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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

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Simplicity

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 and with or without levodopa. 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. Overdose: Symptoms reported following rasagiline overdose (3-100mg) included dysphoria, hypomania, hypertensive crisis and serotonin syndrome. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Do not use in patients with severe hepatic impairment. 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 (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants, and MAO inhibitors. Cases of serotonin syndrome have been reported post-marketing in patients treated concomitantly with antidepressants/SNRIs and rasagiline. 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. Cases of elevated blood pressure have been reported in the post-marketing period, including one report of hypertensive crisis associated with the ingestion of unknown amounts of tyramine. **Undesirable effects in clinical trials:** Monotherapy: >1%: headache, influenza, skin carcinoma, leucopenia, allergy, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, musculoskeletal pain, neck pain, arthritis, urinary urgency, fever, malaise. <1%: decreased appetite, cerebrovascular accident, myocardial infarction, vesiculobullous rash. Adjunct therapy: >1%: dyskinesia, decreased appetite, hallucinations, abnormal dreams, dystonia, carpal tunnel syndrome, balance disorder, orthostatic hypotension, abdominal pain, constipation, nausea and vomiting, dry mouth, rash, arthralgia, neck pain, decreased weight, fall. <1%: skin melanoma, confusion, cerebrovascular accident, angina pectoris. Please refer to the SmPC for the rates 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:** December 2009. **Further information available from:** Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

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Editorial board and contributors

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

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

David J Burn is the editor of our Conference News Section and is Professor in Movement Disorder Neurology & Honorary Consultant, Newcastle General Hospital. He runs Movement Disorders clinics in Newcastle-upon-Tyne. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

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

Alastair Wilkins is our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.

Nicki Cohen is ACNR's Neuropathology Editor. She is a Specialist Registrar in Neuropathology at Southampton and has a DPhil in Neuroscience. Her research interests lie in CNS stem cell biology, and the brain's response to injury.

Peter Whitfield is ACNR's Neurosurgery Editor. He is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.

Heather Angus-Leppan is ACNR's ABN representative on the Editorial Board. She is Head of the Neurology Department at Barnet Hospital and Consultant Neurologist, Honorary Senior Lecturer and Epilepsy Lead at the Royal Free Hospital, London, UK. She is the Honorary Assistant Secretary of the Association of British Neurologists, Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and current Chair of the Map of Medicine Epilepsy Group, UK.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital.

Professor Klaus Berek, Austria: Head of the Neurological Department of the KH Kufstein.

Professor Hermann Stefan, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nürnberg.

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

Professor Alan Thompson elected Fellow of the AAN

Professor Alan Thompson has been elected as a Fellow of the American Academy of Neurology. Professor Alan J Thompson is an international authority on demyelinating disease, and in particular, on the diagnosis, measurement, and management of Multiple Sclerosis. He is Vice-Dean of the Faculty of Biomedical Sciences at University College London, Director of the UCL Institute of Neurology, and Programme Director for the Neurological Disorders theme of UCL Partners (Academic Health Science Centre). Professor Thompson received his undergraduate and postgraduate degrees from Trinity College Dublin, and has been awarded an honorary doctorate by Hasselt University, Belgium.

David Werring wins funding for 5-year research programme

David Werring (Department of Brain Repair and Rehabilitation, Stroke Research Group, Institute of Neurology, London) has been awarded a £940,000 joint programme grant from the Stroke Association and British Heart Foundation. The funding will support a 5-year programme of stroke brain imaging and genetic research.

The team will try to find new ways to predict the risk of intracranial bleeding associated with blood thinning drugs (eg warfarin). New types of magnetic resonance imaging (MRI) scans, and testing for genetic factors that affect the fragility of brain blood vessels, will be developed. David explains: "Although blood thinning (anticoagulant) drugs after ischaemic stroke due to atrial fibrillation are very effective, a small minority of patients are at risk of devastating brain haemorrhage. In some cases it is very hard to know the best thing to do – on the one hand there is a high risk of recurrent blood clots to the brain, on the other – a danger of bleeding. We want to identify those at highest risk of bleeding using special MRI techniques to detect microbleeds. Microbleeds are now quite commonly found in our stroke patients, but we don't yet know their full significance. In patients with a lot of microbleeds, anticoagulant drugs might cause a life-threatening large haemorrhage. If this theory is correct, screening for microbleeds could help target the right anticoagulant treatment to the right patients, making them much safer to use."

MS Society calls on stem cell researchers for grant applications

The MS Society has called for researchers and scientists to come forward with research projects investigating the potential benefit of stem cells in multiple sclerosis (MS). A new partnership between the MS Society and the UK Stem Cell Foundation has levered £1million to be specifically ring-fenced for translational, pre-clinical and clinical trials. Currently there are limited treatment options available for people with MS, especially for progressive forms of the condition, and the identification and development of disease modifying therapies for MS remains a major priority for the MS Society. At an International Stem Cells and MS Consensus Meeting, organised by the MS Society and held in London in May 2009, it was announced that a concerted effort in stem cell research and clinical trials of stem cell therapies for MS is now needed. The MS Society and UKSCF partnership was set up as a direct result of this work.

For more information contact The MS Society on T. 020 8438 0700.

Gowers' awards 2010

The UK Chapter of the International League Against Epilepsy invite entries for the Gowers' Awards 2010. Entries are welcome from within the UK, must be in English and not more than 5,000 words.

1. Gowers' Young Physician Award (£1,000): A dissertation on any aspect of epilepsy. Entrants must be no older than 35 years on December 31st 2010.
2. Gowers' Medical Student Award (£500): A dissertation on any aspect of epilepsy, including case histories of a patient personally observed by the student. Entrants must be bona fide medical students.
3. Gowers' Combined Nursing & Health Profesional Award (£1,000): A dissertation on any aspect of epilepsy, by a member of the nursing profession or recognised health profession related to epilepsy care.

For more details please contact Ms. Juliet Solomon, T. 0207 837 3611 Extn. 4285.
E j.solomon@ion.ucl.ac.uk

Roger Barker, Co-Editor.

ACNR has now entered its tenth year and I want to begin by thanking you for all your encouragement and support during this time. To celebrate this significant milestone, we thought it might be interesting to invite back some of the early contributors to the journal, to allow them to comment on what they see as having changed in their field over the last decade.

In our review article, we therefore have Angela Vincent discussing antibodies and neurological disease – an area that has expanded enormously of late, in no small part because of the pioneering work of Angela and her team. Her continued high quality contribution to the field of neuroimmunology obviously goes back many years, and the other article written by Angela in this issue of ACNR takes us back to these early days as she describes the life and work of the late John Newsom-Davis. This account forms part of our series on the inspirational neurologists of our time, and this article reveals the true genius of John and his ability to inspire and instruct a whole generation of neurologists and neuroscientists.

The rehabilitation article takes as its theme the management of traumatic spinal cord injuries. In an age of evolving high tech strategies for effecting repair in the CNS, it is comforting to know that one of the main recommendations for managing this condition optimally is to have a good well integrated multi-disciplinary team of complementary therapists and doctors.

The piece in our Personal Perspective section is a very moving account by Tony Judt about his motorneuron disease. The article (which has been published elsewhere as well) describes the traumas of one night with this condition and highlights how trivial movements and excursions normally keep us comfortable such that when our motor systems are robbed of power, these minor activities take on a grotesque significance.

Mark Manford treats us to his personal view on 10 years of epilepsy research and therapeutics and seeks to try and convince us to move away from stopping seizures and move towards treating epilepsy – getting to the root cause of the problem rather than just its electrical expression. This article whilst highlighting the major advances in the genetics of epilepsy also is sobering in terms of how many really novel therapeutics have come to clinic for this all too common condition.

Nicki Cohen and Roy Weller have also kindly taken us back over 10 years of advances in Neuropathology — much of which has been in the field of glioma and stem/cancer cell biology as well as neurodegenerative disorders of the CNS. In addition they applaud the move towards a more joined up approach to brain banking and how this is likely to pay dividends in the years to come.

Erlick Pereira and colleagues, in their contribution to the Neurosurgery series, have written a gripping account of Neurosurgery past, present and future. This engaging account highlights the contribution of the UK to modern neurosurgical practice whilst discussing how it has evolved both in terms of a discipline and the training of those interested in this area of surgery.

In the Research Series, edited by Boyd Ghosh, we call in at the Academy of Medical Sciences to discover their important and growing role in fostering clinical academic work. In addition we hear about how being an NHS consultant should not stop one from doing research especially as claiming to do this will now come under closer scrutiny in the annual debate with managers over job plans.

In the Paediatric Neurology series Rachel Bower tells us about developmental milestones, which are not just the domain of parents and paediatric neurologists. For many of us, knowing what is supposed to happen in the life of the developing child can be very informative in assessing some adult neurological cases.

Finally, we have our usual collection of reviews, including a marvellously useful summary of the big new trials in MS by Alasdair Coles.

So, we hope that you have enjoyed the last decade of ACNR and do let us know what we can do to make it better over the next decade! ◆

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

It's hard to live life to the full if part of you is always expecting the next seizure. VIMPAT® is an anti-epileptic drug with an innovative mode of action.[1,2] In clinical trials, VIMPAT® has shown improved seizure control when added to first and second generation AEDs.[3] Prescribe VIMPAT® when you want your patients to look forward with the confidence of additional seizure control.[1,3]

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PRESCRIBING INFORMATION (Please consult the Summary of Product Characteristics (SPC) before prescribing.) **Vimpat® Lacosamide Active Ingredient:** *Tablets:* lacosamide 50 mg, 100 mg, 150 mg and 200 mg. *Syrup:* lacosamide 15 mg/ml. *Solution for infusion:* lacosamide 10 mg/ml. **Indication:** Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. **Dosage and Administration:** *Adults and adolescents from 16 years:* Recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after 1 week. Maximum daily dose of 400 mg (in two 200 mg doses). For *solution for infusion:* Infused over a period of 15 to 60 minutes twice daily. Can be administered i.v. without further dilution. *Elderly:* No dose reduction necessary. Age associated decreased renal clearance with an increase in AUC levels should be considered. *Paediatric patients:* Not recommended. *Patients with renal impairment:* No dose adjustment necessary in mild and moderate renal impairment. Dose adjustment is recommended for patients with severe renal impairment and patients with end-stage renal disease (see SPC). Dose titration should be performed with caution. *Patients with hepatic impairment:* No dose adjustment needed in mild to moderate impairment. In accordance with current clinical practice, if Vimpat has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week). **Contraindications, Warnings, etc:** *Contraindications:* Hypersensitivity 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 **Marketing Authorisation Number(s):** 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: £10.81; 100 mg x 14 tabs: £21.62; 100 mg x 56 tabs: £86.50; 150 mg x 14 tabs: £32.44; 150 mg x 56 tabs: £129.74; 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. **Marketing Authorisation Holder:** UCB Pharma SA, Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com **Date of Revision:** 01/2010 (10VPE0010). Vimpat is a registered trademark **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 2010. 10VPE0024

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ACNR is celebrating the first issue of its tenth volume.

Error in ACNR supplement on multiple sclerosis

In our supplement on multiple sclerosis, which came with your last issue of ACNR, I commented on the BMJ article by Mike Boggild and others (BMJ 2009 Dec 2;339:b4677) that "having recruited 5583 patients, two years of data was only available on 1479 (34.5%) relapsing-remitting patients". I was vaguely critical of this...

Mike Boggild has kindly written in to explain that I was completely wrong! He says: "Just for the record the 1479 figure was the number of RRMS patients who had reached their third [my emphasis] assessment by the time of the analysis (which was undertaken when everyone had reached year 2, only ~50% of patients had reached year 3 by that point) and allowed us therefore to 'confirm' their 2nd year score".

In fact, the article clearly states that 2901 of 4293 patients had valid year 2 data. This is 68% of patients; much more representative than the 34.5% figure I quoted.

With apologies to all concerned...
Alasdair Coles

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APO-GO® APOMORPHINE HYDROCHLORIDE. ABBREVIATED PRESCRIBING INFORMATION. Consult Summary of Product Characteristics before prescribing. **Uses:** The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic 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:** Apomorphine should not be used in pregnancy unless clearly necessary. 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. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. **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. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitus. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. 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. Dizziness and lightheadiness have also been reported. 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 and thrombocytopenia 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. Yawning and breathing difficulties have been reported as has peripheral oedema. *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: PL 06831/0245. APO-go Pens: PL 06831/0246. APO-go Pre filled syringes: PL 06831/0247. **Legal Category:** POM. **Date of last revision:** February 2010. For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK.

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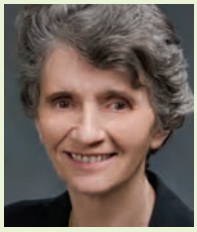
An Update on Antibody-Mediated Diseases



Prof Angela Vincent
is Emeritus Professor of Neuroimmunology at Oxford University. In the 1970s she helped John Newsom-Davis to establish the Neurosciences Group at the Royal Free Hospital, which then moved to the Weatheralll Institute in Oxford. Since his retirement in 1998 she has led the Neuroimmunology Group, which is now exploring the whole spectrum of antibody-mediated diseases of the nervous system.

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It doesn't seem that long since 2001 when I summarised the diseases of the neuromuscular junction caused by autoantibodies to ion channels (VGCC, VGKC) and receptors (AChR, MuSK) but there are, nevertheless, a surprising number of developments that you might like to hear about in this brief review. The table has been updated to include all of the known conditions in which antibodies – if not yet shown formally to be the pathogenic mechanism – are proving crucial to the diagnosis and thence the treatment of patients.

What's been happening at the neuromuscular junction?

Perhaps one of the most important aspects for the general neurologist is the surprising frequency of AChR-Ab positive MG in the elderly a few of whom may have been previously unrecognized, or misdiagnosed as motor neuron disease or stroke.[1] The changing demographics probably reflect better diagnosis, greater awareness and ascertainment, and the increasing age of the population, but there may also be a real increase in the disease in older people.

With the advent of a relatively easy diagnostic testing for MuSK antibodies there have been many studies on MuSK-MG from around the world indicating that it is recognised widely, although the prevalence appears to vary considerably, probably reflecting environmental factors, with the highest prevalence in countries in Southern Europe and the equivalent USA states – the prevalence decreases in countries further north. Whereas the pathogenic mechanisms in AChR-Ab positive MG (AChR-MG) are well established, the mechanisms in MuSK-MG are much less clear. The antibodies bind to the extracellular domains of MuSK and affect remodelling of the neuromuscular junction in various active and passive immunisation models but AChR numbers are not greatly altered in patients and these changes alone would not adequately account for the marked defect in neuromuscular transmission in MG. Moreover, the MuSK-MG patients often have particularly severe bulbar involvement which suggests that these muscles, which are often atrophied, may be particularly susceptible to the effects of the antibodies; this requires further study.[2] Importantly, the thymus is usually normal in MuSK-MG and thymectomy not (in our view) indicated, and although plasma exchange is always effective, MuSK-MG can be relatively difficult to treat; studies on the effects of newer immunotherapies such as rituximab are beginning to appear and may offer hope to those patients with intractable MuSK-MG.[3]

The patients who have neither AChR nor MuSK antibodies by current techniques are still somewhat of a mystery, but there are some developments. For instance, using AChRs expressed in a human kidney cell line (HEK 293 cells), and clustered into dense arrays similar to those on the postsynaptic membrane of the NMJ, we found binding of antibodies in patients previously negative for AChR antibodies, and a similar method has also improved the detection of MuSK antibodies; unfortunately these techniques are not yet adapted for routine diagnostics.[4] By contrast, there have been few developments in LEMS or in acquired neuromyotonia although a number of clinical studies from the Netherlands have detailed the epidemiology, cancer incidence and risk factors in LEMS.[5]

Moving to the central nervous system

Previous generations seemed to have had quite fixed ideas regarding antibodies and CNS disease – understandably drawing attention to the "blood brain barrier" as a reason why antibodies would not get into the parenchyma of the CNS. Nevertheless, there is always some IgG in the cerebrospinal fluid (approximately 1/400 of the serum levels) and quantitative testing can demonstrate the relationship between serum and CSF levels of specific autoantibodies - intrathecal synthesis of specific autoantibodies may be detectable even when the intrathecal concentration of total IgG is within normal limits. However, in my view, we shouldn't necessarily assume that intrathecal synthesis of a particular antibody is required for it to be pathogenic – it is possible that some diseases are caused by local leakage of antibody from the serum into the brain parenchyma. But this view is not shared by many and it's an area for future study!

In 2001 we first showed that VGKC antibodies were associated not only with neuromyotonia but also with both limbic encephalitis and Morvan's syndrome. A patient with marked neuromyotonia, autonomic, sleep disturbance and cognitive dysfunction (Morvan's) had high VGKC antibodies and improved after multiple plasma exchanges, whereas limbic encephalitis that responded to plasma exchange was seen in two women, one with thymoma and MG, and the other with no tumour. Slowly these cases began to be recognised and described and VGKC antibody testing has now become routine, at least in some countries, for patients with unexplained memory loss, seizures and personality/psychiatric

