

ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



INSIDE > Hard times demand that prescribers should seek economic options
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Anthony J Strong

Spreading Depolarisations: Tsunamis in the Injured Brain

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Azilect[®] 1mg tablets Prescribing information (Please refer to the Summary of Product Characteristics (SmPC) before prescribing) **Presentation:** Tablets containing 1mg rasagiline (as the mesilate). **Indication:** Treatment of idiopathic Parkinson's disease as monotherapy or as adjunct to levodopa in patients with end of dose fluctuations. **Dosage and administration:** Oral, 1mg once daily taken with or without food. **Elderly:** No change in dosage required. **Children and adolescents (<18 years):** Not recommended. **Patients with renal impairment:** No change in dosage required. **Patients with hepatic impairment:** Predominant hepatic metabolism. Do not use in patients with severe impairment. Avoid use in patients with moderate impairment. Use with caution in patients with mild impairment and stop if progresses to moderate. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Do not use in patients with severe hepatic insufficiency. Co-administration of other monoamine oxidase (MAO) inhibitors is contraindicated due to risk of hypertensive crises. Concomitant pethidine treatment is contraindicated. Allow at least 14 days off rasagiline before using other MAO inhibitors or pethidine. **Special warnings and precautions:** Administer antidepressants with caution as serious adverse reactions have been reported with concomitant use of selective serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants, MAO inhibitors and a selective MAO-B inhibitor. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use

in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. **Undesirable effects in clinical trials: Monotherapy:** >1%: headache, flu syndrome, malaise, neck pain, dyspepsia, arthralgia, depression, conjunctivitis, allergic reaction, fever, angina pectoris, anorexia, leucopenia, arthritis, vertigo, rhinitis, contact dermatitis, vesiculobullous rash, skin carcinoma, hallucinations, urinary urgency. <1%: cerebrovascular accident, myocardial infarct. **Adjunct therapy:** >1%: abdominal pain, accidental injury, postural hypotension, constipation, vomiting, weight loss, dyskinesia, neck pain, anorexia, dry mouth, arthralgia, tenosynovitis, dystonia, abnormal dreams, ataxia, rash, hallucinations. <1%: angina pectoris, cerebrovascular accident, skin melanoma, confusion. Please refer to the SmPC for a full list of adverse events. **Basic NHS Price:** Azilect[®] (tablets) 1mg x 28 £70.72 **Legal category:** POM **Marketing Authorisation Number:** 1mg tablets (28 pack size) EU/1/04/304/003 **Marketing Authorisation Holder:** Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany **Date last revised:** May 2008 **Further information available from:** Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

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



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Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

Two neurologists join the board of UK Migraine Charity

Two neurologists have joined the board of The Migraine Trust, the UK's health and medical research charity for migraine.

Dr Brendan Davies, Consultant Neurologist and Director of the North Midlands Headache Clinic, University Hospital of North Staffordshire, Stoke-on-Trent, and Dr Mark Weatherall, Consultant Neurologist, Princess Margaret Migraine Clinic, Charing Cross Hospital, London, have been appointed trustees.

They join eminent neurologist Professor Peter Goadsby, from the Institute of Neurology, who is already on the board.

The Migraine Trust's Chief Executive, Wendy Thomas, said: "Migraine causes huge suffering to eight million people in the UK. Our highly skilled trustees will help us raise the profile of this debilitating condition and help us towards better treatment and prevention of migraine."

The Migraine Trust has donated more than £3 million to more than 130 research projects since it was founded in 1965.

Andrew Jordan, Chairman of The Migraine Trust, said: "It's very exciting to welcome these new trustees who will further enhance the work of this small but excellent charity. They clearly bring a lot of energy and expertise and we look forward to working closely with them to improve the lives of people affected by migraine."

Dr Davies will give an overview of headache and migraine at a training day on migraine for health professionals, on 23 April 2009 in Birmingham, hosted jointly by The Migraine Trust and the British Association for the Study of Headache.



Dr Brendan Davies



Dr Mark Weatherall



Professor Peter Goadsby

For more information contact: Kate Scurr on 0207 462 6606 or Frances Perrow on 07779 788018. www.migrainetrust.org

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 for more information about The Migraine Trust



Prestigious award for Professor Hugh Bostock

Congratulations to Professor Hugh Bostock who has been awarded the highly prestigious Grey Walter Medal by the British Society for Clinical Neurophysiology, in recognition of his distinguished contribution to Clinical Neurophysiology. He will also deliver the Grey Walter invited lecture at the scientific meeting of the Society in October 2009. The medal is seldom awarded, but, for example, was given to Mary Brazier the pioneering electroencephalographer.



Professor Hugh Bostock

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

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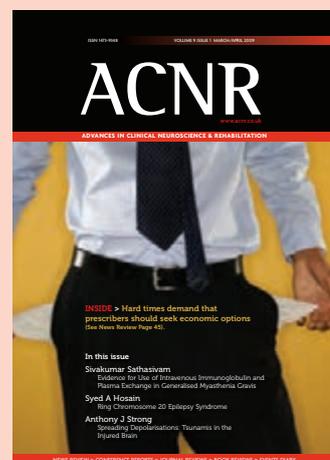
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Cover shows "Empty pockets" taken from the Beacon Pharmaceuticals news items on page 45.

ACNR's Neurology Digest

17th November, 2009, Royal Society of Medicine, London

ACNR is delighted to introduce "Neurology Digest", a new series of half day events run in partnership with Innervate Ltd, the secretariat to the Primary Care Neurology Society.

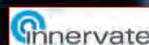
Each event will focus on recently published key papers in neuroscience, neurology and therapeutics including rehabilitation, 'digest' the content of the papers, and offer expert opinion on the implications for clinical practice.

The first event will focus on multiple sclerosis and movement disorders and will be led by Roger Barker and Alasdair Coles, co-editors of ACNR.

Cost: £95 inc VAT.

For more information contact:

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Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient bases; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Caution should be exercised if prescribing apomorphine to pregnant women and women of childbearing age. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Breathing difficulties have been reported. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL04483/0064. APO-go Pens: PL04483/0065. APO-go Pre filled syringes: PL05928/0025. **Legal Category:** POM. **Date of last revision:** October 2008. For further information please contact: Britannia Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK.

References: 1. Pietz K, Hagell P, Odin P, 1998. Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up. *J Neurol Neurosurg Psychiatry*. 65:709-716. 2. Lees A, Turner K, 2002. Apomorphine for Parkinson's Disease. *Practical Neurology*, 2:280-287. 3. Deleu D, Hanssens Y, Northway M G, 2004. Subcutaneous Apomorphine: An Evidence-Based Review of its Use in Parkinson's Disease. *Drugs Aging*, 21(11):687-709. 4. Ellis C, Lemmens G et al 1997. Use of Apomorphine in Parkinsonian Patients with Neuropsychiatric Complications to Oral Treatment. *Parkinsonism & Related Disorders*, 3(2):103-107.

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Managing patients with myasthenia gravis who get acutely worse is often done with supportive treatment and intravenous immunoglobulin (IVIG). However, we are often told by some of our more senior colleagues that plasma exchange (PE) is better under such circumstances. The article by Sivakumar Sathasivam in this issue of ACNR reviews these two immune therapies in myasthenia and concludes that the two therapies appear equal in terms of their efficacy under such circumstances. Indeed he recommends that "As IVIG is easier to administer and associated with fewer adverse events than PE, and the efficacy of the two treatments are similar, the former is commonly preferred to the latter".



In the second of our Neuroradiology series, Justin Cross takes us through the principles of MRI. This extremely well illustrated review summarises the physics underlying this scanning modality before discussing its clinical applications and limitations. This, as with the other article in this series on CT by Justin (ACNR 8.5), is a very helpful guide to those involved with MRI at whatever level, and is especially useful if you and your neuroradiology colleagues are seeing different things on the same scan!

In the neurosurgical series, Andrew Strong reports on spreading depolarisation, a concept developed by Leao in the 1940s and perhaps most commonly thought of in the context of migraine. However, in his article (with exciting video links) he discusses the significance and relevance of this phenomena in the injured brain and a better understanding of it may have clinical implications for the management of patients with brain injuries in the future.

Nicholas Shenker and colleagues explore the mechanisms underlying abnormal pain states in the Complex Regional Pain Syndrome. This involves sensorimotor "incongruence and neuroplasticity" within frontoparietal cortical areas with a particular emphasis on the role of the anterior cingulate cortex in this process. Furthermore they discuss the different pathways that mediate aspects of nociception and pain and how this may be exploited in the treatment of this condition.

Sabahat Wasti in the first of a new series of Neurology from around the world discusses some of the observations he has made whilst serving the people of the United Arab Emirates (UAE). In his article, he presents "new ways of analysing the needs of patients requiring rehabilitation" and that "This analysis should lead to defining the cultural and social constructs of the communities patients originate from, and allow the treating teams to develop Culturally Adjusted Rehabilitation Models (CARM)". A stimulating personal account that raises many interesting questions on how and why we practice medicine, in the way that we do.

In the last issue of ACNR we discussed a common problem for refractory epilepsy, non-compliance. In this issue we discuss a very rare cause for it, namely the Ring 20 Chromosome [r(20)] epilepsy syndrome. This uncommon condition is presented in great depth by Dr Syed Hosain, and throws up many questions as to how this condition causes epilepsy and whether it may be more common than we suspect as it can only be diagnosed by chromosomal testing.

"Recent experiences of surgery for NLPE (Non-lesional Partial Epilepsy) suggests that undertaking an invasive presurgical evaluation in carefully selected patients is worthwhile and gives a reasonable chance of surgical success." So writes Dr Lee and colleagues in an article on the role for surgery in NLPE, and how this can be optimally developed using an array of clinical, imaging and neurophysiological approaches. They show that by carefully selecting the right patient and studying them with a range of state-of-the-art techniques, one can identify some epileptic individuals who will do very well with surgery.

Finally, in his commentary "Living well with Dementia: A National Dementia Strategy", Andrew Lerner discusses this new initiative and how well it will or will not be implemented in the years to come. He concludes that "Formulation of policy (top-down) is relatively easy, whereas implementation (bottom-up) is rather more difficult. Only time will tell whether this policy can be meaningfully delivered."

We also have our usual collection of reviews for you to enjoy, and we are always keen to have more help in this task – so if you are interested in becoming a reviewer for us then do let us know. ♦

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

Life with epilepsy can be much more than just a gap between seizures

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to lacosamide or to any of the excipients. Known second- or third-degree atrioventricular block. In addition for *tablets*, hypersensitivity to peanuts or soya. *Precautions:* Lacosamide has been associated with dizziness. Use with caution in patients with known conduction problems, severe cardiac disease or in elderly. Excipients in the *syrup* may cause allergic reactions (possibly delayed), should not be taken by those with fructose intolerance and may be harmful to patients with phenylketonuria. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. *Interactions:* Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. *Pregnancy and Lactation:* Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. *Driving etc.:* Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities. **Adverse Effects:** *Very common (≥10%):* Dizziness, headache, diplopia, nausea. *Common (between 1%-10%):* Depression, balance disorder, abnormal coordination, memory

impairment, cognitive disorder, somnolence, tremor, nystagmus, blurred vision, vertigo, vomiting, constipation, flatulence, pruritus, gait disturbance, asthenia, fatigue, fall, skin laceration. Adverse reactions associated with PR prolongation may occur. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** *Tablets:* None. *Syrup:* Do not store above 30°C. Use within 4 weeks of first opening. *Solution for infusion:* Do not store above 25°C. Use immediately. **Legal Category:** POM. **Product Licence Numbers:** 50 mg x 14 tabs: EU/1/08/470/001; 100 mg x 14 tabs: EU/1/08/470/004; 100 mg x 56 tabs: EU/1/08/470/005; 150 mg x 14 tabs: EU/1/08/470/007; 150 mg x 56 tabs: EU/1/08/470/008; 200 mg x 56 tabs: EU/1/08/470/011; Syrup (15 mg/ml) x 200 ml: EU/1/08/470/014; Solution for Infusion (10 mg/ml) x 20 ml: EU/1/08/470/016. **NHS Cost:** 50 mg x 14 tabs: £9.01; 100 mg x 14 tabs: £18.02; 100 mg x 56 tabs: £72.08; 150 mg x 14 tabs: £27.03; 150 mg x 56 tabs: £108.12; 200 mg x 56 tabs: £144.16; Syrup (15 mg/ml) x 200 ml: £38.61; Solution for Infusion (10 mg/ml) x 20 ml: £29.70. **Name and Address of PL Holder:** UCB Pharma S.A., Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformation@ucb-group.com. **Date of Revision:** January 2009 (08VPE0353) Vimpat is a registered trade name. **References:** 1. VIMPAT® Summary of Product Characteristics. 2. Beyreuther BK et al. *CNS Drug Rev* 2007; 13(1): 21-42. 3. UCB Data on file. **Date of preparation:** February 2009. 09VPE0029



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For further information please visit www.vimpat.co.uk

Evidence for Use of Intravenous Immunoglobulin and Plasma Exchange in Generalised Myasthenia Gravis



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is a Consultant Neurologist with an interest in Neuromuscular Disorders.

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In 1895, Friedrich Jolly described the electrophysiological feature of fading response of muscles to prolonged electrical stimulation, which is characteristic of the fatigue of myasthenia gravis (MG).¹ MG is an autoimmune disorder of neuromuscular junction transmission that causes fluctuating, painless muscle weakness. It most commonly presents with ocular weakness, manifesting as binocular diplopia and asymmetrical ptosis. In 15% of cases, it remains purely ocular; in the remaining 85% it becomes generalised, usually by descending to involve bulbar, neck, limb and, sometimes, respiratory muscles. Severe involvement of respiratory or bulbar muscles may lead to a myasthenic crisis, necessitating intubation and mechanical ventilation.

The impairment of neurotransmission in MG is usually caused by antibodies to postsynaptic nicotinic acetylcholine receptors (AChRs) which reduce the number of functional AChRs.² Around 15% of patients with generalised MG do not have detectable AChR antibodies.³ Sera from a fraction of these AChR antibody-negative patients contain antibodies to muscle-specific tyrosine kinase (MuSK), although the pathogenic role of the latter have not been established.⁴ Loss of tolerance to self-antigens appears to be important in MG.⁵ T cell tolerance to self-antigens is established in the thymus, and thymic abnormalities are common in MG – 65% of patients have thymic hyperplasia and 10% have thymomas.⁶ B cell and T cell activation are involved in the pathogenesis and immunoregulation of MG.^{7,8}

In the past 70 years, advances in treatment have reduced the mortality of MG from 70% between 1915 and 1934⁹ to less than 5% now.¹⁰ Furthermore, the prevalence of MG has risen from around five per million population between 1915 and 1934,⁹ to about 200 per million now,¹¹ although part of this is due to improved detection of AChR antibodies. Apart from improvements in pulmonary support and ventilation, most of the decrease in mortality has been due to the development of effective treatments based on the

understanding of the pathophysiology of MG.

This review will examine and summarise the evidence of the short-term immunomodulatory treatments intravenous immunoglobulin (IVIg) and plasma exchange (PE) in the treatment of generalised MG.

Intravenous immunoglobulin

The mode of action of intravenous immunoglobulin (IVIg) in MG is not completely understood, but key mechanisms include the neutralisation of activated complement, interference of signalling via Fc receptors, modulation of proinflammatory cytokines and suppression of idiotypic antibodies.^{12,13} IVIg was first used in MG in the mid 1980s.^{14,15}

IVIg showed an improvement of more than 70% in MG in two reviews, which collated results from previously published uncontrolled studies.^{16,17} In addition, two open studies of severe generalised MG with a total of 21 patients showed improvement with IVIg in all patients.^{18,19} IVIg has comparable effectiveness to PE in preoperative thymectomy preparation of patients with MG.^{20,21}

Five randomised controlled trials (RCTs) comparing IVIg with placebo or other treatments in MG have been carried out (Table 1).²² Two trials compared IVIg to placebo. In the first trial of 15 patients with mild to moderate generalised MG, no significant difference between the two groups was observed at six weeks.²³ In the second trial of 51 patients with acute exacerbation of generalised MG, IVIg resulted in significant improvement in muscle strength (measured by the Quantitative MG Score for Disease Severity [QMG score])²⁴ only in the group of patients with severe disease, with a mean difference in the QMG score on day 14 of -3.40 (95% confidence interval [CI] -5.74 to -1.06).²⁵ Two trials compared IVIg to PE. In the first with 87 patients with acute exacerbation of generalised MG, no significant change in muscle strength was observed between day 0 and day 15 between the two treatment groups. In addition, similar efficacy of IVIg was observed

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Adults and elderly: 5000U or 10000U divided between two to four affected muscles. 10000U may increase the clinical benefit. The dose and frequency of administration should be adjusted for each patient depending on the clinical response.

Patients with renal or hepatic impairment: No dose adjustment required. (see SPC)

Children and adolescents under 18 years: Not recommended

Contra-Indications: Hypersensitivity to Botulinum Toxin Type B or any excipient. Individuals with other neuromuscular diseases or neuromuscular junctional disorders.

Pregnancy: Do not use during pregnancy unless clearly necessary. Studies in animals are insufficient and potential risk in humans is unknown.

Lactation: Do not use during lactation unless clearly necessary as it is unknown whether Botulinum Toxin Type B is excreted in breast milk.

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Neuromuscular side effects due to toxin spread have been reported. Development of an immune response and subsequent tolerance can occur after repeated administration. Spontaneous reports of dysphagia, aspiration pneumonia and/or potentially fatal respiratory disease, after treatment with Botulinum Toxin Type A/B have been reported. There is an increased risk of side effects in patients with underlying neuromuscular disease and swallowing disorders. Close medical supervision is advised in patients with neuromuscular disorders or history of dysphagia and aspiration. Seeking medical attention for respiratory difficulties, choking or any new or worsening dysphagia is advised. Dysphagia has been reported following injection to sites other than the cervical musculature. Botulinum Toxin Type B contains human albumin and therefore the possibility of transmitting infectious agents cannot be totally excluded. Dosage units are specific to Botulinum Toxin Type B only and are not relevant to preparations of Botulinum Toxin Type A.

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Table 1: Major randomised controlled trials comparing different types of treatment in generalised myasthenia gravis

Trial	Patients	Intervention	Outcome
Wolfe GI 2002 ²³	15 with stable mild or moderate MG	IVIg v placebo	No significant difference
Zinman 2007 ²⁵	51 with acute exacerbation of MG	IVIg v placebo	Significant improvement in muscle strength in group with severe disease
Gajdos 1997 ²⁶	87 with acute exacerbation of MG	IVIg v PE	No significant difference
Rønager 2001 ²⁷	12 with stable moderate or severe MG	IVIg v PE	No significant difference
Cochrane group ²² (personal communication)	33 with acute exacerbation of MG	IVIg v oral methylprednisolone	No significant difference

IVIg = intravenous immunoglobulin, MG = myasthenia gravis, PE = plasma exchange

whether 1.2g/kg or 2g/kg of IVIG was used.²⁶ In the second trial which had a crossover design with 12 patients with moderate to severe generalised MG in a stable phase, no significant difference between the two groups was detected after 1 and 4 weeks of treatment.²⁷ The Cochrane group also reported that an unpublished RCT comparing IVIG to oral methylprednisolone, which was obtained through personal communication, in 33 patients with acute exacerbation of generalised MG did not show any significant difference between the two treatment arms.²² Finally, another RCT comparing two doses of IVIG in 173 patients with acute exacerbation of generalised MG did not show any significant difference in efficacy between 2g/kg and 1g/kg of IVIG.²⁸

The RCTs of IVIG in generalised MG only show limited evidence that it is effective (class I evidence).²² In acute exacerbation of generalised MG, only one RCT showed efficacy of IVIG over placebo.²⁵ In chronic generalised MG, there is insufficient evidence to determine whether IVIG is effective as the number of patients in each of the two trials was very small.^{28,27} No meta-analysis of the RCTs were possible due to major methodological differences between the trials.²² Common adverse events of IVIG include fever, headache, nausea, and allergic reaction. A severe anaphylactic reaction might occur in patients with IgA deficiency. Volume overload may occur in cardiomyopathy and solute-induced renal failure may occur in patients with pre-existing renal impairment.²⁸ Serious adverse events include thrombosis and stroke, which are associated

with high infusion rates.²⁹ However, adverse events from IVIG appeared less severe than those from PE.^{26,27}

Plasma exchange

Therapeutic PE is an extracorporeal blood purification technique designed to remove large molecular weight particles from plasma. Its mechanism of action is thought to involve the removal of circulating antibodies, immune complexes, cytokines, and other inflammatory mediators.³⁰ In MG, the concentration of AChR and MuSK antibodies have been shown to fall with PE.^{31,32} PE was first used in MG in the mid 1970s.³³

Several relatively large open studies of 20 or more patients each have demonstrated a beneficial effect from PE in MG. Most of the patients in these trials were already on other immunosuppressive / immunomodulatory therapy, or started on these therapies after PE. Of a total of 166 patients with generalised MG, 130 patients (78%) were reported to have improved with PE.^{34,38} Three fairly large retrospective studies totalling 84 patients with generalised MG reported improvement with PE in 81 patients (96%).^{39,41} Another retrospective study comparing PE with IVIG in myasthenic crisis showed that the ventilatory status at two weeks and the functional outcome after one month was better in the PE group.⁴² One non-randomised trial comparing different PE protocols in generalised MG did not reveal any significant difference in efficacy between the treatments.⁴³ Prethymectomy plasmapheresis improves outcome after thymectomy in MG.^{44,45}

One RCT of PE plus prednisolone versus prednisolone alone in 14 patients with generalised MG did not show any significant difference in muscle strength between the two treatment groups after one month.⁴⁶ Two RCTs comparing daily and alternate-day PE in generalised MG have not shown any difference in efficacy between the treatments.^{47,48}

The small number of patients in the RCT of PE in generalised MG makes it difficult to draw any definite conclusion on its effectiveness in generalised MG, despite the fact open or retrospective studies have been encouraging.⁴⁹ However, as mentioned above, a large trial has shown that it is as effective as IVIG in acute exacerbation of MG (class I evidence).²⁶ Most adverse events of PE are related to issues of vascular access such as thrombosis, infection, pneumothorax and, rarely, air embolism. Excessive fluid volume shifts can lead to hypotension or fluid overload and congestive cardiac failure. Citrate infused for anticoagulation may lead to disturbances in acid-base homeostasis and hypocalcaemia.³⁰

Conclusions

IVIg and PE are both used to achieve rapid (days to weeks), temporary improvement in generalised MG. Each treatment is useful as an interim measure while waiting for corticosteroids and other long-term immunosuppressants to take effect. As IVIG is easier to administer and associated with fewer adverse events than PE, and the efficacy of the two treatments are similar, the former is commonly preferred to the latter.⁵⁰ ♦

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daily every two weeks. The lowest effective dose should be used. (For full dosage recommendations see SPC.) **Patients with renal impairment:** Adjust dose according to creatinine clearance as advised in SPC. **Patients with hepatic impairment:** No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended, as the creatinine clearance may underestimate the renal insufficiency. **Contraindications, Warnings etc.:** **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Precautions:** If discontinuing treatment reduce dose gradually as advised in SPC. Due to its excipients, the oral solution may cause allergic reactions (possibly delayed). **Infusion:** Keppra concentrate contains 7.196 mg of sodium per vial. To be taken into consideration by patients on a controlled sodium diet. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc.:** Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Adverse Effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: **Very common** (≥10%): asthenia/fatigue, somnolence. **Common** (between 1%–10%): GI disturbances, anorexia, weight increase, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, balance disorder, disturbances in attention, memory impairment, emotional lability/mood swings,

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Ring Chromosome 20 Epilepsy Syndrome



Dr Syed A Hosain

Dr Syed Hosain is currently Clinical Professor in charge of the pediatric epilepsy and clinical neurophysiology program at the Bristol-Myers Squibb Children's Hospital – Robert Wood Johnson Medical School, USA. His clinical research interest includes study of patients with intractable childhood epilepsies with a particular focus on ring chromosome 20 epilepsy. He is also the principal medical advisor for the Ring Chromosome 20 Foundation and supervises its research mission and patient awareness programs.

