sometimes longer), may reduce inflammation contributing to pain. Topical lidocaine patches as well as aspercreme and flexall 454 may help. The development of other topical anaesthetic agents for PHN sufferers is an important area for future clinical research.

VZV Vasculopathy. In immunocompetent and immunocompromised patients, central nervous system (CNS) complications develop after VZV reactivation when virus spreads to arteries of the brain and spinal cord. Although VZV infection in the CNS is commonly referred to as VZV encephalitis, it is actually a vasculopathy that affects large and small cerebral arteries. Large artery infection predominates in elderly immunocompetent individuals, and is characterised by acute focal deficit that develops weeks-months after contralateral trigeminal-distribution zoster. The vasculopathy is usually restricted to 1-3 large anterior circulation arteries. In contrast, VZV infection of small cerebral blood vessels predominates in immunocompromised individuals and produces features of headache, fever, mental status changes and multifocal deficit, evident by neurological exam and brain MRI imaging. VZV small-vessel disease is often chronic and may develop without zoster rash. Both ischaemic and hemorrhagic infarcts are found in cortical, subcortical gray and white matter (Amlie-Lefond *et al.*, 1995).

Most patients with VZV vasculopathy have a cerebral spinal fluid (CSF) pleocytosis, usually <100 cells (predominantly mononuclear), oligoclonal bands and increased CSF IgG. When large vessels are involved, angiography reveals focal constriction and segmental narrowing. Microscopic and virologic examination of arteries reveals inflammation, multinucleated giant cells, Cowdry A inclusions and herpesvirus particles (all hallmarks of herpesvirus infection), as well as VZV antigen and VZV DNA in affected vessels (Gilden *et al.*, 1996; Melanson *et al.*, 1996).

Because VZV vasculopathy is uncommon, controlled treatment trials

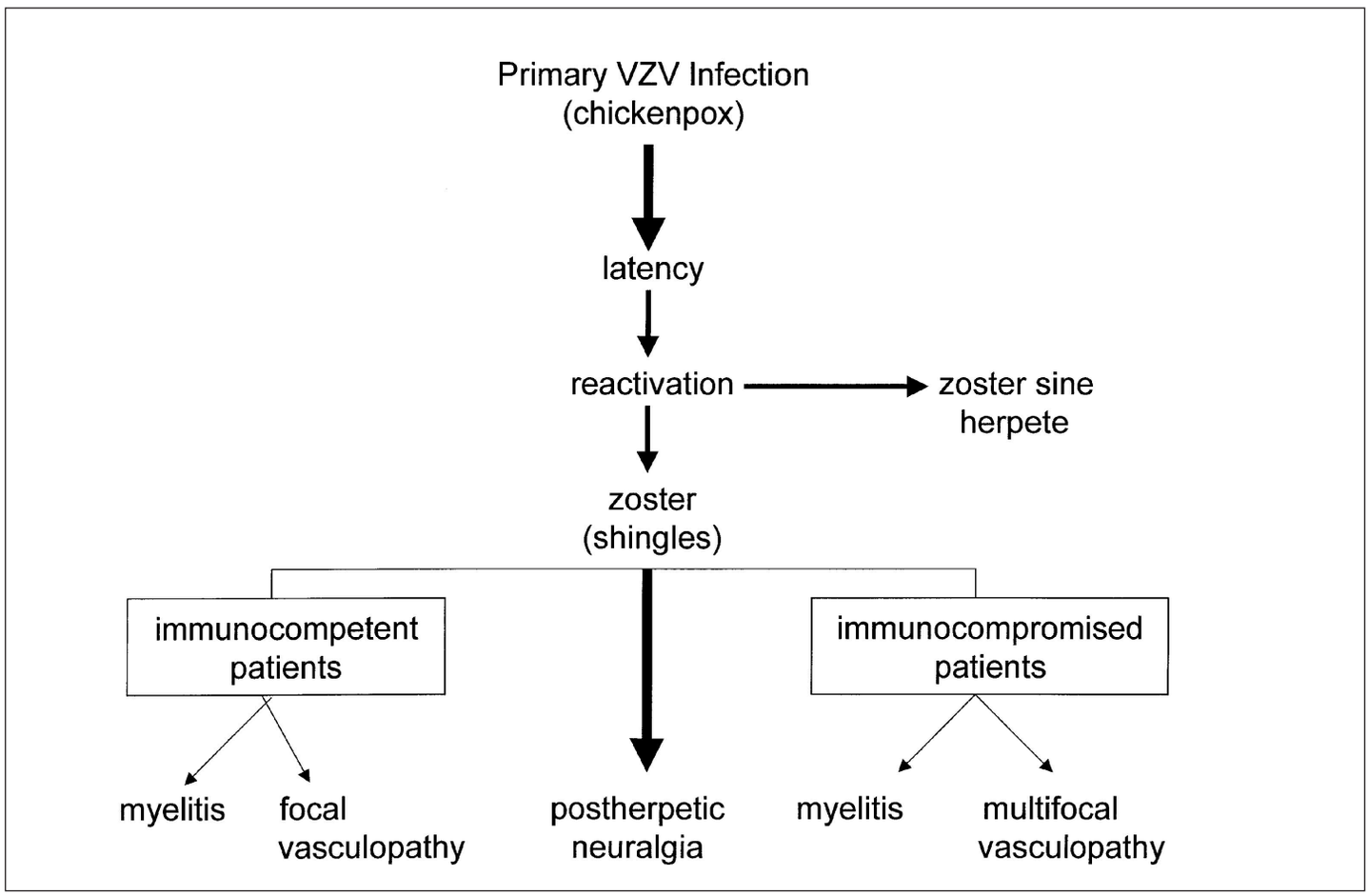

Fig. 1. Neurological Complications of Varicella Zoster Virus (VZV) Reactivation.
Primary encounter (infection) with VZV usually occurs in childhood and produces chickenpox (acute varicella). After chickenpox, VZV becomes latent in ganglia in virtually everyone and remains for the lifetime of the individual. VZV reactivation, usually after age 50, produces a characteristic dermatomal shingles rash (zoster). Rarely, VZV reactivation can also produce pain without rash (zoster sine herpete). In immunocompetent individuals, the main complication of zoster is postherpetic neuralgia (pain that persists more than 6 weeks after rash). After shingles (zoster), immunocompetent individuals may also uncommonly develop central nervous system (CNS) complications of myelitis or a CNS vasculopathy affecting large or small cerebral arteries. Rarely, each of these complications can even develop without clinically recognised rash.

have not been possible. Based on the presence of virus in arteries and variably associated inflammation, we recommend intravenous acyclovir (10-15 mg/kg 3 times daily for 7-10 days) to kill persistent virus, and a short course of steroids (prednisone 60-80 mg daily for 3-5 days) for their anti-inflammatory effect. Immunocompromised patients may need prolonged oral antiviral therapy.

VZV Myelitis. VZV myelitis develops in immunocompetent and immunocompromised patients. In immunocompetent individuals, myelitis is usually monophasic and occurs 1-2 weeks after acute varicella or zoster. Clinical features are characterised by paraparesis with a sensory level and sphincter impairment. The mechanism of post-infectious myelitis is unknown. In contrast, VZV myelitis in immunocompromised patients is often insidious, progressive and sometimes fatal. Spinal cord MRI shows longitudinal serpiginous enhancing lesions. Spinal cord necrosis and intense inflammation with parenchymal invasion by VZV are seen pathologically. Cases of chronic and recurrent VZV myelopathy, responsive to antiviral treatment, have been reported (Gilden *et al.*, 1994a). Like VZV vasculopathy in brain, patients with VZV myelitis do not always have rash. Thus, an early search for VZV DNA or antibody in CSF is essential for diagnosis, particularly since acyclovir treatment, even in AIDS patients, may clear infection.

VZV Infection without Rash. Zoster sine herpete is dermatomal-distribution pain without antecedent rash. Before polymerase chain reaction (PCR), verification was by serologic testing. The first documentation was a physician who described his acute trigeminal distribution pain without rash, associated with a four-fold rise in antibody to VZV, but not to herpes simplex virus (HSV) (Easton, 1970). Demonstration of virus came only after PCR analysis of 2 men without rash who had experienced prolonged thoracic-distribution radicular pain. Amplifiable VZV DNA, but not HSV DNA, was found in their CSF and blood mononuclear cells (MNCs) (Gilden *et al.*, 1994b). Both were treated successfully with intravenous acyclovir. The prevalence of zoster sine herpete awaits virological analysis of additional patients with prolonged radicular pain. Analysis should include PCR to amplify VZV DNA in CSF and blood MNCs as well as a search for VZV antibody in CSF. The existence of ganglionitis without rash is further supported by radicular pain before zoster, so-called preherpetic neuralgia. A report of 6 individuals with preherpetic neuralgia exists. Pain preceded rash by 7-100 days, and was located in dermatomes different from, as well as the area of eventual rash (Gilden *et al.*, 1991).

There are other instances of VZV infection without rash. VZV meningitis and meningoencephalitis without rash were verified by detection of VZV antibody synthesised intrathecally (Vartdal *et al.*, 1982). Two instances of polyneuritis cranialis produced by VZV in apparently immunocompetent men were documented by seroconversion to VZV, but not to multiple other human viruses (Mayo and Booss, 1989; Osaki *et al.*, 1995). Some cases of acute unilateral facial (Bell's) palsy that developed without rash were attributed to VZV (geniculate zoster sine herpete) based on seroconversion (Aitken and Brain, 1933). The most extreme example of VZV infection of the nervous system without rash was an immunocompromised man who developed meningoradiculitis and died 3 weeks later (Dueland *et al.*, 1991). At autopsy, hemorrhagic inflammatory lesions with Cowdry A inclusions were found in meninges and nerve roots extending from cranial nerve roots to cauda equina. VZV, but not HSV or

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Please read Summary of Product Characteristics before prescribing. **Presentation:** Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. **Uses:** Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. **Dosage and Administration:** Oral administration (not to be chewed). Over 16 years: Usually 200–400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Renal disease may require a dose modification. Children 2 to 16: Approx. 5–9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1–3 mg/kg. Sprinkle Capsules should be taken whole or sprinkled on a small amount (teaspoon) of soft food and swallowed immediately. **Contra-indications:** Hypersensitivity to any component. **Precautions and Warnings:** May cause sedation; so caution if driving or operating machinery. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use. Requires discontinuation of Topamax and treatment of symptoms. **Side Effects:** Abdominal pain, ataxia, anorexia, CNS side effects, diplopia, fatigue, nausea, nystagmus, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis. Acute myopia with secondary acute-angle closure glaucoma reported rarely. **Pharmaceutical Precautions:** Tablets: Store in a dry place at or below 25°C. Sprinkle Capsules: Store below 25°C. **Legal Category:** POM. **Package Quantities and Prices:** Bottles of 60 tablets. 25 mg (PL0242/0301) = £22.02, 50 mg (PL0242/0302) = £36.17; 100 mg (PL0242/0303) = £64.80; 200 mg (PL0242/0304) = £125.83. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.88, 25 mg (PL0242/0349) = £25.32 50 mg (PL0242/0350) = £41.60. **Product licence holder:** Janssen-Cilag Limited, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ. UK. **Date of text revision:** November 2001. APIVER141101. **Code:** 02074

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cytomegalovirus antigen and nucleic acid, was detected in all infected tissue.

VZV Diagnosis: Amplifiable VZV DNA by PCR and Antibody to VZV. PCR and antibody testing of CSF to confirm the role of VZV in producing the many varied clinical syndromes of the peripheral and central nervous system is widely available and should be exploited, particularly since effective antiviral therapy exists. In the appropriate clinical setting (i.e. acute or subacute spinal cord disease, acute or chronic progressive encephalitis, or chronic radicular pain with or without rash), the presence of VZV DNA or antibody, or both, in CSF is strong presumptive evidence of infection. Even the detection of VZV antibody in CSF without PCR-amplifiable VZV DNA supports the diagnosis of VZV infection of the nervous system (Gilden *et al.*, 1998). Analysis of serum anti-VZV antibody alone is of no value since VZV antibodies are present in nearly all adults (Vafai *et al.*, 1988).

Acknowledgements. This work was supported in part by Public Health Service grants NS 32623 and AG 06127 from the National Institutes of Health (NIH). We thank Cathy Allen for preparing the manuscript.

References

Aitken RS, Brain RT. *Facial palsy and infection with zoster virus.* Lancet 1:19-22, 1933.
Amlie-Lefond C, Kleinschmidt-DeMasters BK, Mahalingam R, Davis LE, Gilden DH. *The vasculopathy of varicella zoster virus encephalitis.* Ann Neurol 37:784-790, 1995.
Arnold DG. *Herpes zoster as sequel of spinal anesthesia.* J Int Coll Surg 4:66-67, 1941.
Dueland AN, Devlin M, Martin JR, *et al. Fatal varicella zoster virus meningoradiculitis without skin involvement.* Ann Neurol 29:569-572, 1991.
Easton HG. *Zoster sine herpete causing acute trigeminal neuralgia.* Lancet 2:1065-1066, 1970.
Gilden DH, Dueland An, Cohrs R. Martin JR, Kleinschmidt-DeMasters BK, Mahalingam R. *Preherpetic neuralgia.* Neurology 41:1215-1218, 1991.
Gilden DH, Beinlich BR, Rubinstien EM, *et al. VZV myelitis: an expanding spectrum.* Neurology 44:1818-1823, 1994a.
Gilden DH, Wright RR, Schneck SA, Gwaltney JM Jr, Mahalingam R. *Zoster sine herpete, a clinical variant.* Ann Neurol 1994;35:530-533, 1994b.
Gilden DH, Kleinschmidt-DeMasters BK, Wellish M, Hedley-Whyte ET, Rentier B, Mahalingam R. *Varicella zoster virus, a cause of waxing and waning vasculitis.* NEJM case 5-1995 revisited. Neurology 47:1441-1446, 1996.
Gilden DH, Bennett JL, Kleinschmidt-DeMasters BK, Song DD, Yee AS, Steiner I. *The value of cerebrospinal fluid antiviral antibody in the diagnosis of neurologic disease produced by varicella zoster virus.* J Neurol Sci 159:140-144, 1998.
Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. *Neurologic complications of the reactivation of varicella-zoster virus.* N Engl J Med 342:635-645, 2000.
Lapresle J, Lasjaunias P. *Cranial nerve ischaemic arterial syndromes: a review.* Brain 109:207-216, 1986.
Mayberg MR, Zervas NT, Moskowitz MA. *Trigeminal projections to supratentorial pial and dural blood vessels in cats demonstrated by horseradish peroxidase histochemistry.* J Comp Neurol 223:46-56, 1984.
Mayo DR, Booss J. *Varicella zoster-associated neurologic disease without skin lesions.* Arch Neurol 46:313-315, 1989.
Melanson M, Chalk C, Georgevich L, *et al. Varicella-zoster virus DNA in CSF and arteries in delayed contralateral hemiplegia: evidence for viral invasion of cerebral arteries.* Neurology 47:569-570, 1996.
Osaki Y, Matsubayashi K, Okumiya K, Wada T, Doi Y. *Polyneuritis cranialis due to varicella-zoster virus in the absence of rash.* Neurology 45:2293, 1995.
Sweeney CJ, Gilden, DH. *Ramsay Hunt syndrome.* J Neurol Neurosurg Psychiatry 71:149-154, 2001.
Tyring S, Nahlik J, Cunningham A, *et al. Efficacy and safety of famciclovir in the treatment of patients with herpes zoster: results of the first placebo-controlled study.* In: Program and Abstractions of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Oct. 17-20, 1993. New Orleans: American Society for Microbiology, p. 400, 1993.
Vafai A, Mahalingam R, Zerbe G, Wellish M, Gilden DH. *Detection of antibodies to varicella-zoster virus proteins in sera from the elderly.* Gerontology 34:242-249, 1998.
Vartdal F, Vandvik B, Norby E. *Intrathecal synthesis of virus-specific oligoclonal IgG, IgA and IgM antibodies in a case of varicella-zoster meningoencephalitis.* J Neurol Sci 57:121-132, 1982.
Wood MJ, Johnson RW, McKendrick MW, Taylor J, Mandal BK, Crooks J. *A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster.* N Engl J Med 330:896-900, 1994.

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Glioma therapy

Gliomas are the most common primary intracranial tumours with an annual incidence of approximately 12/100000 persons. They are graded according to their morphological features and range from WHO Grade I (pilocytic astrocytomas) through to the most malignant WHO Grade IV (glioblastoma multiforme GBM). Grade I tumours are usually curable by surgery and will not be considered any further. The median survival for Grade II tumours (diffuse astrocytoma, oligodendroglioma and mixed oligoastrocytoma) is typically between five to seven years, for Grade III tumours (anaplastic astrocytoma) two years and for GBM one year. Treatment of gliomas is limited by their diffusely infiltrative behaviour, the involvement of eloquent brain structures and their tendency to recur at the primary site. The prognosis has improved little over the last thirty years and so we are constantly on the look out for new management strategies.

Author

Dr Jeremy Rees is a Senior Lecturer in Neuro-oncology and honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery (NHNN). He qualified from UCL Medical School in 1988 and trained at the NHNN, Royal Free Hospital, St Thomas's Hospital and Memorial Sloan Kettering Cancer Center, New York. His research interests include paraneoplastic neurological disorders and low-grade gliomas.

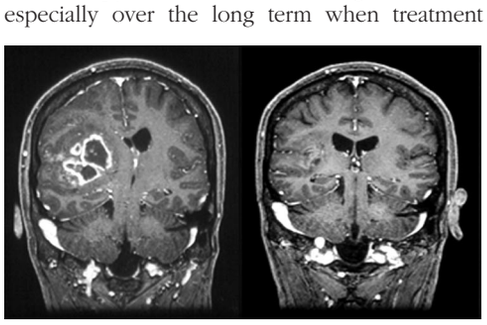
Surgery

Brain tumour surgery has come of age. Open craniotomy with direct visualisation and reliance on angiography with the associated high morbidity and mortality is no longer practised. In their place, surgeons have high quality pre-operative and, in some centres, peri-operative MRI, functional imaging with PET/SPECT or fMRI and stereotactic systems that allow precise computer aided navigation to avoid eloquent areas and blood vessels. This has led to dramatic changes in the risks associated with surgery but whether these advances have been translated into improvements in prognosis is not known. We still need prospective randomised controlled studies to determine if surgery has any role at all in improving outcome. Studies showing a relationship between extent of resection and prognosis are all retrospective and suffer from the natural bias of surgeons who select the best preoperative cases to operate on. A recent meta-analysis of surgery for low-grade gliomas concluded that the only management standard based on high-quality evidence was tissue diagnosis. All other treatment methods are "practice options" supported by evidence that is inconclusive or conflicting. Similarly a meta-analysis of surgery in malignant gliomas found only 4 out of 20 studies reporting a relationship between extent of resection and survival. In two of these, it followed age, performance status and histological findings in importance suggesting that any benefit from the surgical resection is modest. Therefore the crucial question as to whether resection can be recommended over biopsy to prolong survival has yet to be answered.