Focus on concordance in epilepsy

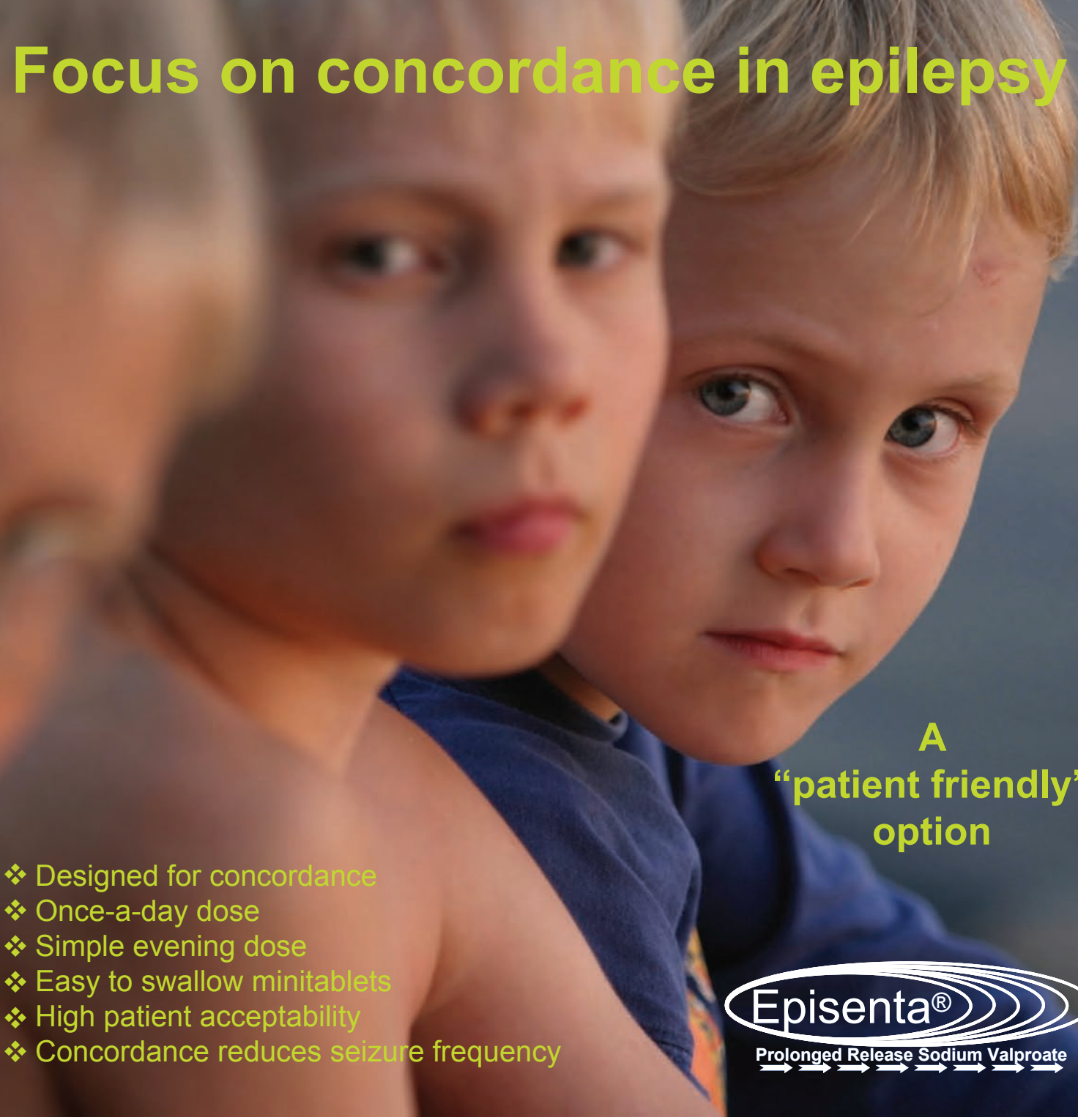

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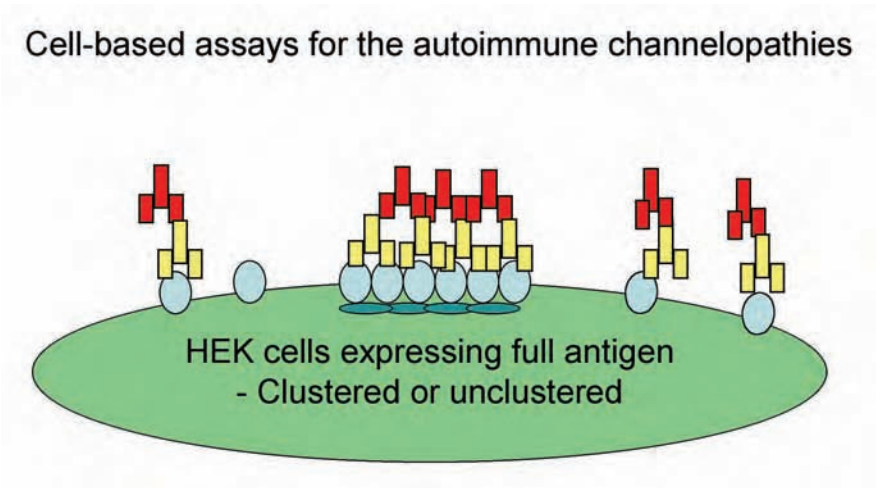
Table: Update on antibody targets and associated conditions

TARGET	ANTIGEN USED FOR ASSAY	CONDITIONS	NEW DEVELOPMENTS SINCE 2001
AChR	125I-bungarotoxin-AChR (fetal and adult)	Myasthenia gravis Arthrogryposis multiplex congenital	Cell-based assay using clustered AChR to increase sensitivity
MuSK	Recombinant extracellular domain of MuSK on ELISA	Seronegative (or MuSK antibody positive) myasthenia gravis	Commercially available radioimmunoprecipitation assay and cell-based MuSK expression to increase sensitivity
VGCC	125I-conotoxin-MVIIC VGCC	Lambert Eaton myasthenic syndrome with or without small cell lung cancer	
VGKC	125I-dendrotoxin-VGKC	Acquired neuromyotonia Limbic and hypothalamic syndromes with or without neuromyotonia	
NEW TARGETS	**ASSAY METHOD**	**CONDITION**	**TREATMENT EFFECT**
VGKC	125I-dendrotoxin-VGKC but cell-based methods will be developed for new antigens	Increasing recognition of "VGKC" antibodies in limbic or epilepsy syndromes and in Morvan's syndrome.	Usually very immunotherapy-responsive. There can also be frequent brief partial seizures.[18]
Aquaporin 4	Various including NMO-IgG and cell-based, ELISAs	Distinguishes neuromyelitis optica from multiple sclerosis or other causes of optic neuritis or transverse myelitis	Requires aggressive immunotherapies to treat and prevent relapses
NMDAR	Cell based expression of NR1/NR2B	A newly-described syndrome including both limbic and subcortical features with prominent movement disorders often in young adults and children. Often associated with ovarian teratoma but can be non-paraneoplastic.	Either by tumour removal, and/or by immunotherapies.
AMPAR or GABA(B)R	Cell based expression of GluR2/3 Cell based expression of GABA(B)R	Limbic encephalitis often associated with tumours Limbic encephalitis often associated with tumours	Immunotherapy responsive but can relapse Immunotherapy responsive
GlyR	Cell based expression of GlyR1alpha	Progressive encephalomyelitis with rigidity and myoclonus, or stiff person syndrome or hyperekplexia	Probably very rare Immunotherapy responsive
Glutamic acid decarboxylase	Various assays employing recombinant GAD	Increasing recognition of the usefulness of GAD antibodies as a marker for stiff person syndrome, autoimmune cerebellar ataxia or limbic encephalitis	Variably immunotherapy responsive but treatments may need to be started early

GABAR = gamma-amino butyric acid receptor

disturbance.[6,7] In fact, although the antibodies are still measured by the radioimmunoprecipitation assay (see Table), it has become clear that most of the antibodies in the patients with CNS diseases are not directed against the VGKCs themselves but against associated proteins that are part of the VGKC-complexes found in the CNS and PNS. This new knowledge will begin to provide an explanation for the differing clinical phenotypes associated with "VGKC" antibodies (Irani and Vincent in preparation).

The next major development concerned a completely different sort of channel antibody. Aquaporin4 (AQP4) is a water channel and the target for antibodies in neuromyelitis optica.[8] Measurement of the antibodies is best determined using a cell-based approach (as used for several assays, see Figure), although there are now commercial ELISAs and other assays appearing. It is proving to be very helpful in distinguishing these patients from typical MS, and by so doing this ensures that they receive appropriate treatments. The antibodies are also found in



Cell based assays are proving to be the best method for the detection of antibodies to membrane proteins. The antigen (pale blue) is expressed on the surface of a cell transfected with cDNAs encoding the antigen subunits. The patient's antibodies (yellow) are detected by binding of a fluorescent anti-human IgG (red). The antigens can be tagged with another fluorescent colour if required (eg. green, not shown), and sensitivity can be increased by clustering the antigen using naturally occurring intracellular scaffold proteins –eg. RAPsyn (dark green) that clusters AChRs at the neuromuscular junction.

Collectively these (CNS) syndromes are now proving to be some of the most satisfying diseases to encounter, and our laboratory is detecting one or other of these antibodies in around up to 20 patients each week

children with this condition.[9] The antibodies are complement fixing and damage astrocytes directly, and probably neurons and oligodendrocytes indirectly.[10] There are recent reports of passive transfer models that demonstrate the pathogenicity of the antibodies.

Also exciting has been the discovery of NMDAR antibodies in patients with a complex neurological syndrome often associated with ovarian teratomas in young women.[11] The antibodies were first detected by binding to the neuropil of the hippocampus in rat brain sections – a technique which illustrates the presence of a highly specific antibody but does not identify the target. Hippocampal neuronal cultures showed that the antibodies were directed towards cell-surface determinants and were likely to be pathogenic (in comparison with many of the antibodies detected by binding to brain tissue sections, such as anti-Hu, or anti-Yo, which are directed towards intracellular antigens and merely markers for a paraneoplastic disease process rather than pathogenic[12]). The target was identified as the NMDAR. Whereas at first the antibodies were thought to be predominantly against the NR2B subunit, they are now known to be mainly against the NR1 subunit. They are best identified by binding to the surface of cells expressing the NR1/NR2B subunit complex and are now being found in many patients with an acute onset of neurological disturbance that includes combinations of amnesia, seizures, personality change or frank psychosis, with movement disorders, autonomic disturbance and brain stem signs. Curiously, despite the very dramatic and disturbing clinical picture, the MRIs can be normal or non-specific. Now it is recognized that NMDAR antibodies can be present without tumours in both sexes (Irani et al submitted) and in children.[13] We found the same antibodies in children who had been given a diagnosis of dyskinetic encephalitis lethargica[14] – a rather satisfying development in the understanding of this historic disease of the early 20th century.

Three other antibodies to look out for in the future are AMPAR or GABA(B)R in limbic encephalitis and GlyRs in stiff person syndrome and its variations. Each of these antibodies has been recently identified by one group only, and their frequency is not yet clear. Nevertheless, since the syndromes associated with these antibodies appear to be immunotherapy responsive, and may be associated with tumours (AMPAR, GABA(B)R) their use in routine screening is likely to be taken up.

Finally, antibodies to GAD have always been a bit confusing. GAD is an intracellular enzyme and antibodies to it should not be pathogenic - unless they can get into the cell, or unless GAD is also expressed on the cell surface, neither of which have been convincingly demonstrated. Nevertheless, GAD antibodies at very high titres are being identified in patients not only with stiff person syndrome or autoimmune cerebellar ataxia but also in a few epilepsy patients and now in limbic encephalitis.[15] Unfortunately, the GAD antibodies are seldom sought early on in the disease course, and treatments are not often effective, but it seems highly likely that GAD antibodies are a marker for an immune–mediated process that might respond well to treatments if started early enough.

These brief comments highlight the marked change in direction that antibody-mediated conditions are undergoing and the importance of being aware that CNS conditions can be antibody-mediated and treatment responsive.[16,17] Although individually not very common, collectively these syndromes are now proving to be some of the most satisfying diseases to encounter, and our laboratory is detecting one or other of these antibodies in around up to 20 patients each week. All that is required now is for companies to take up this area enthusiastically in order to provide the most sensitive assays. The cell-based approach is being used for most of the membrane receptor antigens (see Table and Figure) and is not easy to provide in a suitable form for routine diagnostic testing, but this is a challenge that must be overcome. ◆

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Evolution Not Revolution:
epilepsy in the last ten years

Mark Manford
trained in neurology at the National Hospital where he obtained his MD researching into clinical patterns of epilepsy, and at the Wessex Neurological Centre. He has been a Consultant Neurologist at Addenbrooke's and Bedford Hospitals since 1997 and has continued his interest in epilepsy, including writing a greatly under-rated textbook on the subject. He is also extensively involved in undergraduate medical training in Cambridge.

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The new millennium ushered in the age of communication and ACNR has spearheaded high quality, accessible neurology. As a keen new consultant, I was delighted to be asked to write a series of articles about various aspects of epilepsy. Now ten years on, the editors in their desperation have charged me with looking back and asking what's new, acorns, green shoots or grand oaks? There follows an unapologetically personal and perhaps hugely biased mosaic of those areas which have stuck in my mind.

I was grabbed by the identification of fast ripples (100-500Hz) described in animals and then in human intracranial EEG studies, described as "field oscillations composed of hypersynchronous action potentials"[1] possibly mediated via gap junctions, rather than synapses. Ripples may precede the onset of a seizure by a considerable period of time and are blocked by inhibitors of glutamate. They open a new vista in consideration of epilepsy mechanisms and treatment, which has yet to be realised and this reflects the core theme of my article; that, to date, our treatments deal with seizure expression, and not root causes. Of course, the most powerful tool we currently have to look into causes is genetics. Monogenic epilepsies (Table 1) have been identified[2], starting with autosomal dominant frontal lobe epilepsy (ADNFLE). Most of these monogenic epilepsies are disorders of ion channels or neurotransmitters, which is reassuring when considering the mechanisms of action of all the anti-epileptic drugs we possess. We have known since the work of William Lennox over half a century ago that there is a strong genetic component to the idiopathic generalised epilepsies but the search for their genetic basis is proving frustratingly slow. Some genes have been identified underlying monogenic pedigrees which are phenotypically similar to the sporadic diseases. These may inform the mechanisms underlying commoner disorders and we shall know more as the technology improves, and larger numbers of patients and genes can be tested quickly; I hope that, if I am asked to write another article in another ten years, the answer will be very different. Even with monogenic disorders, mapping clinical syndrome to gene defect has not proved altogether straightforward, with significant heterogeneity and a "many-to-many" map. So what influences the variable expression of genetic abnormalities? In some disease it may be the type of genetic abnormality; deletion or point mutation or the locus within the gene or else presumably other variable genes playing a part.

Even now that we know more about ion channels they are becoming predictably more complex. In neonates GABA is an excitatory neurotransmitter[3] – who would have guessed that? This and other maturational changes, including the progressive myelination of the young brain, may go some way to explaining why childhood epilepsy is such a different disease to adult epilepsy with all those strange syndromes that no self-respecting adult neurologist can ever remember. In ADNFLE, seizures may result in a gain in inhibition in a homozygous mouse model. So a traditional view of drugs as uppers and downers of cortical activity, whilst appealing, is clearly simplistic and what may be important is the role of the neurotransmitter in neuronal synchronisation in the light of modified anatomy and physiology.[4] Identifying the gene is only one step, moving on to determining pathophysiology in different patients with different expressions and designing effective and safe drugs, is quite another. The next phase will be slower but therapeutically more rewarding. Genes may be tricky but are perhaps easier to investigate than environment and the clearest example of their interaction is the doubling of the risk of epilepsy in those with a major head injury who also have a family history of epilepsy.

There has been a burgeoning of anti-epileptic medications in the last ten years. But my guess is your clinic is as full as ever it was, even if NHS coffers are considerably emptier. So what do the new drugs offer? A few patients have become seizure-free who would never have been seizure-free before. Some patients have fewer or milder seizures. We can now achieve similar results with fewer adverse effects, less drug interactions and simpler pharmacokinetics. Why AED all-too-often do not work has also been the subject of work in the area of pharmacogenomics, but studies remain at a very preliminary stage. On a more positive note, the SANAD study has given us good quality data showing that lamotrigine, of the drugs tested, had the highest retention rate in focal epilepsy[4] and valproate was far and away better in generalised epilepsy than lamotrigine or topiramate.[5] The results are interesting, both in their clinical relevance and also in telling us that focal and generalised epilepsies really are two different diseases and diagnosing them properly is very important. At the same time, the UK register of epilepsy and pregnancy, which collects prospective data on about half of pregnant women with epilepsy in the UK, and whose results are about to be expanded by other major registers, has given us the first robust and clinically useful data on AED and major malformations.[6] Only our data on lamotrigine, carbamazepine

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Table 1: Monogenic Epilepsies

Gene	Gene product	Clinical syndrome
ChRNA2, CHRNA4, CHRNB2	Different subunits of the nicotinic acetyl choline receptor.	Autosomal dominant nocturnal frontal lobe epilepsy
KCNQ2 KCNQ3	Neuronal voltage gated potassium channel (M current)	Benign familial neonatal seizures
SCN2A	Neuronal voltage-gated sodium channel α1 subunit	GEFS+, Dravet syndrome, febrile seizures
SNC1B	Neuronal voltage-gated sodium channel β1 subunit	GEFS+
GABRG2	γ2 subunit of the $GABA_A$ receptor	GEFS+, Dravet syndrome, febrile seizures Childhood absence epilepsy
GABRD	δ subunit of the $GABA_A$ receptor	GEFS+
GABRA1S	α1 subunit of the $GABA_A$ receptor	Juvenile myoclonic epilepsy
CLCN2	Voltage gated chloride channel	Various types
CA2CNA1H	Neuronal voltage gated T-type calcium channel	Chidlhood absence epilepsy
EFHC1	Myoclonin, function unknown	Juvenile myoclonic epilepsy

GEFS+ Generalized epilepsy with febrile seizures plus.

and valproate are statistically significant to date and whilst reassuring in the case of the first two, valproate emerges as the bad boy on the block. This combined with preliminary data suggesting that the verbal IQ of children exposed to valproate in utero may be reduced,[7] is a major cause of concern for a drug which may be the only option for some women with, for example, severe juvenile myoclonic epilepsy.

When treating our refractory patients, it is as well to bear in mind studies suggesting that the main determinants of quality of life are related to depression and adverse effects of medication and not to seizure frequency.[8,9] Poring over a seizure diary to see if seizures have been reduced by 35% or 50% is not of relevance to many patients but it is the measure used in regulatory studies prior to drug marketing. Smarter studies would be helpful but this needs a change in regulatory requirements. Sometimes the most important manifestation of a disease is not the most obvious; Parkinson's disease doctors have learned to think about non-motor manifestations and epilepsy doctors must consider their co-morbidities. Some new ones have gained prominence in the last ten years, in particular new memory disturbances such as accelerated forgetting;[10] the tendency for memories to drop out over a few weeks, which is not detectable in the short time frame of standard psychometric testing and transient epileptic amnesia,[11] which has some similarities to transient global amnesia but episodes are briefer, often first thing in the morning and more prone to recurrence.

The approach to treatment is maturing, parallel with a change in culture across medicine, clinicians and patients partners in seeking goals of key importance to the patient. With this has come improvements in sharing of information, often led by patient groups and charities; we have a representative in our clinic giving out information to patients at each epilepsy clinic. Epilepsy nurses are now a widespread and invaluable resource, acting as a bridge for the dissemination of knowledge into the community. However, some key pieces of our knowledge jigsaw are missing. The natural history of epilepsy is, in my view, still not clear and without this we make guesses, which are only partly educated, in helping patients to make choices. Studies are conflicting but my overall impression is that if you follow patients long enough, many will enter into a remission but many will also relapse, with or without the withdrawal of treatment; for many, epilepsy seems to be chronic relapsing and remitting disease.[12] The suggestion that failure to respond to two AED[13] makes it unlikely that the epilepsy will respond to any drug is widely quoted and is more pessimistic than some studies[14], but gives a basis for a sensible dialogue with a patient about the pros and cons of the "stick or twist" decision of trying new drugs from amongst the ever-increasing choice available. Sudden unexplained death in epilepsy, long recognised but under-rated is now given the prominence it deserves, thanks largely to the efforts of the charity "Epilepsy Bereaved" and although I still do not know the right way of handling the issue, it is something at the forefront of my mind. Investigation of epilepsy mortality has led to a practical change with a regular search for and occasional discovery of seizure-induced cardiac arrhythmia, particularly in epilepsy patients who develop drop attacks.[15]

High quality structural imaging continues to provide new insights into epilepsy.[16] A more powerful magnet (3T) may find structural abnormalities in 20% of patients with normal standard imaging and voxel-based morphometry can identify subtle changes, not obvious on standard imaging. The neurophysiology purists argue that conventional imaging looks at structure and epilepsy is a disturbance of function, but new methods such as diffusion tensor imaging and tractography may identify changes in connectivity which may be of significance in a disorder which is a disturbance of networks. Tractography is also of value in presurgical evaluation for temporal lobectomy, determining the location of Meyer's loop and so being able to predict those patients more at risk of visual field defects.[17] But the approach is multifaceted and even in patients whose structural MRI is normal,[18] investigators have become better at identifying the region of epileptogenesis with a combination of functional imaging and neurophysiology, such that successful outcomes of surgery are increasingly reported in these patients (Figure 1), although it can be argued that the definition of a normal scan depends on the type of scan used. Diffuse brain disease is also not a contraindication to surgery if it can be shown that the epilepsy satisfies conventional criteria of focal onset and good surgical outcomes can be seen in patients with apparently diffuse disorders such as tuberose sclerosis or severe learning disability and even in patients with apparently diffuse electrical abnormalities[19] but focal congenital structural lesions. In malformations of cortical development, the combination of EEG, structural and BOLD MRI is helping to elucidate the relationship of the lesion to the electrical disturbance; it appears that the overlying cortex is the key player in many cases, which has implications for surgical treatment.[20] So it seems that neuroimaging and EEG both have their place; neither should be over-interpreted in pre-surgical evaluation.