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Ring chromosome 20 epilepsy syndrome [r(20)], has a striking association with seizures, whereas in other aberrations of chromosome 20 seizures are infrequent. This syndrome is characterised by medically intractable complex partial epilepsy, nocturnal subtle seizures, behavioural problems and mild mental impairment. Chromosomal abnormalities are rarely considered in patients with severe, young onset epilepsy with no dysmorphism or intellectual impairment, but this is the usual phenotype of ring chromosome 20. Chromosomal analysis, relatively simple and cheap, may save complex and unnecessary evaluation at a later stage. This syndrome is undoubtedly an under-diagnosed condition as chromosomal testing is not routine in epilepsy patients. Diagnosis is often delayed for many years after onset of seizures.

Borgaonkar and colleagues at Johns Hopkins University catalogued ring chromosome 20 syndrome as a genetic syndrome in 1976. Since then, over 60 cases of r(20) have been reported in the literature. To date there is still no published data on the incidence and prevalence of this syndrome. This disorder appears to be pan-ethnic and non-gender specific. Cases of this syndrome have been reported from many different parts of the world involving different ethnicities. Almost all cases reported are sporadic except a few with known family history. With more widespread cytogenetic chromosomal karyotyping in non-aetiological cases of epilepsy, more cases of r(20) will undoubtedly be recognised.¹

Phenotypic characteristics

Epileptology

Epilepsy is a constant feature of this syndrome and typically starts in early childhood and in many cases is intractable and drug resistant. Seizure onset has been reported between 1 and 17 years of age. Seizures are often complex partial in type and reported as episodes of altered consciousness with staring, oral automatisms, unspecified automatic behaviour, focal motor symptoms and/or head turning. Periods of intense fear and sometimes prolonged confused states lasting for several minutes to hours are described (non-convulsive status epilepticus). Subtle nocturnal behavioural changes such as stretching, rubbing and turning have been observed which resemble normal arousal behaviour. Generalised tonic-clonic seizures are rarely reported. In addition, subtle nocturnal seizures (SNS) and nocturnal frontal lobe seizures (SNFLS) are also reported. Seizures can be easily mistaken for non-epileptic events. Features of frontal lobe epilepsy are often recognised. Seizures are difficult to control with antiepileptic medications and if the diagnosis of

r(20) has not been made patients are subjected to epilepsy surgery workup and unnecessary investigations.^{2,3,4,5}

Cognition & Behaviour

Cognition is usually normal before the onset of epilepsy; however, there is the possibility of mental impairment if seizures are frequent and persistent. Individuals may have normal cognition despite periods of poorly controlled epilepsy and others may have profound learning disabilities and require help with all aspects of daily life. Behavioural problems can vary from minor concentration and attention difficulties with high levels of activity to profound problems. Several of the children reported in the medical literature have been described to have periods of very difficult behaviour, often associated with poor seizure control. The behaviour and cognitive difficulties do vary with time and may worsen with increasing seizures. However, the child may regain these lost skills with improved seizure control.⁶

Physical Features

Abnormal physical features are often lacking. Major and minor malformations including facial dysmorphism are subtle or absent. This lack of dysmorphic features and often omission of chromosomal testing in patients with refractory epilepsy leads to delayed diagnosis. Rare cases of r(20) syndrome with dysmorphic features published in the literature consist of microcephaly, plagiocephaly, dental malocclusions, micrognathia, cauliflower-shaped ears, and coarse facial features with slanting eyelids (obliquely downward and outward).⁷ Occasional renal and cardiac abnormalities are also reported in the syndrome.

Neurophysiology

Electroencephalography (EEG)

No characteristic electroencephalographic (EEG) features distinguish r(20) syndrome from other refractory epilepsies, therefore diagnosis alone cannot be suspected by EEG. A wide spectrum of EEG abnormalities has been described. Interictal EEG (Figure 1) may be normal to mildly slow, and in some cases bifrontal spikes and sharp waves may be seen. Burst of sharply contoured theta activity has also been described. Interictal patterns are often more pronounced in sleep and may share similarities with other epileptic encephalopathies such as Lennox-Gastaut syndrome (LGS) and Landau-Kieffner syndrome (LKS).

Ictal EEGs (Figure 2) may show prolonged runs of diffuse slowing with frontal dominance intermixed with bifrontal sharp wave discharges. Ictal



Figure 1: Interictal EEG showing rhythmic sharp theta burst.



Figure 2: Ictal EEG showing predominant bifrontal slowing and sharp wave discharges.

r(20) karyotype

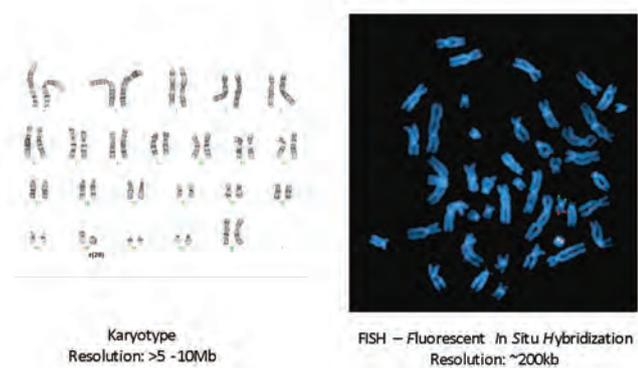


Figure 3: Diagnosis of r(20) syndrome.

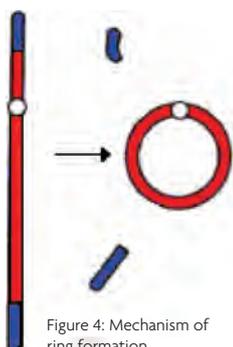


Figure 4: Mechanism of ring formation.

Early chromosomal testing to look for ring 20 mosaicism may avoid misdiagnosis

patterns often raise the possibility of a frontal lobe focus. In patients with non-convulsive status epilepticus the above described patterns may be combined with large portions of normal appearing EEG activity.^{8,9}

Magnetoencephalography

Ictal magnetoencephalography (MEG) has been performed on one patient with r(20) syndrome. MEG and EEG were simultaneously recorded and the equivalent current dipoles (ECD) of ictal discharges on MEG were localised to the medial frontal lobe. The authors suggested that the mechanism of underlying epilepsy in r(20) syndrome may be similar to medial frontal lobe epilepsy.¹⁰

Neuroimaging

A wide spectrum of structural and functional neuroimaging studies has been performed in patients with r(20) syndrome. In the majority of the patients structural abnormalities are not seen. In a few patients minor structural abnormalities have been reported. A recent [18F] fluoro-L-DOPA PET study in patients with r(20) showed decreased uptake in the basal ganglia bilaterally. The authors discussed the possible role of subcortical structural abnormalities in epileptic mechanisms.¹¹

Differential diagnosis

Both clinical and electroencephalographic findings in patients with r(20) syndrome can be confused with other refractory epilepsy syndromes. This syndrome can be misdiagnosed as Lennox-Gastaut syndrome (LGS) which is characterised by medically refractory mixed intractable seizures. Tonic and atonic seizures characteristic of LGS are rarely seen in r(20) syndrome. Non-aetiological frontal lobe epilepsy is another frequent consideration and has phenotypic and EEG similarities with r(20) syndrome. Identifying r(20) syndrome in patients suspected of intractable frontal lobe epilepsy is critical to avoid unnecessary investigations and treatments. Unlike r(20) syndrome, the seizures in autosomal dominant nocturnal frontal lobe epilepsy (ADNFE) are predominantly nocturnal and rarely refractory. The nocturnal EEG pattern in r(20) may also have overlapping features of continuous spike and wave discharges in slow wave sleep (CSWS) and electrical status epilepticus in sleep (ESES). Early chromosomal testing to look for ring 20 mosaicism may avoid misdiagnosis.¹²

Diagnosis and genetics

Diagnosis of ring chromosome 20 syndrome can be made by recognition of certain characteristic clinical features, however definitive diagnosis requires chromosomal testing. This is most easily done by looking at the chromosome pattern (karyotype) in blood cells but any other tissue including skin could be examined (Figure 3).

At least 50-100 cells should be cytogenetically analysed to diagnose mosaic ring 20. Analyses of fewer than 50 cells may not reveal ring mosaicism. Cytogenetic testing is most easily done by looking at the chromosome pattern (karyotype) in blood cells but any other tissue including skin could be examined. Since chromosomal analysis is not a routine investigation when epilepsy first presents, the diagnosis of r(20) syndrome may be delayed or go unrecognised. Almost all parents of individuals with r(20) syndrome have no evidence of r(20) syndrome in their own blood chromosome analysis (personal communication – Spinner laboratory – Children’s Hospital of Philadelphia). A few individuals, typically relatives of affected children, have been found to have a ring chromosome 20 without any evidence of symptoms.

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See Full SmPC for Details. Episenta 150mg & 300mg capsules and Episenta 500mg & 1000mg sachets contain prolonged release sodium valproate minitables. **Indication:** The treatment of all forms of epilepsy. **Dose:** Give in 1 - 2 single doses. **Monotherapy: Adults:** Start at 600mg daily increasing to 1000-3000mg at three day intervals to a max of 2500mg/day until control is achieved. **Children over 20kg:** Initial dosage - 300mg/day increasing to max. of 1000mg/kg bw/day until control is achieved. **Children under 20kg:** 20mg/kg bw/day; max 40mg/kg/day. **Patients with renal insufficiency:** May require decreased dosage. **Combined Therapy:** Dosage adjustments may be required. **Administration:** Swallow without chewing the prolonged-release minitables. **Contraindications:** Liver disease. Personal or family history of hepatic problems. Porphyria. Hypersensitivity to valproate. **Precautions:** Suicidal ideation reported. The onset of acute illness is an indication of the early stages of hepatic failure and requires immediate withdrawal of the drug. Routinely measure liver function in those at risk before and during the first six months of therapy. Discontinue if signs of liver damage occur or if serum amylase levels are elevated or if spontaneous bruising or bleeding occurs. Review patients who have issues with pancreatitis, renal insufficiency, SLE, hyperammonaemia, weight gain, diabetes or blood test abnormalities. Withdrawal of sodium valproate should be gradual. **Interactions, Pregnancy and Lactation:** See full SPC. **Undesirable Effects:** See full SPC. **Further Information & MA Holder:** Beacon Pharmaceuticals Ltd. 85 High St., TN1 1YG UK. **Presentations & Prices:** POM. Episenta 150mg capsule x 100 PL 18157/0021, Episenta 300mg capsule x 100 PL 18157/0022, Episenta 500mg sachet x 100 PL 18157/0023, Episenta 1000mg sachet x 100 PL 18157/0024 have the following NHS prices: £5.70, £10.90, £18.00 & £35.00 respectively. **Date of text:** Oct 2008. Advert prepared Feb 2009

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 Beacon

Chromosome 20ater - Genes

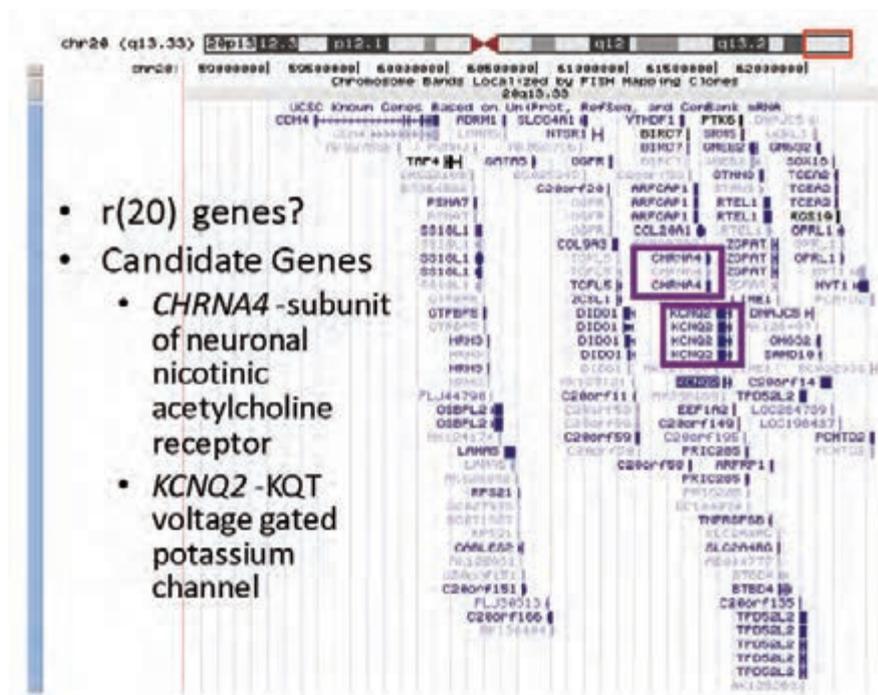


Figure 5: Candidate Genes.

Most individuals with r(20) syndrome have some cells which have two normal chromosome 20s and others which have a normal and a ring chromosome. Studies have shown that a higher degree of mosaicism is associated with earlier age of seizure onset and malformations. However, the degree of mosaicism does not determine response to drug treatment. The range in age of onset of seizures and IQ for a given mosaic ratio is relatively wide. Therefore the prediction of phenotype from the mosaicism ratio should be done with caution with regards to genetic counseling.¹³

Ring chromosome 20 results from a chromosomal break on each arm resulting in ring formation (Figure 4).

Deletion of the short arms (p) of chromosome 20 does not appear to result in epilepsy however terminal deletion of the long arm (q) is associated with epilepsy. In r(20) syndrome the breakpoint in most patients is in the p13q13.33 region of chromosome 20. The genes involved in this region (q13.33 region of chromosome 20) have yet to be identified, however this telomeric region includes two genes that are related to other distinct epilepsy syndromes; these are autosomal dominant nocturnal frontal lobe epilepsy (ADNFE) and benign familial neonatal convulsions (BFNC).

The genes identified in ADNFE and BFNC are the nicotinic acetylcholine receptor alpha-4 subunit (CHRNA4) and potassium voltage-gated

channel subfamily KQT member 2 (KCNQ2) respectively (Figure 5).

Mutations in these genes are responsible for the clinical manifestations in these disorders. Haploinsufficiency of these candidate genes may account for clinical symptoms of r(20) syndrome. Previous studies have not reported deletion in these candidate genes. However, Spinner and colleagues utilising newer array based techniques (personal communication) have identified deletion in both candidate genes associated with a worse phenotype.^{14,15} The recurrent risk for r(20) syndrome is very low, as the chromosomal ring formation is usually a 'de novo' event.

Treatment and outcome

Management of children with r(20) is symptomatic. Seizures are typically difficult to treat. No comparative studies have been done between the older and newer antiepileptic drugs (AEDs). From the review of published literature, no one drug seems to be better than any other drug and patients are frequently exposed to multiple AEDs. Unfortunately seizures are difficult to control with antiepileptic medication and may require consideration of alternative treatments. Epilepsy in r(20) syndrome is not amenable to resective surgery. Few patients have undergone epilepsy surgery without any benefit. Vagus nerve stimulation (VNS) treatment has been reported to have a good outcome in a few cases. There are no published reports on use of ketogenic diet in patients with r(20) syndrome, however its efficacy and safety is well established in other intractable epilepsies like Lennox-Gastaut syndrome. The role of other unconventional treatments of epilepsy is not established for the treatment of r(20) syndrome.¹⁶

The long term outcome of the syndrome is not known. It is not lethal; however, r(20) patients, like other refractory epilepsies, are at risk of other complications of epilepsy including status epilepticus and sudden unexpected death in epilepsy (SUDEP). The best predictor of outcome is likely to be the degree of seizure control. ♦

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Date of preparation: February 2009.

REB09-0035

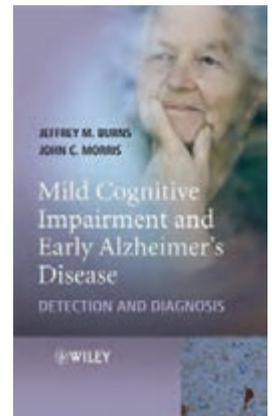


Mild Cognitive Impairment and Early Alzheimer's Disease. Detection and Diagnosis

Identification of early, preferably presymptomatic, Alzheimer's disease (AD) is now deemed the most likely way to achieve meaningful therapeutic intervention, through use of disease-modifying agents when these become available. Although there are some existing texts on mild cognitive impairment (MCI; e.g. see review in *ACNR* 2003;3(5);23), a new volume may be thought welcome, especially when one of the authors (John Morris) has been an important player in the field.

This slim volume covers neuropathology, detection, aetiology, and treatment of MCI, as well as presenting three case histories. As to be expected, the emphasis is that of the Washington University group, with diagnosis of early AD based largely on subjective information gathered from a reliable informant, rather than depending on patient performance in cognitive test batteries (e.g. pp 65–68, and case histories), with immediate commencement of symptomatic therapy when diagnosis is made (p71; of course, not possible in UK if following NICE guidance). The distinction of “worried well” (= self-report of lapses in memory retrieval) from incipient AD (= loss of self-appreciation) is helpful (p53).

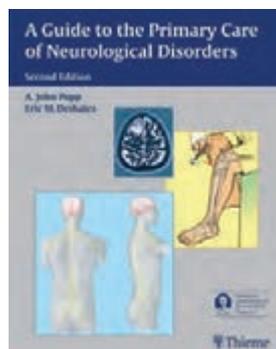
This book will serve as a useful introduction for those approaching this area for the first time, although experienced cognitive neurologists will already be familiar with much of the content. However, the book is seriously marred by inadequate proof-reading and/or copy-editing. There are many typographical errors (e.g. “Neurotic and inflammatory responses”, p85), a non-existent figure is referred to (p64), factual errors occur (surely 18, not 15, patients developed meningoencephalitis in the AN1792 amyloid vaccine trial? p88), a note to “add a reference” has not been deleted from the text (p54), and the references are inconsistent, being neither sequential nor in alphabetical order, beginning at reference 12. With the exception of the first 11 references, none are more recent than 2004 (indeed one 2004 reference is “in press”). If I may indulge in some amateur sleuthing in textual criticism, I would speculate that the book was originally written in 2004, then languished until 2006 when additions were tacked on, rather than fully integrated into the text; perhaps the two authors wrote their sections separately. The other consequence of this is that parts of the book are seriously out of date, e.g. trials of cholinesterase inhibitors in MCI (p69) have now been published; “more than 50” presenilin 1 mutations described (p103; now in fact more than 160). Likewise, the 2007 revised diagnostic criteria for AD, which suggest elimination of the MCI category, are not discussed. ♦



Author: Burns JM, Morris JC
Published by: John Wiley, 2008
Price: £21.00
ISBN: 9780470319369

Reviewed by:
 AJ Larner,
 Cognitive Function Clinic,
 WCN, Liverpool, UK.

A Guide to the Primary Care of Neurological Disorders, Second Edition



Editors: Popp JA, Deshaies EM
 Published by: Thieme, 2007
 Price: \$79.95
 ISBN: 978-1-58890-525-3

Reviewed by:
 CAH Fisher,
 Marches Surgery,
 Leominster, UK.

A primary care neurology textbook edited by two American neurosurgeons may raise eyebrows. As will a glance at the list of contributors – ten neurologists, fourteen neurosurgeons, four psychiatrists, two radiologists... The list goes on, and yes, does include two primary care physicians (one in private practice). The result is a text with scope way beyond that required by a British GP, but hidden within it are some nuggets worth finding.

This is a thoroughly American book, as witnessed by references to websites, and the recommended reading at the end of each chapter. As a paperback, it is somewhat unwieldy in its sub-A4 size. The text is dense, with few diagrams, and those that there are can be daunting (e.g. the neuroanatomy of the vestibular apparatus) or of no practical use (that showing the Hallpike manoeuvre would be of no help to anyone not experienced in its use). Tables abound, and some of these are of much greater value – that outlining medication options for essential tremor has led me to try mirtazapine for a patient. The index is excellent and without doubt it is through this that the book should be accessed.

The text is divided into four sections, covering an overview of “primary care and the neurosciences”, diagnosis (in general terms), diagnosis and management of common neurological symptoms, and finally, management of specific conditions. Chapter 1 provides a remarkably informed description of the nature and role of primary care, written by a paediatric neurosurgeon! But only the most dedicated would plough on through subsequent chapters, describing the history and scope of the neurosciences, with a strong American emphasis, and legal and ethical issues of the same (though reference to the issue of physician-assisted suicide in Oregon is interesting). A chapter on ambulatory nurses is of no relevance to UK practice, and another purporting to describe the effective use of diagnostic tests was a dry list of statistics. In section 2 (diagnosis) there is only the briefest review of symptoms, though it is good to be reminded that “TIAs very seldom cause loss of consciousness or memory”. A rather poor description of examination techniques includes some unfamiliar suggestions, such as examination of the ethmoid arteries and the Shirley Wray sign. By contrast, much detail is given in sections on neuroimaging and neurophysiological tests, surely of limited use to even an American family physician.