Radiotherapy

Unlike the situation with surgery, radiotherapy has been shown in two separate trials to prolong survival in patients with malignant gliomas. The situation with low-grade gliomas is less clear-cut. One dose-response study found no difference in median survival between a low dose (45 Gy) and a high dose (54.9 Gy) protocol. A subsequent study, comparing radiotherapy at diagnosis versus radiotherapy at progression found no difference in overall survival after a median follow-up of 4.6 years although there was a tendency for a longer progression-free survival in the irradiated group. Because of this and because radiotherapy is associated with a significant incidence of CNS toxicity, especially over the long term when treatment fields are large, my practice is only to recommend treatment when there is clinical and radiological evidence of malignant transformation or in medically-intractable epilepsy.

There have been many attempts to increase the radiation dose to the tumour while minimising the dose to surrounding normal tissue but none have proven more successful than a standard course of external beam radiation delivered to the tumour plus a 2-3 cm margin of normal tissue. Examples include interstitial radiotherapy (brachytherapy), stereotactic boosts, radiation sensitisers and hyperfractionation regimens.



Coronal T1W MRI scans with gadolinium enhancement before and after 4 cycles of PCV showing right frontal anaplastic oligodendroglioma presenting with subacute left hemiparesis. The symptoms and signs resolved completely after the first cycle. The scans show disappearance of mass effect and contrast enhancement with shrinkage of both the cystic and solid elements of the tumour.

Chemotherapy

In general, the use of chemotherapy for the treatment of gliomas has been disappointing, partly because of intrinsic chemoresistance and partly because of problems of drug delivery across the blood-brain-barrier. Adjuvant chemotherapy i.e. used in addition to radiotherapy does not provide a significant survival benefit although it is used routinely in the United States.

The most significant advance in recent years for chemotherapy of gliomas has been the realisation that anaplastic oligodendrogliomas with loss of chromosome 1p and 19q are exquisitely chemosensitive. Such tumours, previously regarded as highly malignant with a poor prognosis, show prolonged and reliable responses to a standard chemotherapy regime incorporating procarbazine, CCNU and vincristine (PCV). However these are rare tumours accounting for less than 5% of all primary brain tumours and the excellent results have not yet been translated to other more common glioma subtypes.

The other important advance in chemotherapy of gliomas has been the introduction into clinical practice of a new imidazotetrazine compound called temozolomide, an oral alkylating agent, which has recently been approved by NICE for the second line treatment of recurrent malignant gliomas. A phase III MRC sponsored trial is due to begin this year which will determine whether temozolomide, for all its hype, is better than conventional first line treatment with PCV for recurrent disease. Unfortunately, patients with recurrent malignant gliomas have a uniformly dismal prognosis and so interest is focusing on other potential applications of this new drug.

Because of the multiplicity of confounding factors which affect our ability to assess the true effectiveness of a drug in the setting of recurrent disease, further trials should examine promising new agents in primary treatment i.e. in newly diagnosed patients who have not received any other chemotherapy or radiotherapy and who have measurable disease. An example of such a study has been reported for temozolomide which, in preliminary results from an open label phase II study of 51 patients, produced a response rate of 39% (complete and partial responses). Furthermore the drug was well tolerated with only occasional severe myelosuppression, nausea and constipation.

In addition, a recently completed trial using temozolomide given on a daily basis during radiation therapy in newly diagnosed patients with glioblastoma multiforme followed by standard cycles after radiotherapy has shown early encouraging results with a twelve month survival estimate of 67%. A phase III trial is planned and hopefully results will be available next year.

New drugs are continuously being evaluated for efficacy in malignant gliomas because of the poor response rates from standard regimens. For example, preliminary data for the new drug irinotecan (CPT-11), a topoisomerase inhibitor has shown only modest activity.

Conclusions

Gliomas are still incurable tumours which has led to a considerable degree of therapeutic nihilism associated with their treatment. Surgery may be useful, radiotherapy prolongs survival but is not curative. Chemotherapy is being increasingly used in and new indications are emerging.

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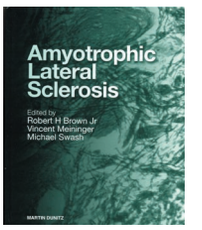
Amyotrophic Lateral Sclerosis



Author: Robert H Brown Jr,Vincent Meininger, Michael Swash (eds.).
Published by: Martin Dunitz 2000
Pages: 496
ISBN No: 1-85317-421-1
Price: £75

Motor neurone disease is one of the most feared of medical conditions. The image of the profoundly disabled, anarthric, wheelchair bound patient remains with us and is amplified in the public arena by high profile legal cases relating to end of life decisions. Despite these gloomy perceptions the reality of motor neurone disease at the start of the 21st century is rather different. The past decade has seen a dramatic growth in our knowledge of the nature of the condition and a parallel improvement in our ability to treat the patient and deal with the most troublesome clinical concerns. These advances are well reflected in this excellent multi-author textbook. The book is divided into six sections dealing with clinical features, patient care, pathology, physiology, pathogenesis and therapeutic approaches. Each section has much to commend and the entire book maintains a reasonable coherence despite almost 60 contributing authors. There is some repetition of material but it is refreshing that the editors are prepared to include chapters expressing contradictory viewpoints - I particularly enjoyed Appel's review of the immunology of motor neurone injury followed by Drachmann's rebuttal. Such an approach challenges the specialist but may be of less value to the general neurologist. Following the discovery that mutations of the SOD1 gene were associated with familial motor neurone disease, genetic research has burgeoned. This is well reflected in a detailed review by Andersen *et al* which is clear and comprehensible even to those of us who are non-geneticists. Similarly reviews of the roles of excitotoxicity, oxidative stress and neurotrophism are each of high quality and informative.

For the clinician there is a clear and well-presented section dealing with typical and atypical presentations. The first chapter concerning symptomatic treatment is entitled. 'A treatable disease: a guide to the management of ALS' This title immediately warmed me to Gelinas and Miller's outstanding contribution. They cover the treatment of the familiar symptoms but also focus on aspects which are often poorly described in the literature, areas including the management of sleep disturbance, laryngospasm, GI reflux, pain and pressure sores. Terminal management and end of life decisions vary across Europe and The United States, however the contributions here reflect the range of options and the necessity to tailor clinical decisions to the need of the individual patient, particularly when considering the need for ventilatory support. I would quibble a little about the rather poor coverage of the landmark trials with Riluzole and nothing is said about the role of this drug in clinical practice. The review of health outcome measures is thorough but includes little information relating to studies of the validity and repeatability of these measures - nor does it reflect the anxiety that troubles many concerning the administration of questionnaires to patients with motor neurone disease or their carers.

The study of MND has often been limited by the difficulty in bridging the gap between laboratory and clinic. This book represents an important attempt to draw the strands together - it is informative, well written and well edited and should be considered a true textbook of MND. I would thoroughly recommend it to all neurologists with an interest in the pathogenesis or management of this wretched condition.

Robin S Howard, National Hospital, Queen Square.

Clinicians Guide to Epilepsy

Author: P E M Smith, S J Wallace
Published by: Arnold 2001
Pages: 275
ISBN No: 0-340-76293-4
Price: 29.99

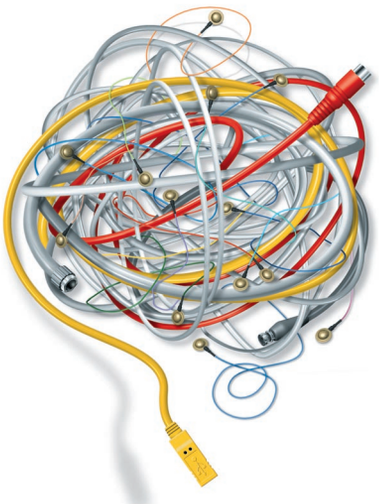
This dual authored 265-page, 10-chapter offering is a comprehensive canter up hill and down dale through the evolving landscape of epilepsy. Specialists within the field choking at the juxtaposition of the term "comprehensive" in an opus comprising a mere 265 pages will rightly surmise that much must be omitted or savagely reduced to permit such brevity in an area as vast as Epilepsy. This point is further magnified as one realises, with a rapid sense of unease and rising epigastric fullness, that paediatric epilepsy features in this book with a prominence which, were it mirrored in the outpatient clinic, would promote a less than comfortable feeling in this (adult) neurologist.

A popular and unsettling question to ask these days is "what's it for?" In that respect this book provides a platform of solid, broad, practical, and pragmatic information and references to prepare individuals embarking on their initial journeys into the increasingly complex network of epilepsy management. A tougher question would be "who is this book for?" Clearly it is aimed at the younger end of the market. Had I known this stuff as a final year medical student I would have shone blindingly and irritatingly in front of exhausted housemen and peri-MRCP SHOs. I suspect that fledgling neurology SpR's not already neuronally migrated to epilepsy would pick up many tips and new information, too. For those longer in the tooth, two useful chapters at the back outline practical advice in concise terms regarding the thorny questions of lifestyle including mortality issues, that mean so much to the patient but feature little if at all in standard texts on the "medicine" of epilepsy. My favourite chapter entitled "Epilepsy in special client groups" has 23 pages devoted to those "clients" younger than teenagers and 21 pages that cover teenagers, women's issues, and the elderly. Whether patients see themselves as clients is not specifically discussed.

I would recommend this book to those starting out in medicine who will, like it or - even more importantly - not, be involved in the care of patients with epilepsy. If you only ever read (rather than purchase, place on the bookshelf, and never open again) one book on epilepsy you could do a lot worse than this. Considering how common seizure disorders are many junior doctors (and their clients!) would benefit from reading this book.

John Bowen, Royal Hospital Haslar, Gosport.

ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS



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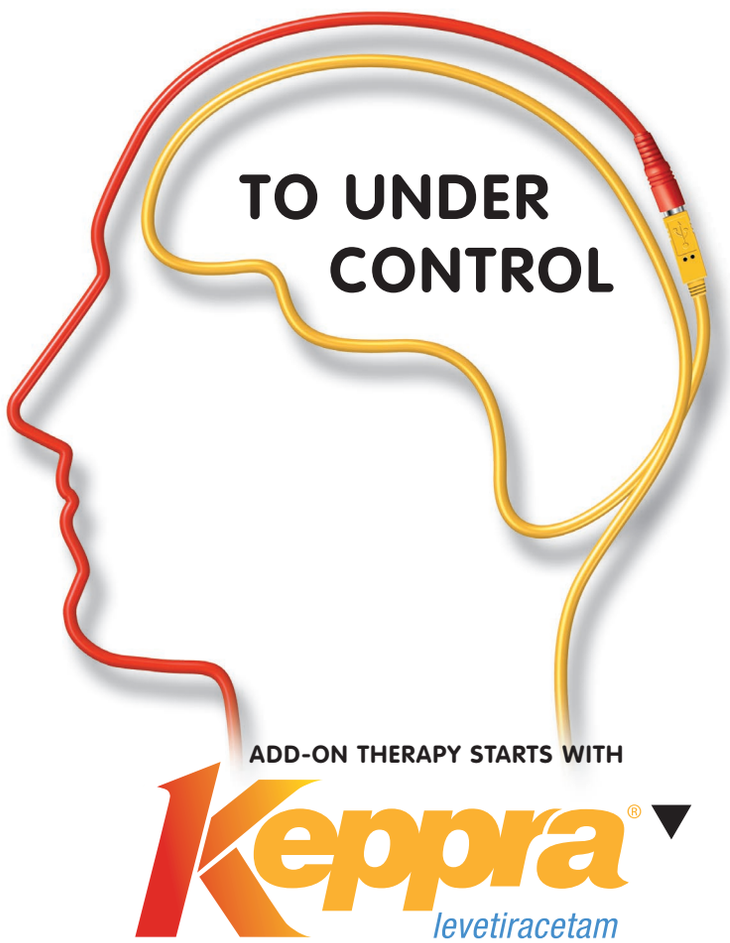

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Further information is available from: UCB Pharma Ltd., 3 George Street, Watford, Herts WD18 0UH. Tel: 01923 – 211811 or e-mail medicaluk@ucb-group.com
Date of Preparation: February 2002.
References:

1. Shorvon S et al. Pooled efficacy and safety data of levetiracetam (LEV) used as adjunctive therapy in patients with partial onset seizures. *Epilepsia* 1999;40,S7:76,abstract B.01.
2. Cereghino J et al. Levetiracetam for partial seizures. Results of a double-blind, randomized clinical trial. *Neurology* 2000;55:236-242.
3. Ben-Menachem E et al. Efficacy and tolerability of levetiracetam 3,000 mg in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 2000;41,10, 1276-1283.
4. Shorvon S et al. Multicenter, double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *Epilepsia* 2000;41,9,1179 -1186.
5. Data on file, UCB Pharma Ltd.
6. Patsalos P. Pharmacokinetic profile of levetiracetam: towards ideal characteristics. *Pharmacol Ther* 2000;85(2):77-85.

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SIMPLIFYING SEIZURE CONTROL

Inflammatory Muscle Disease

Gillian Hall

Introduction

Inflammatory muscle disease is a generic term used to include polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM). The latter does not respond to immunosuppression suggesting that the inflammation may be a secondary phenomenon rather than a causal factor. PM and DM on the other hand, are immune mediated.

Epidemiology

The prevalence and incidence figures vary widely from study to study. The prevalence of PM is in the order of 1-7/100,000 and DM 1-10/1,000,000. DM is the commonest childhood myositis with a prevalence of around 3/1,000,000 children.

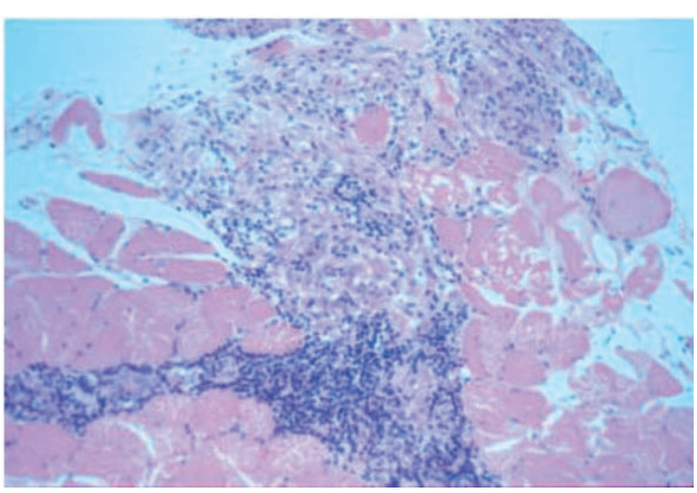
Both PM and DM affect woman approximately twice as often as men. Whereas PM is a disease of adults (with only rare exceptions), DM affects both adults and children showing 2 peaks between the ages of 14-16 and 45-65. IBM is a disease predominantly of older men. It affects men three times as often as females and is only rarely seen under the age of 50.

Association with an underlying malignancy

Again the figures vary from report to report. What can be said with more certainty is that an associated malignancy is not a feature of childhood myositis or of IBM. Some reports suggest an underlying malignancy is only found with DM whereas others with both DM and PM. More recent studies suggest a modest increase in relative risk with PM and a more significant increase with DM especially in patients over 50 (reviewed in 1). Therefore, particularly in older patients, a search for an underlying malignancy is warranted. This should include a physical examination concentrating on breast, lungs and abdomen and pelvis and appropriate blood analysis and radiological screening. Initial screening may be normal and the malignancy declare itself sometime (maybe years) after presentation with myositis. For this reason, some authors advocate repeat screening at 6 monthly intervals for several years[2].

Overlap Syndromes

In some cases myositis is seen as part of a wider autoimmune condition, often associated with systemic lupus erythrematosus, rheumatoid arthritis, scleroderma, mixed connective tissue disease etc. In Sjögren's syndrome myositis is associated with interstitial lung disease. Antibodies to histidyl-tRNA synthetase, known as Jo-1, are found in the majority of patients with myositis and interstitial lung disease and may indicate a worse outcome secondary to respiratory distress syndrome. Interstitial lung disease is found in approximately 10% of patients with DM and PM.



Muscle from patient with polymositis. Dense inflammatory cell infiltrate is shown.

Presentation

PM has a sub acute, insidious onset over months. Patients experience proximal weakness often without myalgia. Cardiac involvement includes both problems with conduction and cardiomyopathy. DM is an easier diagnosis due to the characteristic rash that may precede the muscle involvement. One sees a heliotropic rash around the eyelids that may spread to the cheeks and erythematous, raised scaly lesions on the knuckles (Gottron's patches) and similar lesions on the elbows. Calcinosis of the subcutaneous tissue and intermuscular fascia, which may ulcerate, is mainly seen in the childhood form of DM but is occasionally seen in adults. Other manifestations include dysphagia, cardiac and pulmonary involvement (as above), associated vasculitis and contractures (childhood DM). Systemic features including fever, malaise and weight loss may be seen in either PM or DM.

Focal myositis is an entity that does exist. It is mostly restricted to the thigh, neck or shoulder girdle and occasionally large limb muscles such as in the forearm but is also reported in small foot muscles[3]. Focal myositis may present as a local pseudotumour or may have systemic features.

Whereas PM and DM tend to have symmetrical presentations, IBM is usually asymmetrical. It again tends to affect proximal muscles particularly the quadriceps femoris but often affects the long finger flexors early such that patients may present with complaints such as being unable to use aerosols. There is also preferential involvement of iliopsoas, biceps and triceps. Mild facial weakness (not a feature of PM or DM) is seen in 60% of cases and dysphagia common.

Diagnosis

Serum creatine kinase (CK) is not necessarily raised. In PM and DM it is very occasionally normal though is usually raised and may be 50 times the upper limit of normal or higher (may be in excess of 10,000 units/litre). In IBM the CK is normal or shows only a mild elevation.