The assessment of cognitive function in epilepsy is often in preparation for surgery and for half a century the Wada test has been the gold-standard but this has been

How will restless legs syndrome affect your patients today?

The symptoms of RLS can flare up at any moment, day or night. Neupro® can help no matter when your patients suffer most. Its 24-hour continuous delivery system helps RLS patients to rest, live and sleep.[1,2]

Restless Legs Syndrome

Neupro®

rotigotine transdermal patch

Rest, live, sleep

PRESCRIBING INFORMATION

(Please consult the Summary of P oduct Cha acteris ics (SPC) befo e p escr bing)

Neupro®

Rotigotine

Active Ingredient: Rotigotine. *1 mg/24 h transdermal patch* is 5 cm^2 and contains 2.25 mg otigotine, eleasing 1 mg otigotine over 24 hours. *2 mg/24 h transdermal patch* is 10 cm^2 and contains 4 5 mg otigotine, releasing 2 mg otigotine over 24 hours. *3 mg/24 h transdermal patch* is 15 cm^2 and contains 6.75 mg rotigotine, releasing 3 mg rotigotine over 24 hours **Indication:** Neupro is indicated for the symptomatic t eatment of mode ate to seve e idiopathic Restless Legs Syndrome in adults. **Dosage and Administration:** Neupro is applied to clean, hea thy, intact skin once a day. The patch emains on he skin for 24 hours and will then be eplaced by a new one at a diffe ent application site. T eatment initiated at 1 mg/24 h and may be inc eased in weekly increments of 1 mg/24 h to a maximal dose of 3 mg/24 h. The need for t eatment continuation should be reconside ed every 6 months. *Hepatic and renal impairment:* Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients wi h mild to seve e renal impairment including those equiring dialysis. Caution is advised and dose adjustment may be needed when t eating patients with seve e hepatic impairment. *Children and adolescents:* Not ecommended. *Treatment discontinuation:* If t eatment is to be withdrawn, it should be gradually reduced, in steps of 1 mg/24 h wi h a dose eduction preferably every other day, to avoid the possibility of developing neu oleptic malignant syndrome. **Contraindications, Warnings, etc:** *Contraindications:* Hypersensitivity to otigotine or to any of the excipients. Neupro should be emoved prior to Magnetic Resonance Imaging (MRI) or ca dioversion to avoid burns. *Precautions:* External heat should not be applied to the patch. Dopamine agonists a e known to cause hypotension, and monitoring of blood p essure is ecommended. Whe e somnolence or sudden sleep onset occurs, or whe e here is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of herapy. Rotate he site of patch application to minimise the risk of skin eactions. In case of gene alised skin reaction associated wi h use of Neupro, discontinue treatment. Avoid exposu e to di ect sunlight until the skin is healed. Pathologic gambling, inc eased libido and hypersexuality have been eported in patients treated with dopamine agonists, including Neup o. Hallucinations have been reported and patients should be informed that hallucinations can occur. Oph halmologic monitoring is recommended at regular intervals or if vision abnormalities occur. Augmentation may occur. Conside ation should be taken when p escribing Neupro in combination with levodopa in PD patients as a gene ally higher incidence of some dopamine gic adverse events have been observed. *Interactions:* Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients taking sedating medicines or o her dep essants in combination with otigotine. Neup o may potentiate he dopaminergic adverse reaction of levodopa. Co-administ ation of otigotine (3 mg/24 h) did not affect the pharmacodynamics and pharmacokinetics of o al contraceptives (0.03 mg ethinylest adiol, 0.15 mg levonorgestrel). *Pregnancy and lactation:* Neup o should not be used during p egnancy. Breast-feeding should be discontinued. *Driving etc.:* Neupro may have major influence on he ability to drive and use machines. **Adverse Effects:** *Very common (>10%):* Nausea, application and instillation site eactions, fatigue, headache. *Common (between 1%-10%):* Vomiting, dyspepsia, irritability, hypersensitivity, somnolence, sleep attacks, sexual desire diso der, insomnia, sleep diso der, abnormal d eams, pruritis, hypertension. Consult SPC in relation to o her side effects. **Pharmaceutical Precautions:** Sto e in a efrige ator (2°C - 8°C). Sto e in he original package. **Legal Category:** POM. **Marketing Authorisation Numbers:** 1 mg x 28 patches: EU/1/05/331/040; 2 mg x 28 patches: EU/1/05/331/002; 3 mg x 28 patches: EU/1/05/331/049. **NHS Cost:** 1 mg x 28 patches: £77.24; 2 mg x 28 patches: £77.24; 3 mg x 28 patches: £97.48. **Marketing Authorisation Holder:** SCHWARZ PHARMA Ltd, Shannon, Industrial Estate, Co. Cla e, I eland. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshi e, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com. **Date of Revision:** 10/2009 (09NE0262). Neup o is a registe ed t ademark.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk
Adverse events should also be reported to UCB Pharma Ltd.

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Date of literature preparation: February 2010

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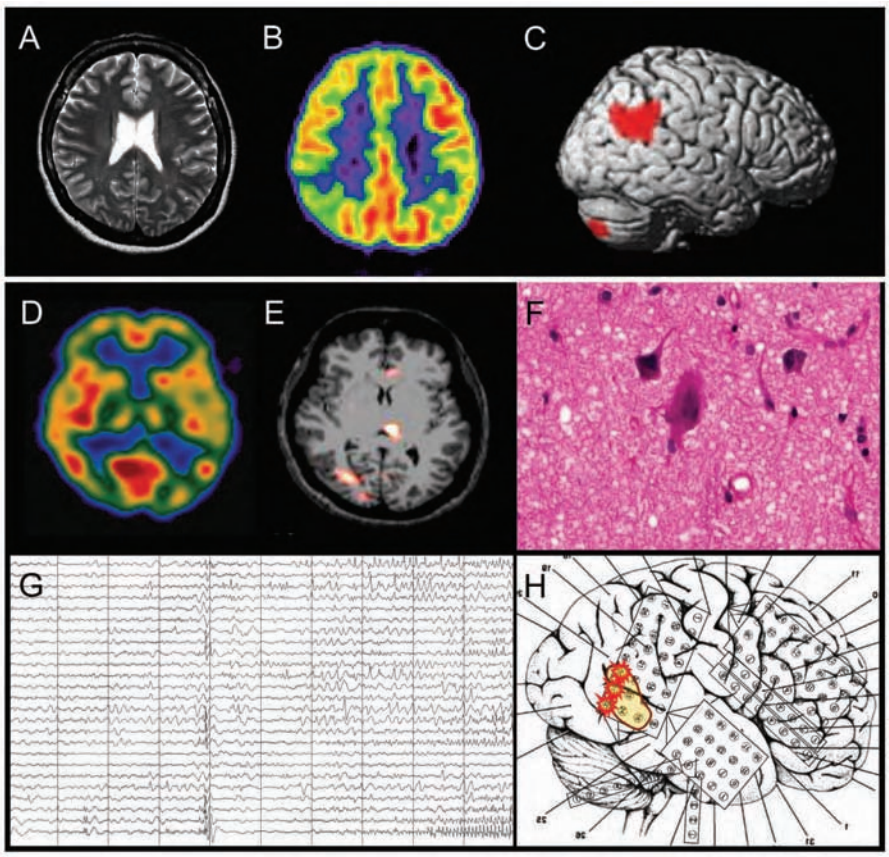

Figure 1: A 38-year-old right-handed woman who underwent resective surgery for chronic intractable complex partial seizures and secondarily generalised tonic-clonic seizures. T2WI-MRI showing no specific abnormality (A). Decreased metabolism in the right parietal region by both 18F-FDG-PET (B) and PET-SPM (C). Ictal SPECT (D) and SISCOM (E) delineated the region of increased blood flow. Pathology of the specimen shows a dysmorphic neuron, consistant 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). Photograph used with kind permission from Dr Byung In Lee, Yonsei University, Korea.

questioned with the development of functional neuroimaging techniques, which in some centres have taken over altogether from Wada testing and in others supplement it.[21] Not without risk, distressing for the patient and difficult to interpret, even though the Wada test must be one of the most dramatic investigations in medicine, its passing is a blessing for patients.

Where drugs and resective surgery do not work, it is now commonplace for patients to be considered for palliative surgery in the form of vagus nerve stimulation. I have moved from being something of a sceptic in the technique to a modest supporter on the basis that although it does not make patients seizure-free, it probably does give a useful improvement in seizures in 25%-40% of patients and does so without the cognitive and psychiatric side effects of anti-epileptic drugs which patients find so distressing.[22]

So my summary of the last ten years is that we do what we always did and I think we do it a little better and more sensitively with a growing understanding of what is tediously called patient-focussed (otherwise known as good) practice, but we have not had any quantum leap in understanding, which would really allow us to make inroads into the enormous psychosocial morbidity of uncontrolled epilepsy, still the commonest serious neurological disease. We have many new strings to our pharmaceutical bow, but we need a new instrument. Where Alzheimer's disease modifying drugs are around the corner and MS disease modifying drugs are with us already, epilepsy disease modifying drugs don't even know where the bus-stop is. So my hopes for the next ten years: firstly, not another drug that controls seizures by blocking electrical activity, although a really good one would do no harm, but one that interferes with epileptogenesis that we can give patients after major head injuries, encephalitis and haemorrhages, which we know carry a high risk of later epilepsy. Arguably, we may have filled in some gaps in the picture left to us by Hughlings Jackson over a century ago but our conceptual framework has advanced only a little and my second hope is of increasing knowledge of the mass action of neurons, what makes them synchronize into pathological networks and how we can interfere with that process. Hopefully knowing the genes will start to inform what goes on inside cells as well as on their surfaces. We need to treat epilepsy and not just seizures. Finally, we need to keep doing epidemiological studies, because without knowing the natural history of the disease we are treating, we are navigators without a map. ◆

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VNS Therapy could help your patients to experience reductions in the frequency and intensity of their seizures. Furthermore, your patients may feel improvements in terms of their mood, alertness and sense of control.

In essence, the aim of VNS Therapy is to help your patients to experience increased confidence, independence and enjoyment of life.

The reality is that there are a limited number of options in dealing with difficult-to-treat epilepsy. By choosing VNS Therapy, you might well find the option that will best suit your patients.

EUROPEAN INDICATION FOR USE:
The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalisation) or generalised seizures, which are refractory to antiepileptic medications.

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Brief Summary[1] of Safety Information for the VNS Therapy™ System [Epilepsy and Depression Indications] (March 2007)

1. INTENDED USE / INDICATIONS Epilepsy (Non-US) — The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to antiepileptic medications. Depression (Non-US) — The VNS Therapy System is indicated for the treatment of chronic or recurrent depression in patients that are in a treatment-resistant or treatment-intolerant depressive episode. 2. CONTRAINDICATIONS Vagotomy — The VNS Therapy System cannot be used in patients after a bilateral or left cervical vagotomy. Diathermy — Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with a VNS Therapy System. Diagnostic ultrasound is not included in this contraindication. 3. WARNINGS — GENERAL Physicians should inform patients about all potential risks and adverse events discussed in the physician's manuals. This document is not intended to serve as a substitute for the complete physician's manuals. The safety and efficacy of the VNS Therapy System have not been established for uses outside the "Intended Use/Indications" section of the physician's manuals. The safety and effectiveness of the VNS Therapy System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated. Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. It is important to follow recommended implantation procedures and intraoperative product testing described in the Implantation Procedure part of the physician's manuals. During the intraoperative System Diagnostics (Lead Test), infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate <40 bpm), or a clinically significant change in heart rate is encountered during a System Diagnostics (Lead Test) or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS). Difficulty swallowing (dysphagia) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties are at greater risk for aspiration. Dyspnea (shortness of breath) may occur with active VNS Therapy. Any patient with underlying pulmonary disease or insufficiency such as chronic obstructive pulmonary disease or asthma may be at increased risk for dyspnea. Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or prolonging "OFF" time may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder. Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage. Patients should be instructed to use the Magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation. Patients with the VNS Therapy System or any part of the VNS Therapy System implanted should not have full body MRI. Excessive stimulation at an excess duty cycle (that is, one that occurs when "ON" time is greater than "OFF" time) has resulted in degenerative nerve damage in laboratory animals. Patients who manipulate the Pulse Generator and Lead through the skin (Twiddler's Syndrome) may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve. 4. WARNINGS — EPILEPSY The VNS Therapy System should only be prescribed and monitored by physicians who have specific training and expertise in the management of seizures and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device. The VNS Therapy System is not curative. Physicians should warn patients that the VNS Therapy System is not a cure for epilepsy and that since seizures may occur unexpectedly, patients should consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, and in strenuous sports that could harm them or others. Sudden unexplained death in epilepsy (SUDEP): Through August 1996, 10 sudden and unexplained deaths (definite, probable, and possible) were recorded among the 1,000 patients implanted and treated with the VNS Therapy device. During this period, these patients had accumulated 2,017 patient-years of exposure. Some of these deaths could represent seizure-related deaths in which the seizure was not observed, at night, for example. This number represents an incidence of 5.0 definite, probable, and possible SUDEP deaths per 1,000 patient-years. Although this rate exceeds that expected in a healthy (nonepileptic) population matched for age and sex, it is within the range of estimates for epilepsy patients not receiving vagus nerve stimulation, ranging from 1.3 SUDEP deaths for the general population of patients with epilepsy, to 3.5 (for definite and probable) for a recently studied antiepileptic drug (AED) clinical trial population similar to the VNS Therapy System clinical cohort, to 9.3 for patients with medically intractable epilepsy who were epilepsy surgery candidates. 5. WARNINGS — DEPRESSION This device is a permanent implant. It is only to be used in patients with severe depression who are unresponsive to standard psychiatric management. It should only be prescribed and monitored by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device. Physicians should warn patients that VNS Therapy has not been determined to be a cure for depression. Patients being treated with adjunctive VNS Therapy should be observed closely for clinical worsening and suicidality, especia ly at the time of VNS Therapy stimulation parameter changes or drug or drug dose changes. Excessive stimulation: Note: Use of the Magnet to activate stimulation is not recommended for patients with depression. 6. PRECAUTIONS — GENERAL Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy physician's manuals. Prescribing physicians should be experienced in the diagnosis and treatment of depression or ep lepsy and should be familiar with the programming and use of the VNS Therapy System. Physicians who implant the VNS Therapy System should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the VNS Therapy System. The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy. VNS should be used during pregnancy only if clearly needed. The VNS Therapy System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The VNS Therapy System is indicated for use only in stimulating the left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve. It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the procedure. The VNS Therapy System may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable pacemaker, defibrillatory therapy or other types of stimulators, careful programming of each system may be necessary to optimize the patient's benefit from each device. Reversal of Lead polarity has been associated with an increased chance of bradycardia in animal studies. It is important that the electrodes are attached to the left vagus nerve in the correct orientation. It is also important to make sure that Leads with dual connector pins are correctly inserted (white marker band to + connection) into the Pulse Generator's Lead receptacles. The patient can use a neck brace for the first week to help ensure proper Lead stabilization. Do not program the VNS Therapy System to an "ON" or periodic stimulation treatment for at least 14 days after the initial or replacement implantation. Do not use frequencies of 5 Hz or below for long-term stimulation. Resetting the Pulse Generator turns the device OFF (output current = 0.0 mA), and all device history information is lost. Patients who smoke may have an increased risk of laryngeal irritation. 7. ENVIRONMENTAL AND MEDICAL THERAPY HAZARDS Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a Pulse Generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation. VNS Therapy System operation should always be checked by performing device diagnostics after any of the procedures mentioned in the physician's manuals. For clear imaging, patients may need to be specially positioned for mammography procedures, because of the location of the Pulse Generator in the chest. Therapeutic radiation may damage the Pulse Generator's circuitry, although no testing has been done to date and no definite information on radiation effects is available. Sources of such radiation include therapeutic radiation, cobalt machines, and linear accelerators. The radiation effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage, and may not be detectable immediately. External defibrillation may damage the Pulse Generator. Use of electrosurgery [electrocautery or radio frequency (RF) ablation devices] may damage the Pulse Generator. Magnetic resonance imaging (MRI) should not be performed with a magnetic resonance body coil in the transmit mode. The heat induced in the Lead by an MRI body scan can cause injury. Additionally, in vitro tests have shown that an intact Lead without an implanted Pulse Generator presents substantially the same hazards as a full VNS Therapy System. If an MRI should be done, use only a transmit-and-receive type of head coil. MRI compatibility was demonstrated using 1.5T General Electric Signa and 3.0T Philips MR systems. Use caution when other MR systems are used, since adverse events may occur because of different magnetic field distributions. Consider other imaging modalities when appropriate. Procedures in which the radio frequency (RF) is transmitted by the body coil should not be done on a patient who has the VNS Therapy System. Thus, protocols must not be used that utilize local coils that are RF receive-only, with RF-transmit performed by the body coil. Note that some RF head coils are receive-only, and that most other local coils, such as knee and spinal coils, are also RF-receive only. These coils must not be used in patients with the VNS Therapy System. See MRI with the VNS Therapy System (Non-U.S. version) for details. Extracorporeal shockwave lithotripsy may damage the Pulse Generator. If therapeutic ultrasound therapy is required, avoid positioning the area of the body where the Pulse Generator is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the Pulse Generator output to 0 mA for the treatment, and then after therapy, reprogram the Pulse Generator to the original parameters. If the patient receives medical treatment for which electric current is passed through the body (such as from a TENS unit), either the Pulse Generator should be set to 0 mA or function of the Pulse Generator should be monitored during initial stages of treatment. Routine therapeutic ultrasound could damage the Pulse Generator and may be inadvertently concentrated by the device, causing harm to the patient. For complete information related to home occupational environments, cellular phones, other environmental hazards, other devices, and ECG monitors, refer to the physician's manuals. 8. ADVERSE EVENTS — EPILEPSY Adverse events reported during clinical studies as statistically significant are listed below in alphabetical order: ataxia (loss of the ability to coordinate muscular movement); dyspepsia (indigestion); dyspnea (difficulty breathing, shortness of breath); hypesthesia (impaired sense of touch); increased coughing; infection; insomnia (inability to sleep); laryngismus (throat, larynx spasms); nausea; pain; paresthesia (prickling of the skin); pharyngitis (inflammation of the pharynx, throat); voice alteration (hoarseness); vomiting. 9. ADVERSE EVENTS — DEPRESSION Implant-related adverse events reported during the pivotal study in ≥ 5% of patients are listed in order of decreasing occurrence: incision pain, voice alteration, incision site reaction, device site pain, device site reaction, pharyngitis, dysphagia, hypesthesia, dyspnea, nausea, headache, neck pain, pain, paresthesia, and cough increased. Stimulation-related adverse events reported during the acute sham-controlled study by ≥ 5% of VNS Therapy-treated patients are (in order of decreasing occurrence): voice alteration, cough increased, dyspnea, neck pain, dysphagia, laryngismus, paresthesia, pharyngitis, nausea, and incision pain.

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[1] The information contained in this Brief Summary for Physicians represents partial excerpts of important prescribing information taken from the physician's manuals. (Copies of VNS Therapy physician's and patient's manuals are posted at www.VNSTherapy.com/manuals.) The information is not intended to serve as a substitute for a complete and thorough understanding of the material presented in all of the physician's manuals for the VNS Therapy System and its component parts nor does this information represent ful disclosure of a l pertinent information concerning the use of this product, potential safety complications, or efficacy outcomes.