In section 3, there is more of interest to be found. A whole chapter dedicated to low back pain would be more expected in an orthopaedic text, and UK readers will note a complete absence of reference to “red flags”. But it is interesting to note that “home cervical traction” is recommended for cervical disc herniation – perhaps worthy of consideration this side of the Atlantic. We are also reminded that vertebroplasty may have a role in compression fractures of the

spine. In a chapter on headache there is reference to the use of barbiturate compounds (butalbital) for acute relief of tension headache and, interestingly, advice to increase doses of amitriptyline up to 125mg in prevention, or to try fluoxetine. The author of the headache chapter repeats his salutary warning that use of analgesics should be restricted to no more than 2-3 days per week, and opiates to just one day per week. Dripping 4% lignocaine into the nostrils is less familiar advice!

This is a thoroughly American book, as witnessed by references to websites, and the recommended reading at the end of each chapter

Section 4 probably contains most of interest, though once again there are whole chapters that might be better placed in other texts, including a whole one on hearing loss, and another on psychiatry. There are good overviews of neuropathies and myelopathies, movement disorders, neuro-ophthalmology, and dementia/delirium, including the hardly required dictum “early diagnosis of dementia can be difficult”. In managing the latter, “daily supplementation with vitamin E is now accepted as standard practice”, and thioridazine is still advocated as an option for management of agitation. A detailed chapter on coma and brain death could simply have been excluded, as could much of others on head injury, spinal injury, and “The Role of the Emergency Department...” An otherwise useful account of cerebrovascular disease has no reference to the ABCD stratification of TIAs, but those on neuro-oncology, infections and MS provide good overviews, and another covering neurology applied to paediatrics is an unexpected bonus.

In these days of ready and quick access to clinical information via one's PC, the role of textbooks is perhaps in decline, and it is difficult to imagine this one making it onto the shelves of many British GPs. But for those lucky enough to have access to a copy, it can certainly provide some useful insights as a reference text. A third edition would benefit from UK input if it is to aspire to a readership in this country. ♦

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o rachael@acnr.co.uk

Workforce Planning: is there an impending crisis in consultant posts available for neurology trainees?



Biba Stanton,
Secretary ABNT.

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The last two years have seen a significant expansion in the number of neurology registrar posts in response to the crisis caused by MMC. While this has been generally welcomed, there are concerns about whether there will be sufficient consultant posts for these trainees to move into, when they obtain their CCTs. In neurosurgery, trainees have predicted that there will be a deficit in consultant posts available for trainees finishing between now and 2012.

It is surprisingly difficult to find accurate information about the current numbers of neurology trainees and consultant posts. The most complete information for England comes from the NHS Workforce Review Team, who use data from Deaneries and a survey of Trust payrolls, but even this has proved to be inaccurate. Boyd Ghosh, ABNT Treasurer, has therefore undertaken a major piece of work to obtain more accurate information on the current numbers of neurology registrars in England. Boyd has combined data from the Workforce Review Team with information from Deaneries, programme directors, the Royal College of Physicians and individual trainees (including deferred posts). Boyd's figures indicate that there are almost 100 more registrars due to complete training by 2014 than the Workforce Review Team were aware of. There is likely to be a "bulge" of trainees completing their CCT in 2011 due to expansion associated with MMC (red line in Figure 1).

According to Workforce Review Team data there were 539 NHS consultant posts in England

in 2007. To make predictions about likely vacancies, they assume a net figure of 6 young consultants leaving each year, due to maternity leave or other movements, as well as assumptions about retirements. Boyd has extrapolated the consultant expansion of the last 10 years, 7% annually, to give a likely number of consultant posts in the future. Using these assumptions (green line in Figure 1), the number of consultant vacancies should be sufficient for all registrars completing training until 2012. However, making slight changes to these assumptions changes these predictions substantially. For instance, if we were to gain 9 international consultants per year, as the workforce review team have assumed in their figures, and not have the predicted 6 young leavers, there would be insufficient consultant posts to accommodate the "bulge" of trainees completing in 2011 (black line in Figure 1).

So what's the bottom line? Based on the best data available, it doesn't seem that there is a looming crisis in the number of consultant posts for neurology trainees as has been predicted in neurosurgery. However, accommodating all current trainees will certainly require ongoing consultant expansion in the specialty. Existing official sources of data on trainee numbers are worryingly inaccurate. The ABNT will try to maintain more accurate data, and will continue to make the case for ongoing consultant expansion in neurology. It may also be time for a wider debate about whether the role of consultant neurologists may need to broaden or change if we are to be successful in achieving this. ♦

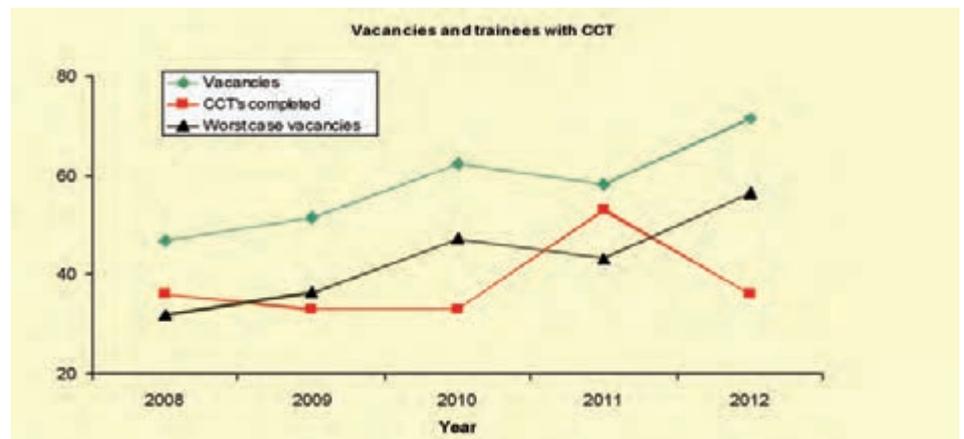


Figure 1: Graph showing trainees completing CCT by year and assumed vacant consultancy posts based on two different assumptions. See text for details.

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References: 1. Rudick RA *et al.* *Neurol* 1997; **49**: 358-63. 2. Jacobs LD *et al.* *Ann Neurol* 1996; **39**: 285-94. 3. Rudick RA *et al.* Poster presented at ECTRIMS. October 2007; Prague, Czech Republic. 4. Devonshire V *et al.* Poster presented at ECTRIMS. September 2006; Madrid, Spain. 5. Reynolds MW *et al.* Poster presented at ECTRIMS. October 2007; Prague, Czech Republic.

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teaching and research of the highest quality in
neurology and the neurosciences*

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 9 April, 2009

2009

MARCH

VIREPA, the Virtual Epilepsy Academy
Distance learning courses. Genetics of Epilepsy, EEG in the diagnosis and management of epilepsy, Neuroimaging and Clinical Pharmacology and Pharmacotherapy.
www.epilepsy-academy.org

Multiple sclerosis: origins, pathogenesis and treatment

5 March, 2009; London, UK
T. 020 7290 2984/3941
E. cns@rsm.ac.uk

British & Irish Neurologists' Movement Disorders Meeting

5-6 March, 2009; London, UK
E. Itaib@ion.ucl.ac.uk

Interventions in Neurodisability - what works?

6 March, 2009, 2009; Derby, UK
Ms Kelly Robinson
T. 020 7092 6083
E. kelly.robinson@rcpch.ac.uk

1st UAE International Meeting on Diagnosis and Treatment of the Neurogenic Bladder in Children and Adolescents

7-8 March, 2009; Abu Dhabi, UAE
E. mpatricolo@skmc.gov.ae

Restauracion Neurologica - 3rd International Conference

9-13 March, 2009; Havana, Cuba
E. rn2009@neuro.ciren.cu
Professor Jorge Bergado
E. Jorge.bergado@infomed.sld.cu
W. www.ciren.cu

Fundamentals of Neuroradiology Sheffield Course

11-13 March, 2009; Sheffield, UK
T. 0114 2712957
E. Linda.Milnes@sth.nhs.uk

9th International Conference on Alzheimer's and Parkinson's Diseases - ADPD 2009

11-15 March, 2009; Prague, Czech Republic
Natalie Shabi
T. 41 229 080 488
E. adpd@kenes.com

Normal Gait

12 March, 2009; Derby, UK
T. 01332 254679
W. www.ncore.org.uk

Talent and Autism Public Lecture

12 March, 2009; London, UK
E. events@royalsociety.org
W. <http://royalsociety.org/event.asp?id=8200>

5th World Congress World Institute of Pain

13-16 March, 2009; New York, USA
Natalie Shabi
T. 41 229 080 488
E. wip@kenes.com

4th Fred J. Epstein International Symposium on New Horizons in Pediatric Neurology, Neurosurgery and Neurofibromatosis

15-19 March, 2009; Eilat, Israel
Hannah Baum
T. 972 3 517 5150
E. newhorizons@targetconf.com

9th Advanced Prosthetic & Amputee Rehabilitation Course

16-18 March, 2009; London, UK
E. admin@bsrm.co.uk
T. 01992 638865

Taking Leisure Seriously

16 March, 2009; London, UK
E. lgriffiths@rhn.org.uk
W. www.rhn.org.uk/institute/doc.asp?catid=1477&docid=3278

Arrhythmia Alliance Regional Meeting
19 March, 2009; Stratford Upon Avon, UK
Melanie Quinlan

E. events@stars.org.uk
W. www.hearhythmcharity.org.uk

Understanding Migraine and Other Headaches Study Day for Nursing Staff

20 March, 2009; Glasgow, UK
E. events@migrainetrust.org
T. 020 7462 6606

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

21 March, 2009; London, UK
E. yogini.naidu@uhl.nhs.uk

The Upper Limb: ACPIN National Conference
The Association Of Chartered Physiotherapists Interested In Neurology

21 March, 2009; Northampton, UK
E. Anne.rodger@hotmail.co.uk

Recognising Post Traumatic Stress

24 March, 2009; Derby, UK
T. 01332 254679
W. www.ncore.org.uk

Arrhythmia Alliance Regional Meeting

25 March, 2009; London, UK
Melanie Quinlan
E. events@stars.org.uk
W. www.hearhythmcharity.org.uk

British Neuropsychological Society Annual Meeting

25-26 March, 2009; London, UK
E. a.a.beaton@swansea.ac.uk

UK Neuromuscular Translational Research Conference

26-27 March, 2009; Newcastle, UK
E. z.scott@ion.ucl.ac.uk

The Bakerian Prize Lecture - Mathematics in the real world: From brain tumours to saving marriages

26 March, 2009; London, UK
W. royalsociety.org/event.asp?id=8195&month=3,2009
E. events@royalsociety.org

Marseille Neurosurgery 2009 Joint Annual Meeting of the European Association of Neurosurgical Societies (EANS) and the French Neurosurgical Society (SFNC)

27-31 March, 2009; Marseilles, France
W. www.kenes.com/eans-sfnc

Practical Paediatric Neurology Study Days

30 March-3 April, 2009; London, UK
T. 020 7405 9200,

CBT approaches to physical rehabilitation

30 March, 2009; Derby, UK
T. 01332 254679
W. www.ncore.org.uk

9th London International Eating Disorders Conference

31 March-2 April, 2009; London, UK
Amy Tranter
T. 0207 5016 711
E. amy.t@markallengroup.com

Brain Repair Spring School 2009

31 March-2 April, 2009; Cambridge, UK
T. 01223 331160
E. pj214@cam.ac.uk

11th International Neuroscience Winter Conference

31 March-4 April, 2009; Sölden, Austria
Professor Tsolakis
T. 43 51 250 423 715
E. philipp.tsolakis@i-med.ac.at

APRIL

PCNS Neurology Update Workshop

1 April, 2009; Liverpool, UK
W. www.p-cns.org.uk

Recent Advances in Movement Disorders

2 April, 2009; London, UK
T. 020 7290 2984/3941
E. cns@rsm.ac.uk

2nd International Conference on Psychogenic Movement Disorders and Other Conversion Disorders

2-4 April, 2009; Washington, US
E. LSevcik@movementdisorders.org
T. 001 414 276 2145

MS Trust Cardiff Study Day for Health & Social Care Professionals with an interest in MS

2 April, 2009; Cardiff, UK
T. 01462 476704
E. education@mstrust.org.uk
W. www.mstrust.org.uk/studydays

European Psychiatric Association Sevetion of Neuroimaging

The 5th Annual Meeting: Genes, Brain, Behaviour
9-10 April, 2009; Edinburgh, UK
E. epaneuroimaging2009@iop.kcl.ac.uk

Arrhythmia Alliance Regional Meeting

15 April, 2009; Bristol, UK
Melanie Quinlan
E. events@stars.org.uk
W. www.hearhythmcharity.org.uk

UKNG - state of the art, education, update!

16 April, 2009; London, UK
E. sellarannie@hotmail.com

Speciality Revision Series - Neurology

17 April, 2009; London, UK
T. 020 7290 2984/3941
E. cns@rsm.ac.uk

7th Staffordshire Conference on Clinical Biomechanics

17-18 April, 2009; Staffordshire, UK
W. www.staffs.ac.uk/scsb

20th National Meeting of the British Neuroscience Association

19-22 April, 2009; Liverpool, UK
Dr Yvonne Allen
E. bn2009@liv.ac.uk

Parkinson's Awareness Week

20-26 April, 2009; UK
W. <http://www.parkinsons.org.uk>

Wiring the Brain

21-24 April, 2009; Adare, Ireland
E. wiringthebrain@gmail.com
W. www.wiringthebrain.com

Posture & Balance in Neurological Conditions - Upper Limb Qualified staff

22-23 April, 2009; Derby, UK
T. 01332 254679
W. www.ncore.org.uk

BISWG Conference-Counting the Cost -Financial Issues after Brain Injury

23 April, 2009; Manchester, UK
T. 0208 780 4530
E. psimonsen@rhn.org.uk

Getting to Grips with Migraine and Other Headaches

23 April, 2009; Birmingham, UK
E. events@migrainetrust.org
T. 020 7462 6606

61st Annual Meeting of the American Academy of Neurology

25 April - 2 May, 2009; Seattle, WA, USA
W. www.aan.org

Cognitive Rehabilitation Workshop

27-28 April, 2009; Kamloops, BC, Canada
E. hplumbley@therehabgroup.ca
W. www.cogrehabworkshop.info/

Arrhythmia Alliance Regional Meeting

29 April, 2009; Knutsford, UK
Melanie Quinlan
E. events@stars.org.uk
W. www.hearhythmcharity.org.uk

PCNS Neurology Update Workshop

29 April, 2009; Sevenoaks, UK
W. www.p-cns.org.uk

MAY

2nd International Epilepsy Colloquium: Pediatric Epilepsy Surgery

3-6 May, 2009; Lyon, France
W. <http://epilepsycolloquium2009ams.fr>

Developing Insight/Awareness following brain injury

4-5 May, 2009; Vancouver, BC, Canada
E. info@jrrehab.ca
W. www.jrrehab.ca/

Neuropsychiatric, Psychological and Social Developments in a Globalised World

5-8 May, 2009; Athens, Greece
Mrs Demy Kotta
T. 302-106-842-663
E. appachellas@yahoo.com

Mending the Brain: Advances in Neurosurgical Techniques

7 May, 2009; London, UK
T. 020 7290 2984/3941
E. cns@rsm.ac.uk

Measuring Mobility: 28th Scientific meeting of the Physiotherapy Research Society

7 May, 2009; Glasgow, UK
E. m.grant@gcal.ac.uk

24th International Training Institute in Neurologic Music Therapy

7-9 May, 2009; London, UK
E. lgriffiths@rhn.org.uk
W. www.rhn.org.uk/institute/doc.asp?catid=1477&docid=3277

Window on Tomorrow: Advancements in the Science and Medicine in Neuromuscular Conditions

7-9 May, 2009; Auckland, New Zealand
T. +64 9 845 5540
E. events@iconevents.co.nz
W. www.nma2009.org.nz

24th International Training Institute in Neurologic Music Therapy

7-9 May, 2009; London, UK
E. lgriffiths@rhn.org.uk
W. www.rhn.org.uk/institute/conferencesNMT
T. 020 8780 4500 ext 5140

Molecular Mechanisms Of Neurodegeneration

8-10 May, 2009; Milan, Italy
Angelo Poletti
T. +390250318215
E. triplets@unimi.it

5th ISPRM World Congress

9-13 May, 2009; Istanbul, Turkey
E. traceymole@wfnr.co.uk

UCL May Short Courses

11-15 May, 2009; London, UK
T. 020 7692 2346
E. J.Reynolds@ion.ucl.ac.uk

The Nottingham Systematic Review Course 2009

12-15 May, 2009; Nottingham, UK
Jun Xia T. 0113 3058303
E. jun.xia@nottingham.ac.uk

Health Care Records

12 May, 2009; Derby, UK
T. 01332 254679
W. www.ncore.org.uk

Intensive Neuroendocrinology Course

13 May, 2009; Coventry, UK
E. rachel.davies2@uhcw.nhs.uk

6th Baltic Congress of Neurology

13-16 May, 2009; Vilnius, Lithuania
Dainora Bandziute
T. 37 0 52 120 003
E. info@balcone2009.com

Joint BSRM/IARM Spring Meetin

14-15 May, 2009; Dublin, Ireland
T. 01992 638865
E. admin@bsrm.co.uk

19th International Symposium on ALS/MND

Conference details: 3-5 November, 2008, Birmingham, UK. **Reviewed by:** Belinda Cupid, Research Manager, Motor Neurone Disease Association, UK.

"These are tremendously promising times for scientists working in MND," commented Lord Drayson, Science and Innovation Minister, during his opening speech. Organised by the MND Association, UK, the meeting is a careful balance of presentations discussing biomedical research, clinical research and the clinical management of the disease, mostly organised in parallel sessions.

One of the biggest advances in the field of MND research in the last year has been the causal link between TDP43 and MND. In February 2008, mutations in the TAR DNA binding protein gene were found in two families affected by familial ALS. This new knowledge followed the discovery of aggregates of the encoded protein in the more common sporadic cases of MND, cases of MND with frontotemporal dementia and those with frontotemporal dementia alone. Presentations at the symposium gave delegates an update on the focus of research since February. These included confirming the link between TDP43 and the pathogenesis of the disease, establishing the function of wildtype protein and the interaction of TDP43 with other processes within the motor neurone.

As the knowledge and availability of non invasive ventilation (NIV) to help people with MND with respiratory symptoms improves, compliance continues to be a concern. A novel way to improve this was presented by Anabela Pinto from Lisbon. She explained that a lack of compliance is associated with the presence of abnormal breathing patterns. Half of the participants in her study used specially adapted ventilators, where parameters around their use were recorded. Recorded data were transferred via the internet to a central monitoring room on a weekly basis. Using these data, health professionals were able to adjust the ventilator settings remotely to better suit the patient. The group with the adapted ventilators achieved a high rate of compliance compared to those whose ventilator use was monitored during clinic appointments. Dr Pinto also found that they adapted more quickly to NIV.

Depressingly, the results of earlier drug clinical trials presented at the meeting were negative. The results of the latest insulin-like growth factor trial and that of co-enzyme Q10 showed no beneficial effects for people with MND. We must hope that that Trophos' study and others in the pipeline will bring happier news. Reasons for the poor track record of ALS clinical trials could be attributed to a number of factors in preclinical studies. Discussions at the International Symposium ranged from the entertaining (if you were not falling foul of his



Lord Drayson, Science and Innovation Minister, opening the 19th International Symposium on MND/ALS.

rules) presentation from Professor Chris Liplinski, to a number of sessions discussing disease models for MND/ALS. Prof Lipinski is a medicinal chemist. His 'rule of five' physico-chemical properties that potential drugs should meet go a long way to determining the likelihood of success of these drugs in the clinic.

Perhaps the most well known of disease models of ALS/MND is the (mutant Cu,Zn-superoxide dismutase 1) SOD1 transgenic mouse and more recently transgenic rat. The first transgenic mouse was created in 1996. Since then, literally hundreds of compounds have been tested in these mice for a beneficial effect. However, only one of these, riluzole, has made it to the clinic, leading to doubts on the validity of this model. The use of the SOD1 mouse in understanding the disease and developing treatments for it was discussed in a session encompassing a series of short pre-

sentations and a Panel question and answer discussion. Choice of SOD1 mutant, copy number, mouse genetic background and study design (drug administration pre- or post- symptom onset and robustness of phenotypic characterisation) were considered. In summing up the Chair concluded that we should not, as one of the speakers put it 'throw the baby out with the bath water', but that robust guidelines should be developed and implemented for their use. These would provide clarity for the biomedical researchers conducting these studies and also for their clinical colleagues seeking to interpret the results when considering whether to initiate clinical trials.

Transgenic rodents were not the only models of ALS/MND that were under discussion, one of the highlights was a talk from Joan Coates, presenting her data on the first sporadic ALS animal model – in dogs. Using a whole genome scan approach Prof Coates discovered that Canine degenerative myelopathy-affecting Pembroke Welsh corgis has a missense mutation in the SOD1 gene. Further investigation found this mutation, and spinal cord pathology similar to human ALS, in four other dog breeds. This research was published in PNAS in February 2009 (Awano et al DOI: 10.1073/pnas.0812297106).

It was encouraging to hear researchers talk about feasible applications for stem cells that may translate into the clinic. Nick Maragakis from Johns Hopkins University showed that transplantation of glial precursor cells into the cervical spinal cord of SOD1 rats resulted in the maintenance of respiratory function, longer survival and slower decline in forelimb (but not hindlimb) muscle strength. Over 85% of the glial precursor cells injected differentiated into astrocytes. These were unaffected by MND – their function was maintained and they did not contain protein aggregates. He concluded that this approach may have future application for preservation of respiratory function in the clinic.

In the closing session of the Symposium, Prof Clive Svendsen talked about a different approach for a cell based therapy. He has manipulated human mesenchymal stem cells to deliver an ex vivo gene therapy of GDNF into the muscles of a SOD1 rats. These injections slowed the progression of the disease and extended survival.

As over 800 delegates packed their bags to go home, I hope that it proved to be a thought provoking and memorable few days – memorable not just because this was the week that Lewis Hamilton became F1 world champion and the US voted for a new stem cell president! ♦

There were over 800 people talking about MND research for three days, from 7 in the morning until 10 at night – the buzz was fantastic



British Neuropathological Society Summer School

8-10th July 2009

The BNS Summer School: **Recent Advances in Neuropathology & Applied Neurobiology** will be held at the Royal Agricultural College, Cirencester. In-depth sessions including lectures and workshops will mix basic neurosciences and applied neurobiology to link with human diseases. Neuroscience workers interested in translational research, researchers working on human tissues, clinical neuroscience specialists updating their basic neuroscience understanding, trainees in clinical neurosciences and post-doctoral workers in neurosciences should attend. The informal atmosphere will provide the opportunity for participants to meet and make new contacts.

For further information please visit:
<http://www.bns.org.uk/>



Getting to grips with migraine and other headaches – training day

Thursday 23 April 2009

As a health professional you will be aware that Migraine and headache have a considerable impact on the lives of sufferers and that their needs are poorly addressed within the health service.