Electromyography may be indistinguishable between PM, DM and IBM. Myopathic motor units are seen with increased insertional activity and fibrillations indicative of active disease. Non-specific complex repetitive discharges may be seen suggesting chronicity. All changes may be patchy and fibrillation potentials (often most reliably detected in the paraspinal muscles) may be the only abnormality.

Muscle biopsy provides histological confirmation of disease. Again, findings may be patchy and several levels need to be examined. Small biopsy samples may not include foci of disease. In PM and sporadic IBM the inflammatory infiltrate is endomysial and predominantly CD8+ve T cells and macrophages. Invasion and necrosis of individual muscle fibres is seen (Figure). In DM there is perifascicular atrophy and perimysial infiltration with predominantly CD4+ve T cells and B cells. Micro infarcts may be seen. MHC class I is unregulated only on perifascicular cells in DM but on all mature muscle fibres in PM. In IBM, MHC class I tends only to be expressed on those fibres that show partial invasion by the inflammatory infiltrate.

Focal myositis may have distinct, more benign pathological features[4].

Treatment

As mentioned in the introduction, only PM and DM respond to treatment. IBM does not and will not be discussed further.

Steroids are the mainstay of treatment, but not without side effects. Some cases will fail to respond to steroids alone and in other cases avoidance of steroids might be desirable (e.g. brittle diabetes).

Treatment is largely empirical in the absence of adequate trials. A typical regime will commence with between 60 and 100mg of oral prednisolone per day depending on weight (approximately 1mg/kg). Occasionally intravenous methyl prednisolone (1g/day for 3 days) is used to get on top of aggressive disease. The patient is usually embarking on long-term therapy and appropriate bone prophylaxis should be instituted. This initial dose is continued for 4 weeks or until CK has normalised. The prednisolone is then gradually reduced by 5 mg/day at weekly intervals until the patient is taking 20mg per day at which time further reductions may be made more slowly. Some authors

prefer alternate day steroids. There is probably no difference in efficacy but there is some suggestion that it may lessen certain side effects but others, in particular impaired glucose tolerance, are more difficult to manage. Certainly, prednisolone should be taken in a single morning dose. Obviously, the exact details of a drug regime need to be tailored to the individual patient.

Addition of a 'steroid sparing' agent from the onset is a matter of clinical preference. Azathioprine (1.5-3mg/kg as tolerated) is the normal used. It does, however, take some time for the full affects of azathioprine to kick in and hence the preference of many clinicians to prescribe it from the outset. Azathioprine is usually well tolerated but an impairment of liver function necessitates discontinuation. A small degree of anaemia or drop in white cell count may be accepted.

Other immunosuppression

There is evidence from a single, randomised controlled trial in adults and from one uncontrolled trial in children supporting the use of intravenous immunoglobulin (IVIg) in DM (reviewed in 5). There are no controlled trials of IVIg in PM. Based on this the Association of British Neurologists' guidelines on the use of IVIg state that '*..IVIg has a role in dermatomyositis in adults and children which is refractory to other treatments. There is insufficient evidence supporting use as primary or long-term treatment. In severe refractory polymyositis there may also be a place for IVIg but this is not substantiated and in these cases reinvestigation should first consider the possibility of inclusion body myositis*'[6]. In the same document it is highlighted that randomised controlled trials have failed to demonstrate a benefit in IBM, therefore IVIg is not recommended for treatment of IBM[5,6].

Methotrexate has a faster mode of action than azathioprine and may have a role in severe or steroid resistant disease. A usual oral regime commences with 7.5mg weekly adjusted according to response increasing in 2.5 mg increments per week to a total of 15 mg as required and tolerated. Occasionally 20mg per week may be required. Bloods must be monitored closely (see BNF). A complicating factor when using methotrexate is methotrexate pneumonitis that resembles the interstitial lung disease associated with some inflammatory muscle disease described above.

In non-responsive disease, other agents including cyclophosphamide, cyclosporin and chlorambucil have been tried with varying results.

The important issues with regard to treatment are that one must treat the patient and not the CK. CK may fall in response to treatment prior to clinical improvement. Also, patients who fail to respond completely to long-term steroid therapy may be developing a steroid myopathy. Their weakness will, of course, only be exacerbated by the further use of steroids. This can be a confusing clinical scenario and may only be resolved by a repeat biopsy.

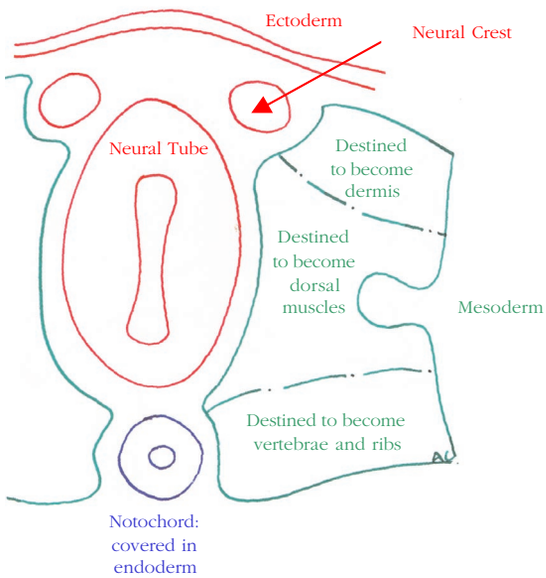
Acknowledgements

Thank you to Professor James Ironside for providing the histology slide.

References

1. *Myositis diagnosis and management*. G Chevrel, N Goebels, R Hohlfeld. Practical Neurology 2002;2:4-11.
2. *Inflammatory myopathies*. M C Dalakas, G Karpati. In Disorders of Voluntary muscle 7th Edition 2001, Edited by G Karpati, D Hilton-Jones and R C Griggs. Cambridge University Press.
3. *Myositis of small foot muscles*. P Kalden, T Krause, B Volk, H H Peter, J von Kempis. Rheumatol Int.1998;18:79-82.
4. *Clinical and pathological features of focal myositis*. A G Smith, S Urbanitis, M Blaivas, W Grisold, J W Russell. Muscle Nerve 2000;23:1569-1575.
5. *Intravenous immunoglobulin in neurological disease: a specialist review*. C M Wiles, P Brown, H Chapel, R Guerrini, R A C Hughes, T D Martin, P McCrone, J Newsom-Davis, J Palace, J H Rees, M R Rose, N Scolding, A D B Webster. JNNP 2002; 72: 440-448.
6. Wiles CM, Brown P, Chapel H, Guerrini R, Hughes RA, Martin TD, McCrone P, Newsom-Davis J, Palace J, Rees JH, Rose MR, Scolding N, Webster AD. *Intravenous immunoglobulin in neurological disease: a specialist review*. J Neurol Neurosurg Psychiatry. 2002 Apr;72(4):440-448. Download from http://www.theabn.org/downloads/IVIgGuidelines.pdf

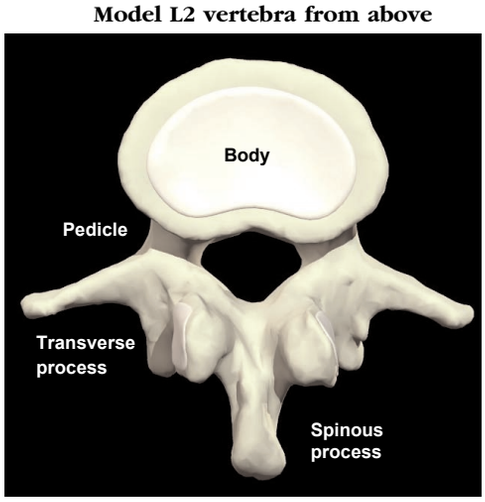
Radiological anatomy: The Lumbar Vertebrae



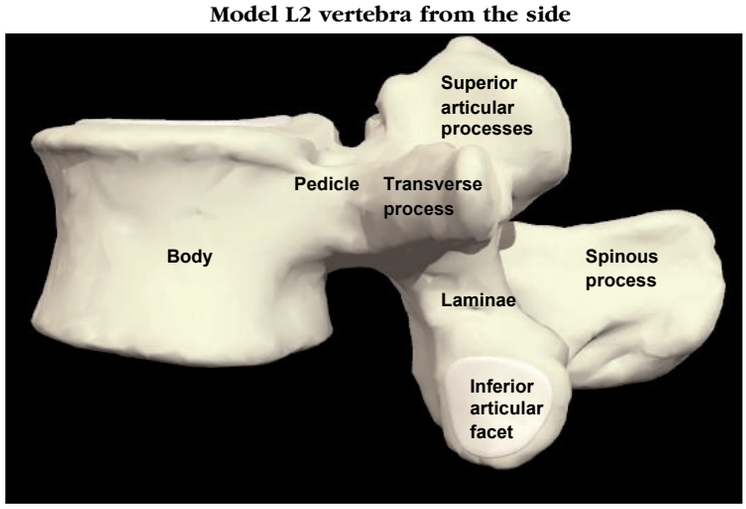
The Basics. Lumbar roots emerge below their respective vertebra. Thus the L4 root emerges from the L4/5 interspace. The root emerges high in the intervertebral foramen, between the pedicles of L4 and L5. A disc lesion at L4/5 may well miss the L4 root. If lateral (the more usual) a disc protrusion will go on to cause a L5 lesion instead, but if central, then lower roots may be affected and the lesion incorrectly localised to a lower segment.

Development: By embryological day 15, the notochord has begun to push aside the ectoderm and endoderm. The mesoderm forms either side of it, bunching into parallel somites which organise themselves segmentally around the notochord, to produce the vertebrae and spinal muscles. (The notochord is squeezed into the tiny "mucoid streak" in the centre of the vertebrae by this process.) The ectoderm folds in, to form the neural tube (which will become the spinal cord) and the neural crest gets isolated under the ectoderm to become ganglia and nerve fibres.

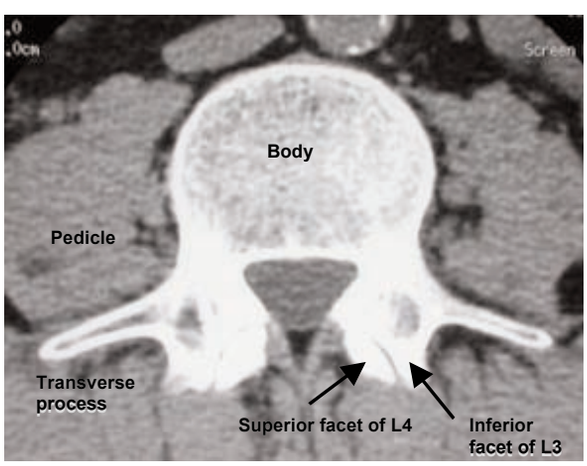
Model L2 vertebra from above



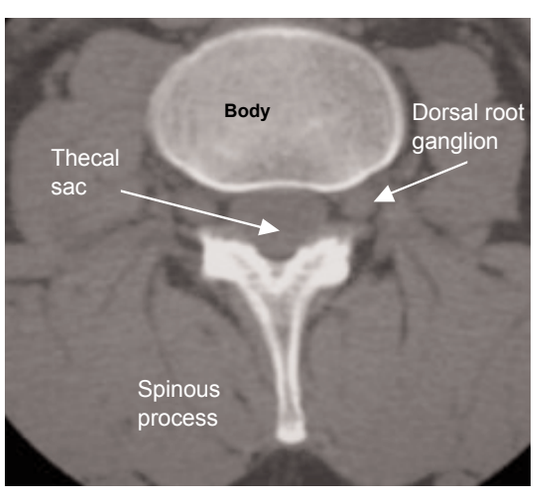
Model L2 vertebra from the side



Axial CT section at L3

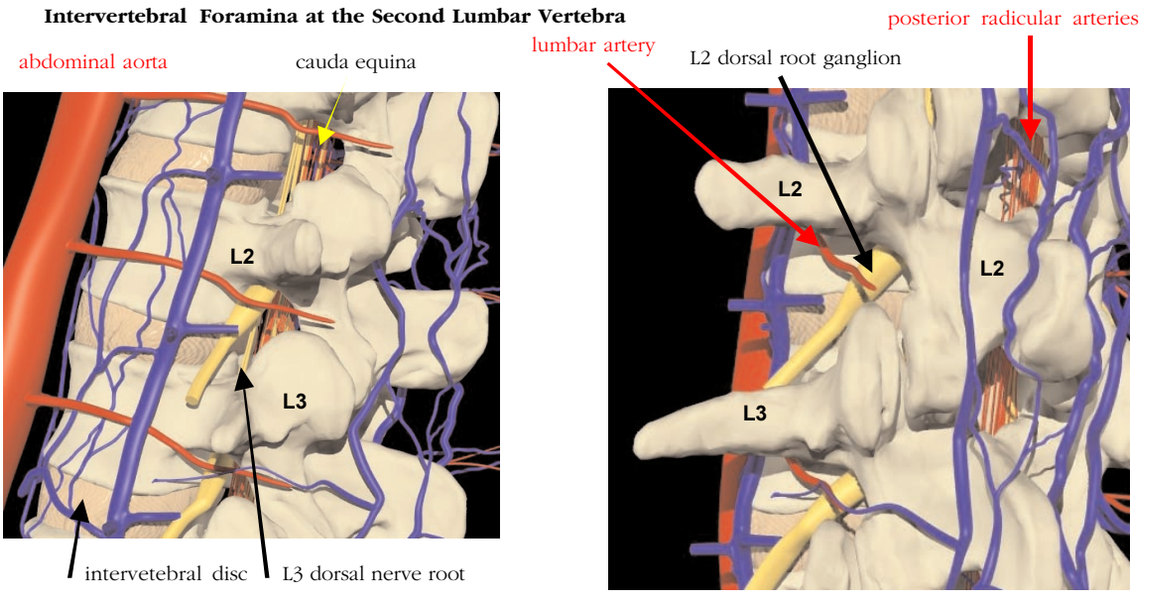


Axial CT section at L3/4

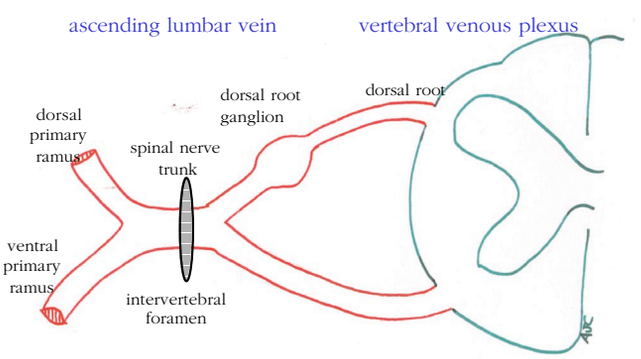


Justin Cross and Alasdair Coles

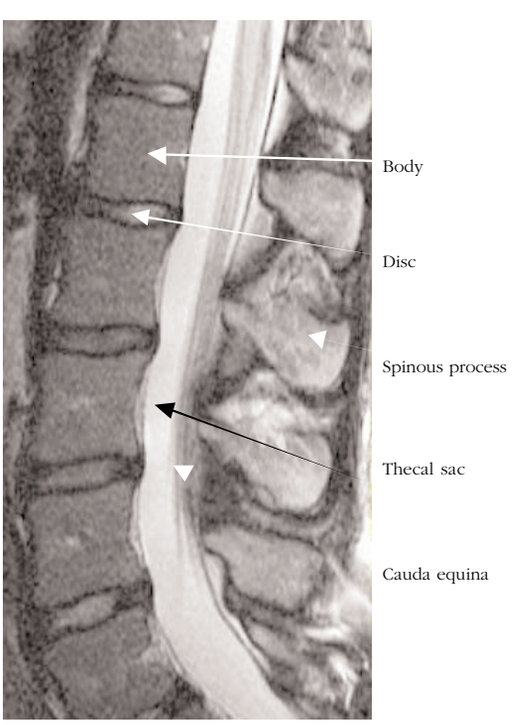
Intervertebral Foramina at the Second Lumbar Vertebra



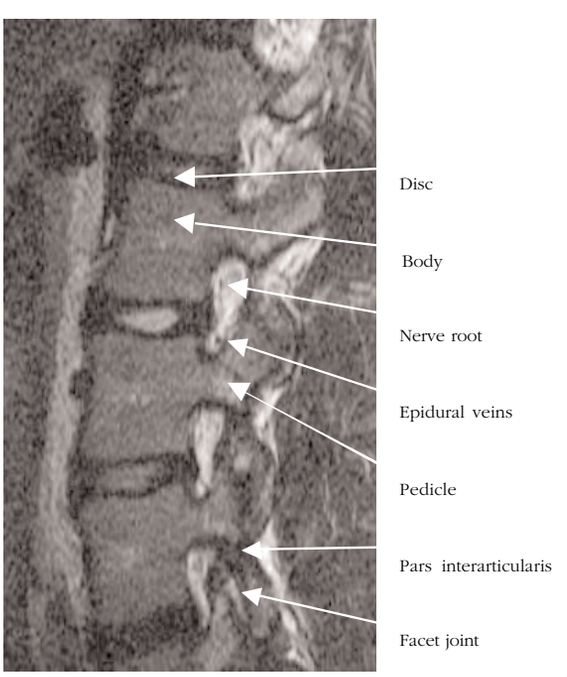
The dorsal and ventral roots emerge from the spinal cord and unite to form the spinal nerve trunk, either at or just distal to the intervertebral foramen. On exiting, the trunk divides: the dorsal rami supply the back and the ventral rami supply the trunk and limbs.



Sagittal T2 weighted MR image



Parasagittal T2 weighted MR image



References:
The Interactive Spine. CD-ROM. Primal Pictures. 2001

Picture credit:
With thanks to Primal Pictures for the images.

Randomisation in single-case experimental designs

Author

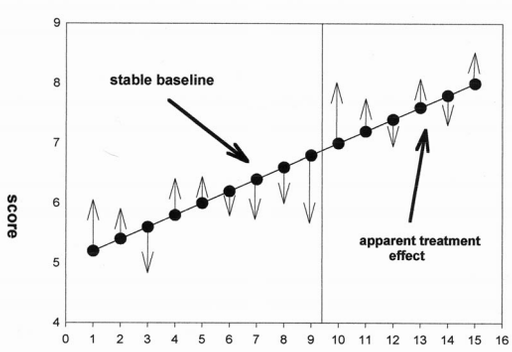
John Todman is Professor of Applied Cognitive Psychology in the Department of Psychology at the University of Dundee. He has worked in the Department for 26 years and, apart from his work on single-case experimental methodology, he engages in research on the development and evaluation of conversation aids for people without speech.