PhysAdGenA4BS08-11-1000-EC

Development and Developmental Assessment

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This article will give you a structure on which to base a developmental history, review usual milestones, and give an understanding of structured developmental assessment. The aim is that you will be able to identify key warning signals and know the practical relevance to your current practice.

The fundamental difference between paediatric and adult neurology is that children continue to grow and develop. This process continues into young adulthood beyond what is conventionally regarded as the "cut off" for paediatric services.

For many paediatricians, let alone adult physicians, developmental assessment is an area where they express a lack of competence and confidence. Remembering that your own child was walking on their first birthday and could just about put on his own shoes when he started at nursery does not qualify you as a confident assessor of child development!

Basic concepts in child development

Developmental progress is about gaining functional skills which will over time allow a child to become independent of its adult caregivers.

Developmental skills are achieved sequentially following a remarkably consistent pattern, there is however a wide normal range.

Development is considered within four fields in the young child:
1. Gross Motor
2. Vision and Fine Motor
3. Hearing, Speech and Language
4. Social, Emotional and Behavioural

Hearing and vision are grouped with the skills which are most contingent on them. Important consideration must be given to these areas as impairments can have important consequences for other areas of development and early intervention is crucial.

Difficulties within one developmental field can lead to delays in the acquisition of skills in another field. The child with a significant hearing impairment may be late to speak, this limits his play opportunities with other children and consequently his social development.

Development should always be a process of progression, any suggestion of developmental standstill or loss of previously attained skills is a cause of significant concern.

The abnormal persistence of immature aspects of behaviour can also be a cause for concern eg mouthing approach to toys beyond 12 months of age.

Cognitive development

In the school aged child skills become more complex and progress tends to be judged by cognitive rather than physical development. That is not to say that cognition can not and should not be assessed in the younger child. Concepts which can be covered in a routine assessment include object permanence, recognition of self and symbolic thought (see Table 1).

Infancy – a child sees himself as the centre of the world, thought processes relate to immediate experiences.

Preschooler – inanimate objects are alive with feelings and events have a magical nature.

School age – the dominant mode of thought is practical and relates to specific circumstances and experiences.

Mid teens – abstract thought begins to develop with the ability to test hypotheses and manipulate more complex concepts.[2]

Important influences on development

Development occurs as a result of an interplay between hereditary factors and the environment. In order for development to occur a child's basic physical and psychological needs must be met.

Case 1

A 10-month-old baby boy attends clinic as he is not crawling. He has three siblings under the age of 5, the household is very busy. You discover he spends large parts of his day in the buggy or car seat. On examination he sits independently but gets upset in the prone position and makes no attempt to crawl.

Case 2

An 18-month-old girl is referred for assessment of delayed development by her social worker. She has no recognisable words and crawls but does not walk. In the clinic room she does not appear to know what to do with toys simply putting them in her mouth, is quiet and reluctant to interact with you. On examination she has a small head 2nd centile, weight on 75th centile you wonder if she is dysmorphic in facial appearance. The social worker tells you that her mother has a long history of drug and alcohol misuse.

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Zebinix®▽
(eslicarbazepine acetate)

Please refer to the SmPC before prescribing. ***Presentation:*** Tablets containing 800 mg eslicarbazepine acetate. ***Indication:*** Adjunctive therapy in adults with partial-onset seizures with or without secondary generalisation. ***Dose and administration:*** May be taken with or without food. Starting dose is 400 mg once daily which should be increased to 800 mg once daily after one or two weeks. The dose may be increased to 1200 mg once daily. Withdraw gradually to minimise the potential of increased seizure frequency. ***Elderly patients:*** Caution (See SmPC). ***Children and adolescents <18 years of age:*** Not recommended. ***Patients with renal impairment:*** The dose should be adjusted according to creatinine clearance (CL_{CR}) (see SmPC). Not recommended in severe impairment. ***Patients with hepatic impairment:*** No dose adjustment in mild to moderate impairment. Not recommended in severe impairment. ***Contra-Indications:*** Hypersensitivity to the active substance, other carboxamide derivatives (e.g. carbamazepine, oxcarbazepine) or any excipients. Known second or third degree AV block. ***Pregnancy:*** No data on the use of Zebinix in pregnant women. If women receiving Zebinix become pregnant or plan to become pregnant, the use of Zebinix should be carefully re-evaluated. Minimum effective doses should be given. Zebinix interacts with oral contraceptives. An alternative, effective and safe method of contraception should be used during treatment and up to the end of the current menstrual cycle after treatment has been stopped. ***Lactation:*** Excretion in human breast milk is unknown. Breastfeeding should be discontinued during treatment. ***Warnings and precautions:*** Zebinix has been associated with some CNS reactions such as dizziness and somnolence. Concomitant use with oxcarbazepine is not recommended. Rash has been reported. If signs or symptoms of hypersensitivity develop, Zebinix must be discontinued. Presence of HLA-B*1502 allele in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine. Screening for this allele should be undertaken in such individuals. Serum sodium levels should be examined before and during treatment in patients with pre-existing renal disease or in patients concomitantly treated with medicinal products which may lead to hyponatraemia. Serum sodium levels should be determined if clinical signs of hyponatraemia occur. If clinically relevant hyponatraemia develops, discontinue Zebinix. Use in primary generalised seizures is not recommended. Prolongations in PR interval have been observed. Caution in patients with medical conditions or when taking concomitant medicinal products associated with PR prolongation. Monitor for signs of suicidal ideation and behaviours. Appropriate treatment should be considered. ***Drug interactions:*** In vitro eslicarbazepine is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. In vivo eslicarbazepine may have an inducing effect on the metabolism of medicinal products which are mainly eliminated by metabolism through CYP3A4 or conjugation through the UDP-glucuronyl transferases. When initiating or discontinuing treatment with Zebinix or changing the dose, it may take 2 to 3 weeks to reach the new level of enzyme activity. Time delays must be taken into account when Zebinix is being used just prior to or in combination with other medicines that require dose adjustment when co-administered with Zebinix. Eslicarbazepine has inhibiting properties with respect to CYP2C19. Interactions can arise when co-administering high doses of eslicarbazepine acetate with medicinal products that are mainly metabolised by CYP2C19. Phenytoin: concomitant use may require an increase of Zebinix dose and a decrease of phenytoin dose. Lamotrigine and topiramate: no dose adjustments are required. However, clinical review should be considered. Valproate and levetiracetam: Concomitant administration with valproate or levetiracetam appeared not to affect the exposure to eslicarbazepine but has not been verified by conventional interaction studies. Carbamazepine: Concomitant treatment with carbamazepine increased the risk of the diplopia, abnormal coordination and dizziness. An increase in other adverse reactions caused by co-administration of carbamazepine and eslicarbazepine acetate cannot be excluded. Carbamazepine increases eslicarbazepine clearance. Zebinix slightly increases the clearance of carbamazepine. Oral contraceptives: Interacts with the oral contraceptive. Women of childbearing potential must use adequate contraception during treatment with Zebinix, and up to the end of the current menstruation cycle after the treatment has been discontinued. Warfarin: Zebinix has been shown to decrease exposure to S-warfarin. There are no effects on R-warfarin or coagulation. Monitoring of INR should be performed in the first weeks after initiation or ending concomitant treatment. Digoxin: no effect. MAOIs: an interaction between eslicarbazepine acetate and MAOIs is theoretically possible. ***Side effects:*** Adverse reactions were usually mild to moderate in intensity and occurred predominantly during the first weeks of treatment with Zebinix. Very common effects (≥1/10): dizziness, somnolence. Common effects (≥1/100, <1/10): Headache, abnormal coordination, disturbance in attention, tremor, diplopia, vision blurred, vertigo, nausea, vomiting, diarrhoea, rash, fatigue, gait disturbance. Uncommon (≥1/1,000 to <1/100): anaemia, hypersensitivity, hypothyroidism, increased appetite, decreased appetite, hyponatraemia, electrolyte imbalance, cachexia, dehydration, obesity, insomnia, apathy, depression, nervousness, agitation, attention deficit/hyperactivity disorder, confusional state, mood swings, crying, psychomotor retardation, stress, psychotic disorder, memory impairment, balance disorder, amnesia, hypersomnia, sedation, aphasia, dysaesthesia, dystonia, lethargy, parosmia, autonomic nervous system imbalance, cerebellar ataxia, cerebellar syndrome, grand mal convulsion, neuropathy peripheral, sleep phase rhythm disturbance, nystagmus, speech disorder, dysarthria, hypoaesthesia, ageusia, burning sensation, vision disturbance, oscillopsia, binocular eye movement disorder, ocular hyperaemia, saccadic eye movement, eye pain, ear pain, hypoacusis, tinnitus, palpitations, bradycardia, sinus bradycardia, hypertension, hypotension, orthostatic hypotension, dysphonia, epistaxis, dyspepsia, gastritis, abdominal pain, dry mouth, abdominal discomfort, abdominal distension, duodenitis, epigastric discomfort, gingival hyperplasia, gingivitis, irritable bowel syndrome, melaena, odynophagia, stomach discomfort, stomatitis, toothache, liver disorder, alopecia, dry skin, hyperhidrosis, erythema, nail disorder, skin disorder, myalgia, back pain, neck pain, nocturia, menstruation irregular, asthenia, malaise, chills, oedema peripheral, adverse drug reaction, peripheral coldness, blood pressure decreased, weight decreased, blood pressure diastolic decreased, blood pressure increased, blood pressure systolic decreased, blood sodium decreased, haematocrit decreased, haemoglobin decreased, heart rate increased, transaminases increased, triglycerides increased, triiodothyronine (T3) free decreased, thyroxine (T4) free decreased, drug toxicity, fall, joint injury, poisoning, skin injury. For rare side effects see SmPC. When treated concomitantly with carbamazepine, diplopia, abnormal coordination and dizziness are reported more frequently. Use of Zebinix is associated with an increase in the PR interval. Adverse reactions associated with PR interval prolongation may occur. No second or higher degree AV block was seen in Zebinix treated patients. Rare adverse reactions such as bone marrow depression, anaphylactic reactions, severe cutaneous reactions (e.g. Stevens-Johnson Syndrome), systemic lupus erythematosus or serious cardiac arrhythmias did not occur during clinical studies. However, they have been reported with oxcarbazepine and their occurrence during treatment with Zebinix cannot be excluded. ***Legal Category:*** POM. ***Basic UK NHS cost:*** Zebinix 800 mg: pack of 30 £154.20. ***Marketing authorisation numbers:*** EU/1/09/514/012-020. ***Marketing authorisation holder:*** Bial-Portela & Cª., S.A. À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado – Portugal. ***Further Information from:*** Eisai Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, UK. ***Date of preparation:*** July 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 Eisai Ltd on 0208 600 1400/0845 676 1400 or Lmedinfo@eisai.net

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Eisai

TABLE 1: Key concepts of cognitive development in the young child.

Cognitive concept	Description	Milestones	Relevance
Object permanence	The concept that an object remains even when it is not visible.	At 2-3 months a baby will glance fleetingly after an object that is lost from view. By one year a child will search for an object they have seen covered by a cloth.	Important for emotional security, maturation and language development.
Recognition of self	The ability of a child to see herself as a person separate from others.	In the first 2 months a baby probably sees herself as an integral part of her mother. By 8-12 months she develops an awareness of the effect she can have on other things (subjective self). By 2 years recognition of herself as 'a girl' or 'a child' recognising herself in the mirror.	Essential to develop a sense of self evaluation.
Symbolic thought	The recognition that something can stand for something else.	Early evidence in second year of life with deferred imitation of things seen previously and evolves into symbolic play e.g. using a stick as a sword.	Precursor for language, as words are symbols of things.

A baby will develop motor skills if:
- he has a normal central nervous system
- he has motivation to practice new skills
- he has the opportunity to practice new skills

In case 1 the child lacks the opportunity and motivation to practice new skills.[3]

In case 2 the central nervous system may not be normal as illicit drug and alcohol use in pregnancy are both associated with significant effects on the developing foetus. Parents who misuse substances may expose their children to significant neglect both physically and emotionally, compounding any underlying neurological problem.

The developmental history

The developmental history needs to be taken within the context of a full assessment as described in the previous article in the series.[4] Development is highly influenced by the environmental context in which a child exists, the history is your chance to gain an insight into this.

Begin at the beginning. Concerns may have arisen antenatally on the basis of family history or screening tests. In the birth history it is important to identify prematurity, which should be corrected for until two years of age when considering development. A child born at 30 weeks gestation may not smile until 15 weeks of chronological age, corrected for gestation five weeks, and be normal. A sensitive but thorough social and family history is vital.

Developmental milestones

A developmental milestone is an important developmental skill. For each skill there is a normal range of time for a child to develop it within. A median age is the age at which half of children acquire a skill.

A limit age is the age at which a skill should have been achieved, it reflects two standard deviations from the mean. Failure to achieve these warrants more detailed assessment, investigation or intervention.

This concept can be demonstrated with respect to walking unaided:
- 25% by 11 months
- 50% by 12 months
- 75% by 13 months
- 90% by 15 months
- 97.5% by 18 months[2]

Of those not walking by 18 months some will be normal late walkers. However, 20% will have a significant problem including cerebral palsy, Duchenne muscular dystrophy or global developmental delay.

It is important to have a feel for which milestones are most consistent. Smiling socially by the age of eight weeks is a very consistent milestone and failure to achieve this is a real cause for concern. Crawling is a very inconsistent milestone, it occurs at a widely varying point and some children with normal development never learn to crawl.

It is important to have a few key milestones on which to base your assessment and to know where to go for more detail (see Table 2).

Developmental assessment

You can gain a brief idea of a child's developmental level by asking a few targeted questions depending on their age and making a careful observation of their behaviour in the clinic room without recourse to more formal assessment.

These questions form the 'Parent Evaluation of Developmental Status' (PEDS). A study using this in children aged 21 to 84 months found it to be as good as most developmental screening tests. [1]

Please tell me any concerns about the way your child is behaving, learning and developing.

Any concerns about how she
understands what you say?
talks?
makes speech sounds?
uses hands and fingers to do things?
uses arms and legs?
behaves?
gets along with others?
is learning to do things for herself?
is learning preschool and school skills?

A range of formal developmental tests exist which are based on cross sectional observations of many children. They require specialist training to deliver, but can generate useful information.

Those in common use include:
- Bayley II Scales of Infant Development
- Griffiths Abilities of Babies and Young Children

In school age children assessments would tend to be made by educational psychologists using a different range of standardised tools:
- WISC-III UK3 (Wechsler Intelligence Scale for Children)
- BAS II (British Abilities Scales 2nd Edition 1997)

Testing of development is not without pitfalls, points to consider include:
- Testing reflects a single observation and a child who is unwell, tired, hungry or

TABLE TWO: Developmental Milestones.

Age	Gross Motor	Fine Motor and vision	Hearing, Speech and Lanuage	Social, Emotional/Behavioural.
6 weeks	Head level with body in ventral suspension	Fixes and follows	Stills to sound	Smiles
3 months	Holds head at 90 degrees in ventral suspension	Holds an object placed in the hand	Turns to sound	Hand regard, laughs and squeals
6 months	No head lag on pull to sit Sits with support In prone lifts up on forearms	Palmar grasp of objects Transfers objects hand to hand	Babbles	Works to reach a toy May finger feed
9 months	Crawls Sits steadily unsupported and pivots around	Pincer grasp Index finger approach Bangs 2 cubes together	2 syllable babble	Waves bye bye Plays pat a cake Indicate wants
12 months	Pulls to stand Cruises Stands alone (briefly) Walks alone	Puts block in cup Casting	One or two words	Imitates activities Plays ball Object permanence established
18 months	Walks well Runs	Tower of 2-4 cubes Scribbles	6-12 words	Uses spoon Helps in house Symbolic play
2 years	Kicks ball Climbs stairs 2 feet per step	Tower of 6-7 cubes Circular scribble	Joins 2 -3 words Knows 5-6 body parts Identifies 2 pictures	Removes a garment e.g. a sock
3 years	Throws overarm Stands briefly on one foot Climbs stairs 1 foot per step	Tower of 9 cubes Copies a circle Cuts with scissors	Talks in sentences Names 4 pictures	Eats with fork and spoon Puts on clothing Names friend

It is important to have a feel of which milestones are most consistent. Smiling socially by the age of eight weeks is a very consistent milestone and failure to achieve this is a real cause for concern. Crawling is a very inconsistent milestone, it occurs at a widely varying point and some children with normal development never learn to crawl

anxious may not perform at their usual level.

- Many tests rely heavily on motor skills and a child with difficulties in this area may under perform.
- Some test components do not stand the test of time, most children's shoes fasten with Velcro now, tying shoe laces is a lost art! To gain a skill you must have experience of it.
- Some tests in widespread use were designed many years ago and may not reflect current societal norms. Children from some ethnic groups may therefore appear to be disadvantaged because of this.

Performing one of these tests of development gives a horizontal assessment of the child in comparison with other children of the same age at a point. In a child about whom there are concerns, a vertical assessment of their abilities over time will allow you to assess rate of progress and skill acquisition.

Key messages

- Parents who are concerned that there is something wrong with their child are usually right.
- A history of loss of skills i.e. regression implies a progressive underlying cause for developmental delay.
- Delayed gross motor development, (sitting and walking) is the least significant pointer to a general delay, but can be the most obvious and most worrying for the parents.
- Almost all normal babies born around their expected due date smile by 8 weeks. Failure to do so should alert you to the possibility that there is a problem.
- Children not walking at 18 months have a 1 in 5 chance of having a significant problem.

Conclusion

Child development can seem baffling to those not used to thinking about it. However, like most things in medicine it is straightforward if you familiarise yourself with what is normal and develop a system for trying to identify what is abnormal. Abnormal patterns or delays in development are essential to recognise in order to identify causes and institute appropriate support. ◆

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Night

Tony Judt

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I suffer from a motor neuron disorder, in my case a variant of amyotrophic lateral sclerosis (ALS): Lou Gehrig's disease. Motor neuron disorders are far from rare: Parkinson's disease, multiple sclerosis, and a variety of lesser diseases all come under that heading. What is distinctive about ALS – the least common of this family of neuro-muscular illnesses – is firstly that there is no loss of sensation (a mixed blessing) and secondly that there is no pain. In contrast to almost every other serious or deadly disease, one is thus left free to contemplate at leisure and in minimal discomfort the catastrophic progress of one's own deterioration.

In effect, ALS constitutes progressive imprisonment without parole. First you lose the use of a digit or two; then a limb; then and almost inevitably, all four. The muscles of the torso decline into near torpor, a practical problem from the digestive point of view but also life-threatening, in that breathing becomes at first difficult and eventually impossible without external assistance in the form of a tube-and-pump apparatus. In the more extreme variants of the disease, associated with dysfunction of the upper motor neurons (the rest of the body is driven by the so-called lower motor neurons), swallowing, speaking, and even controlling the jaw and head become impossible. I do not (yet) suffer from this aspect of the disease, or else I could not dictate this text.

By my present stage of decline, I am thus effectively quadriplegic. With extraordinary effort I can move my right hand a little and can adduct my left arm some six inches across my chest. My legs, although they will lock when upright long enough to allow a nurse to transfer me from one chair to another, cannot bear my weight and only one of them has any autonomous movement left in it. Thus when legs or arms are set in a given position, there they remain until someone moves them for me. The same is true of my torso, with the result that backache from inertia and pressure is a chronic irritation. Having no use of my arms, I cannot scratch an itch, adjust my spectacles, remove food particles from my teeth, or anything else that – as a moment's reflection will confirm – we all do dozens of times a day. To say the least, I am utterly and completely dependent upon the kindness of strangers (and anyone else).