The Migraine Trust in association with the British Association for the Study of Headache are organising a day on headache. Topics will include diagnosis, management and support dealing with all types of headache. The day is being subsidised by the Migraine Trust and will only cost £85 to include lunch and refreshments.

To make a booking please email events@migrainetrust.org or write to Education & Research Dept, The Migraine Trust, 55 Russell Square, London, WC1B 4HP or contact *kate Scurr* on 020 7462 6606 by 19 March 2009.



UNIVERSITY OF CAMBRIDGE

CAMBRIDGE CENTRE FOR BRAIN REPAIR

SPRING SCHOOL 2009

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31 March to 2 April 2009,
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Now open for registration:
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For further information contact:

Trish Jansen
01223 331177
pj214@cam.ac.uk

BRAIN INJURY
REHABILITATION TRUST

Looking ahead



Innovations:

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New developments in neuroscience and rehabilitation practice

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email frances.pitwell@thedtgroup.org or visit www.birt.co.uk

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BIRT is a division of The Disabilities Trust Registered Charity No 800797

June 20–24, 2009

Milan, Italy

Neurology: Learning, knowledge, progress and the future

Key symposia:

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

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

Abstract Submission Deadline: February 11, 2009

Early Registration Deadline: April 22, 2009

For further information please contact:

ENS 2009, c/o AKM Congress Service

Association House, P.O. Box, CH-4002 Basel / Switzerland

Phone +41 61 686 77 77 Fax +41 61 686 77 88 Email info@akm.ch

Commentary on Living Well with Dementia: A National Dementia Strategy



Dr Andrew J 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.

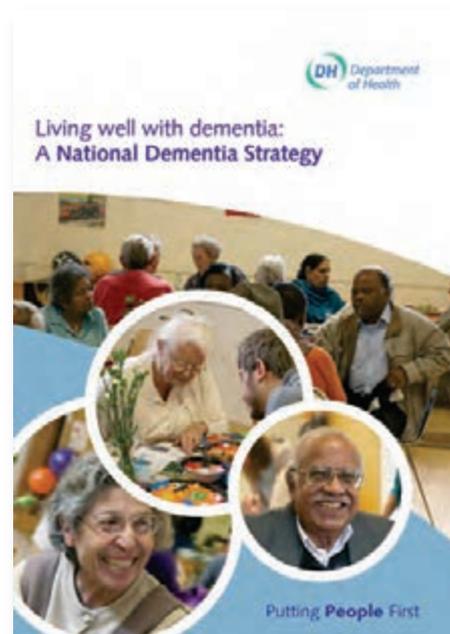
Correspondence to:

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Walton Centre for Neurology
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Lower Lane, Fazakerley,
Liverpool, L9 7LJ, UK.
E. a.larner@thewaltoncentre.nhs.uk

Who can legislate for snow? After months of waiting, a (or is it "the?") National Dementia Strategy (NDS)¹ was officially launched on 3rd February, 2009 (this was originally planned for October, 2008), but its media impact was somewhat diluted by the obsession with snowfall and the resultant school closures and cancellation of London's buses. Brief items appeared on BBC News, but nothing in the next day's *Guardian*.

The NDS builds on a consultation document² issued by the Department of Health in June 2008. Both propose three key themes to address the problem of dementia: improved awareness, early diagnosis and intervention, and a higher quality of care. There are 17 "key objectives", but many of these fall outwith the clinical domain, such as an information campaign to raise awareness and reduce stigma, improving community personal support services, housing support and care homes. Perhaps consistent with this is the fact that hospital clinicians without managerial roles are conspicuously absent from the NDS target audience (p2). Moreover, the NDS is explicitly not detailed clinical guidance, since the NICE/SCIE guidelines of 2006 are said to fulfil that role (p15), a document which has previously been commented upon in these pages.³ There is, however, a proposed care pathway for the implementation of the strategy (p22), although specified roles for specified specialists at specified times are not suggested (cf. ref 4).

For clinicians, the key chapter will be that devoted to early diagnosis, and particularly objective 2, "good quality early diagnosis and intervention for all" (p33). This is to be delivered by "commissioning of a good quality service, available locally, for early diagnosis and intervention in dementia, which has the capacity to assess all new cases occurring in that area". According to the NDS, diagnosis should be carried out by "a clinician with specialist skills" (p35), and this will require the commissioning of a specific service for early diagnosis and intervention (p36), rather than utilising existing services. This is because old age psychiatry services are said to be focused on the severe and complex end of the spectrum leaving early diagnosis unaddressed, whilst geriatricians and neurologists are "saturated at present with their current work with those referred to them with dementia and complex physical comorbidity and younger and atypical presenta-



tions respectively" (p36). The proposed new service would focus solely on early diagnosis and intervention and would be complementary to the work of old age psychiatry, geriatrics, neurology and primary care (p37). This new service, the applicability of which is based on the Department of Health pilot study in the Croydon Memory Service,⁵ "might be provided by any of a number of types of specialist with diagnostic skills in dementia (e.g. old age psychiatrists, geriatricians, neurologists, or GPs with a specialist interest) or combinations thereof". It will be based on "local decisions ... based on existing service provision and where local skills and enthusiasm lie". There is no expectation that all areas will implement the strategy within 5 years (p13).

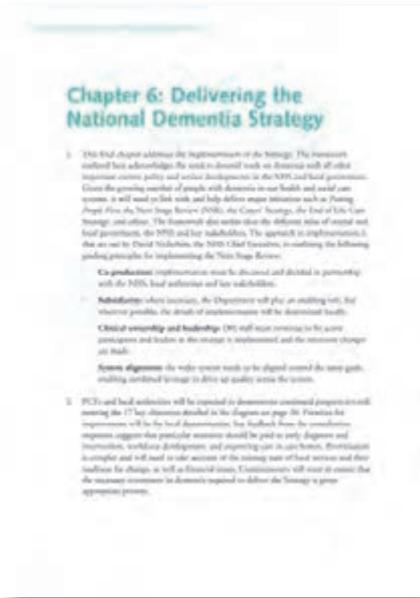
Whilst the NDS goals are self-evidently laudable, the pragmatics are that everything seems to hinge on commissioning, to which end something called "World Class Commissioning" guidance for dementia will operate (an 18-page Annex is devoted to this creation). Nonetheless, one suspects that there will be differences of interpretation and hence different service models emerging in different areas, dependent upon the views of individual managers. As an example, one NDS objective is the appointment of "demen-

tia advisers” to facilitate easy access to appropriate care, support and advice for those diagnosed with dementia and their carers (p11). About 2 years ago we proposed a similar post of “dementia care manager” be set up at this centre to coordinate referrals between our diagnostic service and social care services, but this was summarily rejected.

Septic that I am, I find the idea of a new service devoted to early diagnosis a little perplexing. Isn't this just an extension of existing services, the more so if it is to be provided by those with specialist skills (e.g. old age psychiatrists, geriatricians, neurologists) already providing the existing service? The approach of extending existing services is apparently good enough in other circumstances: on the issue of inappropriate use of antipsychotic drugs in patients with dementia, it is suggested that “commissioning an extension of the existing role of the old age community mental health teams ... rather than ... setting up a separate service” would be appropriate (p60). There also seems to be an expectation that early diagnosis of dementia is always a straightforward matter, whereas empirically it is often difficult, requiring patient follow-up and reassessment over time. There is, as far as I can see, no explicit acknowledgement that dementia is aetiologically a heterogeneous syndrome, which may require rather different diagnostic skills and interventions dependent upon cause.

Furthermore, what case mix would an early diagnosis service see? I think many of its clients would be the “worried well”, those with self-reported and physiological memory lapses, rather than those with pathological neurodegeneration. Would such a service be able to deal with these issues, or would there be a need for onward referral for assessment of the non-demented? Top-down policies may have consequences contrary to those expected, for example, despite the expectation in some

Formulation of policy (top-down) is relatively easy, whereas implementation (bottom-up) is rather more difficult



quarters that NICE/SCIE guidelines would make a neurology-led cognitive clinic redundant, such that managers mooted its closure, referral numbers have in fact increased significantly.⁶

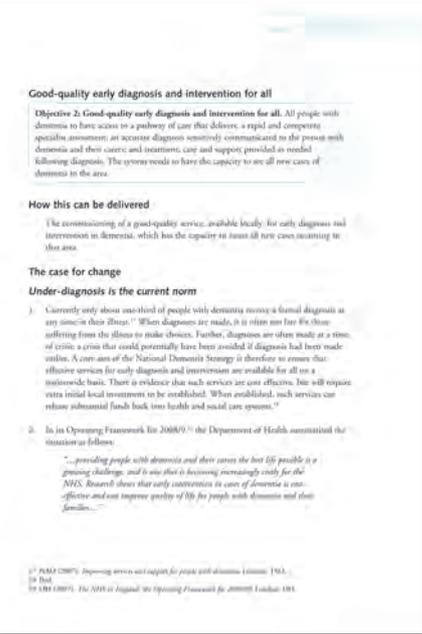
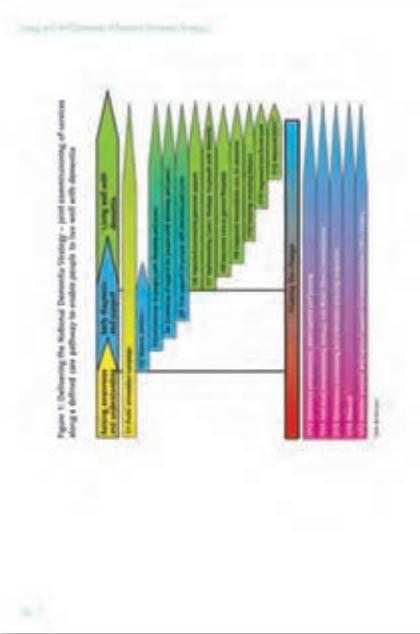
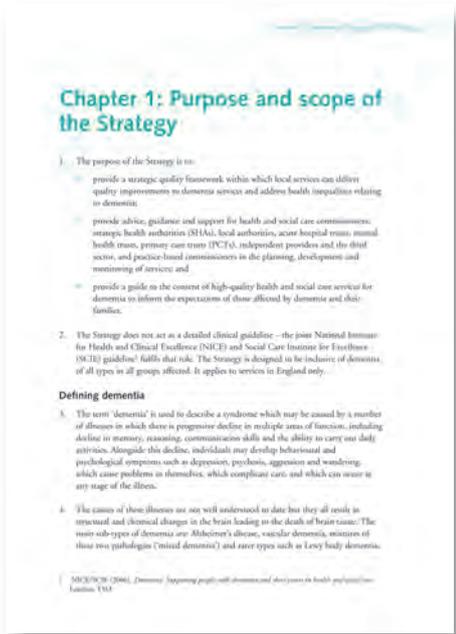
NDS is a five-year plan (a name which will inevitably, for the historically minded, conjure visions of Stalin), and seems to be one part of a unified plan, if not for the whole of society then for much of the care sector, since it is pro-

posed to dovetail with the Carers' Strategy, the National End of Life Care Strategy, NHS Next Stage Review, *Putting People First*, and possibly others (p64). Whilst integration is of course desirable, policy does not appear to be entirely joined up, since early intervention will not, of course, include cholinesterase inhibitors if the NICE 2006 cholinesterase inhibitor guidance is followed.

Formulation of policy (top-down) is relatively easy, whereas implementation (bottom-up) is rather more difficult. Only time will tell whether this policy can be meaningfully delivered. ♦

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- Transforming the quality of dementia care: consultation on a National Dementia Strategy*. London: Department of Health, 2008.
- Doran M, Larner AJ. *NICE/SCIE dementia guidance: time to reconsider*. *Advances in Clinical Neuroscience & Rehabilitation* 2008;8(1):34-35.
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- Banerjee S, Willis R, Matthews D, Contell F, Chan J, Murray J. *Improving the quality of care for mild to moderate dementia: an evaluation of the Croydon Memory Service Model*. *Int J Geriatr Psychiatry* 2007;22:782-788.
- Larner AJ. *Impact of NICE/SCIE dementia guidelines in a neurology-led memory clinic*. *Clin Med* 2009;9:in press



Principles of MRI



Dr Justin Cross

trained in neuroradiology at Addenbrooke's Hospital, Cambridge UK and at the University of Toronto, Canada. He has a special interest in paediatric neuroradiology and has published articles on the measurement of cerebral tumour volume, carotid imaging and the use of spectroscopy in clinical practice.

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Hills Road,
Cambridge CB2 0QQ, UK.

Table 1: Materials that are of high signal intensity on T1 weighted MRI

Lipid and cholesterol
Subacute blood product (Met-Haemoglobin)
Gadolinium
Melanin, mucin and other proteins
Calcification (rarely)
Copper in Wilson's disease

Basic MRI physics

Frequency and Phase

The rotation of protons can be described in terms of frequency and phase. In a magnetic field, the protons spin around the axis of the magnet at a given frequency which is proportional to the field strength. This is governed by the Larmor equation: frequency = Larmor constant x magnetic field strength.

In addition to frequency, protons rotating in a magnetic field have a property known as phase. In the resting state, the protons are not in phase (Figure 3a). However, when particular radiofrequency pulses are used, the protons can be brought into phase (Figure 3b). When the radiofrequency is turned off, they dephase again. The ability to manipulate the phase of protons is important for differentiating tissues (see T2 weighted imaging) and for the spatial localisation of signal intensity (see spatial localisation).

Understanding spatial frequencies

MR images are acquired and processed in terms of spatial frequency rather than pixel by pixel. This is necessary to overcome the difficulty in localising the origin of MR signal intensity (see spatial localisation). An image is made up of pixels that have amplitude (degrees of greyness) and position. One row of pixels can be represented by a waveform which plots amplitude on the y-axis and distance (position) on the x-axis (Figure 6). A mathematical operation known as a Fourier transform breaks this wave form down into constituent sine waves of differing amplitudes and frequencies. Fourier mathematics can be used to encode a 2D image entirely in terms of spatial frequencies rather than for each row of pixels in turn. This is difficult to conceptualise, but the spatial frequency representation of an image is referred to as k-space.

Spatial localisation

(i) Slice selection

A magnetic gradient is applied along the axis of the magnet. Since protons resonate at frequencies depending on the applied field strength, slices can be selected by varying the radiofrequency energy used to acquire data (Figure 7).

(ii) In slice localisation

We learnt earlier that MR images are obtained in terms of spatial frequency. This followed a breakthrough in spatial localisation known as phase encoding. The phase of protons was discussed earlier, as well as the ability to manipulate phase using magnetic gradients and radiofrequency. Phase encoding is a brilliant way of localising signal intensity. We have seen that data is being obtained slice by slice by varying the magnetic field along the length of the patient and using a radiofrequency to which only protons in the slice of interest will resonate (Figure 7). How can

we localise signal intensity within the slice? Imagine applying a gradient along the x-axis of the slice which causes phase to vary by 3×360 degrees across the region of interest (Figure 8). If there is a uniform distribution of protons in this area, signal intensity will cancel out to zero. However, if there are three blocks of protons evenly spaced out, signal intensity from these protons will summate giving a strong signal. This gradient can be said to be sensitive to spatial frequencies of three per unit length. The gradient can be varied to detect any spatial frequency required.

T1 and T2 relaxation times

T1 and T2 are rate constants governing the return of protons to a resting state following excitation by a combination of applied radiofrequency energy and magnetic field changes.

T1 refers to the recovery of the protons' magnetic field along the axis of the magnet. When radiofrequency is applied, the protons are deflected away from the magnetic field and when it is turned off, the protons re-align with the field. During this process, electromagnetic radiation is emitted. The rate constant governing the return of longitudinal magnetisation is called T1. T1 is governed by the interaction of protons with large molecules such as cell membranes, lipids and myelin and is sometimes referred to as spin-lattice relaxation. Protons that are heavily bound have a rapid recovery of magnetisation and a short T1. There are a few substances that have a particularly short T1 (see Table 1) so that lesions that are high intensity on T1 can be easily characterised. Protons that are free to move, for example in solution, have a long T1.

T2 governs the loss of phase that occurs when a radiofrequency pulse is switched off. T2 is dominated by interaction with other protons (spin-spin interactions). Protons that are closely packed influence each other more than those in free solution. Thus water (very loosely packed) has a long T2 and tissues with little water content have a short T2. T2 is particularly useful in detecting the water content of tissues and is sensitive to pathologies that generate oedema (inflammation, infection, ischaemia, neoplasia etc).

Artefacts

Ghosting

If errors are made in the detection of spatial frequency data, ghosts of the image are generated usually to the left and right side of the main image in the phase encoding axis. This can occur because of patient motion or from flowing blood which has a different phase to the surrounding tissues. The mathematical explanation for this phenomenon is beyond the scope of this article but can be found in an MR physics text.

Gibbs or truncation artefact

We saw earlier that MRI has difficulty in representing straight lines and sharp edges. When there is a

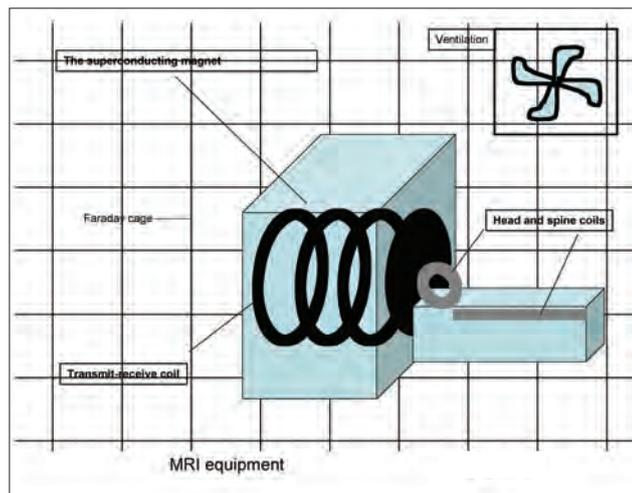


Figure 1 - MRI equipment

- A superconducting magnet made of millions of turns of wire consisting of Niobium-Titanium alloy embedded in copper. This is maintained at a temperature below 7.7K by liquid helium which in turn is kept cold by a refrigeration unit (cold head). Helium is slowly lost from the system and must be refilled every 2-3 years.
- Transmit-receive coils made of copper which emit radiofrequency energy when an electrical current is passed through them. When radiofrequency passes through them an electrical current is induced and this is how magnetic resonance signal intensity is detected.
- Motorised table
- Faraday cage – copper wires are built into walls and ceiling to prevent extraneous radiofrequency energy entering the room.
- Ventilation is required to maintain oxygen levels, which can become depleted if helium slowly leaks into the room even during normal operation of the magnet. If cooling of the magnet fails, the coils will become resistive causing a sudden rapid rise in temperature, a process known as quenching. This will result in a large release of helium gas, and facilities must be in place to allow this to be safely vented to the outside of the building.

straight line, such as the interface between the cord and CSF; multiple lower intensity lines may be repeated on either side of the interface. This can be mistaken for an intrinsic cord abnormality. The artefact is named after Willard Gibbs (1839-1903) an American physicist who first described this phenomenon in relation to Fourier transforms. It is also referred to a truncation artefact because the problem would not arise if an infinite number of spatial frequencies were used (in practice the number of frequencies is truncated to allow a reasonable imaging time).

Phase wrap

If the field of view selected is smaller than the slice, signal from outside the field of view may be projected on top of the desired image. This artefact can be avoided by selecting a larger field of view or nulling the signal from areas that are not of interest.

Susceptibility

If there is material in the region of interest which modifies the magnetic field, signal in adjacent tissue is modified and spatially misrepresented. This leads to distortion of the image, usually with loss of signal in adjacent tissues.

Chemical shift

Protons in fat resonate at slightly different frequencies to protons in water when the same magnetic field strength is applied. This results in slight spatial misregistration of signal from fat. ♦

REFERENCE

McRobbie DW, Moore EA, Graves MJ, Prince MR. MRI: From picture to proton. Cambridge University Press, 2003.

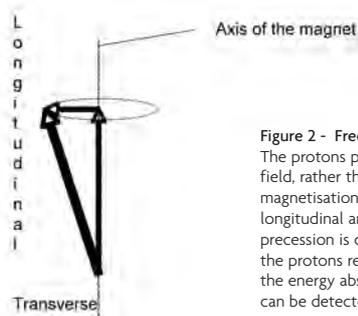


Figure 2 - Frequency

The protons precess around the axis of the magnetic field, rather than being precisely aligned with it. The magnetisation of the proton can be resolved into longitudinal and transverse components. The frequency of precession is crucial to magnetic resonance imaging, because the protons resonate to radioenergy of that frequency, and the energy absorbed is later re-emitted in radiowaves that can be detected.

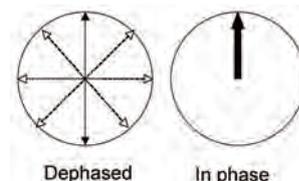


Figure 3 - Phase

Phase is a separate property of precessing protons which may either rotate asynchronously or in synchrony (in phase). The phasing and dephasing of protons is an important contributor to tissue contrast in MRI, particularly for T2 weighted and flow related imaging (MR angiography).

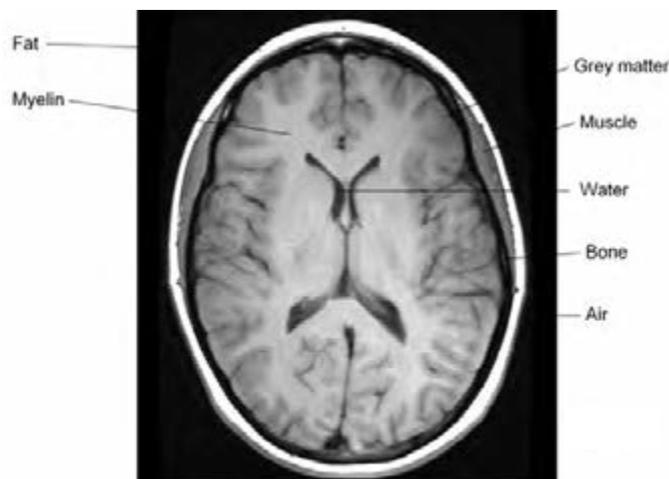


Figure 4 - T1 weighting

This is sometimes referred to as spin-lattice imaging as it is influenced by the interaction of protons with large molecules. These molecules tend to shorten T1 and this effect is displayed as high intensity on MR images. On this T1 weighted image, subcutaneous fat and myelin are shown as high intensity; grey matter and muscle are intermediate intensity; water is low intensity; bone and air are very low intensity.