Response-guided intervention in phase designs

There is a strong tradition of response–guided intervention in single-case rehabilitation studies. This is perhaps most noticeable in phase (eg, AB, ABA etc.) designs, where the common recommendation is to continue with baseline observations until the baseline stabilises; that is, several observations in a row show little variation.[1,2] Regardless of whether visual or statistical analysis of the data follows, this response-guided determination of the point at which the treatment intervention is introduced creates a bias in favour of finding a treatment effect where none exists. This is illustrated with some simulated data pertaining to an AB design.

Figure 1 displays simulated data representing a linear trend, such as might be associated with a practice effect, but with random variations around the linear trend. The equation used to generate the linear trend was: score = 5 + 0.2(obs. no.). Thus the regression line meets the score axis at 5 and for every increase of 1 observation, the score increases by 0.2 of a score unit. The vertical arrows indicate random fluctuations of the score introduced at each observation point (ie, random normal deviates set at mean = 0 and SD = 1.5). The important point is that we know there is no treatment effect; just a continuous linear trend with random variations. However, a couple of upward random variations (observations 4 and 5) followed by several downward random variations (observations 6, 7, 8 and 9) may easily be interpreted as stabilisation of the baseline. If the treatment intervention is introduced at this fortuitous point, the expected continuation of the upward trend is likely to appear to be a discontinuity coinciding with the commencement of the intervention. If this led to the inference of a causal relationship between the treatment and the observed discontinuity at the intervention point, it would be an erroneous conclusion.

Figure 1. Data generated by equation: y = 5 + 0.2x with random variation added



It is reasonable to ask how frequently mistaken inferences of treatment efficacy might arise in this way. In a study carried out to assess the risk,[3] 80 graphs were generated using the same equation and random deviate as in Figure 1. In 50 of these graphs a "stabilisation of the baseline" could be discerned and two copies of each of these graphs were prepared. One of each pair had an intervention point (a vertical line) drawn in immediately following the roughly horizontal sequence of observations. The other member of each pair had the intervention point randomly assigned, with the constraint that there must be at least 4 observations in each of the baseline and treatment phases. Twelve psychology students, used to interpreting graphs, were each asked to sort a randomly ordered pile of the 100 graphs into those that did and those that did not appear to show a treatment effect. The mean number of graphs judged to be consistent with a treatment effect was 33.0 for those with response guided intervention points and 11.4 for those with randomly determined intervention points (related t (11) = 9.84; p < 0.001; 2-tailed). Furthermore, the method of assignment of the intervention point accounted for 90% of the variance.

Randomisation tests for phase designs

The bias that has been described above exists whether visual or statistical analysis is used. However, introduction of a random procedure into the design, opens the way for a valid statistical test of the treatment effect. In view of the established difficulty of evaluating causal hypotheses by visual inspection of the data,[4] a statistical test may well be worthwhile, if only to confirm the conclusion from a visual analysis.

Randomisation tests work by considering all possible recombinations of the data, given the randomisation procedure that was used in the study. In the AB example, if it had been decided that there were to be 30 observations in all and that there were to be at least 5 in the baseline and treatment conditions respectively, the randomly determined intervention point could have occurred at any observation from 6 to 26. That is, there were 21 potential intervention points. The difference between actual baseline and treatment means is calculated, as is the mean difference for every split between baseline and treatment observations that could have occurred if a different random intervention point had been selected. If the actual difference is greater than the difference for any other potential intervention point, the probability of this happening by chance is 1/21 = 0.048. In general, the obtained difference between means will be statistically significant at the 5% level if the obtained difference falls in the 5% most extreme differences in the (real) distribution of possible recombinations of the data. Obviously, there must be at least 20 potential intervention points to make possible a significant effect at the 5% level. Thus, many practical applications of the AB design will have quite low power to find a real effect. Power can be increased, however, by adding phases to the design (as in an ABA reversal design) or by introducing multiple baselines.

If a stable baseline is considered necessary for interpretation of an apparent treatment effect, it is possible to have the best of both methodologies by waiting until a "pre-experimental baseline" has stabilised before proceeding to a baseline-treatment experiment with a randomly selected intervention point.

Randomisation tests for other designs

The principles underlying randomisation tests generalise to numerous other possible single-case designs, provided some form of randomisation procedure has been introduced into the design. For example, randomisation procedures (and, hence, randomisation tests) are readily applicable to alternating designs, which are the other major category of single-case designs alongside phase designs. Consider a rehabilitation study designed to compare the efficacy of two prostheses. If we have eight observation periods available, we could make four observations with each prosthesis, with prosthesis type randomly allocated to the observation periods. If the mean score difference between prosthesis types is greater than the mean difference for any other possible split of the data into two piles of four, what is the probability that this was a chance effect? It is 1/70 = 0.014 (i.e., $p < 0.05$). For those who are interested, this result can be obtained using the formula for the number of different combinations possible for N things with n1 and n2 of each of two different kinds:

N!/n1! n2! = 8!/4!4! = 8x7x6x5x4x3x2x1/4x3x2x1x4x3x2x1 = 70.

As the number of observations increases, the number of possible combinations increases rapidly. For example, with double the number of observations with each prosthesis, there are about 600 million possible combinations! This has two implications. First, alternating

designs, where they are practical, can have very high power. Second, powerful computers are required to make randomisation tests routinely available. Programs that allow researchers to carry out randomisation tests for a range of single-case designs within SPSS, Minitab or Excel are now available on CD ROM supplied with a recent book on randomisation tests by Todman and Dugard.[5]

To summarise; just as true experiments in multi-participant designs require random allocation of treatments to participants (and to observation times), so too is some form of random allocation of treatments to observation times essential for internal validity in single case designs. The principle of random allocation is paramount for the establishment of causal effects in single-case as in group designs, whether or not statistical analysis is carried out. The availability of valid statistical tests made possible by the random allocation procedures is "icing on the cake".

References

1. Kazdin, A.E. (1982). *Single-case research designs: Methods for clinical and applied settings*. New York: OUP.
2. Shaughnessy, J.J., & Zechmeister, E.B. (1994). *Research methods in psychology (3rd ed.)*. New York: McGraw Hill.
3. Todman, J., & Dugard, P. (1999). *Accessible randomization tests for single-case and small-n experimental designs in AAC research*. Augmentative and Alternative Communication, 15, 69-82.
4. Franklin, R.D., Gorman, B.S., Beasley, T.M., & Allison, D.B. (1966). *Graphical display and visual analysis*. In R.D. Franklin, D.B. Allison, & B.S. Gorman (Eds.), Design and analysis of single-case research (pp. 119-158). Mahwah, NJ: Lawrence Erlbaum.
5. Todman, J. and Dugard, P. (2001). *Single-case and small-n experimental designs: A practical guide to randomization tests*. Mahwah, NJ: Lawrence Erlbaum.

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Conference Preview

13th European Congress of Physical and Rehabilitation Medicine

28-31 May 2002, Brighton, UK

Those involved in the speciality of Physical & Rehabilitation Medicine (P&RM) – represented in the UK as Rehabilitation Medicine – at a European level know that the discipline is a lot more healthy in some countries than in Britain and that a greater range of clinical activity exists. There are whole areas of work undertaken in continental Europe that are not considered as part of the speciality's area of expertise here. These include cardiac, pulmonary and cancer rehabilitation and span the whole age range. The lack of interest by British doctors in the activities of our colleagues abroad is also surprising and the view was formulated at the European Congress in Rome in 1997 (where there was only a handful of British doctors and not one trainee), that the only way to stimulate some interest was to hold the Congress in the UK and bring Europe to British clinicians.

This will now hopefully happen when, after five years of planning, the 13th European Congress of P&RM comes to Brighton. The European Federation of P&RM granted the Congress to be jointly hosted by the British Society of Rehabilitation Medicine and the multidisciplinary Society for Research in Rehabilitation, which is a new departure for these events and reflects changing practice in Europe. It will also hopefully see the inauguration of the new European Society of P&RM, which will succeed the European Federation. Some of the traditions of recent European Congresses will continue, but Brighton will break new ground in putting on "state of the art" plenary and concurrent sessions, along with practical teaching to meet the demands for continuing professional development and to allow trainees and junior members of staff to acquire new skills. This Congress should interest a wide variety of professionals and trainees in all professions will be particularly welcome.

The event will open on the evening Tuesday 28th May and the three-day scientific programme on the Wednesday, Thursday and Friday, 29th – 31st will be built across three main areas:

- Neurological rehabilitation,
- Musculoskeletal rehabilitation and
- Prosthetics and the technical aspects of rehabilitation.

The Congress will open with a look at Clinical Governance with a guest lecture by Professor Aidan Halligan, who heads up the NHS Clinical Governance Support Team. The themes will change each day and will cover the following through the daily morning plenary sessions:

- Day 1: Clinical standards,
- Day 2: Measurement of outcome
- Day 3: Evidence for effectiveness

There will then be three concurrent sessions throughout the rest of the day covering a range of topics relevant to the speciality's work and it is here that I hope a wider view of specialist rehabilitation will be apparent. There will be three parallel sessions in each 90-minute section across each area of rehabilitation and the aim is to allow suitable discussion during each. There will thus only be two speakers and it is hoped that the experts in the audience will have a real chance to interact with the experts on the podium. Of course, the scientific committee, headed by Professor Lynne Turner-Stokes has encouraged scientific papers and the submission date has now passed. A creditable 240 have been received and scoring has been carried out using the SRR's well-established system. Submitted papers fall into the categories of research, audit and quality of clinical care, clinical cases, technological developments and education. These have been placed into number of topic areas (diagnosis and assessment, management, technological advances, rehabilitation approaches, audit and education) to help delegates categorise them. Poster presentation is the preferred method and there are only a few slots for oral presentations where the point of the paper would be lost in a poster. Posters are thus held in the same esteem as oral papers and this is of particular importance where the authors' first language is not English. In addition, there are a number of workshops, seminars, updates and practical demonstrations covering many aspects of clinical work and the whole experience will be valuable to both established clinicians and to those in training.

The Congress takes over the usual summer meetings of both the BSRM and SRR and an international meeting like this allows greater choice in topics, as well as the chance to "network". There are thus a number of social events to allow delegates to mix and, while the scientific sessions will be in English only, it will be fun to try the odd words of French, German, Dutch, Swedish, Italian or Greek! We in Britain are proud and fortunate to host this exciting event and I hope as many people interested in rehabilitation make the effort to come. The Congress' web site has all the necessary information and can be found by clicking on to:

www.ecprm2002.co.uk

So go on – treat yourself – come to Brighton, acquire new knowledge and skills, renew old acquaintances and make new friends.

Dr Anthony B Ward
President, Organising Committee

Events Diary

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by June 7th, 2002.

2002

May

Strategies for Managing Postural Stability, Falls, Medicines & Pain
9 May 2002; London, UK
Tel. 0208 9770 011, Fax. 0208 9770 055,
E. hmc@hamptonmedical.com

6th Congress of the European Society for Clinical Neuropharmacology (ESCNP)
14-18 May, 2002; Budapest, Hungary
Tel. 0036 1 311 6687, Fax. 0036 1 383 7918,
E. Motesz@elender.hu

PDSNA 2002 Conference
20-21 May, 2002; Nottingham, UK
Tel. Karen Vernon on 01625 661119,
E. petesmithpdns@yahoo.com

Dementia: A Dual Approach
23 May, 2002; Haydock, UK
E. carey.taylor@pharma.novartis.com
Educational meeting sponsored by Novartis

Siemens Sensational CT Symposiums
23 May & also 24th, 2002; Birmingham, UK
Julie Godber, Tel. 01344 396334,
E. godberj@plcbrk.siemens.co.uk

7th Meeting of the European Society of Neurosonology and Cerebral Hemodynamics
26-28 May, 2002; Bern, Switzerland
Tel. 41 41 767 34 49, Fax. 41 41 767 34 00,
E. Neurosonology2002@jacch.jnj.com

Dementia: A Dual Approach
28 May, 2002; Haslemere, UK
E. carey.taylor@pharma.novartis.com
Educational meeting sponsored by Novartis

Cholinesterase Inhibitors: The Evidence Base
28 May, 2002; London, UK
Tel. 020 7290 2984, E. geriatrics@rsm.ac.uk

13th European Congress of Physical Medicine & Rehabilitation
28-31 May, 2002; Brighton, UK
Melanie Ramsdell, Concorde Services.
Tel. 020 8743 3106, www.bsrm.co.uk/ec2002

Siemens Sensational CT Symposium
28 May, 2002; Newcastle, UK
Julie Godber, Tel. 01344 396334,
E. godberj@plcbrk.siemens.co.uk

33rd Scandinavian Neurology Congress
29 May-1 June, 2002; Reykjavik, Iceland
Tel. 00354 585 3900, Fax. 00354 585 3901,
E. Congress@congress.is, www.congress.is

5th Conference on Myasthenia Gravis & Related Disorders
29 May-9 June, 2002; Florida, US
Tel. 212 838 0230 x 327, Fax. 212 838 5640,
E. conference@nyas.org

Dementia: A Dual Approach
30 May, 2002; Rotherham, UK
E. carey.taylor@pharma.novartis.com
Educational meeting sponsored by Novartis

June

Dementia: A Dual Approach
11 June, 2002; Glasgow, UK
E. carey.taylor@pharma.novartis.com
Educational meeting sponsored by Novartis

Dementia: A Dual Approach
12 June, 2002; Swindon, UK
E. carey.taylor@pharma.novartis.com
Educational meeting sponsored by Novartis

ENS 2002
22-26 June, 2002; Berlin, Germany
Tel. +41 61 686 77 11,
Fax. +41 61 686 77 88, E. info@akm.ch

7th Euroacademia Multidisciplinaria Neurotraumatologica Congress
26-29 June, 2002; Newcastle upon Tyne, UK
Tel. 0191 273 88 11 22 999,
E. emn2002@ncl.ac.uk

July

7th Cycle: First Course of the Brain
Wendy Taylor, Tel. 0207 837 7660, Fax. 0207 278 5122, E. W.Taylor@ion.ucl.ac.uk / r.jager@ion.ucl.ac.uk

Dementia: A Dual Approach
2 July, 2002; London, UK
E. carey.taylor@pharma.novartis.com
Educational meeting sponsored by Novartis

MR Symposium
2 July, 2002; Birmingham, UK
Julie Godber, Tel. 01344 396334,
E. godberj@plcbrk.siemens.co.uk

Technological Advances in Diagnostic Radiology - European Cruise
3-15 July, 2002; London, UK
Tel. 800 422 0711, Fax. 727 527 3228,
E. kciotti@continuingeducation.net

ABN one-day joint meeting with RCP
4 July, 2002; London, UK
Susan Tann, ABN, Tel. 020 7405 4060,
Fax. 020 7405 4070,
E. abn@abnoffice.demon.co.uk

EPTA Summer Scientific Meeting
6 July, 2002; Liverpool, UK
E. nigel.hudson@phnt.swest.nhs.uk

10th International Congress of Neuromuscular Diseases
7-12 July, 2002; Vancouver, Canada
Tel. 1 604 681 5226, Fax. 1 604 681 2503, E. Congress@venuewest.com

7th European Congress of Neuropathology
14-17 July, 2002; Helsinki, Finland
Tel. + 3 58 9 56 07-5 00, Fax. + 3 58 9 56 07-50 20, E. Neuropathology2002@congrex.fi, www.congrex.fi/neuropathology2002

6th Conference on Parkinson's Disease & Parkinsonism
17 July, 2002; London, UK
Medical Education Partnership, Tel. 020 7072 4191, Fax. 020 7072 4392,
E. mpaul@mepuk.com

8th International Conference on Alzheimer's Disease and Related Disorders
20-25 July, 2002; Stockholm, Sweden
Tel. 001 312 335 5813, Fax. 001 312 335 5781, E. internationalconference@alz.org, www.alz.org/internationalconference

International Symposium on Neurobiology and Neuroendocrinology of Aging
21-26 July, 2002; Bregenz, Austria
Dr Bartke, Tel. 618 453 1512, Fax. 618 453 1517, E. abartke@siumed.edu

Bridging Basic & Clinical Epileptology
21 July - 4 August, 2002; San Servolo, Italy
E. avanzini@instituto-besta.it

August

Neuropathic Pain Satellite Symposium
14 August, 2002; Tijuana, Mexico
Tel. 52 5 531 6981, Fax. 52 5 531 6977,
E. luemgeo@servidor.unam.mx

29th Scandinavian Congress of Rheumatology
15-18 August, 202; Tromso, Norway
Tel. 4 777 627 294, Fax. 4 777 627 258,
E. 29scr2002@rito.no or revhan@rita.no

WFNRS Symposium Neuroradiologicum XVII
18-24 August, 2002; Paris, France
Tel. 0033 3 83851456, Fax. 0033 3 838 51391

Multiple Sclerosis: Genetics, Pathogenesis & Therapy
18-22 August, 2002; Copenhagen, Denmark
E. benzon@post1.tele.dk

11th European Congress of Clinical Neurophysiology-ECCN
24-28 August, 2002; Barcelona, Spain
Tel. 34 935 101 005, Fax. 34 935 101 009,
E. barcelona@viajesiberia.com,
www.eccn2002barcelona.com

5th International Congress of Neuroendocrinology
31 August-4 September, 2002; Bristol, UK
Tel. 01454 619347,
E. Icn2002@endocrinology.org

Healthcare for Older People
31 August-13 September, 2002; Edinburgh, UK
Rosemary Hector, Tel. 0131 247 3636,
Fax. 0131 220 4393,
E. r.hector@rcpe.ac.uk

September

Better Care for Children & Adults with Epilepsy - A Consensus Conference
4-5 September, 2002; Edinburgh, Scotland
Rosemary Hector, Tel. 0131 247 3636,
Fax. 0131 220 4393,
E. r.hector@rcpe.ac.uk

5th Congress of the European Association for Neuro-Oncology
7 - 11 September, 2002; Florence, Italy
Tel. Carmine Carapella, Tel. 39 064 173 4412,
Fax. 39 064 179 6897, E. eano2002@ifo.it