During the day I can at least request a scratch, an adjustment, a drink, or simply a gratuitous replacement of my limbs – since enforced stillness for hours on end is not only physically uncomfortable but psychologically close to intolerable. It is not as though you lose the desire to stretch, to bend, to stand or lie or run or even exercise. But when the urge comes over you there is nothing – nothing – that you can do except seek some tiny substitute or else find a way to suppress the thought and the accompanying muscle memory.

But then comes the night. I leave bedtime until the last possible moment compatible with my nurse's need for sleep. Once I have been 'prepared' for bed I am rolled into the bedroom in the wheelchair where I have spent the past eighteen hours. With some difficulty (despite my reduced height, mass, and bulk I am still a substantial dead weight for even a strong man to shift) I am manoeuvered onto my cot. I am sat upright at an angle of some 110° and wedged into place with folded towels and pillows, my left leg in particular turned out ballet-like to compensate for its propensity to collapse inward. This process requires considerable concentration. If I allow a stray limb to be mis-placed, or fail to insist on having my midriff carefully aligned with legs and head, I shall suffer the agonies of the damned later in the night.

I am then covered, my hands placed outside the blanket to afford me the illusion of mobility but wrapped nonetheless since – like the rest of me – they now suffer from a permanent sensation of cold. I am offered a final scratch on any of a dozen itchy spots from hairline to toe; the Bi-Pap breathing device in my nose is adjusted to a necessarily uncomfortable level of tightness to ensure that it does not slip in the night; my glasses are removed...and there I lie: trussed, myopic, and motionless like a modern-day mummy, alone in my corporeal prison, accompanied for the rest of the night only by my thoughts.

Of course, I do have access to help if I need it. Since I can't move a muscle, save only my neck and head, my communication device is a baby's intercom at my bedside, left permanently on so that a mere call from me will bring assistance. In the early stages of my disease the temptation to call out for help was almost irresistible: every muscle felt in need of movement, every inch of skin itched, my bladder found mysterious ways to refill itself in the night and thus require relief, and in general I felt a desperate need for the reassurance of light, company, and the simple comforts of human intercourse. By now, however, I have learned to forgo this most nights, finding solace and recourse in my own thoughts.

The latter, though I say it myself, is no small undertaking. Ask yourself how often you move in the night. I don't mean change location altogether (e.g., to go to the bathroom, though that too): merely how often you shift a hand, a foot; how frequently you scratch assorted body parts before dropping off; how unselfconsciously you alter position very slightly to find the most comfortable one. Imagine for a moment that you had been obliged instead to lie absolutely motionless on your back – by no means the best sleeping position, but the only one I can tolerate – for seven unbroken hours and constrained to come up with ways to render this Calvary tolerable not just for one night but for the rest of your life.

My solution has been to scroll through my life, my thoughts, my fantasies, my memories, mismemories, and the like until I have chanced upon events, people, or narratives that I can employ to divert my mind from the body in which it is

encased. These mental exercises have to be interesting enough to hold my attention and see me through an intolerable itch in my inner ear or lower back; but they also have to be boring and predictable enough to serve as a reliable prelude and encouragement to sleep. It took me some time to identify this process as a workable alternative to insomnia and physical discomfort and it is by no means infallible. But I am occasionally astonished, when I reflect upon the matter, at how readily I seem to get through, night after night, week after week, month after month, what was once an almost insufferable nocturnal ordeal. I wake up in exactly the position, frame of mind, and state of suspended despair with which I went to bed – which in the circumstances might be thought a considerable achievement.

This cockroach-like existence is cumulatively intolerable even though on any given night it is perfectly manageable. "Cockroach" is of course an allusion to Kafka's Metamorphosis, in which the protagonist wakes up one morning to discover that he has been transformed into an insect. The point of the story is as much the responses and incomprehension of his family as it is the account of his own sensations, and it is hard to resist the thought that even the best-meaning and most generously thoughtful friend or relative cannot hope to understand the sense of isolation and imprisonment that this disease imposes upon its victims. Helplessness is humiliating even in a passing crisis – imagine or recall some occasion when you have fallen down or otherwise required physical assistance from strangers. Imagine the mind's response to the knowledge that the peculiarly humiliating helplessness of ALS is a life sentence (we speak blithely of death sentences in this connection, but actually the latter would be a relief).

Morning brings some respite, though it says something about the lonely journey through the night that the prospect of being transferred to a wheelchair for the rest of the day should raise one's spirits! Having something to do, in my case something purely cerebral and verbal, is a salutary diversion – if only in the almost literal sense of providing an occasion to communicate with the outside world and express in words, often angry words, the bottled-up irritations and frustrations of physical inanition.

The best way to survive the night would be to treat it like the day. If I could find people who had nothing better to do than talk to me all night about something sufficiently diverting to keep us both awake, I would search them out. But one is also and always aware in this disease of the necessary normalcy of other people's lives: their need for exercise, entertainment, and sleep. And so my nights superficially resemble those of other people. I prepare for bed; I go to bed; I get up (or, rather, am got up). But the bit between is, like the disease itself, incommunicable.

I suppose I should be at least mildly satisfied to know that I have found within myself the sort of survival mechanism that most normal people only read about in accounts of natural disasters or isolation cells. And it is true that this disease has its enabling dimension: thanks to my inability to take notes or prepare them, my memory – already quite good – has improved considerably, with the help of techniques adapted from the "memory palace" so intriguingly depicted by Jonathan Spence. But the satisfactions of compensation are notoriously fleeting. There is no saving grace in being confined to an iron suit, cold and unforgiving. The pleasures of mental agility are much overstated, inevitably – as it now appears to me – by those not exclusively dependent upon them. Much the same can be said of well-meaning encouragements to find nonphysical compensations for physical inadequacy. That way lies futility. Loss is loss, and nothing is gained by calling it by a nicer name. My nights are intriguing; but I could do without them. ◆

Response to... Health Records: out of the frying pan

By Mark Wardle, Specialist Registrar, Neurology, Cardiff.

The article "Health Records: out of the frying pan"[1] provides many interesting and aspirational ideas for National Health Service (NHS)-based computer-based health records. One suggestion is that patient records should be "standardised" across all locations.

However, one must distinguish between the electronic standardisation of data formats, vocabularies and terminologies across the United Kingdom (UK) and that of developing a standard user interface for users. The former include data dictionaries (such as the "NHS data model and dictionary"[2]), terminology references (such as READ codes and SNOMED CT[3]), messaging (such as HL7[4]) and NHS organisational structures[5]. Standardisation of user interfaces results in a uniform look and feel for all users irrespective of organisation or role. Standardisation of data formats, vocabularies and terminologies is a sensible and essential first step to creating electronic systems that can share and interoperate. Relying on a single user interface for all users ignores the variable needs of different stakeholders including clinicians (of all specialties), administrators, managers and patients.

Users should also have access to real-time aggregated patient data – NHS central returns of patient episodes and diagnostic categories are historically inaccurate[6] and yet these data are what shape resource allocation and service development – front-line clinicians ignore such information at their peril. As such, we need access to waiting lists, waiting times, appointments, cancellations, procedures, and diagnoses. It is nonsensical to provide a single portal or user interface for all uses of NHS and patient data – end users need specialised systems to provide specialised services – built upon a standardised and highly structured information base interoperable between NHS organisations.

In addition, we cannot ignore the rapid organisational changes within the NHS in the UK. Indeed, there are four diverging "NHSs" within the UK each with different informatics strategies. As such, it is not possible to create a central top-down implementation of an electronic record or indeed feasible to "cull existing systems" and switch to a new centralised system. We will be faced with connecting heterogeneous and disparate information systems across organisational boundaries for many years to come.

Finally, the article makes no mention of research and recruitment into clinical trials. Electronic patient records must be flexible enough to support a wide-range of uses, including supporting clinicians through capturing clinically-relevant research data when appropriate. Such endeavours would streamline and simplify enrolment and randomisation into clinical trials and allow clinicians to capture data at the bedside relevant to them and their practice in a self-determined and clinician-driven manner. For example, stroke physicians want an easy way of recording the results of the NIHSS[7], multiple sclerosis neurologists want to capture (and graph) the EDSS[8], we all want an easy way to randomise the patient in front of us when we don't have sufficient evidence to know what to do. Why can't our information systems support our practice?

As such, my list of requirements is rather different to that suggested. The first prerequisite is providing a solid backend architectural structure (a scaffolding) to support a host of applications using open, interoperable standards and a centralised approach to patient identification and registration.

What then are the clinical priority areas, particularly when we live in a changing economic climate? Priority areas should be those that improve the care and safety of patients: ordering and receiving results of tests, rapid and safe communication between clinicians, electronic prescribing and viewing medication histories.

The final priority? Developing systems that grow as we need them. Centrally driven, top-down designed systems will not evolve with the changing demands placed upon them; the hope must be that we aspire to create information systems that cope with integrating disparate, evolving and rapidly changing patients, clinicians and demands.

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Developments in Neuropathology in the Past Decade

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Neuropathology is a discipline that has broad applications across clinical and research fields involving the central and peripheral nervous systems and skeletal muscle. As a clinical service, neuropathology defines diseases of the nervous system by their structural features through the macroscopic, microscopic and, occasionally, ultrastructural examination of biopsy and autopsy material. Much of the research in neuropathology is centred on the study of human disease and observations that generate hypotheses to be tested by experiments in animal models or in tissue culture. Conversely, results from experimental studies aid the interpretation of pathological features of human disease.

Scientific and clinical advances in the last ten years affecting Neuropathology have been driven by the introduction of new techniques and concepts and by the need to communicate more effectively with those involved in the direct clinical care of patients and with patients and relatives themselves. A spirit of communication and collaboration has strengthened over the last decade through regular Multidisciplinary Team Meetings and collaborative research projects.

Many developments have occurred in the last ten years across the whole spectrum of adult, paediatric and forensic neuropathology. However, in this article, we focus upon some of the changes that have evolved in tumour pathology, an area of primary responsibility for most practicing neuropathologists, and in muscle pathology. We go on to describe progress in the post-mortem diagnosis and in the understanding of neurodegenerative diseases.

Advances in tumour pathology

Neuropathology is often at the centre of the clinical decision making process. The pathological diagnosis of tumours in patients is crucial for their management and treatment. Major changes in clinical practice in relation to tumours of the nervous system have come with the introduction of molecular diagnostics. Molecular evaluation of tumours is now routine (Table 1), but diagnosis remains dependent primarily on the microscopic appearances of a tumour in routine sections stained with haematoxylin and eosin.

Scientific discoveries that hold most promise for a change in clinical practice in relation to tumours of the nervous system have been due to the application of array-based and deep sequencing technologies and by the use of mouse models as a foundation for in vivo therapeutic testing. During the last decade, application of immunocytochemistry

Table 1: Some of the more commonly investigated molecular characteristics of primary CNS tumours. Citation of all of this work is not possible, for a review see reference 1.

Tumour	Test	Implication
Glioblastoma	EGFR amplification Pten /p53 mutations	Distinguish from anaplastic astrocytoma
	MGMT methylation	Associated with improved response to chemotherapy and improved survival
	IDH-1 or 2	May be associated with progression from a lower grade glial tumour and hence possibly improved prognosis
Oligodendroglioma	1p/19q Loss (qPCR or FISH)	Deletion on both loci associated with superior survival and treatment response. Linked to histopathological features
Medulloblastoma	NMYC / CMYC PCR	Gains associated with poor prognosis
	Wnt pathway mutations	Associated with improved prognosis
Atypical Teratoid Rhabdoid tumour	INI-1 or BAF47 immunohistochemistry	Mutation in this gene is linked closely with development of such tumours sporadically or genetically

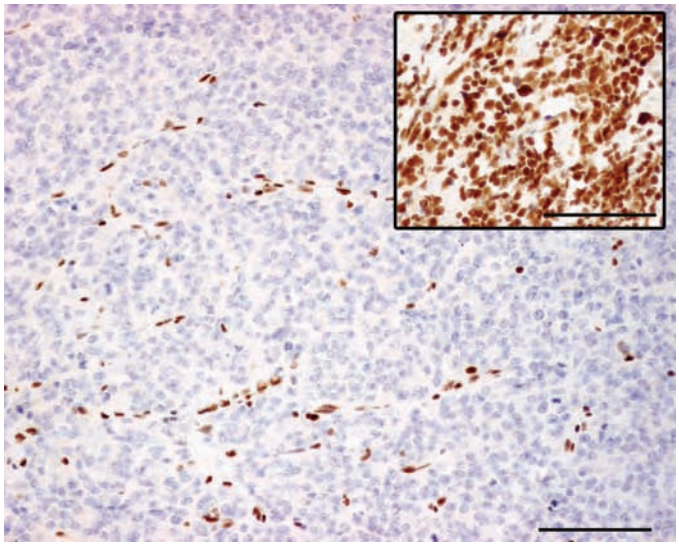

Figure 1: INI-1 immunohistochemistry of an atypical teratoid/rhaboid tumour (main image, no staining within tumour cells but vascular endothelial cells show nuclear brown staining). By comparison, a primitive neurectodermal tumour (PNET), inset, shows strong nuclear staining of tumour cells. Scale bar = 100µm.

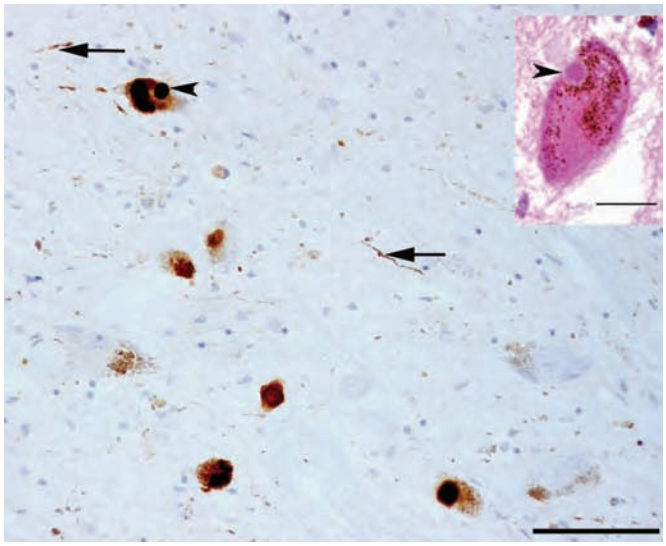

Figure 2: Lewy neurites and Lewy bodies in the substantia nigra of an 82 year-old male with Dementia with Lewy Bodies. Main image – α-synuclein immunohistochemistry showing fine wire-like Lewy neurites (arrows to two) and Lewy bodies (arrow-head to one), scale bar = 100µm. Inset: H&E appearance of a single nigral neuron with some remaining melanin pigment, but also a single Lewy body with a dense core and paler periphery (arrowhead). Scale bar = 20µm.

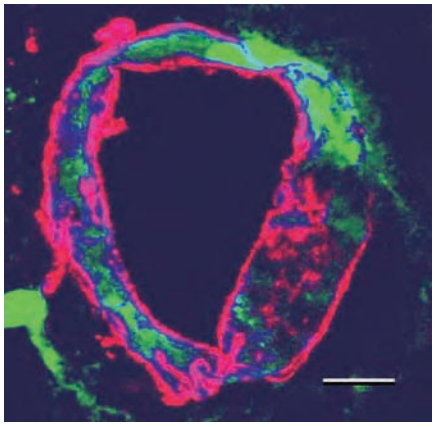

Figure 3: A confocal image of a mouse cerebral artery in transverse section showing how tracers such as dextran (green) can be co-localised with laminin (red) in the artery wall. Co-localisation of dextran and laminin is seen as dark blue. By such use of confocal microscopy it was shown that interstitial fluid and solutes drain from the brain along perivascular basement membranes. Scale bar = 10µm. *Reproduced with permission from reference 9.*

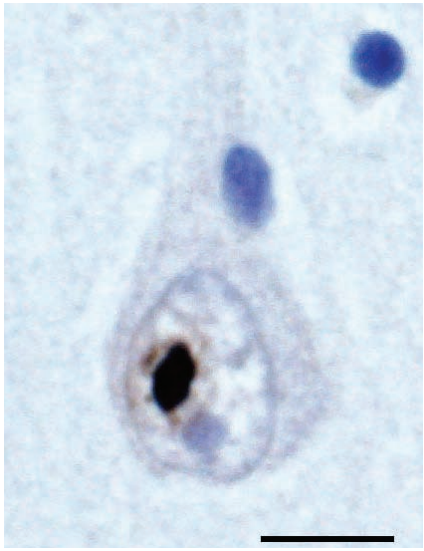

Figure 4: P62 immunohistochemistry labels a neuronal intranuclear inclusion within a cortical neuron in an uncommon neurodegenerative disease associated with dementia. Scale bar = 10µm.

(Figure 1) has greatly improved the classification of brain tumours. In addition, neuropathology plays a key role in establishing the primary diagnosis for tumour tissue used in array-based techniques and fluorescence in situ hybridization (FISH) for the molecular classification of glioblastoma,[1] astrocytoma,[2] oligodendroglioma[3] and medulloblastoma.[4] Such work has had a direct effect on the management and treatment of brain tumours.

Advances in muscle pathology

The characterisation of new forms of inherited muscle disease has grown exponentially over the last ten years. New proteins whose mutations cause certain phenotypes are described several times a year. Basic histological and histochemical evaluation of frozen muscle specimens remains as an important investigation for categorising muscle pathology.[5] More in-depth analysis of biopsies, including genetic testing, is often carried out at NCG (National Commissioning Group) centres. This illustrates one way in which super-specialist high-cost services and professional working practices can be developed and flourish. Data on muscle pathology, biochemistry and genetics are produced at such a rapid rate that published papers and books have difficulty in keeping pace, so many websites (e.g. www.neuromuscular.wustl.edu/) are now the main sources of up-to-date information.

Post-mortem diagnosis and understanding neurodegenerative diseases

Developments in neuropathology in the last decade have played a significant role in the continuing search for the effective diagnosis and treatment of neurodegenerative diseases. An appreciation of neuropathological changes and mechanisms of disease are essential for the interpretation of neuroimaging and of biomarkers in the blood and CSF used in the diagnosis of patients with dementia.[6] Relating the changes in the human brain to those in transgenic mouse models has allowed significant progress in our understanding of disease processes during the last 10 years.

Recognition of genetic abnormalities in familial diseases has had a profound effect on neuropathology and vice-versa. For example, the known genetic causes of Parkinson's disease include mutations in the α-synuclein gene, reported in the late 1990s.[7] The presence of this synapse-related protein, as insoluble accumulations in Lewy bodies and in neurites (Figure 2) in sporadic Parkinson's disease, has stimulated physiological experiments to determine the effects of excessive synuclein on synaptic function. Using transgenic mice that over-express α-synuclein, whole cell patch clamp recordings have shown that high levels of expression of α-synuclein alter synaptic function and suggest that synaptic dysfunction may occur early in Parkinson's.[8]

Technological advances have also increased our understanding of CNS disease. Confocal microscopy, together with continuing advances in immunocytochemistry, have allowed proteins, tracers and ligands to be co-localised with a degree of accuracy that was previously unknown[9] (Figure 3). This has greatly enhanced our capacity to investigate the functional aspects of tissues and cells in the normal and diseased nervous system.