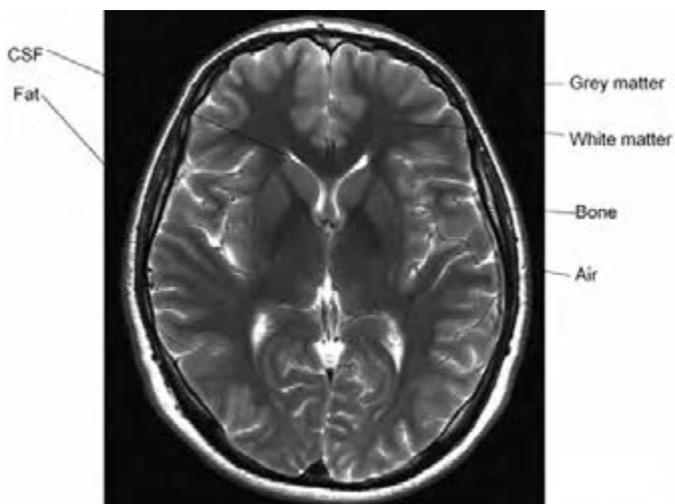


Figure 5 - T2 weighting

T2 weighted imaging may be referred to as spin-spin imaging which describes the effect of neighbouring protons on each other. T2 refers to the rate at which the phase of protons is lost over time. In practice, T2 hyperintensity is strongly influenced by water content, although fat is also hyperintense. On this T2 weighted image, CSF and subcutaneous fat are high intensity; grey matter is higher intensity than white matter; bone and air are very low intensity.

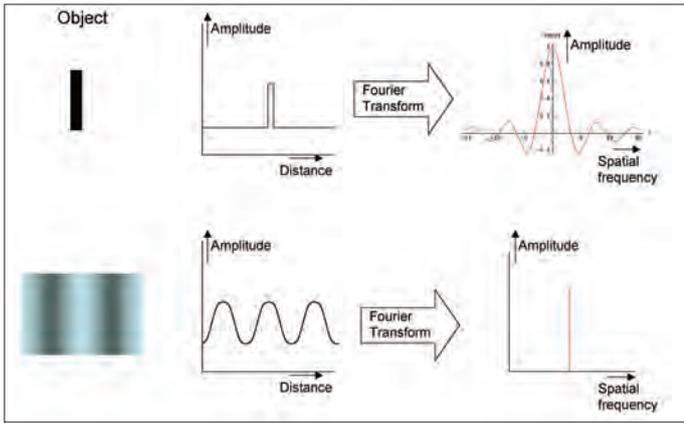


Figure 6 – Spatial frequencies
 For simplicity, the objects chosen on the left vary only in one dimension. The first object, a line, has a single area of increased intensity on the amplitude/distance plot. However, on the amplitude/spatial frequency plot, an infinite number of spatial frequencies are required to capture the imaging data precisely. In particular, smaller and smaller amplitudes are required at higher spatial frequencies to represent perfectly the sharp edges of the line. The second object, a continuously varying background has a sinusoidal pattern on the amplitude/distance plot. This is easily represented in the frequency domain with only a single spatial frequency required. In general, few spatial frequencies are required to define objects with blurred margins whereas a large number are required to reproduce sharp margins.

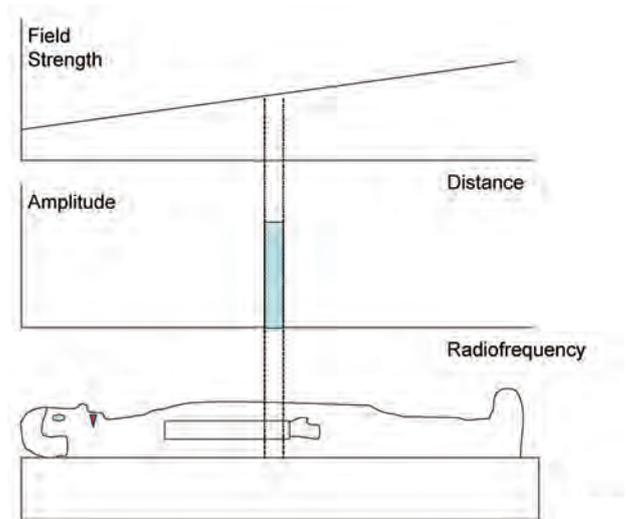


Figure 7 – Slice selection
 The diagram illustrates how a combination of a magnetic gradient and a radiofrequency pulse can be used to excite a particular slice of the body. The thickness of the slice depends on the steepness of the magnetic gradient and on the range of radiofrequencies used (bandwidth).

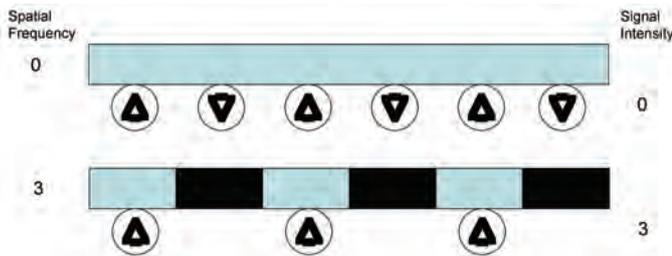


Figure 8 – In slice localisation
 This diagram illustrates the principle of localisation by phase-encoding. A magnetic gradient applied across a slice of tissue will alter the phase of protons along the plane of the gradient. In this case, a gradient has been applied that varies the phase by 3×360 degrees per unit length. In the upper section, protons are evenly distributed and do not generate any signal because of phase cancellation. In the lower section, protons are distributed at a spatial frequency of 3 per unit length. Their signal intensities summate perfectly so that the gradient has sensitivity to spatial frequencies of 3 per unit length. The gradient must be varied to detect all the spatial frequencies required for a complete image (typically 256 frequencies for MRI).

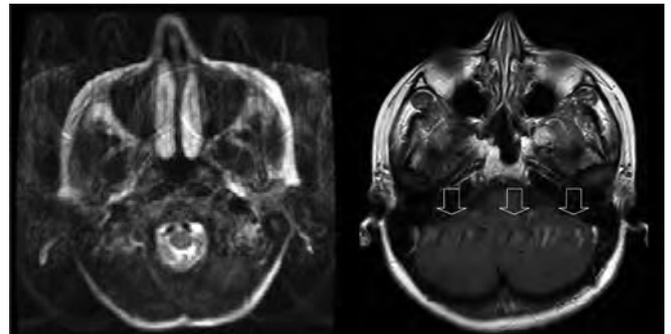


Figure 9 – Ghosting
 Ghosting artefacts are common in MRI and take the form of repeated representations of high intensity areas across the image. Motion is one of the frequent causes (Fig 9a left). Flowing blood also produces ghosts across the image which are more obvious on gadolinium enhanced acquisitions and may be mistaken for enhancing lesions (Fig 9b right).

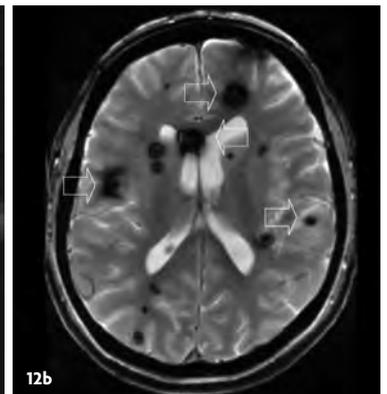
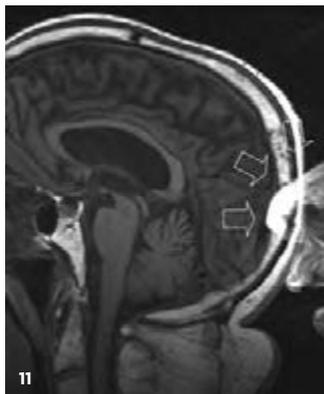
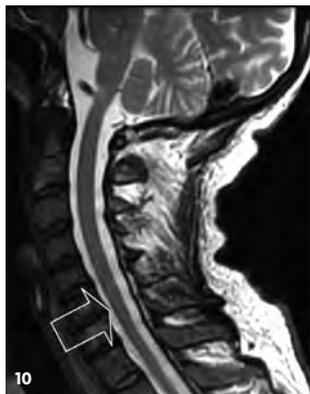
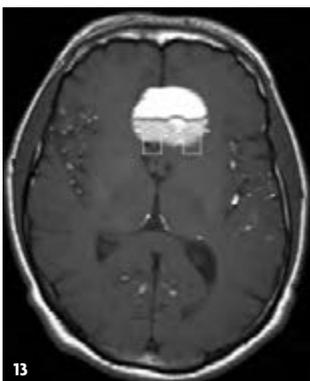


Figure 10 – Gibbs artefact
 This is usually seen in images of the thoracic cord, particularly those obtained on large fields of view.

Figure 11 – Phase wrap
 This artefact is usually easily recognised, but can cause confusion, occasionally mimicking intracranial masses.

Figure 12 – Susceptibility
 This artefact gives rise to signal loss around ferromagnetic metallic implants (Fig 12a). It can be used to advantage to demonstrate iron deposition in areas of chronic haemorrhage in cavernomas (Fig 12b)

Figure 13 – Chemical shift
 Protons in fat resonate at a slightly different frequency and phase to those in water. Since spatial localisation depends on these properties, protons in fat are slightly misregistered in space giving rise to a dark edge next to areas of fat. It is as though the fat has been shifted by a pixel or so. This image shows a dermoid with posterior soft tissue and anterior lipid layer.



Spreading Depolarisations: Tsunamis in the Injured Brain



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Glossary:

COSBID: Co-Operative Study of Brain Injury Depolarisations (www.cosbid.org)

CSD or SD: cortical spreading depolarisation (usually implies that the vascular response is vasodilator)

PID: peri-infarct depolarisation (usually quickly followed by vasoconstriction of varying duration)

DC: direct current

ECoG: electrocorticogram

Ke: extracellular potassium ion concentration

NADH: nicotinamide adenine dinucleotide (reduced state)

TBI: traumatic brain injury

History and basic neurophysiology

"Spreading depression of activity in the cerebral cortex" is the title of a paper by Aristides Leão that reported his finding of an apparent wave of silence in the electrocorticogram (ECoG) that spread backwards from a site of electrical stimulation on the frontal lobe of rabbits at a rate of some 3mm/minute.¹ Leão's aim had been to establish a model of Jacksonian epilepsy, and the unexpected result stimulated him to further work. The title has stood the test of time, and the phenomenon has been the subject of many papers from basic neuroscientists, but as he himself established, its essence is mass depolarisation of cellular elements in the cortex, with the spreading depression of the ECoG that he first observed being an effect of this: the term "spreading depolarisation" (SD) best identifies the fundamental event. Leão thought that his phenomenon might be the basis of the visual aura of migraine, and recent imaging work (see below) confirms directly the longstanding and universally held concept of spatial spread of the phenomenon in the cerebral cortex being analogous with the first ripple that spreads from a stone thrown into a pond (see video 1). That SD is the basis of the visual aura of migraine has also been confirmed.² As Leão recognised, in healthy cortex spreading depolarisation needs to be deliberately induced with some form of mild insult to the cortex, but experimental work over the past 30 years, and especially recently, has emphasised the profound pathogenic potential of many spreading depolarisation events that occur spontaneously, and we shall see below that the analogy of a "tsunami" is very appropriate.

Leão established some important fundamental features of SD. There is marked but transient vasodilation in the pial circulation,³ and surface cortical veins are briefly arterialised. He also found that carotid occlusion delayed recovery of the surface DC potential, indicating the dependence of recovery on energy supply. Grafstein isolated slabs of cortex in situ in rabbits, using subpial transections, and with microelectrodes was able to show a transient phase of mass, uncoordinated neuronal firing that coincided with the onset of the depolarisation.⁴ This is marked by an abrupt negative change in the surface cortical DC potential by some 15 mV, and this rather than ECoG amplitude suppression is the principal marker of a depolarisation, since it can still occur when the ECoG is already flat (see below). Grafstein also proposed that release of potassium

ions into the extracellular space is an important and possibly critical element supporting the spread of depolarisation, and this is closely coupled with glutamate release.⁵ In broad summary, the mechanism of spread of a depolarisation is thought to centre on a massive focal release of potassium in a small focus, in sufficient concentration in the extracellular space of grey matter to depolarise neighbouring neurones (and probably astrocytes), leading to further, "regenerative" depolarisation of adjacent tissue, thus spreading the depolarisation throughout tissue that is susceptible. Multiple areas of grey matter in addition to neocortex have been reported to support spreading depolarisation – hippocampus, basal ganglia, spinal cord, and, if heavily pre-treated, brain stem nuclei. The early 1970s saw the arrival of ion-selective microelectrode technology, bringing support for Grafstein's concept from the use of potassium sensitive electrodes. Soon afterwards, a paper from Branston et al was the first to report spontaneously occurring, transient increases in extracellular potassium (Ke) in the periphery of an ischaemic territory in the primate cerebral cortex.⁶ These transient events were thought by these authors to "resemble spreading depression", and came to be widely recognised as a prominent feature of the ischaemic penumbra in experimental stroke models: peri-infarct depolarisations, PIDs.⁷

"Cortical spreading depression" (SD) versus "peri-infarct depolarisations" (PID): critical differences

Although the basic neurophysiological mechanisms of depolarisation and its spread appear similar in SD and PID,⁸ there are critical differences that are potentially highly relevant to clinical management, now that both phenomena are known to be common events in the injured human brain (see below). SD is associated with profound hyperaemia – up to 400% – that lasts for approximately 1 minute, and is followed by mild oligoemia to some 80-90% of baseline,⁹ and it now seems clear that hyperaemia is what ensures that SD is not associated with tissue damage. That restoration of resting membrane potential following SD imposes a large metabolic load on grey matter was shown by Shinohara and colleagues, who found that local cerebral glucose utilisation was doubled during recovery from SD.¹⁰ It is possible that the hyperaemia is not sufficient to meet the demand, even with full, aerobic oxidation of glucose, since it has been shown that tissue extracellular glucose is

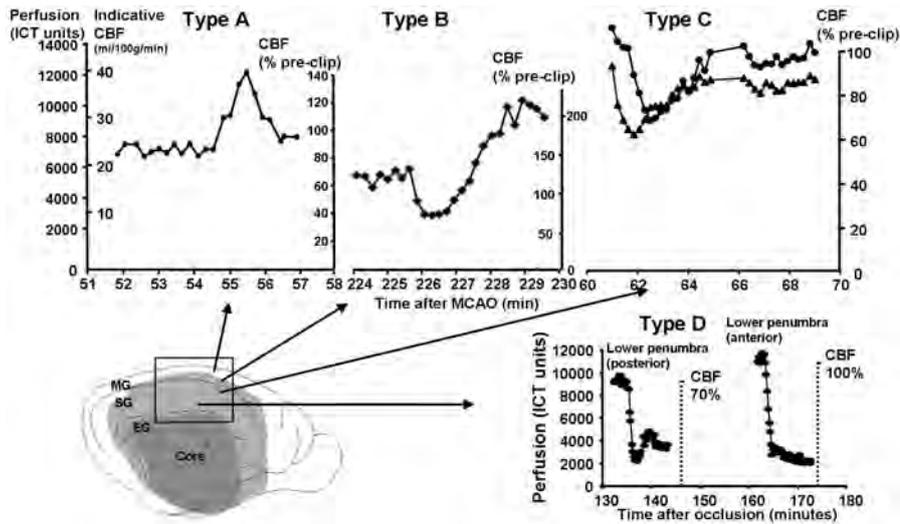


Figure 1: (Figure and legend based on (Open Access) Strong et al. 2007.¹⁹ Brain 130(4):995-1008)

Examples of four different patterns of transient (A, B, C) and sustained (D) changes in perfusion that propagate in penumbral or near-normal gyri linked to depolarisations following experimental middle cerebral artery occlusion in the cat. For upper three panels, speckle contrast and indicative CBF scales are shown to the left, and individual reactivity scales to the right of each figure. Type A: monophasic transient increase in perfusion, typical of near-normal/normal cortex (unshaded, medial ribbon of MG (marginal gyrus) uppermost in diagram, perfused largely by the anterior cerebral artery). Type B: biphasic, consisting of a transient fall in perfusion (approximate half-time for recovery to baseline 0.5-1.5min), followed by hyperaemia, typically lasting 5-10min,

typical of upper penumbra (shaded portion of MG in diagram). Type C: monophasic transient decrease in perfusion, with varying rate of recovery, which was sometimes incomplete, approximate half-time 2-30min. The panel illustrates effects on perfusion of a single Type C event propagating forward through two ROIs, here in upper penumbra (lateral MG). Type C events were more typical of intermediate penumbra, as illustrated by arrow. Type D: examples of abrupt, marked falls in perfusion, with no or minimal recovery, associated here with two separate spreading events, some 40min apart, on lower penumbra; indicative CBF fell to $-10\text{ml}/100\text{g}/\text{min}$, i.e. core conditions. Dotted calibration bars indicate CBF change as percentage pre-occlusion.

reduced for up to 30 minutes after SD.¹¹

In contrast, the number of PIDs is closely related to infarct size in stroke models,¹² and has been shown to be the determining variable, rather than simply a marker, of infarct size.¹³ Additional work has suggested that aggregate duration of depolarisations rather than simply their number is the critical factor.¹⁴ As well as the large increase in K^+ with depolarisation, there is also a large inward calcium ion movement which, if at all sustained, initiates both necrotic and apoptotic cascades. The role of PIDs in ischaemia was attributed until recently to energy metabolite depletion and failure of the cortical surface collateral circulation in the penumbra to deliver the increments in perfusion required to achieve repolarisation. This would lead to sustained depolarisation and hence to infarction in the affected area of penumbra, resulting in the stepwise recruitment of penumbra into the expanding core.

Vasoconstriction and spasm associated with focal ischaemia

However, *in vivo* experimental stroke work from several laboratories has now shown that the vascular response to depolarisation in ischaemic boundary zones is – in terms of pathogenesis – much more aggressive than previously thought. Rather than simply a failure to dilate in response to depolarisation, there is active vasoconstriction that is frequently sustained for long periods. In chronological order, Waltz and Sundt published an elegant description of episodic vasoconstriction of surface vessels in the primate cortex following occlusion

of the middle cerebral artery.¹⁵ They attributed this to a process of active vasoconstriction but did not seek or detect evidence of depolarisation events. Dreier and colleagues showed in a series of experimental papers that if the cerebral cortex of rats is superfused with artificial CSF containing haemoglobin and potassium ion, the hyperaemia that spreads in response to a SD (the most extreme challenge to the normal coupling of cerebral blood flow with function and metabolism) is converted to spreading ischaemia,¹⁶ and indeed leads to cortical infarction that closely resembles what is seen in patients who have suffered a fatal aneurysmal subarachnoid haemorrhage.¹⁷ They designated their observation “inverse coupling” of blood flow. Later, using laser speckle imaging of the exposed mouse cortex to map perfusion quantitatively as a marker of depolarisation, Shin and colleagues were able to document recruitment of additional peri-infarct tissue into the area where perfusion was less than 20% of pre-occlusion, in step with each repeated depolarisation event. Importantly, they also showed that the timing of each perfusion event that resulted in a sustained fall followed – rather than led to or caused – the electrophysiological depolarisation.¹⁸ Most recently, Strong et al, also studying the effects of middle cerebral artery occlusion with laser speckle imaging, but now in the gyrencephalic brain (cats), found that the transient perfusion response to a depolarisation could be assigned qualitatively to one of four categories, ranging from sustained (and sometimes profound) reduction in perfusion to normal hyperaemia, depending on proximity of the

focus being assessed to the infarct core (see figure 1 and video 2).¹⁹ This pattern of response is radically different from that of the normally perfused brain, where a wave of hyperaemia spreads as a concentric wave from a point of disturbance, much as Leão envisaged (Video 1). The mechanism of vasoconstriction in ischaemia clearly needs to be understood, and therapies to reverse it devised: activity of, and substrate availability to, endothelial nitric oxide synthase is one possible candidate.²⁰

Other adverse effects of depolarisations

Brain glucose. Technology to sample glucose and lactate in brain microdialysate at high frequency (30 seconds) has detected time signatures typical of peri-infarct depolarisations – a transient or more sustained fall in tissue glucose, accompanied by a rise in lactate,²¹ and it is now clear that even a “normal”, hyperaemic depolarisation is accompanied by a fall in tissue glucose that may last up to 30 minutes.¹¹ Such falls can be cumulative,²² and low levels of brain dialysate glucose are associated with poor outcome in patients with traumatic brain injury (TBI).²³

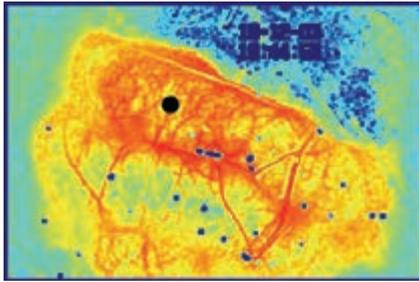
Inflammation. Depolarisations, even in the normally perfused brain, lead to increased levels of matrix metalloproteinase-9, which greatly increases blood brain barrier permeability²⁴; the inflammatory cytokines $\text{IL-1}\beta$ and $\text{TNF}\alpha$ are also upregulated.²⁵ Cyclooxygenase-2 and *c-fos* and *jun-B* are also induced by CSD.^{26,27} In some cases, the association is relatively specific: for example, the degree of induction of the mRNAs encoding brain-derived neurotrophic factor and heat-shock protein-72 in response to CSD induced in the rat is dependent on the number of CSDs.²⁸

Are depolarisations ever beneficial?

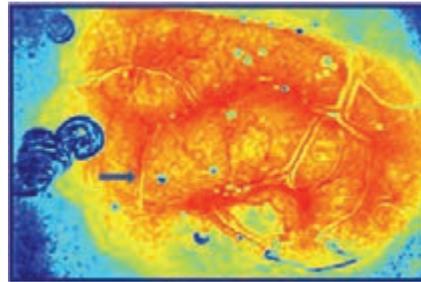
An inflammatory response should not necessarily be considered harmful, and it is easy to envisage that the inflammatory response evolved originally as a beneficial mechanism that only became potentially harmful in the context of cerebral ischaemia – thus largely after the reproductive phase of human life has closed and there is no evolutionary disadvantage from adverse effects of depolarisations. More specifically, experimental induction of depolarisations in rats confers protection from subsequent ischaemia,²⁹ and induces neurogenesis in the subependymal periventricular layer in rats.³⁰

Spontaneous depolarisations in the injured human brain

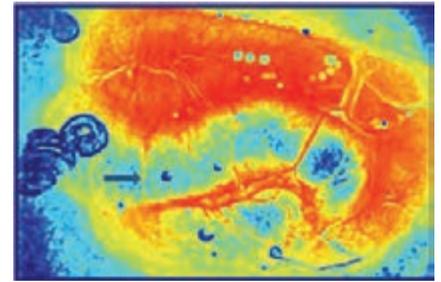
Mayevsky and colleagues used a multiparametric monitoring device located in the right frontal region in patients receiving intensive care following major head injury. They reported observation of linked potassium, perfusion and NADH transient events suggestive of transient depolarisation in one of 14 patients, but at the single observation site could not demonstrate spread of the event (Mayevsky et al. 1996).³¹ Later, Strong et al inserted linear 6- or 8-electrode subdural strips over pericontusional areas following evacuation of a traumatic



Interval image from video 1, indicating site of endothelin injection to initiate a typical hyperaemic depolarisation in the normally perfused brain.