5th International Congress International Society for Neuroimmunomodulation
8-11 September, 2002; Montpellier, France
E. Craig Smith, ccs@codon.nih.gov

Signal Transduction in the Blood-Brain Barriers
12-15 September, 2002; Berlin, Germany
E. bbb@fmp-berlin.de

4th World Congress on Stress
12-15 September, 2002; Edinburgh, UK
Tel. 01355 244966, Fax. 01355 249959, E. stress@glasconf.demon.co.uk

10th Meeting of the European Neuroendocrine Association
12-14 September, 2002; Munich, Germany
Tel. 49 89 5 482 340, Fax. 49 89 54 823 444,
E. ena2002@i-plan.de

BSRM/University of Nottingham Advanced Rehabilitation Course
10-13 September, 2002; Nottingham, UK
E. info@bsrm.co.uk

Epilepsy Specialist Nurses Association Conference
16-17 September, 2002; Sheffield, UK
Tel. Chris Morley on 01482 587011

4th Asian & Oceanian Epilepsy Congress
12-14 September, 2002; Nagano, Japan
Tel. +81 3 3255 0900, Fax. +81 3 3255 7377,
E. aoecsecret@gp.knt.co.jp

Effectiveness of Rehabilitation for Cognitive Deficits
17-19 September, 2002; Cardiff, UK
Tel. Kath Giblin, 029 2087 5356,
Fax. 029 2087 4858

Nordic Movement Disorder Symposium
20-21 September, 2002; Oslo, Norway
Tel. 47 22 561 930, Fax. 47 22 560 541, E. congrex@congrex.no

9th International Child Neurology Congress & 7th Asian and Oceanian Congress of Child Neurology
20-25 September; Beijing, China
Fax. 0086 10 66176450, E. icnc@public3.bta.net.cn

30th Annual Scientific Annual Congress of Neurological Surgeons
22-25 September, 2002; Philadelphia, US
Tel. 847 692 9500, Fax. 847 692 2589

British Human Genetics Conference
22-25 September, York, UK
Tel. 01216 272 634, Fax. 01216 272 634,
E. york2002@bshg.org.uk

Meeting of British Psychophysiology Society
23-25 September, 2002; Glasgow, UK
Hartmut Leuthold, Tel. 0141 330 6847,
Fax. 0141 330 4606,
E. h.leuthold@psy.gla.ac.uk

October

ABN Autumn meeting/British Neuropsychiatry Association
2-4 October; London, UK
Susan Tann, ABN, Tel. 020 7405 4060,
Fax. 020 7405 4070,
E. abn@abnoffice.demon.co.uk

7th International Congress of the World Muscle Society
2-5 October, 2002
Mr Jacob Muller, Tel. 0031 71 527 52 97,
Fax. 0031 71 527 52 62,
E. j.j.l.muller@lumc.nl

EPTA Autumn Scientific Meeting
5 October, 2002; York, UK
E. nigel.hudson@phnt.swest.nhs.uk

5th European Congress on Epileptology
6-10 October, 2002; Madrid, Spain
E.epicongress@eircom.net.

Neurology - European Cruise
7-19 October, 2002; Istanbul, Turkey
Tel. 800 422 0711, Fax. 727 527 3228,
E. kciotti@continuingeducation.net

2nd Latin America Committee for Treatment & Research in MS (LACTRIMS)
9-12 October, 2002; Monterrey, Mexico
www.lactrims2002.com.mx,
E. lactrims@hsj.com.mx

British Geriatrics Society Autumn Meeting
10-11 October, 2002; London, UK
Tel. 01825 768 902, Fax. 01825 768 902,
E. contact@bhm.co.uk

British Society of Neuroradiologists Annual Meeting
10-11 October, 2002; Winchester, UK
Drs Millar or Barker, Wessex Neurological Centre, Tremona Road, Southampton, SO16 6YD

Annual Meeting of the American Neurological Association
13-16 October, 2002; New York, US
Tel. 952 545 6284, Fax. 952 545 6073,
E. lorijanderson@msn.com

ECNR - European Course in Neuroradiology
19-24 October, 2002; Crieff, Scotland
Dr Wendy Taylor,
E. w.taylor@ion.ucl.ac.uk

Alzheimer's Disease International's 18th Annual Conference
23-26 October, 2002; Barcelona, Spain
Tel. 0034 93 201 7571, Fax. 0034 93 201 9789, E. suport@suportserveis.com

Physiotherapy Treatment in the Overall Management of Parkinson's disease
26 October, 2002; Vienna, Austria
Tel. 352 26 53 15 51, Fax. 352 26 53 15 52,
E. mariella.graziano@internet.lu

European Federation of Neurological Societies Congress
26-29 October, 2002; Vienna, Austria
EFNS, Tel. 43 1 880 00270, Fax. 43 1 888 925581, E. headoffice@efns.org

UKABIF in partnership with SHIF

United Kingdom Acquired Brain Injury Forum — Scottish Head Injury Foundation

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SHARING GOOD PRACTICE

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Edinburgh

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Des O'Meara, Service Manager, Northumberland Head Injury Service

Headway in Scotland: Another Piece of the Jigsaw
Tom Greenwood, Scotland Development Manager, Headway

A Neuropaediatric outreach service
Shona Forsyth, Neuropaediatric Outreach Nurse, Glasgow

Implementing an integrated pathway of care for brain injury
Maggie Campbell/Jenny Garber, Brain Injury Co-ordinators, Sheffield

Integrated care in a hospital setting
Brian Pentland, Consultant Neurologist, Astley Ainslie Hospital

Developing a comprehensive service for rehabilitation of acquired brain damage in Glasgow
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Please contact:
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Royal College of Physicians &
Association of British Neurologists

Neurology for the 21st Century

Thursday 4 July, 2002

Royal College of Physicians, 11 St Andrews Place, Regent's Park, London NW1

Audience: Consultant neurologists, general physicians and geriatricians
Purpose: To update specialists on common neurological conditions, particularly emergencies.
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NCYPE
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Association of British Neurologists Spring Meeting 2002

3-5 April 2002, Oxford, UK

The 2002 Spring Meeting of the Association of British Neurologists was organised by the University Department of Neurology, Oxford (Dr. M. Donaghy) and held in the prestigious academic surrounds of the Examination Schools. A number of delegates were soon harking back, not all of them comfortably, to their undergraduate days as they sat surrounded by marble columns and portraits of past academic greats. The venue was excellent, represented for many of us a welcome return to this picturesque city, and reflected the ABN's policy of having meetings outside London.

Four scientific sessions, an educational symposium and a clinico-pathological conference covered a broad range of neurological topics, offering insights into both progress at the research coalface and in some instances how such achievements and understanding may be translated to the clinic.

Drawing heavily from an experienced department in Oxford, the Symposium for Treating Neuromuscular Disease covered a number of topics emphasising treatment and including updates on how to best manage newly diagnosed myasthenia gravis, optimal therapy of chronic inflammatory demyelinating neuropathy (CIDP), inflammatory myopathy and an excellent talk on the use of agents such as riluzole in motor neuron disease and the need to appropriately harness the internet information resource. All talks made reference to the relevant evidence base without overloading the audience and in some case outlining the genuine lack of well-controlled clinical trials in certain areas.

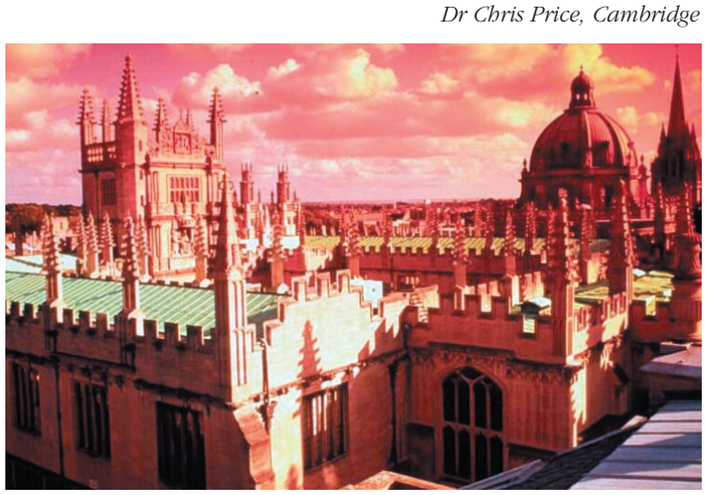
For two of the four, scientific sessions were split into parallel hence covering a broad range of topics. Whilst on the surface this may appear a good idea, it promoted considerable discussion amongst delegates. In particular this discussion focused on the issue of 'dilution' and quality of presentations. Particularly represented on the second day were Parkinson's disease and movement disorders. We heard a fascinating talk about the relatively new disease of neuroferritinopathy from Dr Chinnery (University of Newcastle); this condition appears to be highly heterogenous, genetically mediated in certain families, potentially treatable and may be traceable back to Fletcher Christian and the mutinous days of the Bounty! Dr Khan (Institute of Neurology, London) presented further genetic insights into early onset Parkinson's disease, and Dr Dale (Institute of Child Health, London) presented compelling evidence for an autoimmune mechanism in the pathogenesis of encephalitis lethargica (appropriately combined with video footage and seamless mastering of powerpoint technology!). Dr Pal (King's College, London) provided us with some objective evidence for what we had suspected for some time, namely that asymmetric postural tremor (with or without resting tremor) may be a forerunner for Parkinson's disease. Multiple sclerosis was also represented, and it was refreshing to hear two presentations where the emphasis lay firmly in the domain of pathogenesis. Dr Seidi (GKT, London) gave us an insightful talk on intrathecal production of antibodies to cytoskeletal components, and their correlation to disability over a two-year period. Dr Wilkins (BRC, Cambridge) spoke eloquently about oligodendrocyte derived soluble factors in axonal damage, in particular insulin growth factor 1 (IGF-1), referring to their relevance to future therapeutic strategies. Such insights contrasted with work presented by Dr Ingle (Institute of Neurology, London) on change in long-term ventricular volume in primary progressive disease that had a number of us questioning the relevance of such a technique and how it may relate to our patients in the clinic. Further talks on cognitive dysfunction in 'never encephalopathic' patients awaiting hepatic transplantation (Dr Lewis, Leeds) served to emphasise our lack of mechanistic understanding of such a disease and perhaps also our relatively crude techniques for diagnosing subclinical, but nonetheless clinically significant disease.

> "Neuroferritinopathy... appears to be highly heterogenous, genetically mediated in certain families, potentially treatable and may be traceable back to Fletcher Christian and the mutinous days of the Bounty!"

The third day saw a much welcomed session on cerebrovascular disease. Traditionally, neurologists have taken a rather back seat approach to stroke so it is most refreshing to see this prominent on the agenda. This may reflect an underlying shift in attitude, partly driven by the President's influence (Professor Charles Warlow) and partly from a more generic shift towards neurologists' involvement in acute neurology. Excellent presentations were given by all speakers, in particular Dr Warburton (Cambridge) presenting pioneering work using FDG-PET to examine macrophage activity in symptomatic carotid stenosis and Dr Flossman (Oxford) providing further insights from a well established database on how we should be taking posterior circulation TIAs just as seriously as any other ischaemic event. The session culminated in an excellent clinicopathological conference (CPC) that provided plenty of diagnostic intrigue, serving an important training need as well as illustrating the point that neurological diagnosis can be tricky! The posters throughout the sessions were generally of a very high standard; those that caught my eye included neuroradiologists disagreeing about various aspects of arterio-venous malformations (AVMs), variant CJD in a compulsive jelly eater, tilt table testing from an epilepsy clinic, a paradigm for exploring genetic control of cerebral development and many more.

Overall the meeting managed to combine an excellent venue with a number of presentations most of which were of high quality, although appropriate selection was necessary. The social events at the Natural History Museum and Keble College ensured that a good time was had by all.

Dr Chris Price, Cambridge



The Spring meeting was held in the beautiful city of Oxford.

The 54th Annual American Academy of Neurology (AAN) meeting

13-20 April 2002, Denver, Colorado

The 54th AAN meeting was held this year in Denver, Colorado. Although slightly less tempting on paper than next year's venue, namely Honolulu, the "mile-high" town of Denver provided a more than adequate state-of-the-art conference centre for the 8000 or so delegates from around the world. Founded last century on the back of an abortive gold rush, Denver itself came across as a rather uninspiring place although the picturesque Rockies and associated upmarket ski resorts provided a diverting and impressive backdrop. The altitude together with an action-filled social agenda and, of course, the all-American breakfast seminars combined to produce a week of chronic sleep deprivation and a surreal sense of constant mild hangover (as if!).

The AAN meeting is widely held to be the most important neurology event in the calendar and rightly so. This was my first attendance at such a meeting and it was difficult not to be impressed, if not overawed, by its sheer scale and professionalism. Comparisons with the ABN equivalent in this country would approximate to likening Ben Hur to a donkey derby on Margate sands!

The meeting itself can be divided into three components – the plenary sessions, the scientific programme combining oral presentations and posters, and the educational programme. Dealing with the latter first, this is perhaps the signature aspect of the AAN with almost 200 seminars available from 6:45 in the morning to 11:00 at night over the course of 7 days. Topics were reassuringly broad and included tempting titles such as "Autism across the ages" and "Top ten ophthalmological diagnoses you cannot afford to miss". My experience of several educational sessions and feedback from colleagues would suggest that the quality is usually extremely high with each course providing a comprehensive written syllabus to show the folks back home. Veterans tell me that the trick is to attend a course as far away from one's areas of interest as possible in order to maximise the learning potential. However, depending on one's level of sponsorship, the associated financial gamble might well limit this approach, given that the courses are far from cheap with a price tag ranging from $120 to $600. A popular but again expensive ($200) option was to purchase a CD-ROM containing the text of all educational seminars – if only one had the time to actually read it all! The educational programme clearly brings considerable renumeration to the AAN. Speaking as a purist, one gripe I have of the meeting would be that this aspect was somewhat oversold to the extent that it was often quite difficult to find details and timing of the scientific sessions.

The Colorado Convention Center was designed for meetings and exhibitions. Credit: Denver Metro Convention & Visitors Bureau

I dutifully attended the majority of the plenary sessions and found them extremely rewarding and reassuringly free. These were given by noted international experts in a range of neuroscience topics both clinical and basic. Understandably, not every speaker had English as their first language yet all were impressively eloquent and made full use of the stunning audiovisual aids in the immense exhibition hall. For me there were several highlights including the charismatic Dr Emmanuel Mignot who gave an excellent exposition outlining the recent major advances in understanding the underlying neurobiology of narcolepsy and, indeed, the nature of the sleep/wake cycle. Since this area is a particular interest of mine, I did not learn of any major new findings. However, it was very satisfying to see this leading figure in the sleep world explain the painstaking processes involved in gene-mapping the doberman model of narcolepsy. This has led to the unexpected discovery that deficiency of the neuropeptide, hypocretin, or its receptor, leads to the clinical syndrome. Backed up by knockout mice data and recent human clinical findings, this neat story has almost turned me into a born-again fan of molecular biology, having previously dismissed it as "expensive anatomy".

Another intriguing talk was given by Dr Mel Feany, enigmatically entitled: "Learning about human neurodegenerative diseases from flies and worms". The work followed on from the recent striking findings related to the molecular abnormalities in conditions such as Huntington's and Parkinson's diseases. These have opened up the possibility of exploring the consequences of subcellular protein aggregations in the ubiquitous and highly experimenter-friendly fruit fly. Dr Feany started by reminding us that 70% of our genes are present in the humble drosophila and that homologous areas of the brain exist, even including dopaminergic neurons akin to the substantia nigra. Purposeful mutations of alpha-synuclein in the fly as a model of Parkinson's disease lead to very similar neuropathological and neurochemical consequences. There are even data to suggest that flies with the mutation are slower, less agile and "shakier" than their wild type counterparts. The most interesting aspect, however, relates to the timing of the functional and neuropathological changes. In particular, these occur and progress only when the fly reaches a mature age, adding fuel to the notion that this is a faithful model of a neurodegenerative disease. This impressive type of research leads one to suspect, optimistically, that it can only be a matter of years before we fully understand the fundamental molecular basis of these various neurodegenerative diseases.

The scientific sessions of the meeting were perhaps the least satisfying aspect. This is perhaps not surprising since one is usually already aware of recent significant findings in one's own areas of interest whereas new developments in other areas tend either to be totally incomprehensible or, at best, difficult to appreciate. It is, of course, impossible to summarise the diverse work that was presented although a few papers caught my eye. In particular, the notion that dopamine agonist therapy in Parkinson's disease might in some way slow disease progression, as well as delay motor complications, was given some credence by various presentations of PET data, dopamine transporter markers, as well as histology from marmoset MPTP models. I feel the jury is still very much out on the agonist/L-DOPA debate but the recent cumulative data is starting to look persuasive. It is worth recalling, perhaps cynically, however, that all these studies are funded by the respective interested pharmaceutical companies.

Overall, my experience of the annual AAN meeting was very positive. The size of the meeting and the choice of sessions on offer can easily lead to a sense of disorientation. If I am lucky enough to attend next year's show (any offers?), I feel that my experience of the Denver meeting will allow me to hone in on the really relevant areas to my practice and interests and might be even more worthwhile.

Dr Paul Reading,
Newcastle upon Tyne

EDITOR'S CHOICE

PSYCHOIMMUNOLOGY

Mind over macrophages

One of the expanding areas of immunology nowadays, albeit with fringe elements, is "psycho-immunology": exploring the relationship between neural activity, behaviour and the immune system. This group from New York strayed into this territory by accident, when they made some surprising findings during pre-clinical testing of a novel drug in stroke. CNI-1493 is an inhibitor of macrophage activation by preventing the phosphorylation of p38 mitogen activated protein kinase. Curiously, when injected intraventricularly, CNI-1493 suppresses systemic TNF-α production in response to endotoxin. This paper describes the experiments that explore the mechanism of this effect. First, they showed that the dose of CNI-1493 required to reduce systemic TNF-α is 10,000 times less for intracerebral- as opposed to intravenous- administration. Then they demonstrated that the protective effect of CNI-1493 is mimicked by direct stimulation of the vagus nerve, and abolished if the vagus is surgically cut. The inescapable conclusion is that CNI-1493 acts centrally, via the vagus, to regulate peripheral inflammation, perhaps by vagal release of acetylcholine acting upon the nicotinic receptors found on resident macrophages. There are two important conclusions from this work. First, drugs may control systemic inflammation through an action on the brain and secondly, vagal stimulation may have an immunosuppressive effect. ***-AJC***

Bernik TR, Friedman SG, Ochani M, DiRaimo R, Ulloa L, Yang H, Sudan S, Czura CJ, Ivanova SM, Tracey KJ.
Pharmacological stimulation of the cholinergic antiinflammatory pathway.
JOURNAL OF EXPERIMENTAL MEDICINE
2002 Mar 18;195(6):781-8.