Alzheimer's disease

Alzheimer's disease remains the most common form of dementia world-wide. With an ageing population, it is estimated that there are 700,000 people with dementia in the UK, most of whom will suffer from Alzheimer's disease. Extracellular plaques of insoluble amyloid-β (Aβ) and intracellular, intraneuronal, neurofibrillary tangles

containing tau protein have long been recognised pathological features of Alzheimer's disease. During the last 10 years, there have been very significant advances in our understanding of the disease; too many to mention here. As an example, however, attention has focussed on the failure of elimination of Aβ from the elderly brain and how such a failure may be responsible for dementia. Age brings loss of enzymes that degrade Aβ in brain tissue[10], reduced absorption of Aβ into the blood[11] and impaired elimination of Aβ along perivascular drainage pathways.[12] As the level of soluble Aβ in the brain appears to correlate with cognitive decline in Alzheimer's disease,[13] toxicity of soluble Aβ has also become a focus of research.[14]

Immunotherapy whereby plaques of insoluble Aβ are removed from the brains of patients with Alzheimer's disease has been introduced.[15] Neuropathological studies of post-mortem brains from treated patients have revealed mechanisms by which Aβ is removed from plaques by microglia and how such removal reduces the accumulation of tau in neurites.[16] These observations supply key data for the future development of immunotherapy.

Other studies, using transgenic mice, have shown that tau spreads from neuron to neuron[17] whereas Aβ diffuses through the extracellular spaces and drains along perivascular pathways by which fluid and solutes drain from the brain to regional lymph nodes.[9,18]

Other neurodegenerative diseases

Animal models of prion diseases have been used to distinguish between the toxic and infective roles of prion proteins and this could lead to the development of therapies for Creuzfeldt-Jacob disease (CJD).[19] Just before the present decade began, the UK was in a public health dilemma with the advent of variant CJD contracted by ingestion of meat from cows infected with bovine spongiform encephalopathy (BSE). In the last ten years there has been intense surveillance by neuropathologists to identify any new cases of vCJD as they occur. Biochemical analyses have shown that the prion protein in variant Creutzfeldt-Jakob disease is remarkably stereotyped, in contrast to the considerable heterogeneity that exists in sporadic CJD.[20]

The last decade has seen significant advances in our understanding of frontotemporal lobar degeneration (FTLD)[21, 22] associated with dementia in a slightly younger age group than Alzheimer's disease. Several new types of FTLD have been identified through a combination of gene studies and the neuropathological characterisation of intracellular protein inclusions. One of the more common forms of this disease was previously recognised as a form of motor neuron disease (FTLD-MnD). Particularly significant has been the identification of new pathological proteins in most tau-negative forms of FTLD. P62 is a protein within the ubiquitin functional pathway and immunohistochemistry for p62 has superseded ubiquitin as a diagnostic tool for intracellular inclusions (Figure 4) in FTLD.[21]

The role of neuropathology in Brain Tissue Banks

Although there was much public concern in the UK at the beginning of the decade about retention of brains at post mortem, there have been significant developments in brain and tissue banking during the past ten years. The formation of the Human Tissue Authority and associated Act is an example of this. Brain-banking entails cooperation of patients, carers and relatives, together with the organisational skills and funding from charities and the Medical Research Council (e.g. www.brainsfordementiaresearch.org.uk). Neuropathologists play a key role in brain and tissue banks, not only in the acquisition and storage of the material but also in its accurate diagnosis and documentation.[23] This is an essential service that ensures that researchers who use material from brain banks are supplied with firm and accurate diagnostic neuropathological data. ◆

A spirit of communication and collaboration has strengthened over the last decade through regular Multidisciplinary Team Meetings and collaborative research projects

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The Research Series

In this, our penultimate issue in the series, we look at how to obtain support while you are training to be an independent academic neurologist. Sally Lukins and Peter Hutchinson have written about the role of the Academy of Medical Sciences in supporting researchers as they rise through the ranks. Central to that support are the mentorship programmes that the Academy provide and which they eloquently explain in their article. Our other article is from Nikos Evangelou, who has taken an alternative path to the full time academic. He has combined research with his career in the NHS, and his article gives us a few tips to enable us to follow his lead.

I hope that everyone reading the articles in the research series has enjoyed them. For those of you who are contemplating or pursuing a career in academic neurology, there will be a research forum in the ABN conference at Bournemouth in May. This will be in the form of a series of posters presented by principal investigators from around the country. It will be a fantastic way to network with other researchers as well as discuss projects or posts with potential supervisors or mentors. We will detail this more extensively in the May issue of ACNR, but if you are interested please keep the date in your diary. ◆

ABN conference
Bournemouth 11-14th May.
For more information see
http://abn.org.uk/Meeting.aspx?type=1
or email Beth Mallam at
bethmallam@doctors.org.uk
for details of how to take part

Boyd Ghosh
is currently carrying out research for a PhD in Cambridge, investigating biomarkers and social cognition in progressive supranuclear palsy. He is the current secretary for the ABNT.

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The Academy of Medical Sciences
helping clinical academics to achieve their potential

The Academy of Medical Sciences is the independent body in the UK representing the whole spectrum of medical science. Our mission is to promote advances in medical science and campaign to ensure these are converted into healthcare benefits for society.

Developing the leaders of tomorrow

One of the Academy's strategic goals is to develop the next generation of leading global medical researchers. After the Academy's establishment in 1998, our first piece of work set out to address the decrease in medical trainees pursuing a career in academic medicine. This culminated in the publication of the report 'The Tenured Track Clinician Scientist: a new career pathway to promote recruitment into academic medicine'[1] in 2001. A significant outcome of the report was the creation of the Clinician Scientist Fellowship (CSF) scheme, which provides protected research time to post-doctoral clinical academics. This prestigious scheme has been established across a number of funders, medical research charities and pharmaceutical companies. The Academy partnered with The Health Foundation to award three rounds of Clinician Scientist Fellowships, focussing on boosting capacity in the 'vulnerable' clinical academic specialties, for example, pathology, radiology and surgery. Mr Peter Hutchinson, one of the authors, was one of the first cohort of fellows funded through the Academy's scheme.

Since the development of the CSF scheme, funders have developed a number of initiatives aimed at revitalising the clinical academic workforce, including the National Institute for Health Research (NIHR) Integrated Academic Training Pathway (IATP) scheme, as described in the previous issue of ACNR. The Academy has also developed two new funding schemes to provide opportunities to aspiring medical researchers, outlined in Figure 1.

Figure 1 – Academy of Medical Sciences' funding schemes

Starter Grants for Clinical Lecturers

This £5million grant scheme, funded by the Wellcome Trust, aims to provide 'starter' funds to enable research-active Clinical Lecturers to pursue their research, gather preliminary data and so further strengthen their applications for longer-term fellowships and funding. Grants of up to £30,000 are available and can be spread over two years to contribute towards new and directly incurred research costs such as consumables and equipment.

The Daniel Turnberg Trust Fund UK/Middle East Travel Fellowship Scheme

This scheme provides opportunities for short-term exchange of medical researchers between the UK and countries in the Middle East. It aims to offer applicants the chance to gain further research experience, learn new techniques and to foster scientific collaboration. The aim of the scheme is to encourage researchers to experience an alternative research environment, to learn new techniques and initiate ideas for future collaborations. The Fellowships are aimed primarily at young scientists embarking on a career in research.

For further information please contact: info@acmedsci.ac.uk

Mr Peter Hutchinson
is a Senior Surgical Scientist Fellow, Reader and Honorary Consultant Neurosurgeon. Hutch was one of the first cohort of fellows funded through the Academy's Clinician Scientist Fellowship scheme, in partnership with the Health Foundation. He was awarded a five year Senior Surgical Fellowship in 2003, which was recently renewed. Peter works in the field of Neurosurgery, specifically neurotrauma and intensive care, and his current research is on 'traumatic brain injury: fundamental concepts from resuscitation to rehabilitation'.

Sally Lukins
is a Mentoring and Outreach Officer. The Mentoring and Outreach Scheme is managed by a small team of staff at the Academy. Ms Sally Lukins is responsible for the administration and development of the Academy's mentoring scheme and associated outreach activities. She assists clinical academic trainees to identify and establish a relationship with an appropriate mentor and coordinates a national programme of networking events and training workshops. This work is supported by Dr Nigel Eady, Programme Manager and Dr Suzanne Candy, Director of Biomedical Grants and Policy.

Figure 2 - Academy of Medical Sciences (AMS) mentoring and outreach provision across the clinical academic career grades

Indicates access to scheme activity

Scheme Activity	Clinical Academic Career Stage				Notes
	Pre-doctoral trainee*	Post-doctoral trainee**	Senior Academic	Academy Fellow	
1-2-1 Mentoring		■		■	over 200 pairs
Buddy Groups	■	■	■		28 groups nationwide
Mentor development workshops		■	■	■	2-3 times/year
Outreach events	■	■	■	■	up to 5 per year nationwide incl. Scotland and Ireland
Website	■	■	■	■	www.academicmedicine.co.uk
Communications	■	■	■	■	email mentoring@acmedsci.ac.uk to receive bi-monthly bulletin

* MBPhD students, Academic Foundation Fellows, Academic Clinical Fellows, Clinical Training Fellows
** Clinical Lecturers, Clinician Scientist Fellows

Support through mentorship

An academic career brings challenges, opportunities and rewards. However, many individuals are still in clinical training when they embark on a research career and therefore must fulfil multiple and often competing lines for reporting and assessment. Coping with the demands of working within a highly specialised, competitive and fiercely intellectual culture, while also maintaining a work/life balance brings significant challenges.

Thanks to the efforts of funders, the number of doctors embarking on clinical academic training and pursuing a longer-term academic career continues to grow. In striving to develop innovative ways to support these individuals and respond to the increasing numbers of clinical academics across the training grades the Academy has developed a UK-wide mentoring and outreach scheme. Our portfolio of activities promotes academic medicine to medical students and clinicians in training, and offers support and guidance to individuals as they embark on the academic pathway and progress to become established clinical academics. The range of activities offered are outlined below and in Figure 2.

One to one Mentoring

Post-doctoral clinical academics such as Clinician Scientist Fellows and research-active Clinical Lecturers - irrespective of funder - are welcome to participate in a programme of individual one-on-one mentoring throughout their fellowship. Mentors are drawn from the Academy's 950-strong Fellowship, who are elected for their outstanding contribution to medical science. They represent the UK's leading medical scientists from hospitals and general practice, academia, industry and public service.

Mentors act as role models, inspiring mentees and providing practical advice on how to navigate the clinical academic pathway and meet both research and clinical aspirations. The independence and expertise of Academy mentors enables the dialogue between mentor and mentee to focus on longer term aims as well as day-to-day challenges. Mentors may also act as a signpost to information and resources including people and networks. Crucially, however, skilful mentoring requires that mentors are mindful of staying outside of the mentee's management relationships and their educational and research supervision.

The strength and uniqueness of the Academy's one to one mentoring scheme, is the access trainees have to our pool of medical research leaders. Our mentors span the breadth of medical science, and, as they are located across the UK, aspiring clinical academics or 'mentees' are able to gain personalised, confidential and independent advice from a senior figure outside their institution, specialty and even area of research. For the post-doctoral clinical academic, working towards an independent career, this source of additional support can prove invaluable.

'It is very clear to me that the input of an impartial mentor would be of strong value now. I have been using local mentors in the university so far, which has worked well for my research, but now I am needing to consider advice on longer aims and direction which, I believe, is more difficult for these local mentors to provide impartially.' *Clinician Scientist Fellow*

To support mentors we run a rolling programme of mentor development workshops targeted at Academy Fellows, but the invitation to participate is extended to other senior clinical academics and representatives from institutionally-based mentoring schemes. Workshop participants are introduced to key mentoring topics and given the opportunity to explore issues such as the varying roles of supervisor and mentor, confidentiality and career transitions.

The mentoring scheme started in 2002 and numbers involved in the scheme have steadily grown; the Academy currently supports 200 mentee-mentor pairs.

Buddy group scheme

In addition to the one to one mentoring, we are currently piloting a peer mentoring 'buddy group' scheme. This new initiative draws together small groups of pre-doctoral trainees (Academic Clinical Fellows, Clinical Training Fellows and MB PhD students) supported by a more senior trainee. The groups provide a forum for trainees to discuss career development and share ideas and experiences. There has been a good response to this new scheme from trainees, and 28 groups have now been set up regionally.

'It was great to hear everyone's stories about the specific difficulties they had come up against, as well as all the things they had managed to achieve, and to get tailored advice on how to manage all this. I am very grateful that we have all been put in touch like this.'

Peer mentoring group member

Regional workshops and events

We also provide trainees with a programme of regional workshops and events. Our regional activities link to local mentoring schemes and provide opportunities for trainees to network with senior colleagues and peers. They also provide a forum for knowledge transfer and encourage debate on issues around training, funding and professional development. These events provide trainees with opportunities to:

- Understand how to use mentoring.
- Hear from funders about fellowships and grants.
- Learn about policy developments.
- Engage in open debate.
- Hear inspirational talks.
- Establish effective networks amongst peers and colleagues.

Details of forthcoming events can be found at http://www.acmedsci.ac.uk/p148.html.

Information resources

We continue to develop a range of resources and materials to support our scheme. These include an email bulletin, which goes out to over 1500 trainees, and a practical toolkit of mentoring tips which is published on our academic careers website: www.academicmedicine.ac.uk.

The Academy hopes that the portfolio of support it offers will create a cohort effect amongst clinical academics, reducing isolation and maximising support and collaboration. ◆

The Academy is very grateful to the National Institute for Health Research (NIHR) and NHS Education for Scotland (NES) for funding the Mentoring and Outreach Scheme, and to The Health Foundation, Wellcome Trust and The Daniel Turnberg Trust who financially support the Academy's funding schemes. If you would like further information about any of the activities outlined above, please email mentoring@acmedsci.ac.uk or visit www.acmedsci.ac.uk/p25.html.

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Research as a Clinician

Dr Maria Koufali
is Assistant Director of Research and Innovation at Nottingham University Hospitals. Following a PhD in Neuroscience and 10 years in clinical research, she joined the challenging world of research management. Maria strives to develop research capacity and capability whilst fostering a culture for the diffusion and adoption of innovation within the NHS.

Dr Nikos Evangelou
is a Consultant Neurologist in Nottingham. After his training in Oxford and Nottingham, he was appointed as an NHS consultant in Nottingham. He has special interests in pathology and high field MR imaging of MS. His current role is 80% clinical and 20% research.

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Interested in finding research fellows and collaborators?
The ABNT is collating information to create an interactive research networking database on the ABN website. This will include cross-referenced lists of Academic Neurologists, research groups and research posts available in the UK. If you would like to find out more, or ensure that your group is represented, please contact the ABNT Research Rep, Beth Mallam: bethmallam@doctors.org.uk.

The advantages of research have been described in previous articles – the focus of this piece is to discuss the rewards of research in the context of an NHS job. Research assessment exercises have now become the norm for academics, and with the current recession, there is a threat of significant research redundancies in many UK universities. In this context, having a secure clinical job and doing research for the pure joy that research offers can be liberating. There are certain disadvantages, however, in conducting research while trying to keep an ever demanding NHS manager happy. The crucial problem is time. This can be dealt with by either improving your time management skills, or securing protected research time.

Securing protected research time

The era has passed whereby newly appointed neurologists could simply allocate research time into their job plan. Nowadays, most of us have examples of colleagues who have not really done any research for years, but their timetable has the "traditional" research/audit allocation. With the increasing emphasis on accountability and productivity, it is highly unlikely that any job plans will resist the need for more clinical activity. Essentially then, you have to earn the money for your research time (unless of course you engage in research out of your contracted hours).

One of the most common research income generators involves participating in pharmaceutical sponsored clinical trials. The sponsors compensate for the time taken to recruit and monitor participants. With effective time management, and strong negotiating skills, many clinicians, especially in the field of MS, epilepsy and dementia, can find themselves with significant personal research budgets. The most common way that that money was spent, was to employ full or part time research registrars . Recently, it has also been used to secure dedicated research time for more senior clinicians, such as the consultant neurologist acting as principle investigator for the trials. Profits, of course, can also be invested in smaller and difficult to fund pilot projects, to obtain data for a major funding bid.

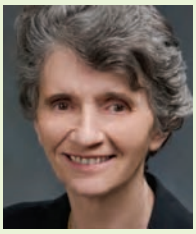
But will the NHS fund research which is led by NHS staff? In recent years there have been dramatic and systematic changes in the structure and funding of research in the NHS. National Institute for Health Research (NIHR) Flexibility and Sustainability Funding is one of the funding schemes that enables NHS consultants (including one of the authors) to spend dedicated time in research. This funding is allocated to research-active NHS organisations, with the amount allocated proportional to the amount of other NIHR income received by that NHS organisation. This funding can cover parts of salaries (PAs) for new research promising posts, for doctors who are in between grants, or preparing grant proposals. This does not cause a permanent change of contract, as the research PA funding is time limited (a few years) and performance managed. Be prepared to present data on grants obtained, number of students supervised, a good publications record etc., if you want your research PAs to continue. Most NHS trusts undertake to take you back at your old, purely clinical, post, if it proves that research is not for you. However, with threatened budget cuts in the NHS, one should be prepared for unexpected twists.

Another source of funding is the NIHR Comprehensive Clinical Research Network (CCRN). It aims to provide infrastructure for clinical trials and other well designed studies in all areas of disease and clinical need within the NHS in England. Ensuring that patients and healthcare professionals from all parts of the country, and from all areas of healthcare, can take part in and benefit from clinical research is a priority for CCRN. It therefore aims to integrate clinical care with high quality research and as such may fund research posts. ◆

Where can you get more information?
Your local R&D office is a good place to start. Much of the research funding comes directly from the NIHR to your trust or university, in which case the R&D offices control the allocation of funds. Other sources of information can be found on www.rdforum.nhs.uk and http://www.crncc.nihr.ac.uk

John Newsom-Davis, MD, FRS, 1932-2007


John Newsom-Davis



Prof Angela Vincent
is Emeritus Professor of Neuroimmunology at Oxford University. In the 1970s she helped John Newsom-Davis to establish the Neurosciences Group at the Royal Free Hospital, which then moved to the Weatheralll Institute in Oxford. Since his retirement in 1998 she has led the Neuroimmunology Group, which is now exploring the whole spectrum of antibody-mediated diseases of the nervous system.

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John Newsom-Davis was a great deal more than a neurologist, of course; he was one of the very few UK clinician scientists of the 1970s and 1980s, and as such had an enormous influence on many who were to come. Here, as well as summarising briefly his achievements, I shall try to draw together some of the aspects of John's early professional life which helped to shape the person that we all admired. Some of the details (given in quotes below) are taken from a transcript of an interview that John gave to the American Neurological Association in 2003, and I am indebted to them and to Barbara Sommer who interviewed him.

John was born the older of twins by a few minutes (his twin sister and older stister are both alive and well). He had a rather conventional middle-class upbringing, but he often admitted that he did not enjoy boarding school (the inference being that he was bullied – probably because he was slight in build and did not enjoy the more macho sports). A much more positive influence was undoubtedly the time he spent in the RAF as a national serviceman (an obligatory two-year stint in one of HM's forces) since he was one of a select few who were trained as pilots. As a result he got his 'wings' in 1953 and flew Metors for a short period before he left the RAF. Meanwhile, he became interested in psychiatry and decided to become a doctor (like his maternal grandfather). He had already been offered a place at Pembroke College Cambridge to read English, but this decision meant that he had to go to a crammer to achieve the necessary higher certificates (A levels) before they would allow him to change to Natural Sciences.

From a relatively undistinguished time in Cambridge he moved to the Middlesex Hospital for his clinical training and it was there that he was particularly influenced by two eminent neurologists: "the first was Dr Michael Kremer, a neurologist who was extraordinarily sharp and who had a remarkable flair for diagnosis, (though it was not always possible – for a medical student – to follow the thought processes by which he reached the right conclusion). But one of his axioms was 'If you can't make the diagnosis, take the history again' – valuable advice that is as relevant now as it was then. The other neurologist who taught me at that time was Professor Roger Gilliatt who had a joint appointment between the Middlesex Hospital and Queen Square. He was a very powerful figure, and a pretty daunting one for a medical student." It was these two who he subsequently acknowledged as the most important in determining his future career.