Sample image from early in video 2, 170 minutes after experimental occlusion of the middle cerebral artery (MCAO), showing restricted area of ischaemia in proximal middle cerebral artery territory (lowermost in figure).



Final image in video 2, 180 minutes after MCAO, showing newly ischaemic territory following spread of a vasoconstrictor depolarisation. Note new spasm in a surface vessel (arrowed in centre and right panels).

LEGENDS TO VIDEOS

(Available for viewing with the online version of ACNR)

Video 1: Time-compressed sequence of pseudo-colour-mapped semiquantitative images of perfusion at the cortical surface (laser speckle method: (Dunn et al. 2001)¹⁸) following a microinjection of 10^{-7} M endothelin at the focus of initiation of the spreading hyperaemia. Animal experiment: chloralose anaesthesia; gyrencephalic brain. Images were acquired at 13-second intervals and illustrate concentric, radiating spread of hyperaemia (as a surrogate marker of depolarisation), at the rate characteristic of spreading depolarisation, approximately

3mm/minute. The wave is seen to disappear into sulci before re-emerging onto an adjacent gyrus.

Video 2: (Reproduced (Open Access) from Strong et al. 2007. *Brain* 130(4): 995-1008)³² Time-compressed sequence of pseudo-colour-mapped semiquantitative images of perfusion at the cortical surface (laser speckle method (Dunn et al. 2001)¹⁸): red = hyperaemia, blue = ischaemia). Animal experiment: chloralose anaesthesia; gyrencephalic brain, 3 hours following occlusion of the middle cerebral artery (MCA). Images of the ischaemic hemisphere were acquired at 13-second intervals. At the start of the sequence, which lasts some 10 minutes, perfusion in the

“resting” state is normal in the majority of the exposed field, but reduced in the initial core area (lowermost). Sustained reduction in perfusion accompanies the depolarisation as it spreads outwards from the core infarct region, and there is a delay as the event traverses the lateral sulcus before emerging on the most medial gyrus. Here, in the outer penumbra (uppermost in image) the vasoconstriction is transient, and is followed by hyperaemia. Some constriction of a surface vessel is seen to the left of the newly ischaemic territory. The final image is at the conclusion of the sequence, and shows the ischaemic territory that has developed as the result of one vasoconstrictor depolarisation.

haematoma (the series –coincidentally also of 14 patients - included 2 patients with ruptured intracranial aneurysms and one with spontaneous hypertensive intracerebral haematoma) and recorded spreading waves of depression of ECoG amplitude, similar to Leão's original finding, in some 71% of patients overall.³² The much higher incidence of depolarisations that they reported (in comparison with Mayevsky et al) seems likely to result from placement of the electrode strips over peri-lesion cortex, and suggests in turn that a depolarisation in the injured human brain may not necessarily invade the whole hemisphere as widely as occurs in lissencephalic and smaller brains. Conversely, the possibility arises that in a patient with multiple areas of contusion, cortex around each contusion may be affected by depolarisations. These authors were subsequently joined by others to commence the CoOperative Study of Brain Injury Depolarisations (“COSBID”, www.cosbid.org): the central goal of the study is to determine which, if any, patterns of depolarisation are independently associated with poor outcome in patients with TBI, higher grade aneurysmal subarachnoid haemorrhage (aSAH), malignant hemisphere occlusive stroke (MHS), or spontaneous intracerebral haematoma (ICH), and a strategy to address this issue is in place. High incidences of depolarisations have now been described by COSBID following aSAH³³ and ICH,³⁴ and in MHS the incidence is 100% if two cases are excluded in which the ECoG strip was placed over the infarct core (Dohmen et al. 2008).³⁵ Refinement of ECoG processing has made it possible to discriminate CSD from PID, on the basis that many depolarisations have been detected in the complete absence of ECoG activity.³⁶

Avoidable factors promoting depolarisations: plasma glucose reduction, pyrexia and arterial hypotension

Some factors have been identified which are likely to promote depolarisation activity and

which deserve attention in clinical management. In the laboratory, there is a robust association of increased frequency of spontaneous PIDs with even mild reduction in plasma glucose (5-6 mmol/L) following middle cerebral artery occlusion (cats)²¹: these data, coupled with much clinical evidence of an adverse effect of levels above 10 mmol/L, suggest that an optimal plasma glucose for a patient with acute brain injury might lie in the region of 7-9mmol/L. While there is evidence, heavily relied upon in general intensive care practice, of benefit from tight glycaemic control to 4-6 mmol/L with insulin in the general ICU population,³⁷ the potential risks of targeting the same levels in patients with acute brain injury have been highlighted.^{11,38,39,40} A high incidence of verified PIDs in association with low plasma glucose has now been reported in a patient with aSAH (Dreier, personal communication, 2008). Pyrexia appears to be associated with increased frequency of depolarisations,⁴¹ and there is emerging evidence to implicate arterial hypotension as a further cause.⁴²

Future clinical and experimental research

A curious feature of depolarisations, seen both in the laboratory and in patients, is a tendency for their occurrence to be grouped in temporal clusters, often with remarkably constant periodicity, usually in the range 20-40 minutes, depending on the precise setting. Since, as we have seen, depolarisations may induce both adverse and beneficial effects, repetition or clustering of depolarisations in the neighbourhood of a focal lesion probably constitutes a powerful mechanism serving to amplify its effects – either for better or for worse.

These uncertainties serve to emphasise the importance of detecting depolarisations in the injured human brain, and of determining whether their effects are likely to be beneficial or harmful in a given patient. At present, it seems that whether the cerebral circulation dilates normally or constricts in response to a

depolarisation event is likely to determine how an ischaemic or traumatic lesion evolves, and hence the clinical outcome. Thus the current challenge to clinical and basic researchers is to understand the nature of the abnormal vasoconstrictor response to depolarisation and how to characterise and reverse it in critically ill patients. In addition, since the need for subdural electrodes as a means of monitoring for depolarisations restricts the study population to patients requiring emergency craniotomy, a noninvasive method for detection of depolarisations would be valuable. ♦

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Culturally Adjusted Rehabilitation Models



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No other branch of medicine is as intrusive as rehabilitation. Treatment programs are personalised to the point of readjusting the very private habitat of an individual. Whilst as rehabilitation teams we state that our work is directed at reclaiming lost function, subconsciously we proceed to readjust functional status. The readjustment process of the personalised style of daily living can inadvertently become a process of remodeling, a step beyond rehabilitation. I have often observed the tragedy of the loss of a person "within" to the enthusiasm of rehabilitation teams and their process of action. Often rehabilitation processes deliver a modified individual, one that is alien to "Self". This sets off a long-term internal battle of acceptance of a very personal nature, as the individual struggles to readjust to his / her new identity. This, indeed, is a battle that is often lost by the one who initiates it. Whilst it is necessary to engineer "Self Alteration" for optimised rehabilitation outcomes in some cases, it should be the last choice of treatment strategy rather than the premier treatment plan.

Although rehabilitation medicine is a relatively young branch of medicine, the practice parameters must continually undergo critical appraisal and it is imperative that the fraternity practising it, should evaluate its current and ongoing practices.

I have now been working in the United Arab Emirates for just under two years. Through my experience of working with a large and varied expatriate community, as well as the indigenous population, I am beginning to learn that the current practice of rehabilitation, mainly developed against the background of modern western lifestyle, is unsuited to the needs of majority of world population. In this article I will argue that we need to develop Culturally Adjusted Rehabilitation Models (CARM) in order to achieve best outcomes for all our patients irrespective of social, cultural and religious backgrounds.

Each community of people has its own needs and life style, one that must be respected by those who seek to serve it. The life structures are constructed upon a framework of religious rituals, linguistic expressions, social demands and practices. These determine the pace and scale of activities, familial and social rights and responsibilities as well as vocational and occupational trends. For rehabilitation practice to be optimally successful in serving a community, rehabilitation teams must educate themselves about the prevalent social, religious and cultural constructs of the community they serve.

It is indeed unrealistically exhaustive to formulate a rehabilitation model for each community of people. However, there is an urgent need to develop a set of general principles that should

enable a rehabilitation team to tune its functioning to the need of the community that it serves.

I will introduce certain concepts that I have formulated during my period of practice in the UAE. I have learnt to give credence to several factors that I never considered objectively important during my years of practice in the United Kingdom. On reflection, it appears to me, that my training and lifestyle in the UK had given me sufficient insight into the life structures of the population I was serving and hence a conscious effort to take notice of such factors was not required. I was subconsciously programmed to design rehabilitation plans that were appropriate for the community I was serving.

Each community of people has a very specific response to disease. Whilst the varied response patterns are appreciated, these have not been accurately evaluated and are often the subject of broad-based statements of cultural sensitivity. The modeling of rehabilitation programmes whilst sensitive, may lack specificity. For example disengagement of family and patient empowerment may be considered rather an uncomfortable issue to approach in a hierarchical family setup but careful tuning of the rehabilitation plan to incorporate this as part of the program is seldom attempted. Having studied such issues I now believe that we must define certain variables that should allow us to tune and model programmes that would suit an individual patient's cultural and social requirements.

The first such variable I have termed "habitualised dependence". Whilst the term habitualised behaviour has been used in relation to societal institutionalisation¹ and on occasion there has been a loose association with dependency, this term has not been used to describe variance within a normal socially and culturally varied group of people. In this context I define "habitualised dependence as developmentally structured and promotional dependence upon artificially acquired facilities and modalities to enhance comfort and ease in daily living and social interactions".

This construct inherently demands a variability of behaviours of people depending upon their habitat, religious beliefs, practices and rituals and social setups. An individual living in the northern hemisphere is more dependent upon the need for a heated home, a hot water supply, well gripping shoes and several layers of clothing. As for a patient in the United Arab Emirates, the need is one for cooling systems, cold and plentiful drinking water supply and light clothing. However, added to the pressures of weather, religious influence maintains a degree of complexity in dressing. Furthermore, influences such as interdependence or interdependence and hierarchical family setup determine an individual's cognitive and

intellectual dependence or independence. Indeed the influence of cultural factors becomes paramount in the area of cognitive and behavioural habituated dependence. For instance a teenager may not have developed a complex decision making capacity in an excessively protective, supportive or dominant family setup. Dependence on maids, servants or helpers may also modify an individual's abilities in activities of daily and advanced daily living. Habituated dependence, or for that matter independence, may curtail or enhance the capacity of a person to interact with self, people and environment as an entirely self reliant individual. In modern times habituated dependence on equipment such as elevators, cars, calculators, computers and telephones must now be considered normal in developed and affluent communities yet is still not readily accessed by the majority of the world population.

In view of the above discussion it is necessary, for treating rehabilitation teams to have in-depth understanding of the prevalent normalised habituated dependence of the community or society that they serve. This should form the pivot around which the individualised rehabilitation plans are developed.

The second variable that I am beginning to take note of is "Impairment Realisation Time (IRT)". I define this as "The time up to the point at which a patient fully and consistently begins to realise that he or she has lost func-

Time (IDAT)". I have defined this as "time from IRT to full appreciation and acceptance of permanent functional loss of a body part due to impairment and clear indication of compensatory strategies being put in place to compensate". I have observed that different communities of people have different time spans over which this status is achieved. Quite interestingly I have noticed that shorter IRTs do not necessarily equate with shorter IDAT. Most available literature on disability acceptance is retrospective⁵ whilst the IDAT has to be based upon prospective observations and evaluations.

The fourth variable that is vital to understand for good rehabilitation is the "Disability Adjustment Time (DAT)". I define this as "Time from acceptance status to a fully compensated and modified status that a disabled individual must achieve in order to establish maximally possible independent or care dependent lifestyle leading to the best achievable level of social and vocational integration or reintegration". Whilst disability acceptance is a widely understood concept,⁶ work on culturally adjusted disability acceptance is rather lacking.

The second, third and fourth variables require scientific evaluation and quantifiable values attached to each. Inherently the studies will require multi-centre and multi-national collaboration. We are presently looking at setting up such comparative studies.

rehabilitation outcome extremely negatively. The treating rehabilitation team must know the prevalent belief systems in the communities they serve in order to pre-empt the risk. Strategies should be put in place early during the acute stages of management to prevent pathological hope taking roots. The task becomes complex as the team must not allow all hope to be extinguished and must avoid cultivating negativity and depression.

As will be seen from the descriptions of the aforementioned variables, rehabilitation models must vary for different communities of people in terms of reclamation and retrieval of lost functional status, time and timings of interventions, length of inpatient and community based rehabilitation and short and long-term supports. I do not believe that North American or Western European standards can be directly imported to and implemented in the United Arab Emirates or for that matter any other area of the world with the exactness with which these are adhered to in the original communities.

In this article I have presented some new ways of analysing the needs of patients requiring rehabilitation. There is a clear need to conduct work in order to quantitatively define the variables. This analysis should lead to defining the cultural and social constructs of the communities patients originate from, and allow the treating teams to develop Culturally Adjusted Rehabilitation Models (CARM). ♦

For rehabilitation practice to be optimally successful in serving a community, rehabilitation teams must educate themselves about the prevalent social, religious and cultural constructs of the community they serve

tion of a body part and that there is a definite likelihood of this loss being partially or completely permanent". Whilst the phenomenon of "Denial" has been widely described,^{2,3} I do not consider this to be same as IRT. Denial implies volitionally generated response whilst I consider IRT to be a conditioned response to injury. This conditioning is influenced by cultural, religious and societal factors. Furthermore denial has been considered as an interim coping strategy⁴ and as such may be one of the expressed psychological phenomenon during IRT. I have further begun to realise that each community is likely to have a mean IRT with individual variations above and below the base line. As a crude observation I can state that patients from South Asia may have less IRT, as in my experience, unless complicated by perceptual deficits they begin to query the permanence of their impairments earlier than patients from other communities. This of course is only an observational statement and one that requires scientific evaluation.

The third variable that I would like to introduce is "Impairment to Disability Acceptance

Finally one other phenomenon that I now recognise is the negative impact of "Hope" on rehabilitation outcome. In the context of rehabilitation I refer to it as "Pathological Hope". I simply define it as "hope generated on the basis of belief that complete or near complete recovery of lost function will occur". The construct of pathological hope has been described in the literature.⁷ Pathological hope takes firm roots in the patient's psyche and becomes so strong that it makes the patient virtually incapable of engaging in processes that invite him, or her, to accept and adjust to impairment or disability. Patients harbouring pathological hope believe that rehabilitative interventions are vehicles to achieving recovery and not modalities that lead to achieving maximum possible function given the level of disability. Patients who hold such hope fail to consider analytically the need for care support or equipment requirements and entertain all such provisions as temporary until near complete or full function is restored. Whilst over an extended period there is some dispensation and weakening of hope, lost time due to the pathological hope impacts on final reha-

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Central Mechanisms in Complex Regional Pain Syndrome (CRPS)

CRPS is poorly defined and usually occurs as a pathological response to injury. Established diagnostic criteria are listed in Table 1.¹ CRPS type 1 (no underlying neural injury) occurs with an incidence of 8-25 / 100,000 with about 75% of cases spontaneously resolving within 1 year.^{2,3} CRPS type 2 may result from any neural injury, but is seen in the UK most commonly in patients with diabetes, stroke and traumatic nerve injury. Efficacious treatments include steroids, bisphosphonates, nerve-altering adjunct analgesics (e.g. gabapentin), physical and desensitisation therapies. Nerve blocks help some patients. Many patients, despite these treatments, have intractable pain with associated loss of functioning and quality of life. Novel therapies are used including intravenous ketamine, intravenous immunoglobulin, tumour necrosis factor (TNF) blockers, thalidomide and intrathecal baclofen. Innovative rehabilitation techniques such as motor imagery programmes, mirror visual feedback and sensory discrimination techniques may also help.^{4,5} Several mechanisms, both peripheral and central, are thought to contribute to the development and propagation of pain in this condition. This review focuses on the brain in patients with CRPS, in particular the symptoms and signs most likely due to brain changes; functional imaging studies to support this; and finally putative mechanisms contributing to the propagation of pain.

Table 1: International Association for the Study of Pain's (IASP) Diagnostic Criteria for CRPS.¹

- 1 Presence of an initiating noxious event, or a cause of immobilisation*.
- 2 Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event.
- 3 Evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain.
- 4 This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction.

*Not required for the diagnosis

Clinical findings to suggest brain involvement in patients with CRPS

Patients with chronic (typically more than 1 year) CRPS1 have disorders in their body perception.⁶ It is unknown how prevalent these clinical features are in patients with CRPS of shorter duration or how frequently they occur in other diseases of the nervous system or chronically painful conditions such as arthritis. The main features are summarised in Table 2.

Most frequently patients with CRPS demonstrate macro- and microsomatognosias (distorted body part size when asked to draw or match a visual image). The majority of chronic cases also have digit misperception (finger agnosia) when they cannot identify correctly a touched finger with their eyes closed.⁷ Finger agnosia was originally described by Gerstmann in 1924 in a group of patients who also had dyscalculia, left-right confusion and agraphia. They all had lesions in the dominant parietal lobe involving the angular gyrus. Finally, patients with CRPS1 demonstrate somatoparaphrenia or a 'neglect-like' state: they have fixed negative beliefs towards their limb; dissociation and depersonalisation (they assign ownership elsewhere ("my hand's not mine", "my leg feels like an alien"); and an autotomy-wish where they desire it to be removed.

Body scheme is an "organised model of ourselves".⁸ It is a sub-conscious representation of the body's position in space. It is related to, but different from, body image which is a conscious representation of the body's position from the outside. Body scheme may be understood as part of a neuropsychological theoretical model of 'executive action' whereby non-routine tasks that

Table 2: Symptoms and signs suggesting brain involvement in patients with CRPS.^{6,7}

- Hostile feelings directed towards the limb, including a desire to get rid of it
- Dissociation from the limb (not feeling as if it belongs to them)
- Disparity between what is apparent and what is felt
- Altered awareness of limb position
- Changes in conscious attention
- Distorted mental image of affected parts
- Digit misperception

require decision-making and self monitoring are performed – i.e. the Supervisory Attentional System.⁹ It receives contributions from touch, proprioception, vision and motor commands. The body scheme has seven properties.¹⁰ It is spatially coded, modular, updated with movement, interpersonal and supramodal, i.e. integrates the different inputs from primary processing. It is adaptable. For example, in monkeys using tools, visual receptive fields of bimodal neurons that previously were linked to hand position become active when vision is directed towards the tip of a tool, or even the visual representation of the tool on a video monitor.¹¹ Finally the body scheme is internally coherent to ensure a continuity of body experience. For example, an illusory extension of the elbow is experienced when the biceps tendon is vibrated while the forearm is held at a fixed angle. If a blindfolded subject holds his nose during this procedure, the nose is perceived to grow in length (Figure 1).¹² Associative cortex, particularly the parietal lobes, is involved in this representation of the body scheme.

Brain changes in patients with CRPS

Functional imaging studies provide evidence for cortical reorganisation in the primary somatosensory (S1) and motor cortex of patients with CRPS1. The extent of functional activity in these areas is correlated with the severity of the pain. Functional activity normalises following successful treatment and pain resolution. For example, Maihofner et al. (2004) found that the extent of the S1 cortex representing the painful upper limb differed to that for the contralateral cortex representing the pain-free side in patients with unilateral upper limb CRPS1.¹³ Symmetry of these magnetoencephalographic functional maps was restored following successful treatment measured by pain reduction (Figure 2). Such cortical reorganisation has an important role in maintaining pain memories suggested by the fact that the amount of cortical reorganisation is correlated with the chronicity and severity of pain in conditions such as fibromyalgia and chronic low back pain.¹⁴

Central mechanisms

As pain is reported as a conscious experience it is helpful to understand the complex nature of consciousness. It is proposed that consciousness is an 'emergent property' of the brain's functioning.¹⁵ The brain may be thought of as a complex system that is composed of separate parts, each of which has a set of internalised rules. The interaction of these separate parts occurs in a non-linear fashion and generates emergent properties that are best studied at a systems level. Another example of a complex system is the combustion engine, each part having a separate function. Linking the separate parts together generates the emergent property of power. Any change to an individual part of the engine may have unexpected effects on power output. In the brain, perceptual categorisation of sensory information combined with value-cat-

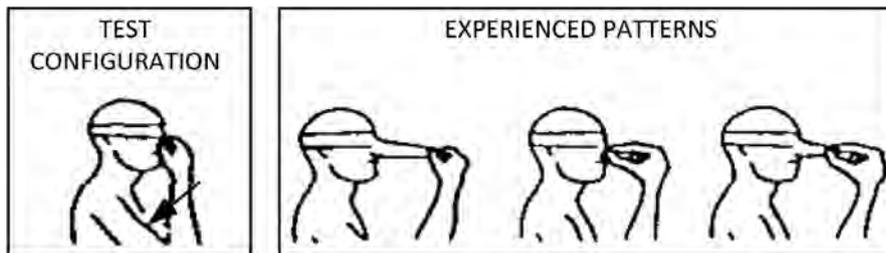


Figure 1: The arrow in the left figure indicates the placement of the vibrator in the physical test situation. Blindfolded subjects experienced their arms extend. In the right, cartoons illustrate the subjective experiences. Most felt their nose elongating, others experienced their fingers elongating but not their noses; a few experienced both elongating (Adapted from Lachner).¹²

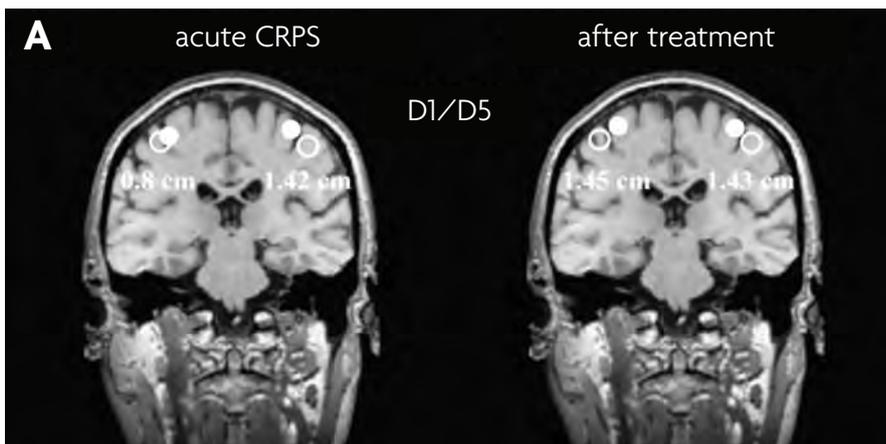


Figure 2: Cortical reorganisation in the primary somatosensory area (S1) in patients with upper limb CRPS. Overlapping representations of thumb (D1) and little finger (D5) resolve following successful treatment.¹³

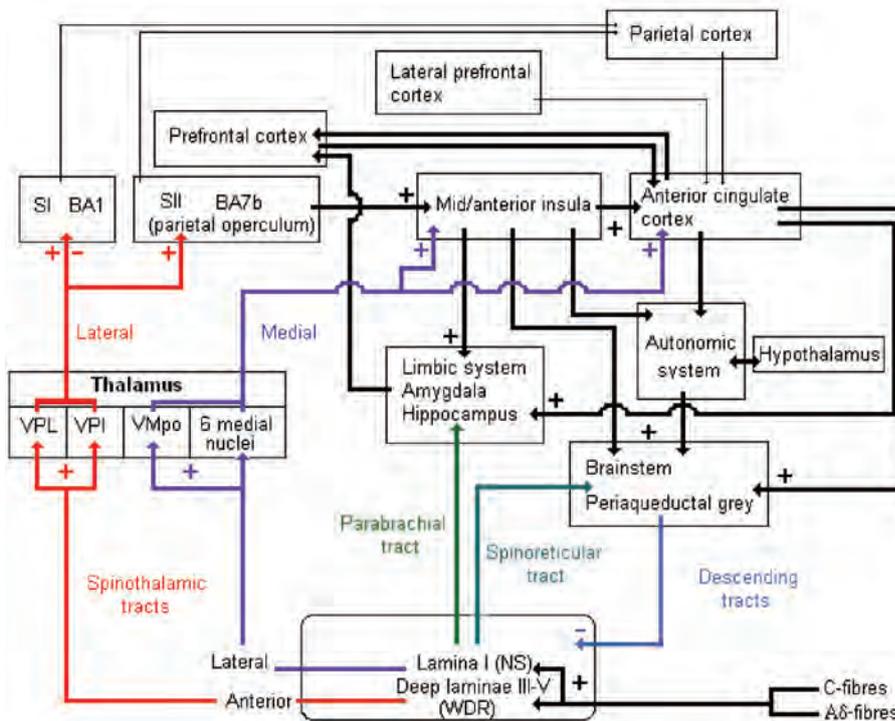


Figure 3: Pathways illustrating neuromatrix representing pain in humans.^{16,17}

egory memory may change the emergent property of conscious 'qualia-space'.¹⁵ It is within this conceptual framework that the sensation of pain may be understood.