Schizophrenia is an autoimmune disease

So claims this paper from Argentina. It is based on the finding of an autoantibody in the sera of patients with schizophrenia that binds to frontal cortical cells. Many claims for autoimmunity in the past have been made on the finding of an autoantibody but we now recognise that this is simply not sufficient evidence. For healthy humans produce antibodies and T cells that react against self. Sterin-Borda's group have amassed, with a technological tour de force, comprehensive circumstantial evidence that the antibodies they have found are pathogenic. Their starting hypothesis is that patients with schizophrenia have antibodies against the particular acetylcholine receptor found in the frontal cortex (the M1 muscarinic receptor: M1mAChR). Happily for the investigators, the rat and human M1mAChR are closely homologous. They demonstrated, by both indirect immunoflourescence and flow cytometry, that sera from 21 patients with paranoid schizophrenia, but not controls, bound to rat fontal cortical cells. They then extracted, from both patient's and controls' sera, an IgG fraction that bound to a peptide representing the sequence of the second extracellular loop of the M1 mAChR. They ran this fraction, in an immunoblot, against a rat frontal cortex membrane and showed that patients' anti-M1 mAChR revealed a band of similar molecular mass to an established anti-M1 mAChR, which could be inhibited by excess peptide, demonstrating specificity. Patients' anti-M1mAChR showed a similar band of much lower intensity, making the point again that low affinity antibodies exist which bind to self in normal people. However, dot blot and ELISA studies showed that the patients' sera, but not controls', show a concentration dependent increase in binding. The next step in their analysis is to see if this binding has any functional effect. They show convincingly that patients' sera and their anti-M1 mAChR fraction act as an agonist at the mAChR and cause a rise in intracellular second messengers (phosphoinositide and cyclicGMP) when applied to rat frontal cortex slices. None of this shows that the autoantibody is pathogenic in patients. To do that would require the classic approaches of transfer of the autoantibody to laboratory animals to see if it causes schizophrenia-like problems (but how are these detected in rats?) and elimination of the antibody in patients (by plasma exchange or other immunosuppression) to see if the disease is modified. ***-AJC***

Borda T, Perez Rivera R, Joensen L, Gomez RM, Sterin-Borda L.
Antibodies against cerebral m(1) cholinergic muscarinic receptor from schizophrenic patients: molecular interaction.
JOURNAL OF IMMUNOLOGY
2002 Apr 1;168(7):3667-74.

PERIPERHAL NEUROPATHY

Anti-MAG antibodies and bad packing

This study, from John Hopkins and involving peripheral neuropathy luminaries Jack Griffin and Richard Hughes, is a neat example of the usefulness of clinical material to the basic sciences. It concerns the packing of neurofilaments within axons. This controls axon calibre, which is so important to their function. It has been proposed that neurofilament packing may be modified at a local level by the phosphorylation of neurofilament sidearms: so increasing the distance between neurofilaments and thus axon calibre. One molecule that may be responsible is myelin-associated glycoprotein (MAG) found on Schwann cells. So the authors studied electron micrographs of sural nerve biopsies from patients with a paraproteinaemic neuropathy and anti-MAG antibody comparing them to other demyelinating neuropathies and normal nerves. The hypothesis was confirmed: the neurofilaments from patients with the anti-MAG antibody were more densely packed than either of the other groups. Neurofilament sidearm phosphorylation was not studied though. This work is useful in two ways. First, it adds to the evidence that the anti-MAG antibody is pathogenic in these patients (always a problem in autoantibodies associated with human disease). Secondly, it suggests a mechanism

whereby a Schwann cell molecule may influence axons and thus perhaps contribute to the axonal degeneration seen in demyelination of both the central and peripheral nervous systems. ***-AJC***

Lunn MP, Crawford TO, Hughes RA, Griffin JW, Sheikh KA.
Anti-myelin-associated glycoprotein antibodies alter neurofilament spacing.
BRAIN
2002 Apr;125(Pt 4):904-911.

NEURO-OPHTHALMOLOGY

Extraocular muscle forever young?

The radically different disease susceptibility between extraocular muscle (EOM) and other skeletal muscle is both well recognised and diagnostically useful in clinical practice. The pathophysiological basis for this difference is poorly understood, but differences in surface antigens might account for selective EOM involvement in the autoimmune disorders myasthenia gravis and Graves disease while a high level of oxidative metabolic activity could explain its susceptibility to mitochondrial disorders. By contrast, EOM is spared in dystrophinopathies despite similar expression levels of dystrophin and related membrane support proteins. EOM is also spared in transgenic animals lacking dystrophin but not in animals lacking both utrophin and dystrophin, which suggests that EOM is uniquely able to successfully substitute utrophin when dystrophin is deficient.

The present study provides exciting new information indicating that mature uninjured EOM fibres continue to incorporate myonuclei from satellite cells at a rate that in other skeletal muscle is only seen following injury. The authors show that EOM satellite cells, unlike those of other skeletal muscles, are continually 'activated' in the healthy adult rabbit. Thus they continue to express the myogenic regulatory factor MyoD and rapidly start dividing following plating without requiring a prolonged activation period. It is particularly interesting to find that satellite cells in uninjured adult EOM muscle continue to incorporate bromodeoxyuridine (BrdU), a marker of cell division.

More compelling still, the presence of BrdU-labelled nuclei in EOM myofibres suggests that satellite cell nuclei are continually being incorporated into healthy fibres. This raises the possibility that active remodelling permits the rapid repair of the sarcolemmal damage associated with deficiency of dystrophin and other members of the dystrophin-glycoprotein complex. A better understanding of why EOM is spared despite sustaining apparently the same pathophysiological insult is likely to provide key insights into both disease mechanisms and potential therapeutic targets in the muscular dystrophies. ***-WR***

McLoon L, Wirtschafter J
Continuous myonuclear addition to single extraocular myofibres in uninjured adult rabbits.
MUSCLE AND NERVE
2002: 25: 348-358

Superior oblique myokymia: a neurovascular compression syndrome?

Superior oblique myokymia (SOM) is an ocular motility disorder characterised by paroxysmal unilateral oscillopsia. (In my practice it is a condition which, once missed, has never been forgotten.) As long ago as 1983 it was suggested that neurovascular compression of the trochlear nerve was the cause, a view supported by occasional reports of successful microvascular decompression surgery. However, neuroimaging studies have hitherto lent no support to the hypothesis. Now, using a specific magnetic resonance imaging protocol (3-D Fourier transform constructive interference in steady-state and 3-D time of flight magnetic resonance angiography +/- Gd-DTPA) which shows small structures surrounded by CSF, further claims for the neurovascular compression hypothesis have been made.

In six patients with SOM, imaging showed contact between branches of the superior cerebellar artery and the trochlear nerve close to or at its point of exit from the midbrain, the root exit zone (REZ). On the contralateral, asymptomatic, side no such contacts were observed (i.e. sensitivity = 100%), although more distal contacts (≥ 3 mm from REZ) were seen. It is argued that the REZ is the critical area since the transition here from PNS to CNS myelin renders the nerve electrophysiologically vulnerable (no epineurium or perineurium in CNS). Whether the patients responded to medical (carbamazepine) and/or surgical (microvascular decompression) therapy is not reported. The specificity of neurovascular contact is lower, since 15% of asymptomatic individuals scanned had this finding: hence it does not reliably predict symptoms.

The data are suggestive, although not compelling, that SOM be regarded as a neurovascular compression syndrome, along with some instances of trigeminal neuralgia and hemifacial spasm. Certainly patients failing carbamazepine might merit detailed neuroimaging to search for neurovascular contact which might potentially represent a surgically remediable cause. ***-AJL***

Yousry I, Dieterich M, Naidich TP, Schmid UD, Yousry TA.
Superior oblique myokymia: magnetic resonance imaging support for the neurovascular compression hypothesis.
ANNALS OF NEUROLOGY
2002;51(3): 361-368

NEUROPHYSIOLOGY

Charging patients

Nerve conduction studies typical involve stimulation at one site and recording a response a few centimetres distant from the stimulation site either on the nerve or muscle. The idea that stimulating a finger and recording from a toe would generate anything diagnostically meaningful seems unlikely and even perhaps a little comical, but such techniques have been used to estimate intracellular and extracellular water volumes (whole body bioelectrical impedance analysis). This relies on a simplified body circuit model and a sizeable number of assumptions and has a somewhat limited application. A more promising avenue with bioimpedance, as a neurological tool, has been investigated by Rutkove and colleagues in which local bioimpedance analysis (LBA) studies of the thigh were performed. A number of electrodes are placed in series along the anterior surface of the thigh, one of which delivers alternating current, parameters defined from recordings of resistance and capacitance are then derived (phase curves). A similar arrangement can also be applied to the forearm. Comparing controls with an eclectic group of patients, with conditions such as inflammatory myopathy, polio and motor neuron disease, differences in these parameters were evident. Changes also paralleled both disease deterioration and improvement in follow up studies extending over 18 months and were not purely dependent on muscle bulk. Tantalising, phase curves appear to be different between these pathologies but this needs further clarification. It is certainly easy to imagine situations where this analysis may be helpful, such as investigating intensive care patients where EMG studies can sometimes be limited by a lack of muscle activation, or following up effectiveness of immunosuppresant treatments in inflammatory myopathies. If this technique is to have a future, then studies comparing age matched controls with a homogenous patient group will be a required and indeed further studies are envisaged. ***-JR***

Rutkove SB, Aaron R, and Shiffman CA.
Localised bioimpedance analysis in the evaluation of neuromuscular disease.
MUSCLE AND NERVE
2002 25, 390-397.

Realising the visual prosthesis

Bypassing the connections from the eye to visual cortex by stimulating the latter artificially may provide a limited degree of functional vision in cases of blindness. Research on this possibility began in the 1960s with intracortical microstimulation techniques. A less invasive

approach utilising painless transcranial magnetic stimulation is currently being investigated, but selecting which subjects may benefit from such an approach remains a problem. One unresolved question is whether long-standing visual deafferentation leads to irreversible impairment of visual cortex function that might impair such technical approaches. To try and address this, Gothe and colleagues have recently assessed different categories of visually impaired subjects with optic atrophy of various aetiologies including glaucoma, retinitis pigmentosa, cone cell dystrophy, and optic nerve meningioma without concomitant damage of post geniculate pathways. The 35 registered blind subjects were compared with 10 controls; the blind subjects were divided into 3 groups dependent on degree of residual vision. The partial or complete long-term deafferentation had been present for at least 10 years. By applying transcranial magnetic stimulation pulses over the occipital skull in normals, perception of brief flashes of white or coloured patches of light (phosphenes) can be achieved. A threshold from the intensity of stimulation and their distribution in the visual field can also be determined. Group 1 patients (visual acuity <20/400) had comparable reponses to the control group. Of the group 2 (light or movement perception only) patients, 60% were able to perceive phosphenes in response to TMS. In group 3, only 2 out of 10 patients reported phosphenes. Surprisingly thresholds for phosphene responses did not significantly differ between controls and patients but active stimulation sites did differ, suggestive of some form of functional remodelling. In conclusion the degree and duration of visual deafferentation needs to be considered in any attempt to artificially revive the dormant visual cortex. ***-JR***

Gothe J , Brandt S, Irlbacher K, Sabel SRB, and Meyer B.
Changes in visual cortex excitability in blind subjects as demonstrated by transcranial magnetic stimulation.
BRAIN
2002 125: 479-490

STROKE

★★★ RECOMMENDED

Chiropractic manipulation and stroke

There are many reports of posterior circulation stroke secondary to vertebral artery dissection seemingly provoked by chiropractic manipulation of the neck. However these are generally anecdotal cases or small series. Thus the true relationship of chiropractic manipulation as a cause of stroke is open to publication, selection and recall bias. This study seeks to determine whether, and if so with what risk, chiropractic manipulation of the neck really does lead to vertebrobasilar infarction.

Each of 582 patients with a posterior circulation infarct admitted to hospital in Ontario were identified retrospectively and matched to 4 controls from the local population. Public health billing records were used to identify all persons having chiropractic manipulation prior to the event date. Patients under the age of 45 were five times (95% CI 1.32-43.87) more likely to have undergone chiropractic manipulation than controls in the week before stroke onset and were five times as likely (95% CI 1.34-18.57) to have made 3 or more visits to a chiropracter for neck manipulation in the previous month. There was no association for patients over the age of 45 yrs.

This is the first population based control study to test the association between chiropractic manipulation and vertebrobasilar stroke and does demonstrate an association for young people. The results correspond to an incidence of 1.3 cases of stroke within 1 week of manipulation per 100 ,000 (greater than the 1 per million previously suggested). However, biases do exist – patients who may have had a subarachnoid haemorrhage from intracranial extension of the vertebral dissection and patients with carotid dissections were excluded. The vertebrobasilar strokes were not all proven dissections. The visit to the chiropracter may have been due to the initial neck pain of a spontaneous dissection and the manipulation was not actually the cause of the dissection (although may have aggravated it). Clearly a large prospective population based case control study is the only way to eliminate such bias but this would require a long study period. Meantime the neurologist who sees a patient with a posterior circulation stroke needs to consider a dissection as a likely cause, patients who have had a previous spontaneous dissection should probably avoid chiropracters and chiropracters should refer on any patient who develops neurological symptoms between or after treatment sessions. Should they warn patients of the risk? Since it is 1:100 000 presumably not. ***-PJM***

Rothwell DM, Bondy SJ, Williams JI.
Chiropractic manipulation and stroke: a population based case control study.
STROKE
2001;32:1054-1059

MOVEMENT DISORDERS

★★★ RECOMMENDED

Neural transplantation for Huntington's disease - the controversy continues

The notion that Huntington's disease (HD) can be cured by the grafting of embryonic striatal tissue has a long experimental history, but relies on the belief that the brunt of the pathology targets this structure. However, there is mounting evidence that the disease is diffuse at onset, although the contribution of these non-striatal pathologies to disease manifestations is not known. Thus much controversy exists as to whether the use of striatal transplants will ever be of value in halting the disease in affected patients, and tends to polarise researchers in those who support this approach and those who believe it is pointless. Proponents of this approach were supported by the successful French study of Peschanski and colleagues published in the Lancet at the end of 2000, but the opponents of the procedure have now been armed by this recent study from Tom Freeman and colleagues in South Florida. As a proponent for the procedure, it should be stated early on that no-one has ever believed that this approach is going to cure patients of HD in much the same way that embryonic nigral grafts do not cure all of the problems in PD (see ACNR 1.2). It has never been seen as an alternative to preventative therapies (see e.g. ACNR 1.5 p31), but may help with some of the core deficits, especially in those with established disease.

In this latest study patients with moderate HD were grafted with a part of the developing human embryonic striatum and then followed up for 12 months. The overall result was that there was no significant benefit from the procedure and that in a number of cases surgical complications were seen such as sub-dural haematomas. This study led Ira Shoulson and Tim Greenamyre to write an editorial in this same issue of Neurology, calling for a halt to this transplant practice in HD. So what conclusions should we draw from this study?

Well, not a lot primarily because not enough information is yet available on this procedure and this recent study does have some major problems with it, namely:

- the dissection of the developing striatal tissue adopted by the team has never been shown to produce functional benefits in animal models of disease, unlike the less selective dissection adopted by the more successful French team;
- the HD patients were followed up for relatively short periods of time, which may have been insufficient to see full clinical effects as evidenced by the earlier French study;
- patients were probably more advanced than those seen in the earlier studies and this may have led to the increased complication rate reported in this study;
- the benefits of transplantation in some patients may have been lost by analysing the group as a whole rather than by individual. It is well-known that neural grafting produces variability between patients often for reasons that are not apparent.

Therefore this negative study should be taken notice of, but it should not be interpreted as providing the final nail in the coffin for grafting in HD. It is still too early to know whether the procedure will be of benefit but premature claims of failure (and success) do more harm than good, and much more is needed before a line can be drawn under this type of therapeutic approach in HD - ***RAB***

Hauser R Furtado S, Cimino CR, Delgado H, Eichler S, Schwartz S, Scott D, Nauert GM, Soety E, Sossi V, Holt DA, Sanberg PR, Stoessl AJ, Freeman TB.
Bilateral human fetal striatal transplantation in Huntington's disease.
NEUROLOGY
2002: 58: 687-695

Wives as well as offspring at risk on Guam

The Guamanian outpost of the National Institute of Neurological Disorders and Stroke has now been studying patients on the "largest land area between the Philippines and Hawaii" since the early '50s. In 1958 a prospective epidemiological study was initiated of the first-degree relatives and spouses of a 5-year cohort of Chamorros with ALS and parkinsonism-dementia complex (PDC) and individually matched controls. The latest analysis of the patient-control registries retains the earlier methodology but the 'ALS + PDC' classification has been abandoned and patients with both diseases have been classified according to the disease with the earlier onset.

Previous registry results already suggested strongly that Guamanian ALS and PDC are familial disorders since the two diseases are frequently seen in the same family as well as in the same individual, and neuronal degeneration in both conditions is characterised by Alzheimer-like neurofibrillary tangles in the brain and spinal cord. Furthermore, parents and siblings are at significantly increased risk of contracting either disease. This is the first follow-up at which sufficient time has elapsed to demonstrate a significantly higher risk for developing either disease among the offspring of patients with PDC but not, apparently, of individuals with ALS. The reasons for this difference are not clear but might be related to the younger age (about 6 years) of the offspring of ALS patients.