He could never understand why, when it came to house-job applications, he was selected for the Professorial Unit at the Middlesex under Prof Moran Campbell but considered that privilege as another major career influence and deeply valued Moran's support thereafter. "He himself was passionately interested in research, and a great teacher and I reckon I owe my career to him. He remained immensely supportive through my early career, and I co-authored a monograph with him and Emilio Agostoni, 'The Respiratory Muscles: Mechanics and Neural Control' while I was still a junior doctor."

From that position it was straightforward to be appointed to the Gilliatt and Kramer firm and he was all set for a successful career in Neurology until Gilliatt decided that John was "too old" for neurology and would be more suited to a less demanding specialty! Nevertheless, after a spell at the Brompton where he developed an interest in the neural control of respiration, he started research with Tom Sears at Queen Square looking at the sensation of respiration which he presented as his MD – winning the Queen Square neurology prize. As a result, he was appointed as a junior resident, working for Sean McArdle and Dennis Williams among others, and ending up as Resident Medical Officer.

During his time in training, he found the investigative aspects of academic medicine as appealing, if not more so, as the clinical aspects, and the supervision and encouragement of these great neurologists was crucial. In fact, it was Moran Compbell who was the willing guinea pig in a highly irregular experiment which demonstrated that the sensation of breathlessness did not occur if the individual was paralysed with curare! John became very interested in hiccough, and both John and Tom Sears frequently stuck microelectrodes into their own or the other's intercostals or diaphragm muscles – leading, on one occasion, to John suffering a pneumothorax that he famously described as a cold fish flapping around in his chest – fortunately it resolved spontaneously.

In order to pursue his blossoming commitment to research he joined Fred Plum in New York who was one of the world authorities on the neurology of breathing He was, perhaps like Roger Gilliatt, a tough boss but "he was a fantastic teacher, hugely knowledgeable, and an excellent clinician" and remained a life-long friend. Returning to Queen Square as a consultant, John began to study the activity of muscle spindles in response to stretch in human intercostal muscles, obtaining them from patients undergoing thoractomies at the London Chest Hospital or undergoing thymectomies at Queen Square.

This was when the switch to myasthenia occurred as John related, "it was in about 1973, and came about in this way. Sir Bernard Katz, the Nobel Prize winner, and Ricardo Miledi who worked with him in the Department of Biophysics, University College, London, were world authorities on the neuromuscular junction and had become interested in myasthenia. They wanted to obtain human intercostal muscle to count the number of acetylcholine receptors using radio-labeled alpha-Bungarotoxin.

Ricardo Miledi knew Tom Sears, my ex-supervisor, who put him in touch with me". John started providing Katz and Miledi with muscle biopsies for the neuromuscular junction and myasthenia studies but he continued to work on the muscle spindles for another couple of years. However, during this time news from the USA highlighted three seminal findings. First, an experimental form of myasthenia could be induced by immunisation against purified (fish) acetylcholine receptors; second, the acetylcholine receptors were reduced in MG muscle (sadly, similar work by Miledi was still in progress at this time and was not, therefore, published until 1978); and thirdly, there were antibodies to AChRs in MG sera. All of these findings pointed to a pathogenic role for the antibodies but the final proof came from two very simple but elegant experiments. In 1975 Toyka et al demonstrated the passive transfer of MG to mice by injection of purified MG IgG, and in 1977 John, Tony Pinching and Keith Peters demonstrated that removal of the circulating antibodies by plasma exchange led to marked improvements. These developments and many others relevant to the field are summarised elsewhere (Vincent Nat Reviews Immunology 2002).

Thereafter John turned most of his attention to myasthenia, recognising the emerging field of neuroimmunology and taking an evening course in immunology at the Middlesex Hospital in order to be better prepared for the future. He started a research group at the Royal Free Hospital recruiting myself (from UCL where I had done much of the myasthenia muscle work) and then Bethan Lang, Nick Willcox and David Beeson over the next eight years, which grew into a very active and multidisciplinary team. It was at this point that he began to apply his investigative bent towards clinical diseases – recognising that Lambert Eaton myasthenic syndrome (LEMS), which had already been investigated physiologically and morphologically by Ed Lambert and Andrew Engel at the Mayo Clinic – was likely also to be antibody mediated. Plasma exchange was effective and Bethan Lang spent months injecting purified IgG into mice which Dennis Wray (recently retired as Professor of Physiology in Leeds) showed had neuromuscular junction defects. Similarly we showed that seronegative MG was also antibody-mediated even though at that stage we had no idea about the nature of the target antigens – that took another 15 years and is still on-going!

When John was appointed in 1987 to the Action Research Chair of Neurology, 16 of us moved from the Royal Free Hospital to the Institute of Molecular Medicine (now Weatherall Institute) in Oxford, as well as neurophysiologist Kerry Mills and anaesthetist Laurie Loh to the Radcliffe Infirmary. There he attracted some excellent clinical fellows from the Commonwealth as well as the UK and continued to lead the research group in myasthenia, concentrating mainly on the more tricky areas of thymic pathology, T cell specificity and potential therapies with Nick Willcox and the team. David Beeson started cloning the acetylcholine receptor genes, mutations in which he subsequently discovered in genetic forms of myasthenia. During this period John spent much of his time in the Radcliffe Infirmary Clinical Neurology Department, where he affiliated Margaret Esiri to a Readership in Neuropathology and established Peter Rothwell and Paul Matthews in positions from which they have both achieved great success. But there was never any doubt in our minds that he was happiest when he could shed the dark suit, don the cords, and join us in the Institute. We heard rumours that he could be quite severe in the clinics, but only once managed to get him to lose his cool in the lab.

Curiously, perhaps the most important development was the most serendipitous as it turns out. This was the discovery of VGKC antibodies in acquired neuromyotonia or Isaacs' disease. John approached the condition in a typically thorough manner. It appeared to be very uncommon but he had just seen his first case on a visit to Athens. He did a medline search and found that some cases were associated with penicillamine treatment, thymomas and/or myasthenia. This was sufficient evidence that it was likely to be autoimmune, so he brought the patient to Oxford for plasma exchange. There was a reduction in the frequency of spontaneous bursts on the EMG (demonstrated by Kerry Mills) and the patient's symptoms were markedly improved. More plasma exchanges and passive transfer experiments confirmed that this was an antibody-mediated disease. He hypothesised that the target was a VGKC since these channels are responsible for modulating neurotransmitter release which is increased in neuromyotonia. The neurotoxin dendrotoxin, that produces rather similar physiological features in experimental animals, was radioactively labeled and used to provide a radioimmunoprecipitation assay for the antibodies. What was not clear at the time is that the antibodies are not necessarily against the VGKCs themselves but can be against other proteins that are part of the membrane complexes that hold the VGKCs in place at the nodes of Ranvier (see my Update). If we hadn't used a rather crude brain preparation of VGKCs and, instead, as one would now, expressed the VGKCs in a cell line using molecular techniques, we would probably not have detected the antibodies in many of the patients! But as a result of the use of simple unsophisticated techniques, one of the legacies of John's career is the major interest in antibody-mediated CNS disease that has followed the work on neuromyotonia.

Quite rightly, John was noted for his modesty, lack of pretentiousness, his carefully conceived but effortlessly given lectures, his ability to enthuse individual doctors at early stages of their careers, and to act as a mentor and role model thereafter. Much of this continued when he retired formally from Oxford in 1998, took over the Editorship of Brain, and began to plan the thymectomy trial that NIH, eventually, funded and which is now led by Gil Wolfe in Dallas. In this phase of his very productive life, perhaps more than in any other, he was able to influence younger colleagues and, in particular, patients worldwide. A remarkable conversationist with an excellent (and highly enviable) memory for faces, names and facts, he was loved by far more people than most of us can remember even knowing. When he died so tragically in a RTA in August 2007 literally hundreds of emails reached us from all over the world – almost everyone said "John was such a good friend". There aren't so many eminent men or women of whom that can be said. ◆

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is a Specialty Registrar in Neurosurgery at the John Radcliffe, Oxford. He studied natural sciences at Trinity College Cambridge before qualifying in medicine at Oxford. His clinical interests are wide-ranging, having published on subjects from paediatric hydrocephalus and head injury to venous stenting and spinal instrumentation. His research, which won the British Neurosurgical Research Group prize, investigates novel approaches and applications in stereotactic surgery. He is enthusiastic about undergraduate teaching and postgraduate surgical training and is a Fellow of Somerville College and Lecturer at Magdalen College, Oxford.

Alex Green

Alex Green is the Spalding Senior Lecturer at the University of Oxford and a Consultant Neurosurgeon at the John Radcliffe, Oxford. He studied medicine at University College London before neurosurgical training in London, Cambridge and Oxford. His MD research in Oxford under the supervision of Professor Tipu Aziz showed that deep brain stimulation of the midbrain periventricular grey region could alter blood pressure, winning the Congress of Neurosurgeons Stereotactic and Functional Neurosurgery Resident of the Year Award. His post-doctoral research focuses upon autonomic function and clinical outcomes in deep brain stimulation. He directs medical student teaching in neurosurgery at the University of Oxford and is a Fellow of The Queen's College, Oxford.

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is a Consultant Neurosurgeon at the John Radcliffe, Oxford and Honorary Senior Lecturer at the University of Oxford. After medical school in London, he trained in neurosurgery in Bristol and Oxford. He completed a DPhil degree in Oxford investigating cellular metabolism in brain injury, subsequently introducing neuroimaging to its study as an academic clinician. He undertakes all aspects of neurosurgery including aneurysm surgery, but has a particular interest in complex spinal surgery including spinal instrumentation, cranio-cervical junction disorders and the rheumatoid spine. He is Chairman of the Intercollegiate Examination Board in Surgical Neurology, a member of the Specialist Advisory Committee in Neurosurgery and Council member of the Society of British Neurological Surgeons.

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Neurosurgery Through the Looking-Glass

The authors reflect upon the past, present and future of British neurosurgery, discussing technological advances, increasing subspecialisation and changes in training and working patterns. They highlight British landmarks and predict some of the next decade's advances in several subspecialty domains - spinal, neurooncological, vascular and stereotactic and functional neurosurgery.

Introduction

Sir Hugh Cairns was the first Nuffield Professor of Surgery at Oxford, and along with Norman Dott and Sir Geoffrey Jefferson, part of the great triumvirate of Harvey Cushing's apostles who established neurosurgery as a distinct specialty in the United Kingdom. At the end of the Second World War, his 29-year-old trainee, John Gillingham, appealed to him for leave to get married. Cairns, a brilliant administrator, arranged the wedding locally in Oxford followed by a reception at his home, such that Gillingham could continue his busy clinical service up to the moment of the wedding, resuming it after just a weekend's honeymoon nearby.[1] Cairns was succeeded by Joe Pennybacker as Head of Neurological Surgery at Oxford and he was approached thirteen years later in 1958 by an also 29 year old Sid Watkins, who inquired, "Mr. Pennybacker, do you really think you could make me a neurosurgeon?" Pennybacker replied with characteristic pith, "Watkins, I could make a neurosurgeon out of a monkey in eighteen months."[2]

Both young men went on to achieve great things in British neurosurgery and also made profound contributions to road safety. Perhaps inspired by Cairns' establishment of motorcycle helmets in British law,[3] Watkins transformed motor racing and Gillingham campaigned successfully for car seatbelt legislation.[1,4] Gillingham also introduced the concept of subspecialty fellowships in neurosurgery in the early 1980s and recently received the fifth ever awarded medal of the Society of British Neurological Surgeons (Figure 1).[5]

Oxford neurosurgery has metamorphosed over the intervening half century, as has the tapestry of British neurosurgery. Alongside the introduction of several technological leaps including the operating microscope, computerised tomography (CT) and magnetic resonance imaging (MRI), Gillingham's visionary subspecialisation has crept in, as have the European Working Time Directive, Modernising Medical Careers, electronic portfolios, revalidation, paternity leave and flexible training – concepts no doubt anathema to Cairns, Dott, Jefferson and Pennybacker.

Neurosurgeons now recognise subspecialties of spine, paediatric, stereotactic and functional, epilepsy, peripheral nerve, trauma, vascular, neurooncology, pituitary and

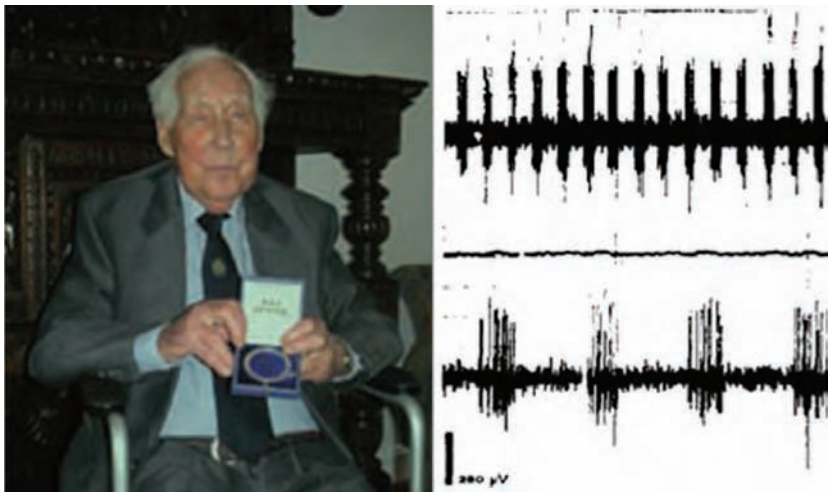

Figure 1: John Gillingham PRCS(Ed) (1916-2010) receiving the fifth Society of British Neurological Surgeons Medal at Magdalen College, Oxford in 2009 (left) and his first microelectrode recordings (right) from the human thalamus showing synchronous bursting with tremor, guiding surgery for Parkinson's disease.[5a]

radiosurgery – the last four complementing the subspecialty of skull base surgery. Cynics fear a craft specialty in turmoil, eroded by diluted training and narrow caseloads. Optimists remain enthusiastic for its future, brightened by scientific advances and enriched by work-life balance, goal-directed training and subspecialisation. Here we attempt stoicism, highlighting British landmarks and future prospects in several neurosurgical subspecialties before discussing training, subspecialisation and the future of British neurosurgery.

Spine

Throughout the late nineteenth century, the Glaswegian, Sir William Macewen (Figure 2), pioneered many surgical techniques, not least the antisepsis advocated by his mentor, Joseph Lister. "He permitted himself to become the object of the derision of his colleagues when he dressed himself for operation in gowns which could be sterilized, but the fulsome criticism of the unimaginative meant nothing to him."[6] Macewen was the first to apply emerging knowledge of cerebral localisation from contemporaries including Paul Broca and David Ferrier to neurosurgical operations of brain and spine, and therefore, some would say, the founding father of modern neurosurgery.[7,8] He first localised and operated upon a spinal tumour in 1883, excising a "fibrous neoplasm of the theca", most likely a meningioma, after a three level thoracic laminectomy. The patient, having a two year history of paralysis, sensory loss and double incontinence, made sufficient recovery to play football five years later![9]

In London, Macewen's contemporary, Sir Victor Horsley (Figure 3), performed a similar feat on a 42-year-old man with a progressive painful spasmodic paraplegia. Horsley could not find the lesion either at his spinal level of exposure nor one level above or below, but was guided in its localisation by the neurologist, Sir William Gowers, who looking over his shoulder advised him to extend his thoracic laminectomy even higher to find the intradural neurofibroma around the fourth dorsal nerve root (Figure 4).[10,11]

Spinal surgery was improved in the twentieth century first by the popularisation of radiographs and more recently by the operating microscope, CT and MRI. Refinements in design and material use for artificial spinal instrumentation have enhanced clinical outcomes in surgery, addressing symptoms of pain, weakness and deformity. While the last decade has seen a shift from decompression alone in degenerative cervical spinal surgery to decompression and fusion, debate continues over whether the removed intervertebral disc should be considered a mobile segment replaced by motion-preserving arthroplasty or a structure best fused by arthrodesis. Our practice is to continue to augment our cervical disc decompressions with fusion, at multiple levels where indicated, until clinical evidence convincingly favours arthroplasty.[12]

While there may become clearer indications for arthroplasty over arthrodesis, we envisage over the coming decade that biological implants derived from tissue-engineered mixtures of bone and cartilage progenitor or stem cells able to osteo-integrate will yield best clinical outcomes once a biomechanical balance between stability and mobility is attained.[13,14] Similarly, progenitor cell research provides hope for a return to neurosurgical intervention after spinal cord injury.[15,16] Nevertheless, alongside minimally invasive and percutaneous techniques, our increasing use of titanium and other modern materials is likely to continue, offering clear benefits over uninstrumented bony fusion alone in terms of symptom relief and restoration of function in spinal stabilisation.

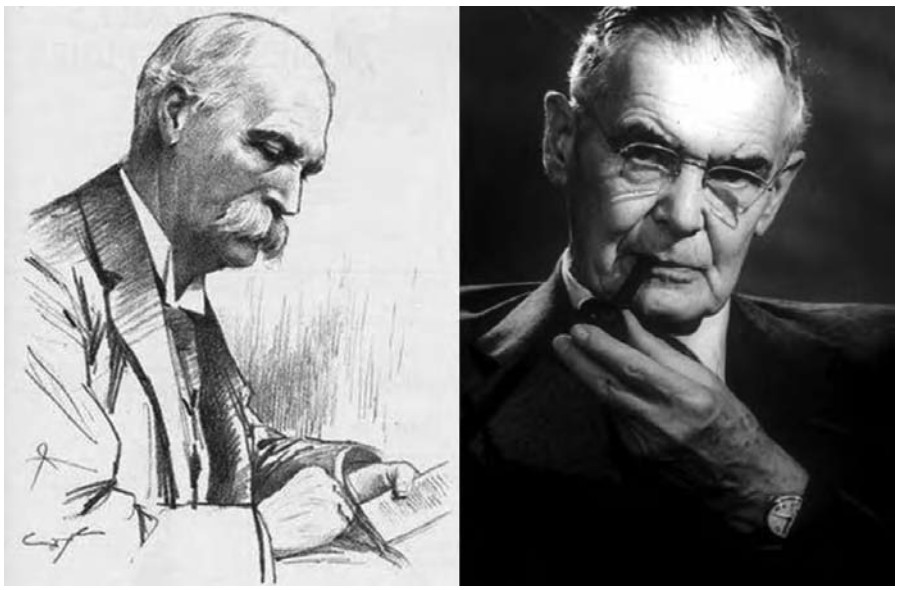

Figure 2: Sir William Macewen, FRS (left; courtesy of the University of Glasgow) and Norman Dott (right; courtesy of the Royal College of Surgeons of Edinburgh).