The distributed neural matrix active during the experience of pain is summarised in Figure 3. This has been mapped under experimental conditions and is based on neurophysiological, neuroanatomical and functional

imaging studies.^{16,17} Nociceptive input is processed by the brain in at least two parallel pathways simultaneously. In general, the lateral pathway (shown in red) contains sensory discriminatory information allowing localisation and characterisation of the nociceptive stimulus. This pathway therefore processes the sensory-discriminative components of pain. The evolutionary older medial pathway

(shown in purple) processes affective information and has influence on cognitive functions concerning pain such as attention. It also has obvious effector pathways enabling both rapid and prolonged changes in the periphery via the sympathetic nervous system and hormonal release via the hypothalamus. This pathway therefore processes the affective-motivational components of pain.

What are the mechanisms for pain in patients with CRPS? Monitoring for incongruence between predicted and actual body states is an important function of the adaptive central nervous system. It has been hypothesised that sensorimotor incongruence involving vision, proprioception, touch and motor programmes generates pain in an analogous fashion to seasickness where incongruent vestibular, proprioceptive, visual and motor programmes generate nausea and even vomiting.¹⁸ By generating such somesthetic incongruence using a mirror and mismatched bilateral movements in healthy volunteers, a proportion (66%) described uncomfortable feelings including pain.¹⁹ Pain is relieved for some patients with CRPS by placing their affected limb behind a mirror and performing congruent bilateral movements while looking at the reflection of their unaffected limb.⁴ It has been demonstrated that sensorimotor incongruence activates an area in the right dorsolateral prefrontal cortex.²⁰ However, verbal semantic, visual and auditory congruence monitoring consistently involves the anterior cingulate cortex (ACC), albeit different areas within the ACC depending on experimental conditions.²¹

CRPS is associated with a neglect-like syndrome and neurological signs

The connectivity neuromatrix (Figure 3) demonstrates that both the lateral prefrontal cortex and parietal cortex have input to the ACC. This provides an anatomical opportunity for potential disruption to sensorimotor congruence monitoring, body scheme and autonomic outflow in the same location.²² ACC activation is important in modifying autonomic outflow responses, particularly the sympathetic nervous system, enigmatically linked to CRPS, a condition previously known as reflex sympathetic dystrophy. Furthermore, the ACC is involved in motor selection responses for noxious stimuli and learning associated with the prediction and avoidance of noxious stimuli.

Case reports of patients with lesions involving the ACC illustrate contralateral hemibody neglect that can be corrected when the affected side is placed in the unaffected visual field.²¹ Monkeys with unilateral cingulate lesions demonstrate motor neglect.²¹ Performing cingulotomies in patients with chronic pain produces a loss of emotional distress, even though the patients still reported that they were in pain – its meaning did not distress them.²¹ Further research into the specific role of the ACC, particularly Brodmann area 24, in the generation of pain, and pain-associated or learned behaviours may allow a better understanding of the neural basis for the bizarre, but consistent, clinical findings in patients with CRPS. Data from such research may illuminate potential therapeutic targets to allow extinction of maladaptive learning and normalisation of cortical function with the associated benefit of pain relief.

Conclusion

Patients with CRPS have abnormalities in body scheme and perception in addition to abnormalities in their peripheral tissues, nociceptive nerves and psychologic functioning when compared to healthy controls. Imaging studies demonstrate cortical reorganisation in areas involved in body perception. In combination these abnormalities may generate brain states that patients report as pain. Potential central mechanisms include sensorimotor incongruence and neuroplasticity and it is likely that the ACC has a pivotal role in this condition. ♦

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Surgery for Intractable Non-lesional Partial Epilepsy

Epilepsy surgery is a well recognised, time-honoured treatment modality for medically intractable partial epilepsy. It is generally recommended if two to three first-line antiepileptic drugs (AEDs) have failed to control seizures and the patient's epilepsy syndrome fulfils the criteria of "surgically remediable epilepsy syndromes (SRES)": SRES indicates an epilepsy syndrome for which (i) the natural history is relatively well known to be medically refractory or even progressive, (ii) presurgical evaluation can be accomplished largely non-invasively, and (iii) surgery offers an excellent chance that disabling seizures will be completely eliminated. Applicable syndromes include mesial temporal lobe epilepsy (MTLE), partial epilepsy with focal lesions, and hemispheric epilepsy in infants and children. The place of resective surgery in the management pathways of other types of epilepsy syndrome is still controversial, and may be considered only after the failure of exhaustive trials of AED therapy.

Resective surgery aims to completely resect or disconnect the "epileptogenic zone (EZ)" without precipitating any new neurological deficits. The EZ is a hypothetical zone defined as the brain area essential and sufficient for the generation of seizures, which can be confirmed only after surgery.¹

Identification and localisation of the EZ is the essential element of presurgical evaluation consisting of a set of different investigative procedures identifying various related zones: symptomatic zone, functional deficit zone, irritative zone, ictal onset zone, epileptogenic lesion, and eloquent cortex. Correct identification and logical correlation of these related zones is essential for the successful localisation of the EZ (Figure 1).

Recently, there has been a growing interest in surgery for partial epilepsy having no demonstrable structural abnormalities on MRI, "non-lesional partial epilepsy (NLPE)". This interest was precipitated by increasing proportions of patients suffering from refractory NLPE in epilepsy clinics, widely available intracranial EEG investigations, and advances in diagnostic technologies spanning from EEG telemetry to high-quality functional neuroimaging studies. Previously, Scott et al.² reported that the chance of successful resective surgery was unlikely in patients with NLPE, however, recent outcome studies for surgery of NLPE have been more encouraging, suggesting that it may provide a good chance of seizure control.^{3,4} McGonigal et al.⁵ reported that the surgical outcome in patients undergoing stereo-EEG investigations was not different between epilepsies with and without MRI lesions.

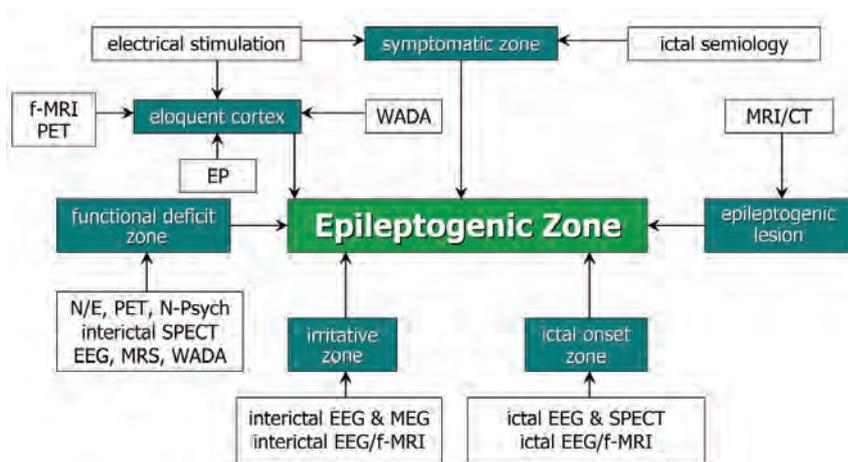


Figure 1: General concept of presurgical evaluation. f-MRI, functional magnetic resonance imaging; WADA, intracarotid sodium amytal test (Wada test); EP, evoked potential; N/E, neurological examination; N-Psych, neuropsychological tests; MEG, magnetoencephalography; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Surgical outcome in non-lesional partial epilepsy

The clinical experience of surgery for NLPE before the beginning of this century was generally unfavourable with the seizure free rate (SFR) ranging from 20% to 50%,^{6,7} which was much poorer than that for lesional epilepsy surgery (55-70%). SFR of non-lesional temporal lobe epilepsy (TLE) was higher than that of extra-TLE: 31-50% vs. 20-29%, respectively. On the other hand, the surgical outcome of NLPE in recent series shows SFR between 36% to 65% (Table 1). There was a trend for SFR being higher in TLE than extra-TLE: 31-70% vs. 17-57% respectively, however, this was not a consistent feature among centres.^{8,9} We found the same trend towards improvement in the surgical outcome of NLPE in our own case series: SFR was only 17% in 18 patients who were operated on in the 1990's,¹⁰ compared to 57% in 14 patients who were operated on after 2005 (unpublished data). Therefore, we are convinced that the surgical outcome of NLPE has greatly improved over the past decade. Although explanations for the outcome improvement are not readily available yet, we speculate that:

- more cautious patient selection for invasive EEG investigations;
- more extensive and comprehensive brain coverage by invasive EEG;
- the advent of high resolution functional neuroimaging studies;
- application of improved analytical methods for data processing⁷
- greater clinical experience with epilepsy surgery in general.

Pathology

The pathological features of NLPE are quite variable but generally can be categorised into normal, nonspecific abnormalities (e.g., gliosis, microdysgenesis, etc), and specific lesions (e.g., focal cortical dysplasia, hippocampal sclerosis, glioma, scars, etc). The relative frequency of each histological category is variable in different studies but approximately 40% may reveal specific lesions, another 40% may show nonspecific pathologies and the remaining 20% may show normal features (Table 2). The correlation of each pathological category to surgical outcome is also variable to individual studies and inconclusive. In our own case series of 14 patients, focal cortical dysplasia (FCD) type II was associated with seizure-free outcome in 5 of 6 patients, while 3 of 6 patients showing normal or nonspecific abnormalities and neither of 2 patients with FCD type I achieved seizure freedom. In addition, patients with FCD type II were more likely to show focal abnormalities on PET (Figure 2); while other pathologies were more often associated with either normal or widespread abnormalities in PET. We speculate that normal or nonspecific pathology may be associated with the development of widespread epileptogenic networks compared to that of specific lesions, thus rendering the complete resection of EZ more difficult.

Authors (year) ^{ref}	F/U (year)	N	Lobar Epilepsy (N)	Engel's classification			
				I	II	III	IV
Siegel et al. (2001) ³	≥ 2	24	TLE (10) Ex-TLE (14)	70% 57%	20% 21%	– –	10% 21%
Blume et al. (2004) ¹¹	≥ 2	70	TLE (43) Ex-TLE (27)	42% 30%	19% 4%	14% 7%	26% 59%
Chapman et al. (2004) ⁸	1-5	24	TLE (13) Ex-TLE (11)	31% 45%	54% 20%	– –	15% 35%
SK Lee et al. (2005) ¹²	≥ 2	89	TLE (31) Ex-TLE (58)	55% 43%	10% 5%	16% 31%	19% 21%
Alarcon et al. (2005) ⁴	≥ 1	19	TLE (13) Ex-TLE (6)	62% 17%	31% 17%	8% 33%	– 33%
RamachandranNair et al. (2007) ⁵	1-5	22	combined	36%	4%	32%	28%
McGonigal et al. (2008) ⁵	≥ 1	20	combined	65%	5%	25%	5%
Jayakar et al. (2008) ⁹	≥ 2	101	TLE (47)	47%	15%	17%	21%
			Ex-TLE (54)	41%	15%	17%	28%

ref = references; F/U = follow-up; N = number of patients; TLE = temporal lobe epilepsy;

Authors (year) ^{ref}	N	Normal	Gliosis/microdysgenesis	Specific lesion†
Siegel et al. (2001) ³	24	13 (54%)	7 (29%)	4 (17%)
Cukiert et al. (2001) ¹³	10	2 (20%)	4 (40%)	4 (40%)
Chapman et al. (2004) ⁸	24	0	13 (54%)	11 (46%)
Alarcon et al. (2005) ⁴	21	0	7 (33%)	14(66%)
SK Lee et al. (2005) ¹²	80	0	9 (11%)	71 (89%)*
McGonigal et al. (2007) ⁵	23	0	11 (48%)	12 (52%)
Jayakar et al. (2008) ⁹	101	18 (8%)	71 (70%)	13 (13%)

ref = references; N = number of patients.
† includes focal cortical dysplasia, hippocampal sclerosis, dysembryoplastic neuroepithelial tumour, scars, etc. * included patients with microdysgenesis

Predictive factors for surgical outcomes

Despite much effort to find meaningful prognostic factors for surgery of NLPE, no agreed-upon specific markers have been identified yet. However, it should be stressed that the demonstration of focal abnormalities in functional neuroimaging studies, localised interictal epileptiform discharges with or without concordant ictal onset discharges in scalp EEG, and the absence of evidence indicating multifocal epileptogenesis^{11,12} are quite important positive features for undertaking intracranial EEG investigations. Preference for specific intracranial electrodes is dependent on the concepts and experiences of individual centers, but most authors agree on the importance of extensive coverage of suspected brain areas.¹³ The interpretation and clinical significance of various electrophysiological features recorded from the intracranial EEG has also

not been fully assessed. However, low amplitude fast frequency discharges, reproducible and stable ictal onset zones, fast repetitive spike patterns, or ictal onset from the margin of subdural electrodes, have all been reported to have prognostic implications.^{10,14} In addition, many other factors including, for example, MEG dipole clusters, Taylor-type FCD and complete resection of the ictal onset zone, have been claimed to be associated with a favourable outcome.¹⁵ However, it should be stressed that the degree of congruence of results from various independent investigations is of the utmost clinical importance rather than relying solely on any specific features of individual tests.

Conclusion

In conclusion, we have seen rapidly improving surgical outcomes for intractable NLPE over the past decade. Explanations for this observation

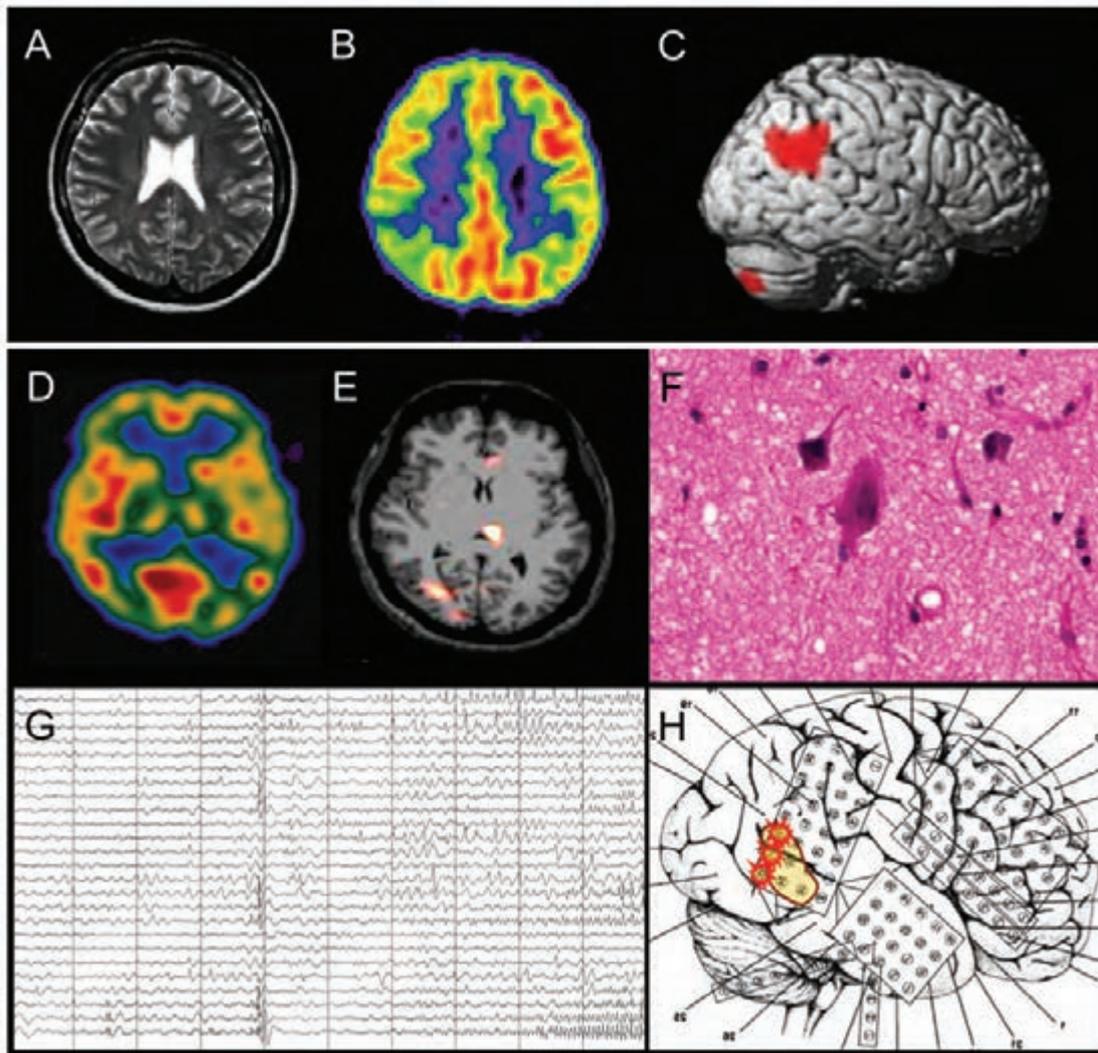


Figure 2: A 38-year-old right-handed woman who underwent resective surgery for chronic intractable complex partial seizures and secondarily generalised tonic-clonic seizures. T2WI-MRI showing no specific abnormality in the right parietal region by both 18F-FDG-PET (B) and PET-SPM (C). Ictal SPECT (D) and SISCOM (E) delineated the region of increased blood flow. Pathology of the specimen shows a dysmorphic neuron, consistent with FCD type IIa (F). Focal rhythmic fast ictal discharges were initiated in the right parietal subdural grid (G; H, red), and then spread to the adjacent electrodes (H, orange).

are not readily available, but, it is likely that a more cautious selection of patients based on the assessment of phase-I investigation (correlation of scalp EEG, clinical and functional neuroimaging studies) as well as a more extensive and comprehensive coverage of the brain by intracranial electrodes might be responsible for this. It is also likely that NLPE consists of heterogeneous epilepsy syndromes related to different

types of pathology. From a limited clinical experience, we speculate that the presence of a specific lesion is associated with a higher chance of detecting focal abnormalities in functional neuroimaging studies and a limited epileptic network amenable to focal resection. In contrast, normal or nonspecific abnormalities are often associated with normal or widespread abnormalities in functional neuroimaging stud-

ies and more widely distributed epileptogenic networks, requiring more extensive coverage of the brain by intracranial electrodes as well as a more extensive resection to achieve a better surgical outcome. Recent experiences of surgery for NLPE suggest that undertaking an invasive presurgical evaluation in carefully selected patients is worthwhile and gives a reasonable chance of surgical success. ♦

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EDITOR'S CHOICE

STEM CELLS: tools for screening drugs in SMA

The ability to make motor neurons from stem cells has always been an attractive prospect given the absence of any effective treatment for motor neurone disease and its variants. Over the years the developmental biologists have been hard at work understanding the normal developmental programme that specifies how a precursor cell ultimately ends up in the ventral horn as a motor neuron. This work, coupled to the exciting new development a couple of years ago on making induced pluripotent stem cells (iPS cells) has now translated into tools that might just lead to cell therapies. The group of Clive Svendsen and colleagues in Wisconsin have generated motoneurons using induced-pluripotent stem cells from a child with type 1 spinal muscular atrophy (SMA) and his unaffected mother. The clones so generated were then propagated and differentiated into motoneurons, and that whilst "iPS-SMA cells can produce similar numbers of neurons and motor neurons initially...the disease phenotype selectively hinders motor neuron production and/or increases motor neuron degeneration

at later time points". So, having set up a nice in vitro model of SMA, they screened for the ability of drugs such as tobramycin and valproic acid to increase production of the SMN protein. This ability to generate motor neurons in this way could simplistically be viewed as a way of trying to make new nerve cells to replace those that are lost in the disease. Obviously in cases where there is a genetic component such as in SMA, the cells would be expected to follow the fate of their predecessors in the host: namely die - as this paper shows in vitro. Perhaps the greatest strength of these cells is not so much as cell replacement but as a model and a cell line by which to study disease pathogenesis and then test therapeutic agents. - **RAB**
Ebert AD, Yu J, Rose FF Jr, Mattis VB, Lorson CL, Thomson JA, Svendsen CN
Induced pluripotent stem cells from a spinal muscular atrophy patient.
NATURE
2009;457:277-81.