So are all cases of ALS and PDC on Guam hereditary? While confirming the familial nature of the disease, the results are against the involvement of simple Mendelian dominant or recessive genes in the aetiology of the disease(s). Indeed, two lines of evidence suggest the additional involvement of extraneous factors. First, there is an increased risk of developing the disease in spouses (wives only) of patients with ALS (but not PDC). Secondly, during the past 30 years, the age at onset for both ALS and PDC has increased by almost 10 years - an observation that has been attributed to the effects of "modernisation" on the island. ***-WR***

Plato CC, Galasko D, Garruto RM, Plato M, Gamst A, Craig U-K, Torres JM, Wiederholt W.
ALS and PDC of Guam: forty-year follow-up.
NEUROLOGY
2002: 58:765-773

GLIOMA

High-grade glioma adjuvant chemotherapy is beneficial

There is no doubt that malignant gliomas carry a particularly bad prognosis, with a median survival of 9 months. Current management involves cytoreductive surgery followed by a course of radiotherapy. Over the last 30 years a number of randomised studies have been undertaken in an attempt to improve this survival by adjuvant chemotherapy (nitrosurea based agents, which are lipid soluble and therefore able to penetrate the blood brain barrier). Each of these studies has failed to provide a conclusive answer to whether or not adjuvant chemotherapy is beneficial or not in patients with high-grade gliomas because of small numbers. It is therefore timely that this meta-analysis has provided evidence that adjuvant chemotherapy provides a small but significant improvement in survival. With data from 12 randomised trials and 3004 patients a 15% relative decrease in the risk of death with adjuvant chemotherapy was calculated. This translates to an increase in survival at 1 year of 6% and a median survival time increase of two months. Subgroup analysis demonstrated no effect on the benefit by histology type, age or sex of patient, resection extent and performance status. Despite beneficial primary outcome measures as mentioned above, data on the quality of life during this extended survival time is essentially absent but the authors comment that nitrosoureas are easily administered and fairly well tolerated. None the less the two most important aspects of this meta-analysis are that high-grade gliomas are chemosensitive and that more work on novel agents should be a matter of priority if any further survival improvements are to be expected. ***-TH***

Glioma Meta-analysis Trialists (GMT) Group.
Chemotherapy In Adult High-Grade Glioma: A Systematic Review And Meta-Analysis Of Individual Patient Data From 12 Randomised Trials.
LANCET
2002: 359:1011-18

MULTIPLE SCLEROSIS

★★★ RECOMMENDED

Failure of remyelination in MS - Inhibition of oligodendrocytes not lack of oligodendrocytes

Understanding why remyelination fails in some MS lesions will allow development of therapeutic strategies to undo the damage inflicted on the nervous system by this disease. If the failure of remyelination is as a result of no infiltrating oligodendrocytes, transplanting oligodendrocytes could be considered a rational therapeutic procedure. It goes without saying then that if the converse is true and oligodendrocytes are present but fail to remyelinate because of a prevailing inhibitory microenvironment then manipulation of this inhibitory environment to create a more permissive environment would be a better treatment option. By being able to define oligodendrocyte precursors, premyelinating oligodendrocytes and mature oligodendrocytes in chronic MS lesions from autopsies, Trapp's group has addressed this question. It is clear that chronic lesions (less than 15 years old) have numerous premyelinating oligodendrocytes, which are associated with axons but fail to remyelinate. This allows the authors to suggest that the machinery for remyelination is in place but there is some as yet undefined inhibition of the remyelination process. However if the lesions are older than 15 years they lose the ability to maintain or produce oligodendrocytes, as there is evidence that these oligodendrocyte precursors undergo apoptosis. It would appear therefore, that there is a window of opportunity for therapeutic intervention before a lesion is 15 years old. ***-TH***

Chang, A, Tourtelotte, W.W, Rudick, R, and Trapp, B.
Premyelinating Oligodendrocytes In Chronic Lesions Of Multiple Sclerosis.
NEW ENGLAND JOURNAL OF MEDICINE
2002: 346:165-73

★★★ RECOMMENDED

Longitudinal correlation between MRI abnormality and disability from MS

Using the well-studied group of patients from the Queen Square cohort who fifteen years ago presented with isolated syndromes suggestive of MS who underwent MRI, Brex and co-workers have studied the progression of the lesions and determined their predictive value. In this group of patients (n=71) 88% of those with abnormal MRI scans developed MS whilst only 19% of those with a normal scan developed MS.

In the earlier years the lesion load (number and extent of lesions) correlated with prognosis and this correlation continues at 14 years.

The 14 year EDSS score correlated moderately with MRI lesion volume at 5 years (r=0.6) and also the increase in lesion volume over the first 5 years (r=0.61). Although there is correlation between early MRI abnormalities and the disability this correlation is modest and the authors suggest early MRI lesion load could provide guidance but should be used with caution in individual decisions pertaining to disease modifying agents. ***-TH***

Brex, P,A, Ciccarelli, O, O'Riordan, J, I, Sailer, M, Thompson, A,J, and Miller, D,H.
A Longitudinal Study Of Abnormalities On MRI And Disabilty From Multiple Sclerosis.
NEW ENGLAND JOURNAL OF MEDICINE
2002: 346:158-64

Antibiotics for multiple sclerosis?

Already a patient with multiple sclerosis (MS) has asked me to prescribe antibiotics for her condition, flourishing a cutting from the *Daily Mail* provoked by this paper.

Rats with experimental allergic encephalomyelitis (EAE), an animal model of MS induced by immunisation with myelin-oligodendrocyte glycoprotein (MOG), were treated with minocycline, a second generation tetracycline. In addition to its antibiotic action, minocycline has anti-inflammatory properties, including inhibition of: microglial activation; synthesis of matrix metalloproteinases (MMP), inducible nitric oxide synthetase, and tumour necrosis factor-_ (TNF-α); and mRNA upregulation of caspases 1 and 3, thought to be involved in apoptosis. It has been reported to slow progression in a transgenic animal model of Huntington's disease (*Nature Medicine* 2000; 6: 797-801).

Rats with MOG-induced EAE treated with minocycline showed reduced disease severity and disease progression compared to sham-treated controls. Histological comparisons showed an absence of T-cell infiltration, reduced MMP expression and no microglial activation in the treated animals. Increased interleukin-10 and reduced IFN-g indicated deviation of the anti-MOG T-cell immune response away from Th1 phenotype (disease-associated) towards the Th2 (immunosuppressive) phenotype. However there was also a rise in TNF-α secretion by T cells, which would tend to promote EAE.

Clearly it is not possible to extrapolate from EAE to MS, but certainly these data suggest that a trial of minocycline in the latter would not be unreasonable. Minocycline is a safe drug, which has been used for extended periods in other conditions (rheumatoid arthritis, acne). Moreover, it is considerably cheaper than some of the drugs currently used in MS. However, its immune effects might have clinical consequences, perhaps leading to the emergence of other autoimmune disorders (as seen with CAMPATH-1H treatment).***-AJL***

Popovic N, Schubart A, Goetz BD, Zhang S-C, Linington C, Duncan ID.
Inhibition of autoimmune encephalomyelitis by a tetracycline.
ANNALS OF NEUROLOGY
2002: 51(2): 215-223

Immunomodulatory effects of Glatiramer Acetate

Glatiramer Acetate (GA) is a random copolymer consisting of glutamic acid, lysine, alanine and tyrosine. It was originally developed, over 30 years ago, to mimic encephalogenic components of myelin basic protein for the induction of experimental autoimmune encephalomyelitis (EAE) in mice – an animal model of multiple sclerosis (MS). However, unexpectedly it inhibited the development of EAE, which resulted in GA being developed as a potential disease-modifying drug in the treatment of MS. Human trials later demonstrated a significant reduction in the relapse frequency when patients with relapsing-remitting multiple sclerosis are treated with GA. However, to date nobody has been able to explain these effects.

In investigating the mechanism of action of GA within both animal models and human trials, an antigen specific Th2 T cell proliferative response to GA has been identified. It was postulated that this might result in bystander suppression of aggressive Th1 cells that recognise 'self' antigens.

However, until now no group had satisfactorily assessed the effect of GA on the CD8+ T cell population, which requires direct immunophenotypic characterisation, due to their relatively low numbers. Karandikar *et al* took on this challenge. They used a combination of flow cytometry to assess the proliferation of T cells and the molecular characterisation of flow sorted T cells subtypes.

They demonstrated that untreated patients with relapsing remitting MS, when compared with healthy controls, have a deficient CD8+ T cell response when their lymphocytes were exposed to GA in vitro. Following the commencement of treatment with GA there is an up regulation of the CD8+ proliferation response, and only a brief statistically insignificant rise in the CD4+ cells. They confirmed that both the CD4+ and the CD8+ cell responses are HLA dependent. The functional profile of the CD8+ cells that were promoted by GA was inconclusive, although suggestive of a regulatory/suppressive nature with increased production of TGFb. However both cell types produced TNFa that may be pro or anti inflammatory in different systems.

This paper therefore raises the possibility that the disease modifying effect of GA may be at least in part via its effects on promoting GA specific CD8+ cell proliferation. As several investigators have identified defective suppressive function in the CD8+ cell population in MS, the group postulate that up regulation of this cell population may explain the effects of GA, and reflect an important target for future disease modifying drugs. The group also raise the possibility of using CD8+ T cell monitoring as a marker for monitoring GA therapy. ***-ALC***

Nitin J. Karandikar *et al.*
Glatiramer Acetate (Copaxone) therapy induces CD8+ T cell responses in patients with multiple sclerosis.
THE JOURNAL OF CLINICAL INVESTIGATION
2002: 109(641-649)

Complimentary Journals Reviewed

We would like to thank the following publishers who have provided us with complimentary review subscriptions to their journals. For subscription details please contact the relevant publisher direct.

Cerebrovascular Diseases, Neuroepidemiology
S. Karger AG - Medical and Scientific Publishers,Allschwilerstrasse 10, CH - 4009 Basel, SWITZERLAND.
Tel. 0041 61 306 11 11, Fax. 0041 61 306 12 34, E-Mail. t.nold@karger.ch www.karger.com

Cerebral Cortex
Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP. Tel. 01865 267154, Fax. 01865 267985.

Clinical Rehabilitation, Multiple Sclerosis
Arnold, 338 Euston Road, London NW1 3BH. Tel. 020 7873 6339, Fax. 020 7873 6325,
E-Mail.arnoldjournals@hodder.co.uk,www.arnoldpublishers.com/journals

Current Opinion in Neurology
Lippincott Williams & Wilkins, 241 Borough High Street, London, SE1 1GB. Tel 0207 940 7564, Fax 0207 940 7530
Email. rmclachl@lww.co.uk, www.Lww.co.uk

Epilepsia
Blackwell Publishing, Commerce Place, 350 Main Street, Malden, MA 02148-5018, USA. Tel. 888 661 5800, Fax. 781 388 8270,
www.blackwellscience.com/epi

FREE RESOURCE

Patients with emergency brain disorders denied specialist care

The majority of patients admitted to hospital as an emergency with brain-related disorders will never be seen by a neurologist. It is a matter of luck and where you live. A report, *Acute Neurological Emergencies in Adults*, published by the Association of British Neurologists (ABN) describes the alarming inequality and lack of specialist treatment throughout the UK because there are simply not enough neurologists to provide adequate care.

Professor Charles Warlow, from Western General Hospital in Edinburgh and President of the ABN said at the launch of the report, "We believe that all hospitals should have a neurological service around the clock to give prompt and accurate diagnosis and treatment to all patients who are admitted with acute neurological illnesses. This is routinely achieved in other European countries. The numbers of neurologists around this country vary significantly, showing there is great disparity in the level of care patients may receive." The ABN is calling on the Government and health authorities to increase the number of neurologists from 350 to 1400 over the next ten years in order to establish a comprehensive UK service. Currently there is just one neurologist for every 177,000 people in the population, which is dramatically worse than all other European countries where these data are available. "We need at least 600 neurologists just to cope with outpatients alone between the hours of nine to five," said Professor Warlow.

Professor Warlow concluded, "Our goals for the next 10 years are ambitious but entirely necessary. The Government must recognise the crisis we and our patients are in."

Acute Neurological Emergencies in Adults is available from the Association of British Neurologists free of charge. Tel. 020 7405 4060, Fax. 020 405 4070, E-Mail. abn@theabn.org

Long-term benefits of Exelon in Alzheimer's disease

Exelon® (rivastigmine) provides sustained benefits for people with Alzheimer's disease for at least two years, according to a large multicentre data analysis presented at the Seventh International Geneva/Springfield Symposium on Advances in Alzheimer's Therapy.

The report included data from the longest studies conducted to date on Exelon, involving over 2,000 patients, and showed the drug slowed cognitive decline compared to placebo or no treatment for up to two years. Exelon is currently approved for treatment of mild to moderate Alzheimer's disease.

"These are important results because they are the first to confirm the benefits of Exelon over such a long period of time and in a large number of patients," said George Grossberg, MD, lead author of the report and Director of Geriatric Psychiatry at Saint Louis University School of Medicine in St. Louis, Missouri, USA. "The finding of a sustained benefit is good news for individuals with Alzheimer's disease and for the physicians and family members who care for them," he said.

For further information contact Novartis Pharmaceuticals UK Ltd, Tel. 01276 692255, Fax. 01276 698427.

Routine testing for anti-ß-interferon binding antibodies in multiple sclerosis?

Patients with relapsing-remitting multiple sclerosis treated with recombinant ß-interferon (IFNß) often exhibit an immune response, with detectable levels of interferon-binding antibodies (Bab) in the peripheral blood. Some of these are neutralising antibodies (NAb) with the capacity to reduce or eliminate the biological activity of the cytokine; for example its' antiviral properties.

The recent PRISMS-4 study[1] showed that efficacy of IFN-ß-1a was reduced in the third and fourth years of treatment in those patients who were NAb-positive. The authors concluded that there were considerable implications for IFNß therapy because the development of NAb may influence treatment decisions, particularly where there is a poor clinical response.

This evidence indicates that regular measurement of NAb levels should now be considered for adoption as a routine procedure to support the clinical assessment of patients receiving IFNß.

The tests used to determine the levels of NAb are complicated bioassays (CPE, MxA etc.), which are not practical for routine application and not widely available. However, since NAb generally do not occur in BAb-negative patients, measurement of BAb levels using a simple immunoassay provides a means of excluding the majority of patients from a further test for NAb[2]. BAb-positive patients, especially those who appear not to be responding well to therapy, may be further investigated for the presence of NAb or for other immunomodulatory markers in order to support any decision either to maintain or modify therapy.

The anti-IFNß- BAb EIA, developed by Bühlmann Laboratories in Switzerland, is a simple enzyme immunoassay kit for the detection of BAb in serum. The test is relatively inexpensive, rapid, easy to perform and uses technology standard in most routine clinical immunology laboratories.

For more information contact Diagenics Ltd on Tel. 01908 376376, Fax. 01908 376375.

1) The PRISMS (prevention of Relapses and Disability byInterferon-ß-1a subcutaneously in Multiple Sclerosis) Study Group; and the University of British Columbia MS/MRI Analysis Group. Neurology 2001; 56 (2 of2):1628-1636.
2) Pachner A R. Neurology 1997, 49: 647-650.

EMG-3 Monitor

If you are involved in Botulinum Toxin injection procedures that require EMG monitoring, then EMG-3 is a cost-effective solution.

EMG-3 is the latest in an established line of portable EMG monitoring equipment and includes a number of improvements on earlier versions, whilst maintaining their essential functionality.

EMG-3's features include: Single-touch function control buttons; Full microprocessor control over all functions; Convenient electrode/skin impedance measurement, giving complete confidence that the reference & ground electrodes are properly connected to the patient; Large area graphic LCD showing highly visible signal bargraph, audio volume setting, display sensitivity, mode selection and battery status; and intelligent volume and sensitivity controls that remember their settings from the previous power-down.

All in all, EMG-3 gives greater control over BT clinic organisation & procedures.

For more details contact The Department of Clinical Engineering, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP UK. Tel: 0151 706 4202, Fax: 0151 706 5803, E-Mail: das@liv.ac.uk

Pediatric Rehabilitation

Pediatric Rehabilitation is a developing speciality in healthcare. The journal, *Pediatric Rehabilitation*, in its new format, promotes greater understanding, research and service development in a wide range of physical and psychological disorders in childhood.

Pediatric Rehabilitation encompasses current practices, new developments, theoretical and historical antecedents in research and service delivery together with ethical and legal perspectives.

The journal welcomes empirical papers, subject reviews and commentaries, single case studies and preliminary reports in animal and human studies.

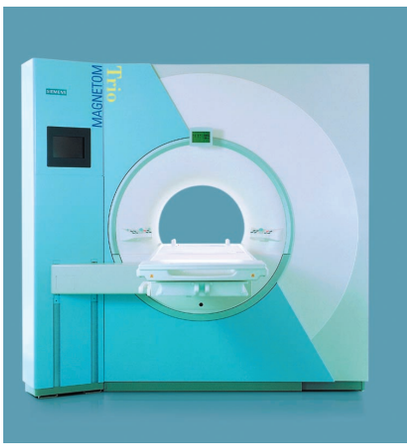
For more details Tel. 020 7842 2282, Fax. 020 7842 2131, or visit www.tandf.co.uk/journals/titles/13638491.html

Successful PD symposium in Oxford

Amersham Health hosted an extremely successful symposium at the ABN in Oxford, attended by over 100 delegates. The symposium, 'Developments in Parkinson's; Imaging and Autopsy studies' featured speakers Professor Andrew Lees, who discussed clinical diagnostic accuracy based on pathological studies, and Professor David Brooks, who looked at neuroimaging of PD. David Burn spoke on the topic of 'Imaging at the Interface of PD and dementia'. The symposium was followed by a dinner at Exeter College, Oxford.

For more information contact Zillah Moore on 01494 798697.

First 3 Tesla whole body systems installed



The Magnetom Trio 3 Tesla magnetic resonance imaging system

The first installations of Magnetom Trio, Siemens 3T whole body system, are demonstrating the benefits of a new concept in Ultra-High Field design, patient friendly systems which provide real patient and clinical benefits on the ideal research platform.

Siemens has, to date, 2 Magnetom Trio systems operational in Europe and 1 in the USA. All systems are providing additional clinical information.

There has also been a tremendous interest in 3 Tesla systems within the UK with a significant number of research sites aspiring to purchase systems this year. These sites will spearhead research to evaluate how the benefits of twice the signal-to-noise translate into clinical performance. Expectations are that neuro imaging including diffusion and spectroscopy, cardiac and very high resolution orthopaedic imaging will all benefit.

New MR Service for Basildon

The new Siemens Magnetom Symphony 1.5 Tesla MR was opened recently at Basildon Hospital.