PARKINSON'S DISEASE: watch out red heads

It seems that there has been a vague story circulating for years, that people with melanoma more frequently get Parkinson's disease... and that people with Parkinson's disease are at increased risk of melanoma...

Alberto Acherio and colleagues from Harvard decided to investigate this association at its most simple and ask: does hair colour (reflecting the quantity and distribution of melanin) influence the risk of Parkinson's? To get sufficient numbers, they ploughed the databases of the Health Professionals Follow-up Study (38,641 men) and Nurse's Health Study (93,661 women). And the result was that PD risk is 1, 1.4, 1.61, 1.93 for black, brown, blond, and red hair. For PD onset before the age of 70, there was an even greater correlation with odds

ratios of 1, 2.25, 2.73, 3.83 for the same hair tones. So, that explains why people with PD are at risk of melanomas... because they are more likely to be fair or red-haired. But why should variable expression of melanin be related to the risk of Parkinson's? Much biochemical hand-waving is the answer, from which I will spare you. No mention of sun-block preventing Parkinson's disease anywhere though, most disappointing. - **AJC**
Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A.
Genetic determinants of hair color and Parkinson's disease risk.
ANNALS OF NEUROLOGY
2009;65(1):76-82.

Journal reviewers

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HEADACHE: Glucose metabolism and headache

Despite the frequency of the problem and the volume of research, many aspects of migraine pathophysiology remain unclear. In particular we don't know what "sets the scene" for migraine, and whether there is something different about the brain of migraineurs. Looking at this question, this study is the first comparison of brain metabolism in migraineurs during headache-free intervals and controls. It examined glucose metabolism at rest in 11 migraineurs and 14 controls using PET scanning.

The study found significantly higher glucose metabolism bilaterally in the posterior subcortical cerebrum and in the cerebellum in those with migraine, during headache-free periods, compared to controls. Involvement in occipito-temporal white matter fits the clinical preponderance of visual symptoms in migraine. It is supported by electrophysiological studies showing increased amplitude of visual evoked responses in migraine, and functional studies showing heightened ability of migraine patients in low-level visual tasks, and heightened sensitivity to certain visual stimuli. The

involvement of the cerebellum is unexpected and the authors conjecture a shared link with essential tremor.

The investigators speculate whether increases in glucose metabolism are due to ischemia or a mitochondrial dysfunction. Given the frequency of migraine, this would have to be a subtle change in a biochemical property, or in metabolic processing under stress. To explain the frequency of migraine, it seems likely that any change is a variation on the biochemical spectrum, activated by other factors. Larger scale studies are important to investigate this further, preferably using functional MRI, avoiding the issue of radiation. It is intriguing, and takes us a step further in understanding possible changes in the brain of migraineurs, which predispose to the cascade of events involved in a migraine. - **HAL**

Kassab M, Bakhtar O, Wack D, Bednarczyk E.
Resting brain glucose uptake in headache-free migraineurs.
HEADACHE
2009;49:90-7.

COGNITION: Language lateralisation and the brachial plexus

Such a simple experiment this, but so profound. This German-Hungarian-American collaboration addresses how language becomes lateralised... Fifteen subjects were studied, who had all had severe brachial plexus injuries at birth so that one limb was flaccid and useless. Those subjects who had injuries to the right arm had – on fMRI testing of word generation – much greater language representation on the right hemisphere than in those with left arm injury. Furthermore, there was a correlation between the degree of injury and the extent of left-to-right shift.

This is exciting because it shows that reduced arm or hand function from a peripheral injury can lead to cortical reorganisation during language development. This implies that lateralisation depends to some extent on hand function. Perhaps our left hemisphere develops language best when we can gesticulate freely with our right hand? – **AJC Auer T, Pinter S, Kovacs N, Kalmar Z, Nagy F, Horvath RA, Koszo B, Kotek G, Perlaki G, Koves M, Kalman B, Komoly S, Schwarcz A, Woermann FG, Janszky J.**

Does obstetric brachial plexus injury influence speech dominance?

**ANNALS OF NEUROLOGY
2009;65(1):57-66.**

HEADACHE: Sodium channels, migraine and epilepsy

This study links a sodium channel gene mutation with familial hemiplegic migraine and epilepsy. It reports a novel mutation in the SCN1A gene. SCN1A mutations are well known in childhood epilepsy. The gene encodes a subunit of the sodium channel, and mutations have been described since 1997 in association with severe myoclonic epilepsy of infancy and “febrile seizures plus” syndromes. Recently, two mutations have been found in patients with pure familial hemiplegic migraine.

This paper describes a Portuguese family with a SCN1A L263V mutation. Five family members had familial hemiplegic migraine, and three of these had epilepsy as well. Importantly, migraine and seizures occurred independently. This description is a clear example of a molecular link between migraine and epilepsy. Many studies, going back over more than a century, have highlighted a link between migraine and seizures clinically, but this has simply been a clinical correlation. This study extends the spectrum of disease associated with epilepsy and migraine. The mechanism of this link between familial hemiplegic migraine and seizures is uncertain, but it seems most likely that there is more than one molecular pathway involved, given the difference in time course and manifestations of a migraine and a seizure. – **HAL**

Castro M-J, Stam AH, Lemos C, de Vries B, Vanmolkot KRJ, Barros J, Terwindt GM, Frants RR, Sequeiros J, Ferrari MD, Pereira-Monteiro JM & van den Maagdenberg AMJM.

**First mutation in the voltage-gated NaV1.1 subunit gene SCN1A with co-occurring familial hemiplegic migraine and epilepsy.
CEPHALALGIA
2009;29:308–13.**

EPILEPSY: plumbing the sulcal depths for seizures

Some patients present with highly focal clinical seizure patterns, which make one feel that there must be some structural abnormality underlying it, but standard neuroimaging is usually depressingly normal. There is a good chance that what is being missed is a cortical dysplasia, the commonest cause of refractory focal epilepsy after mesial temporal sclerosis. A number of imaging techniques have been devised to try and identify the location of subtle lesions, missed on eyeballing the scan.

In this study the authors studied scans of 43 patients whose initial assessment had not revealed a structural cause of their seizures, using a variety of techniques, including surface rendering, curvilinear reformatting (creating slices parallel to the brain surface), texture based analysis and voxel based morphometry. When an area of FCD was indentified, they used an automated technique of sulcal extraction and went on to measure the depth of the sulci. Eighty-six percent of small FCD lesions were located at the base of the sulci and these sulci were deeper than those in normal controls. The authors discuss how this may arise. They relate the lesions to the mechanism of sulcus formation, which is thought to be due to mechanical factors generated by cortico-cortical connections and subcortical connections. There is lower cell density in FCD than in normal cortex, and they hypothesise that this, combined with altered connectivity may alter local tensions to create a deeper sulcus than normal.

The type of dysplasia found was most commonly Taylor-type dysplasia, which has a better prognosis following surgery, so it is important not to miss these cases and clinical and electrographic clues can now help target a neuroradiological search, which it would appear is more likely to bear fruit if it plumbs the sulcal depths. – **MRAM**

Besson P, Andermann F, Dubeau F, Bernasconi A.

Small focal cortical dysplasia lesions are located at the bottom of a deep sulcus.

**BRAIN
2008;131:3246-55.**

PARKINSONISM-DYSTONIA: a surprising connection

Just occasionally genetics can corral together the most unlikely bed-fellows. Take this work from Queen Square, in which studies of two consanguineous families have shown the cause of an adult parkinsonism-dystonia complex, which is L-dopa responsive and not associated with iron deposition, is a mutation in the 741 amino acid of a protein made by the gene snappily called PLA2G6. This turns out to be exactly the same mutation as that which causes infantile neuroaxonal dystrophy and also a subset of cases with neurodegeneration with brain iron accumulation... This all appears to make sense at a molecular level (!) when it emerges that if you replace arginine at position 741 by glutamine in both copies of the gene, then you get adult parkinsonism-dystonia complex. Whereas if you replace the arginine with a tryptophan then either neuroaxonal dystrophy or neurodegeneration with brain iron accumulation results... depending on exactly what the mutation was. Now how do we make sense of that? – **AJC**

Paisan-Ruiz C, Bhatia KP, Li A, Hernandez D, Davis M, Wood NW, Hardy J, Houlden H, Singleton A, Schneider SA.

Characterization of PLA2G6 as a locus for dystonia-parkinsonism.

**ANNALS OF NEUROLOGY
2009;65(1):19-23.**

PARKINSON'S PLUS: and riluzole

Perhaps it is not that surprising, but it is disappointing nonetheless: riluzole does not work in PSP and MSA. So says the phase 3 NNIPPS study, which was a three-year placebo-controlled trial of 363 PSP and 4040 MSA patients from King's, Paris and Ulm. The unexpected finding was that during the three years of follow-up, 45% of the PSP and MSA populations died, much more than you might have predicted. – **AJC Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN; NNIPPS Study Group.**

Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study.

**BRAIN
2009;132(Pt1):156-71.
Epub 2008 Nov 23.**

Guidelines, outcomes, cost effectiveness and valproate

There are a number of different treatment options for patients with epilepsy and there has been much debate about the most appropriate medicine. NICE recommends treatment with the older antiepileptic drugs such as sodium valproate or carbamazepine initially unless there are particular reasons why they may be considered unsuitable. More recent studies such as SANAD confirm good outcomes from the use of sodium valproate and its cost effectiveness.

Although valproate is an inexpensive option there can be considerable differences in price between different formulations and this has been accentuated by price increases of 20% to Epilim Chrono and Epilim Syrup in February 2008. The prices of Episenta have not increased and according to Beacon Pharmaceuticals are now 35% less than Chrono and 50% less than the syrup.

For more information T. 01892-600930.



Nikon extends its diagnostics portfolio to include sample preparation

Nikon Instruments Europe and SLEE Medical GmbH have announced an agreement for a distribution partnership that appoints Nikon as the official European distributor of SLEE's pathology specimen preparation equipment. Nikon will distribute the full range of SLEE's precision-made instruments and consumables to the clinical market, including hospitals and academic medical centres within Europe.

Welcoming the new agreement, Peter Drent, General Manager, Biosciences at Nikon Instruments Europe said, "There is a synergy between us, making this an ideal partnership. SLEE has over 50 years' heritage in offering high quality instruments for histopathology sample preparation. Starting with the development of the first ever cryostat, SLEE has gained a reputation in this area for technological innovation and precision. With over 90 years' heritage, Nikon pioneers microscopy technology, using its advanced technologies to develop innovative imaging solutions. By offering these instruments alongside Nikon's microscopes and digital cameras, we are now able to offer the clinical laboratory the complete pathology solution."

For more information contact Nikon Instruments Europe, E. info@nikoninstruments.eu
www.nikoninstruments.eu/slee



Invitrogen receives approval from Health Canada for system to help determine organ transplant compatibility

Invitrogen, a division of Life Technologies Corporation, has announced that its DynaChip® HLA Antibody Analysis System has received approval from Health Canada's Medical Device Bureau for the detection and identification of antibodies to human leukocyte antigen (HLA) markers, which is an essential step in determining the compatibility of organ donors.

HLA markers are proteins found on the surface of certain cells in the body. They are used by the body's immune system to identify material that is foreign, such as viruses or bacteria. HLA antibody identification is important for organ transplant donor-recipient matching because, in the case of organ donation, a patient's immune system may fight cells from the donor, causing organ failure or rejection.

The DynaChip HLA Antibody Analysis System, which received US Food and Drug Administration clearance in 2008, is the only automated chip-based system for HLA antibody detection and identification. It consists of the following three parts:

- The DynaChip Processor, which automates assay processing, including dispensing, incubation and washing to image detection and results analysis;
- The DynaChip protein array, which allows users to test for multiple antibodies at the same time;
- The DynaChip interpretation software, which provides rapid, efficient and automated analysis.

"Health Canada has joined a growing list of medical agencies that have approved the DynaChip HLA Antibody Analysis System to help make clinical transplant decisions," said Jim Janicki, Head of Clinical Diagnostics for Life Technologies. "This system is an important tool that can help doctors make transplant decisions more quickly and accurately."

For more information see www.invitrogen.com

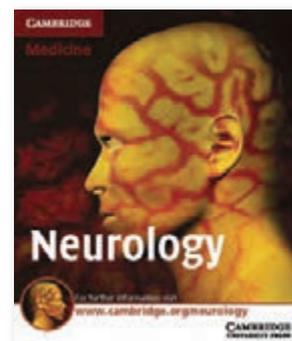
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Chelsea and Westminster Hospital enhances stroke services with new CT scanner

Chelsea and Westminster Hospital NHS Foundation Trust in London has installed a SOMATOM® Definition AS+ CT scanner from Siemens Healthcare. This adaptive imaging solution is the first to be installed into a National Health Service hospital and is currently being used for a wide range of procedures as well as supporting the cardiac and stroke related services.

The new scanner is situated in a back-to-back CT suite that also contains a Siemens SOMATOM Definition AS. This setup has increased staffing efficiency whilst giving a greater degree of scanning flexibility. Whilst the AS+ is used in stroke imaging and cardiology, the AS has been equipped with an interventional modality for radiofrequency ablation and



The SOMATOM Definition AS at Chelsea and Westminster Hospital. (Left to right): Alan Kaye, Radiology Services Manager, Gary Cook, Siemens Regional Sales Manager, Simon Padley, Consultant Radiologist, Olivia Egan, CT Superintendent Radiographer, Dan Gibbons, Siemens CT systems Applications Specialist.

oncology work. By having two adaptable CTs in place, patients can quickly be transferred from Accident and Emergency (A&E) for instant diagnostic scans on the AS+ whilst routine imaging needs are dealt with by the AS.

Chelsea and Westminster also offers a hyper acute stroke service for thrombolysis on the AS+. With its 'Adaptive 4D Spiral', this system goes beyond structural information to provide details on function. By providing whole organ coverage in 4D for stroke perfusion, clinicians can assess the complete picture instead of preselecting a narrow section to evaluate for perfusion defects.

For more information T. 01276 696317,
E. mike.bell@siemens.com
www.siemens.co.uk/healthcare

Elekta delivers advanced 3D brain mapping tool for research

Elekta Neuromag, the world-leading equipment for non-invasive measurement of brain activity using magnetoencephalography (MEG) technology has been ordered by the Moscow Municipal University of Psychology and Education (Moscow, Russia) and the University of Trento (Trento, Italy).

MEG is a powerful tool for studying normal brain function and brain disorders. Elekta Neuromag is the world's most advanced and most used MEG system, providing real-time mapping of brain activity by non-invasively measuring the magnetic fields produced by the brain. Electrical activity in neurons in the brain produce magnetic fields that pass through brain tissue and the skull, which can then be recorded outside the head using Elekta Neuromag.

The first whole-head MEG in Russia, neuroscientists and those in related fields at the Moscow Municipal University of Psychology and Education, plan to use Elekta Neuromag for clinically oriented research applications, such as



autism in children. The University also plans to employ MEG technology for cognitive neuroscience and neuropsychology research such as the study of human emotion and brain abnormalities.

Dedicated to brain and cognitive neuroscience research, a large group of researchers at the University of Trento's Center of Mind/Brain Sciences (CIMeC) plan to use Elekta Neuromag to explore various fields of neuroscience such as sensory processing, attention and action control, language, formation of concepts and cognitive development.

For further information see www.elekta.com

Fast FRET! Image capture at two wavelengths simultaneously

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

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



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

For more information contact
Nikon Instruments Europe,
E. info@nikoninstruments.eu
www.nikoninstruments.eu/ti/

Revolutionary treatment option offers new hope to Russian cancer patients

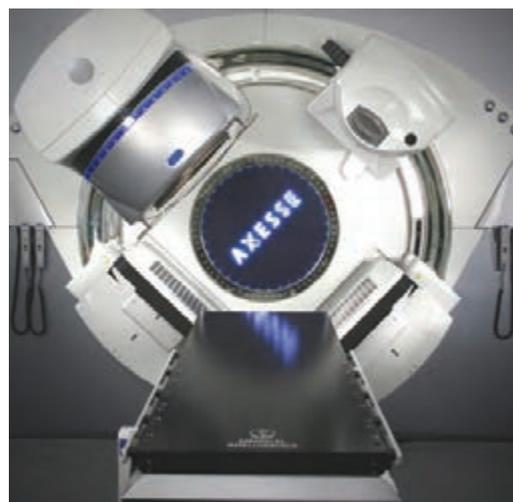
Two of Russia's leading research centers, The Meshalkin Research Institute of Circulation Pathology (NRIBCP, Novosibirsk, Russia) and the Hertenzen Moscow Oncology Research Institute (MORI, Moscow, Russia), have purchased Elekta Axesse systems which will, for the first time in Russia, allow clinicians to treat cancer tumours throughout the body with ultra-high precision while minimising damage to surrounding healthy tissue.

"Elekta Axesse will help us to build one of the most advanced cancer centres in Russia," says Professor Alexander M. Karaskov, Director of the Meshalkin

Research Institute. "The system combines speed and accuracy with the ability to target tumours throughout the body."

Elekta Axesse will be delivered with the latest technology, Elekta VMAT (Volumetric Modulated Arc Therapy), which enables faster treatment time and more accurate targeting of the dose. Hertenzen MORI will be the first clinic in Russia to provide this technology to patients.

For further information
E. rolf.kjellstrom@elekta.com



Point-of-care ultrasound hits the mark for orthopaedics



The latest point-of-care ultrasound technology from SonoSite has been chosen for its easy portability and excellent image quality by consultant orthopaedic surgeon Harry Brownlow, at the Royal Berkshire Hospital in Reading, to help in the diagnosis and treatment of a whole range of shoulder and elbow injuries.

"I have used ultrasound for several years and was just bowled over by how good the images from SonoSite's M-Turbo" system are compared to those from similar systems," explained Mr Brownlow. "I routinely work at different hospital sites so it is important for me to have a light, truly portable system that is easy to carry round and is, at the same time, robust enough to withstand any knocks or bumps. With the M-Turbo system I can also export images onto USB which is really important for me." He added, "My anaesthetist colleagues frequently borrow the system to guide nerve blocks and they are achieving excellent results."

Mr Brownlow said, "If you can show a patient exactly what's going on, it gives them a great deal of confidence in my abilities and the diagnosis I'm giving. It often saves on the need for MRI scans and is also great for guiding needles for injections."

For more information about SonoSite products contact Alexander House, 40A Wilbury Way, Hitchin SG4 0AP. T. 01462 444 800, F. 01462 444 801, E. europe@sonosite.com www.sonosite.com

National Guidelines for botulinum toxin in the management of adult spasticity

New national guidelines are available to provide clinicians with the knowledge and tools to use botulinum toxin in the management of spasticity. Produced with the assistance of an educational grant from Ipsen Ltd and published by the Royal College of Physicians, the guidelines entitled 'Spasticity in Adults: Management using Botulinum Toxin: National Guidelines' are aimed at doctors and health professionals involved in the management of spasticity, and also the providers and purchasers of rehabilitation services.

Commenting on the new guidelines, Professor Lynne Turner-Stokes, the chair and lead editor said "A substantial evidence-base exists for the overall effectiveness of botulinum toxin in the treatment of spasticity. It is important to use it correctly and these updated guidelines detail patient



selection, the establishment of clear goals for treatment and appropriate follow-up therapy - all essential for successful intervention."

Botulinum toxin should only be injected by clinicians experienced in the diagnosis and management of spasticity.

The mainstay of spasticity management is stretching and correct positioning. Botulinum toxin should therefore not be used in isolation, but as

part of a co-ordinated multidisciplinary approach involving physical handling and therapy to achieve the desired effect.

For copies of 'Spasticity in Adults: Management using Botulinum Toxin: National Guidelines' T. 01753 627609, E. access.coordinator@ipson.com

VIMPAT[▼] (lacosamide), given SMC approval

UCB's new treatment for epilepsy has been accepted for use in Scotland by the Scottish Medicines Consortium (SMC) for adults with partial onset seizures, as an add-on to patients' current therapy. All NHS health boards in Scotland will now consider the SMC's advice and ensure that this new treatment is made available where there is a clinical need. The SMC advise use in patients with refractory epilepsy.

The efficacy of VIMPAT[▼] as adjunctive therapy at recommended doses (200 mg/day, 400 mg/day) was established in 3 multicentre, randomised, placebo-controlled clinical trials with a 12-week maintenance period. Overall the proportion of patients with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, Vimpat 200 mg/day and 400 mg/day, respectively. In addition, results from an open-label extension

study demonstrate long-term retention; of the 370 patients enrolled, 77% were still taking Vimpat after one year.

Between 20,000 – 40,000 adults in Scotland have epilepsy. In the UK, it is estimated that around a third of people with epilepsy still experience seizures despite treatment with these medications. Commenting on the SMC approval, Dr. John Paul Leach, Southern General Hospital, Glasgow said, "This acceptance by the SMC means that specialists have another therapeutic choice to offer those patients in Scotland not achieving adequate seizure control."

For further information contact Dr Ian Weatherhead, T. 01753 447 950, E. ian.weatherhead@ucb-group



Confidence to take action everyday

COPAXONE® (glatiramer acetate) PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. Indication – Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. Dosage and administration – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. Children (12 – 18 years) No specific studies. Data suggests safety profile similar to that seen in adults. Children (<12 years) Not recommended. Elderly No specific data. Impaired renal function No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. Contra-indications – Known allergy to glatiramer acetate or mannitol (excipient). Pregnancy. Special warnings and precautions – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. Interactions – No formal evaluation. Increased

incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. Pregnancy and lactation – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. Undesirable effects – Injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, lipodystrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 41% of patients receiving Copaxone compared to 20% of patients receiving placebo. >1%: Nausea, anxiety, rash, hyperhidrosis, chills, face oedema, syncope, vomiting, lymphadenopathy, oedema, nervousness, tremor, herpes simplex, skin benign neoplasm, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions, convulsions, shifts in white blood cell counts, elevated liver enzymes (with no evidence of clinical significance) and skin necrosis at injection sites. Please refer to the SPC for a full list of adverse events. Overdose – Monitor, treat symptomatically. Pharmaceutical Precautions – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Legal Category – POM. Package Quantity and Basic NHS Cost – 28 pre-filled syringes of Copaxone: £524.31. Product Licence Number – 10921/0023 Further Information – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. Date of Preparation: January 2009.

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

Date of Preparation: February 2009

C0109/537a



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