"The addition of MRI to the services offered by the Imaging Department has been of enormous benefit to our patients," said Tina Faulkner, Imaging Manager at the Hospital. "Previously we had access to a shared service, which was restrictive in scanning time and involved significant travelling for patients. This was inconvenient for out-patients and of real concern when transferring sick inpatients. This new facility occupies a purpose-designed area, which is patient and staff friendly."

(L to R) Tina Faulkner, Imaging Manager, Chris Quinn, Senior/Lead Radiographer MRI, Lesley Hearn (seated), Senior/Lead Radiographer MRI, Dr Pam Cory, Consultant Radiologist and Graham Walker, Siemens Medical Solutions Sales Manager.

The service was fortunate to acquire the skills of experienced MR radiographers, to establish and lead the service and a significant reduction in waiting times has already been achieved.

The Siemens Magnetom Symphony 1.5T MRI features its unique Integrated Panoramic Array coil design, which speeds both set-up times and patient throughput. The system also speaks Syngo™, Siemens common hardware and software platform for all imaging modalities, enabling users to work with all their equipment with the minimum of additional training.

For further information contact Mike Bell at Siemens, Tel. 01344 396317.

FREE RESOURCE

Celance (Pergolide) 30 Day Starter Pack

The dopamine agonist Celance is well established in adjunctive use with levodopa in Parkinson's disease. In late 2000 the licence for Celance was extended to include monotherapy of Parkinson's disease.

This has created a need for a new starter pack to assist with dose titration, because it can sometimes appear complex to patients. Recognising this, Lilly have worked with packaging experts to develop a simple starter pack which takes patients from Day 1 to Day 30 of a course of monotherapy. On Day 1 the patient takes one 50 microgram tablet building to a dosage of six 250 microgram tablets by Day 30. This is achieved by use of thirteen wallets containing from one to four days therapy. The wallets allow an individual day's therapy to be removed from the pack whilst ensuring they are protected from damage.

As the new pack takes the patient to Day 30 of therapy the dosage of 1.5mg per day is closer to a maintenance dose than would be achieved with the earlier 14 Day Starter pack, designed for adjunctive therapy. Whilst this is clearly beneficial it remains important for the patient's dose of Celance to be adjusted following the initial 30 Day period to ensure an optimal response to therapy.

For more information, or an empty starter pack which can be used to show patients and carers how to initiate therapy, Tel. 01256 315999 and ask for Celance marketing.

The Association of Physiotherapists in Parkinson's disease: Europe (APPDE)

The APPDE is a new Association which was launched by Mrs Mary Baker, President of the European Parkinson's Disease Association, on 3rd October 2000 in Brussels.

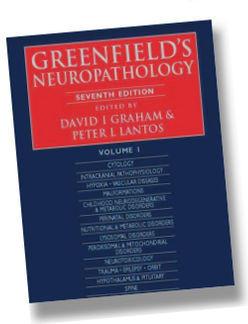
The aim of the association is to provide a forum where physiotherapy management and treatment of Parkinson's disease can be developed and disseminated throughout Europe. Membership comprises physiotherapists, medical and non-medical professionals and people with Parkinson's disease together with other organisations (voluntary, statutory and private), working in this field.

The APPDE will hold a conference "Physiotherapy treatment in the overall management of Parkinson's disease", on 26th October 2002 in Vienna. This conference is part of the programme of the European Federation of Neurological Societies (EFNS). The conference is organised by the APPDE and the European Federation of Neurological Associations (EFNA).

The APPDE are particularly keen to attract nurses to this conference, as they recognise the importance of the multidisciplinary team in the management of Parkinson's disease.

For further information contact Mariella Graziano, Tel. 352 26 53 15 51, Fax. 352 26 53 15 52, E-Mail. mariella.graziano@internet.lu

Greenfield's Neuropathology



The 7th edition of *Greenfield's Neuropathology* will be available from 1st June, greatly revised, containing new material and research, and accompanied by a CD ROM containing over 2,000 illustrations. *Greenfield's Neuropathology, 7th ed* and *Greenfield's Neuropathology Illustrated* are available separately or as a set. Order before June 1st and save up to £80.

For more information, visit www.arnold-publishers.com/greenfields, contact Arnold publishers on 020 7873 6355, or E-Mail. healthsci.marketing@hodder.co.uk

ReQuip slows progression of Parkinson's disease compared with L-dopa

A groundbreaking new study presented at the 54th Annual Meeting of the American Academy of Neurology showed that the dopamine agonist ReQuip® (ropinirole) significantly slows the progression of early Parkinson's disease compared to treatment with L-dopa. This 2 year, double-blind, multinational study used 3D PET to measure changes in ^{18}F-dopa uptake, a marker of dopamine function, in the putamen and substantia nigra. Central analysis of putamen ^{18}F-dopa uptake showed significantly slower disease progression with ReQuip (-13% ReQuip vs -20% L-dopa, p=0.022). Statistical parametric mapping detected significantly greater dopamine function in both the putamen and substantia nigra in the ReQuip group (putamen: -14% ReQuip vs -20% L-dopa, p=0.034; substantia nigra: +3% ReQuip vs -8% L-dopa, p=0.035). A significantly lower incidence of dyskinesias was also seen in patients taking ReQuip (3% ReQuip vs 27% L-dopa, p< 0.001). "These impressive results should certainly have an impact on the way we treat early Parkinson's disease in the future", commented Professor David Brooks, lead investigator and Hartnett Professor of Neurology, Hammersmith Hospital, London.

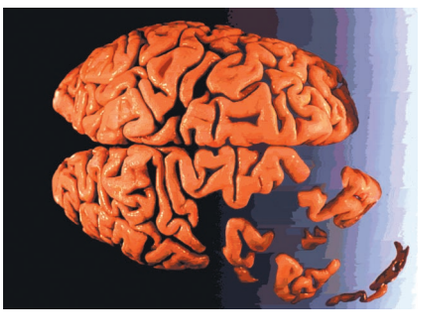
For further information contact Glaxo SmithKline on Tel. 020 8990 9000, Fax. 020 8990 2937.

Art and science meet HEAD ON

The Science Museum in London has unveiled **Head On**, a new exhibition based in the new gallery sponsored by the Wellcome Trust. **Head On** showcases artists' insights into the relationship between art and science and features sculpture, painting and other installations. Well-known works such as Mark Quinn's 'Self', a cast of his head filled with frozen blood, sit alongside specially commissioned collaborations between artists and high profile scientists.

Commissioned collaborations between artists and scientists include: Osi Audu and Professor Christopher Kennard, Imperial College School of Medicine, London; Andrew Carnie and Dr Richard Wingate, at the MRC centre for developmental neurology at King's College, and Professor Richard Frackowiak, Head of the Functional Imaging Laboratory at the Institute of Neurology, London; Annie Cattrell and the Royal Institution of Great Britain Director, Professor Susan Greenfield, and Dr Mark Lythgoe, Great Ormond Street Hospital; Katharine Dowson and Dr Piers Cornelissen, Newcastle University, and Dr Peter Hanson, Oxford University; Gerhard Lang and Professor Uta Frith, University College, London; Tim O'Riley and Professor Christopher Kennard, Imperial College's School of Medicine and Professor Chris Frith, the Institute of Neurology, UCL, and curators at the Science Museum.

For more information contact Matt Moore, The Science Museum, on 020 7942 4364, E-Mail. m.moore@nmsi.ac.uk



Our front cover picture, 'Superior aspect of a human brain falling to pieces' is taken from the exhibition, courtesy of Heidi Cartwright/Wellcome Photo Library.

Movicol for use in extended constipation

Norgine Ltd have been granted an extension to the Movicol product licence for maintenance use. Long-term use of laxatives may be required for many patients who suffer from chronic constipation as a result of a primary disease or as a side effect of drug treatments.

Movicol is licensed for maintenance use in: Patients with severe chronic or resistant constipation; patients whose constipation is secondary to neurological conditions such as Multiple Sclerosis or Parkinson's Disease; and constipation induced by regular constipating medicines (eg opioids or antimuscarinics).

For further information, please contact Norgine on 01895 826600 or E-Mail medinfo@norgnie.com

Use of cannabis in MS

The Multiple Sclerosis Trust (MS Trust) has welcomed the possibility of cannabis based medicines being available on prescription, but is cautious about the involvement of NICE.

Nicola Russell, Director of Services of the MS Trust said, "Many of the 85,000 people with MS in Britain suffer from symptoms such as muscle stiffness, spasms and pain. For many of these people, cannabis has provided significant relief from these and other symptoms, seemingly without side-effects. We are hopeful that this latest announcement has brought the possibility of licensed cannabis based medicines a step closer. We understand that NICE is to be asked to review the situation and we have some concerns that this may lead to a delay in these new medicines being made available to patients, as has been the case with beta interferons. Let us hope that the process can be streamlined and that we do not end up in the situation where yet another treatment is denied to people with MS."

For further information contact the MS Trust on Tel. 01462 476700.

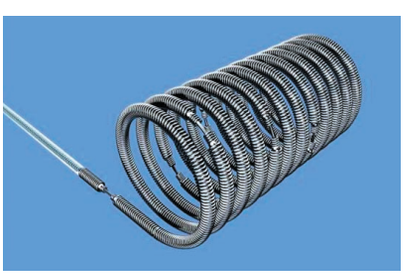
FREE RESOURCE

The new unique variable detachment coil from Dendron

Neurotechnics Ltd has announced the first UK insertion of the Dendron VDS coil at the Southern General Hospital Glasgow. The patient was treated by Dr J Bhattacharya and Dr E Teasdale. The VDS is the first variable detachment coil offered to the market and allows for the coil to be detached at various lengths, which allows the aneurysm to be packed as dense as necessary and alleviates the risk of a protruding coil in the parent artery.

Ian Graney, Neurotechnics Managing Director said, "This is a major step forward for the neuroradiology market, it now means that neuroradiologists can use less coils to treat the patient and will potentially have less wastage of difficult- to-position coils. We believe that this new product range will greatly support the neuroradiologist and help meet the financial challenges that hospitals face today."

For further information and a free product CD, contact Neurotechnics on Tel. 01844 260777, E-Mail. info@neuro-technics.com



Neuro-imaging data shows Parkinson's drug may slow progression of the disease

A new study presented at the AAN showed evidence that patients with Parkinson's disease may benefit if treated initially with Mirapexin™ (pramipexole) in the early stages of the disease rather than with levodopa. The findings support recently presented laboratory studies from the UK that also suggest that pramipexole may slow the loss of dopaminergic neurones in Parkinson's disease.

This study used SPECT (single photon emission computed tomography), an established imaging technology that measures functional changes in the brain. Investigators found that patients who started treatment with pramipexole demonstrated a significant reduction in the rate of loss of striatal β-CIT uptake as compared to patients initiating treatment with levodopa. β-CIT is a marker for dopamine neurone function. The difference between patients treated with pramipexole and patients treated levodopa was approximately 40% after 46 months.

Professor Anthony Schapira, Chairman of the University Department of Clinical Neurosciences, Royal Free and University College Medical School, London, led the laboratory studies to assess whether pramipexole may exert a modifying effect on Parkinson's disease progression. He said, "Protection in cell and animal models against a variety of toxins, including MPTP (and-erase) 6-hydroxydopamine and rotenone, confirms that this agonist has an in vitro and in vivo neuroprotective action. Evidence is now emerging that some of this effect might be mediated by direct action on mitochondrial membrane potential and the inhibition of apoptosis. This laboratory evidence is complementary to the SPECT data and provides a scientific rationale for a possible mechanism of action of pramipexole."

For further information contact Pharmacia on Tel. 01908 661101.

British Epilepsy Association launches Epilepsy Action

On May 1st Epilepsy Action was introduced as the working name for British Epilepsy Association. With a new logo and a striking new colour scheme, Epilepsy Action aims to raise the profile of this often forgotten condition.

Epilepsy is the UK's most common serious neurological condition affecting 450,000 people but there are still too many myths and misunderstandings surrounding it.

Epilepsy Action is the largest member led epilepsy organisation in the UK with 22,000 members. As well as campaigning to improve epilepsy services and raise awareness of the condition, the organisation also offers help and support through a national network of branches, accredited volunteers, regular regional conferences and a Freephone Epilepsy Helpline (0808 800 5050).

Epilepsy Action also provides a website www.epilepsy.org.uk, which is the most frequently visited epilepsy website in Europe.

epilepsy action

Controls seizures

Has no effect on shopping

Lamictal™
lamotrigine

Epilepsy treatment with women in mind

Lamictal (lamotrigine)

Brief Prescribing Information. Presentation: Pale yellow tablets containing 25mg, 50mg, 100mg and 200mg lamotrigine, and white dispersible/chewable tablets containing 2mg, 5mg, 25mg and 100mg lamotrigine.

Uses: *Monotherapy:* Not recommended in children under 12 years. Adults and children over 12 years for partial epilepsy with or without secondarily generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. *Add-on therapy:* Adults and children over 2 years for partial epilepsy with or without secondary generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. Seizures associated with Lennox-Gastaut syndrome.

Dosage and Administration: Initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash. *Monotherapy:* Initial dose is 25mg daily for two weeks, followed by 50mg daily for two weeks. Dose should be increased by a maximum of 50-100mg every 1-2 weeks until optimal response. Usual maintenance dose is 100-200mg/day in one dose, or two divided doses. *Add-on therapy: Adults and Children over 12 years:* To sodium valproate with or without ANY other antiepileptic drug (AED), initial dose 25mg every alternate day for two weeks, followed by 25mg/day for two weeks. Dose should be increased by 25-50mg every 1-2 weeks until optimal response. Usual maintenance dose 100 to 200mg/day in one dose, or two divided doses. To enzyme inducing AEDs with or without other AEDs (but NOT valproate), initial dose is 50mg daily for two weeks, followed by 100mg/day in two divided doses for two weeks. Dose should be increased by 100mg every 1-2 weeks until optimal response. Usual maintenance dose is 200 to 400mg/day given in two divided doses. *Children aged 2-12 years:* To be dosed on a mg/kg basis until the adult recommended titration dose is reached. Add-on to sodium valproate with or without ANY other AED, initial dose is 0.15mg/kg bodyweight/day given once a day for two weeks, followed by 0.3mg/kg/day given once a day for two weeks. Dose should then be increased by a maximum of 0.3mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 1 to 5mg/kg/day given in one dose, or two divided doses. Add-on to enzyme-inducing AEDs with or without other AEDs (but NOT valproate) is 0.6mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2mg/kg/day for two weeks given in two divided doses. Dose should then be increased by a maximum of 1.2mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 5-15mg/kg/day given in two divided doses. Weight of child should be monitored and dose adjusted as appropriate. If calculated dose is 1-2mg/day then 2mg may be taken on alternate days for the first two weeks. *Dose Escalation:* Starter packs covering the first four weeks treatment are available for adults and children over 12 years. When the pharmacokinetic interaction of any AED with Lamictal is unknown the dose escalation for Lamictal and concurrent sodium valproate should be used. *Elderly patients:* No dose adjustment required.

Contra-indications: Hypersensitivity to lamotrigine.

Precautions: Adverse skin reactions, mostly mild and self-limiting, may occur generally during the first 8 weeks of treatment. Rarely, serious, potentially life threatening rashes including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Patients should be promptly evaluated and Lamictal withdrawn unless the rash is clearly not drug related. High initial dose, exceeding the recommended dose escalation rate, and concomitant use of sodium valproate have been associated with an increased risk of rash. Patients who acutely develop symptoms suggestive of hypersensitivity such as rash, fever, lymphadenopathy, facial oedema, blood and liver abnormalities, flu-like symptoms, drowsiness or worsening seizure control, should be evaluated immediately and Lamictal discontinued if an alternative aetiology cannot be established. *Hepatic impairment:* Dose reductions recommended. *Withdrawal:* Avoid abrupt withdrawal, except for safety reasons. *Pregnancy:* **Lamictal was not carcinogenic, mutagenic, teratogenic or shown to impair fertility in animal studies. There are insufficient data available on the use of Lamictal in human pregnancy to evaluate its safety. Lamictal should not be used during pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risk to the developing foetus.** *Driving:* As with all AEDs, the individual response should be considered.

Interactions: Antiepileptic drugs which alter certain metabolising enzymes in the liver affect the pharmacokinetics of Lamictal (see Dosage and Administration). This is also important during AED withdrawal.

Side and Adverse Effects: With monotherapy: headache, tiredness, rash, nausea, dizziness, drowsiness, and insomnia. Other adverse experiences have included diplopia, blurred vision, conjunctivitis, GI disturbances, irritability/aggression, agitation, confusion, hallucinations and haematological abnormalities. Also movement disorders such as tics, unsteadiness, ataxia, nystagmus and tremor. Severe skin reactions including SJS and TEN have occurred rarely, with or without signs of hypersensitivity syndrome. Elevations of liver function tests and rare reports of hepatic dysfunction.

Legal category: POM.

Basic NHS costs: £16.45 for Monotherapy Starter Pack of 42 x 25mg tablets (PL0003/0272); £27.98 for Non-Valproate Starter Pack of 42 x 50mg tablets (PL0003/0273); £8.23 for Valproate Starter Pack of 21 x 25mg tablets (PL0003/0272). £64.37 for pack of 56 x 100mg tablets (PL0003/0274); £109.42 for pack of 56 x 200mg tablets (PL0003/0297). £21.95 for pack of 56 x 25mg tablets (PL0003/0272). £37.31 for pack of 56 x 50mg tablets (PL0003/0273). £8.75 for pack of 28 x 5mg dispersible tablets (PL0003/0346). £21.95 for pack of 56 x 25mg dispersible tablets (PL0003/0347). £64.37 for pack of 56 x 100mg dispersible tablets (PL0003/0348). £9.37 for pack of 30 x 2mg dispersible tablets (PL0003/0375).

Product Licence Holder: The Wellcome Foundation Ltd, Middlesex UB6 0NN. Lamictal is a Trade mark of the GlaxoSmithKline Group of Companies.

Further information is available from **GlaxoSmithKline UK Limited**, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

Note: If changes in AED medication are to be made they should be completed before conception.* The UK Pregnancy Register (0800 389 1248) is collecting prospective data on the effects of all AEDs in pregnancy. Please phone for information or to register a patient.

customercontactuk@gsk.com
Customer Services Freephone 0800 221441

*Crawford P *et al*. Seizure 1999; **8**: 201-217.

LAM/FPA/02/692 - MWL February 2002