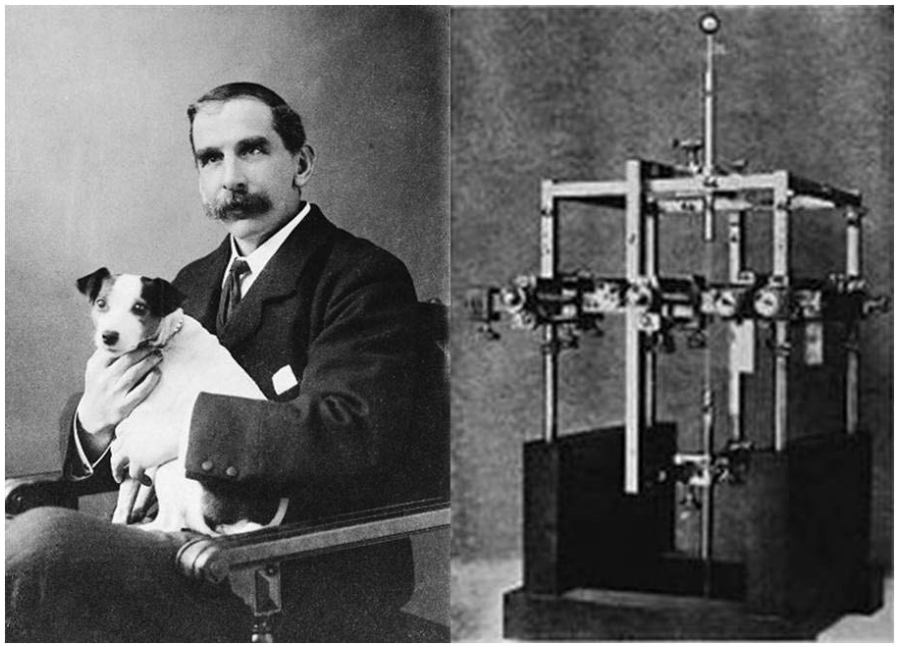

Figure 3: Sir Victor Horsley, FRS (left) and the Horsley-Clarke stereotaxic apparatus (right). (courtesy of the Wellcome Library, London).

Neurooncology

The first known glioma resection was performed by an Englishman, nephew of Joseph Lister and later President of the Royal College of Surgeons of England, Sir Rickman Godlee, at the Regents Park Hospital in London in 1884. A 25-year-old man with focal seizures and progressive left hemiparesis was diagnosed as having a right cortical tumour in the motor region (Figure 5). The patient survived the procedure but succumbed to purulent cerebritis one month later following wound dehiscence.[17,18] A year earlier, the editor of the Lancet had commented that "if Dr. Ferrier's suggestions meet with much practical response, it is to be feared that cerebral localisation will soon have more deaths to answer for, than lives to boast of."[19]

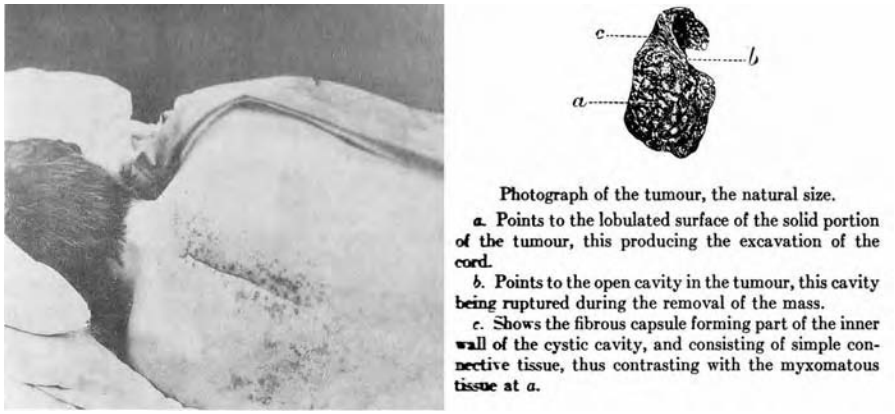

Figure 4: Horsley's thoracic incision for an intradural, extra-axial spinal tumour resection (left) and his artist's impression of the removed tumour (right).[10]

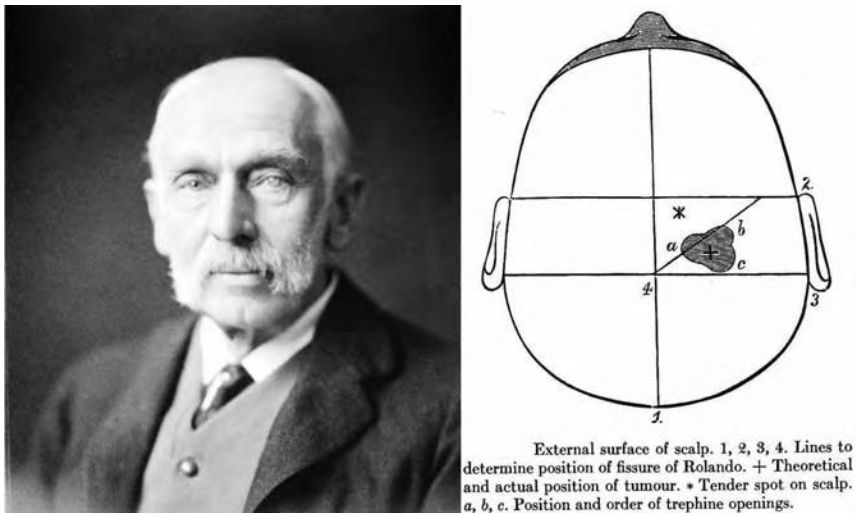

Figure 5: Sir Rickman Godlee, PRCS(Eng) (left) (courtesy of the Wellcome Library, London) and his diagram (right) showing his pre-operative localisation of the first resected brain tumour.[17]

While survival after diagnosis remains dismal and of the order of months for glioblastoma, the most prevalent and aggressive of primary brain tumours, several advances have been made not just in the organisation of neurooncology services nationwide, but in operative neurosurgery, chemotherapy and radiotherapy. MRI has improved pre-operative specificity of diagnosis and guided surgical management. Image-guided stereotactic techniques have become established in the last decade, enabling minimally invasive mini-craniotomies directly over brain tumours, maximising resections while avoiding important adjacent neurovascular structures and increasing the safety of deep brain biopsies. Intra-operative MRI has become available to augment resection extent but whether this improves clinical outcomes remains to be proven by randomised, controlled, clinical trials.[20] Similarly, fluorescent tracers distinguishing tumour from normal brain tissue can guide resection extent and potentially reduce recurrence rates.[21] We envisage increasing use of both over the coming decade as data relating long-term survival to resection extent by these newer techniques becomes available. Nevertheless, widespread uptake will be limited both by cost-benefit concerns and a need for increasing miniaturisation of intra-operative neuroimaging technologies to make them less cumbersome for operating theatre teams.

Patients with gliomas frequently proceed to radiotherapy and chemotherapy, all nowadays after management plans made in multidisciplinary neurooncology meetings. Temozolamide has emerged over the past decade as an important adjuvant chemotherapeutic agent in prolonging survival and improving quality of life, alongside the more established combination chemotherapy of procarbazine with lomustine and vincristine (PCV).[22] Molecular techniques are also being trialed to determine patients who could benefit more from particular chemotherapeutic regimes. For example, the DNA repair enzyme, O6-methylguanine methyltransferase (MGMT), if identified in tumour tissue as epigenetically inactivated by methylation at its promoter site, is a significant prognostic factor for gliomas independent of resection extent. This biomarker is likely to enter the clinic, once its assays are standardised and its prognostic and predictive values are ratified and stratified for primary brain tumours with different regimes of resection, radiotherapy and chemotherapy. Such advances herald a pharmacogenomic era of even more personalised tumour management over the coming decade as related genetic tests and targeted molecular therapies are developed.[23,24]

Vascular

Cushing may also have been speaking of Macewen, but it was only after training and subsequently visiting and entering a lifelong correspondence with Norman Dott (Figure 2) in Edinburgh that he commented, "should you scratch deeply enough a man of pioneering spirit, the chances are that you will draw Scottish blood."[25] Dott indeed pioneered many operative approaches in skull base and pituitary surgery and he is notably credited as being the first to perform an intracranial operation to treat a saccular aneurysm in 1931, wrapping muscle around it at the bifurcation of the left anterior and middle cerebral arteries after a subfrontal approach (Figure 6). He was also first to perform angiography to demonstrate an intracranial aneurysm before treating it in 1933.[26,27] Hunterian ligation of a carotid artery had previously been performed, first serendipitously by Horsley a quarter of a century before Wilfred Trotter in London in 1924 then four years later by the American Walter Dandy.[28,29] During a decade, Dott treated 39 patients with subarachnoid haemorrhage, operating upon 11 of them, classifying its presentations into oculoparetic, apoplectic and tumour-like and its aetiologies into hypertensive, syphilitic and tumour associated. His initial clinical management of bedrest, analgesia and avoidance of straining at stool has stood the test of time. Back then, angiography and Cushing's silver clips, first used on an aneurysm by Dandy, improved treatments, followed by the operative microscope, CT and MRI.

The last major advance to transform the fields of both intracranial aneurysm and arteriovenous malformation treatment has been endovascular neurosurgery, now also known as interventional neuroradiology and an expanding subspecialty in its own right. While percutaneous Seldinger catheterisation techniques for accessing the intracranial vasculature have been applied for half a century with numerous glues and polymers trialed for the embolisation of arteriovenous malformations, it was not until Guglielmi and Sepetka's development of detachable platinum coils less than two decades ago that aneurysm treatment was changed forever.[30,31] In the last decade, the ISAT trial led from Oxford provided clinical evidence showing coiling to confer better clinical outcomes than clipping after one year and five years for certain common types of ruptured intracranial aneurysms.[32,33] Surgery remains necessary for aneurysms that cannot or fail to be coiled and for complications of coiling. Furthermore, systematic reviews argue that aneurysm obliteration appears more definitive and complete with clipping, yet clinical outcomes overall continue to appear better with coiling.[34] Clearly, both treatment modalities continue to be important and we await longer-term outcomes from ISAT and other trials over the coming decade.

Further endovascular technological advances enable us now to stent not just intracranial arteries but also veins,[35] and we pre-

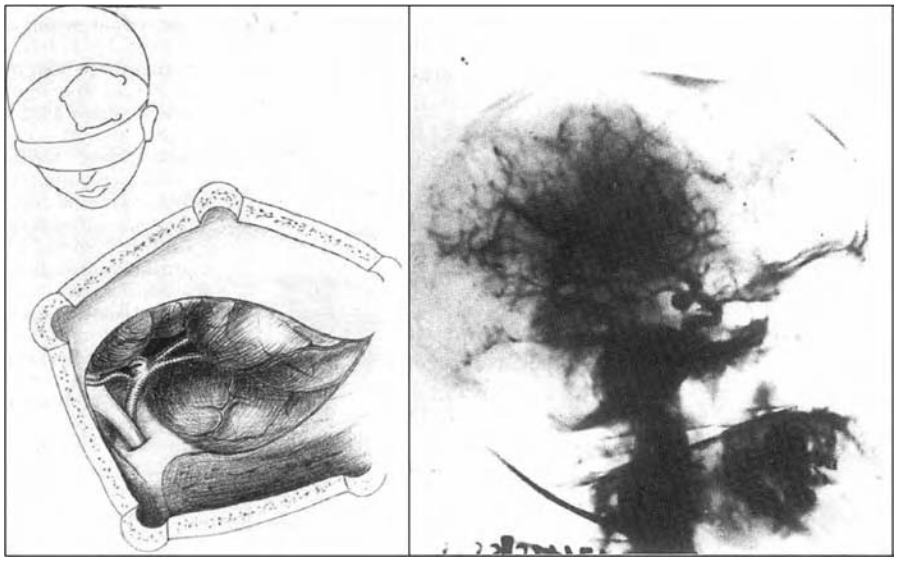

Figure 6: Dott's drawing of his left subfrontal approach, exposure and wrapping of a middle cerebral artery aneurysm (left) and his first use of angiography (right) by Thorotrast injection after direct carotid puncture showing an internal carotid artery aneurysm, guiding subsequent carotid ligation.[27]

dict a growth in endovascular techniques over the coming decade. Both the endovascular and surgical armamentarium have reduced the number of aneurysms deemed untreatable. Contemporary aneurysm surgery requires neurosurgeons versed in vascular neurosurgery, able to perform extracranial-intracranial bypass, use sharp dissection and perform microscopic neurosurgery with minimal retractor use to minimise brain damage. Such skills require intensive training in subspecialty fellowships, often abroad in countries of higher aneurysm incidence like Finland and Japan. Away from the operating theatre, the next decade is likely to yield further understanding of the aetiology of aneurysms, especially regarding their genetics and risk factors. Such knowledge is likely to impact upon screening programmes and consequently upon surveillance and management of increasing numbers of patients with newly detected unruptured aneurysms.[36]

Stereotactic and functional

Sir Victor Horsley arrived at neurosurgery from animal neurophysiology. He was intellectually consumed by the experimental challenges of cerebral localisation of motor function, following the seminal work of Hughlings Jackson, David Ferrier and contemporaries. In 1905, his colleague Robert Clarke built with him an apparatus which could be clamped to an animal's head, fixing the device to a Cartesian coordinate system (Figure 3).[37,38] By this means, Horsley was able to study the deep cerebellar nuclei in cats and non-human primates. Despite his Canadian student Aubrey Mussen's evolution of a human version of the frame,[39] clinical application of stereotactic surgery was not made until after the Second World War.[40]

Subsequent pioneering British contributions to stereotactic and functional neurosurgery are too numerous to list here and we detail them elsewhere.[41] Highlights include Watkins' development of two human brain atlases to improve deep brain targeting in movement disorders and pain,[42,43] and Gillingham's first use of microelectrode recordings to distinguish functionally between deep brain structures in patients and relate rhythmic thalamic neuronal discharge to parkinsonian tremor (Figure 1).[44] In the half century since then, the limitations and side-effects of dopamine therapy for Parkinson's disease and the benefits of subthalamic nucleus deep brain stimulation (DBS) have been firmly established by randomised, controlled clinical trials.[45,46] Thalamic stimulation for tremor, first pioneered two decades ago in France,[47] and pallidal stimulation in dystonia and Parkinson's disease have also become established.[48]

The last decade has seen novel clinical indications for DBS gather significant case series, including psychiatric disorders of obsessive-compulsive disorder, depression and Tourette's syndrome. Chronic pain continues to be relieved with success in experienced centres with cluster headache and epilepsy also treated.[49] The next decade is likely to see an expansion in established clinical indications for DBS to include some of the above and investigations of further novel clinical indications such as obesity, autonomic failure and addiction. Increasing sophistication of neurostimulatory technologies to incorporate smart, demand-driven stimulation responsive to symptom severity is likely to occur over the coming decade, as are dramatic improvements in rechargeable battery and pacemaker miniaturisation and robustness. Improvements in neuroimaging and frameless stereotactic guidance technologies will also continue to improve the accuracy, safety and efficacy of such procedures.

Concomitant with increased uptake of DBS, its limitations will also continue to be clarified and a resurgence of stereotactic ablative surgery in appropriate patients and resource limited settings is predicted. Scientific progress in fields of neurorestoration is also likely to reach the clinic, in particular the fields of gene therapy, nanotechnology and optogenetics.[50,51] Such advances will continue to rely upon rigorous pre-clinical research in appropriate animal models of neurological disorders like non-human primates.[52]

Discussion

It is now over eighty years since Sir Geoffrey Jefferson led others to form the Society of British Neurological Surgeons, "as much a small scientific club as a formal Society".[53] Much has happened since to improve neurosurgery, not least by pioneering British advances. Half a century ago, Gillingham was invited to summarise current and future trends in British neurosurgery.[54] He observed that "future developments in surgical neurology are broad and exciting, and will depend on wide and continuing contacts within the whole of surgery and medicine, technology, and the basic sciences. We cannot afford to remain long within our own four walls." We are certainly beyond our walls now, most of our subspecialties naturally having paired with a complementary medical specialty: spine with orthopaedics; neurooncology with oncologists; pituitary with endocrinologists; functional with neurologists and vascular with radiologists to name but a few. The floor has almost certainly been raised with technological advances rendering the previously untreatable treatable, but has the ceiling been lowered by standards of training?

In contrast to half a century ago, it would now be considered unreasonable for the first author's programme director to request clinical service on their wedding day and return to work a couple of days afterwards as Cairns did of Gillingham. Unlike their predecessor Pennybacker, it is also no longer possible for the senior authors to train a monkey to be a neurosurgeon in eighteen months. It now takes a decade from graduation in a seven year long specialty registrar post followed by at least one year of subspecialty fellowships.[55] Even towards the end of that, having plausibly obtained a portfolio of competencies using the intercollegiate surgical curriculum programme,[56,57] the non-human primate remains likely to come unstuck by the written papers or later fall at the final hurdle of vivas for their FRCS(SN) intercollegiate neurosurgical examinations. Standards for training, while they have changed in need and emphasis, aim to be maintained, despite reduced training hours, by formalising contact with supervisors, continuing examinations and ongoing emphasis upon a trainee's surgical logbook.

It is too early to predict whether the recently reformed British neurosurgical 'run-through' training will promote or stifle the rich British tradition of surgeon-scientists pioneering advances of which we have described just a handful here. As has been observed, "one disappointing area at present is the reluctance of United Kingdom trainees to commit themselves to a career in academic neurosurgery, the majority preferring the seemingly more secure and definitely better remunerated posts in the National Health Service."[58] Further challenges to British neurosurgical training include a

European Working Time Directive limiting doctors' working hours to 48 per week since last year, increasing the tensions between training and service.[59] Yet standards have remained constant over the last decade,[60] and may be augmented by the structure of competence based progression implemented by Alan Crockard.[61] We maintain that British-trained consultant neurosurgeons must continue to be excellent general neurosurgeons well versed in the anatomy of their procedures and able to deal with all potential complications, that they must master the cantatas before they attempt the fugues. Eight decades after Dott first wrapped an aneurysm, few new British consultants have ever clipped one. Yet all are likely to have other subspecialty talents in their repertoires.

We have not summarised many tremendous advances in neuroanaesthesia and neurointensive care and in neuroradiology that continue to radically transform the landscape of our clinical practice. These are beyond the scope of such a brief overview. Similarly, a brief review limits our opportunity to discuss in more depth several neurosurgical subspecialties mentioned previously. They are testament to neurosurgery growing as a specialty both in breadth and depth, with individual consultants now frequently having expertise in one subspecialty alone, compared to just a decade let alone a century ago, their focus continuing to improve clinical standards. ◆

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Management of Traumatic Spinal Cord Injuries:
current standard of care revisited

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Traumatic spinal cord injuries (TSCI) are life changing events. With expert, early, simultaneous Active Physiological Conservative Management (APCM) of the injured spinal cord and its effects, the impact on the patient and family members can be minimised in both the short and long term. Without surgical, pharmacological, or biological intervention over 70% of patients with complete motor paralysis but with sparing of pin prick sensation in the first 72 hours of injury recover motor power to ambulate. Those presenting within 72 hours of injury with motor sparing, however minimal, have an even better chance to walk, also without surgical, pharmacological or biological interventions. Patients who do not recover ambulation can, with APCM, ongoing expert monitoring, care and support, lead healthy, fulfilling, productive and competitive lives.

Active Physiological Conservative Management

Active simultaneous, non surgical management, from the early hours of injury, of

- the injured spine,
- the multisystem neurogenic effects of spinal cord injury on respiratory, cardiovascular, urinary, gastrointestinal, dermatological, sexual, reproductive functions,
- the associated psychological, effects,
- rehabilitation and
- environmental modifications

Unfortunately surgery has become the preferred method of management, also known as the "Standard of Care", of traumatic spinal injuries. Currently, about 80% of patients with TSCI are surgically decompressed and stabilised without the rigours of adequate research methodology or demonstration of superiority of neurological and/or other outcomes over APCM. This can be contrasted with practice in my orthopaedic institution (with four dedicated spinal surgeons) where less than 15% of patients are surgically managed and the majority of patients undergo APCM.

Currently, resources are relatively easily found for surgical implants and surgical procedures in both the developing and developed world. However, it is increasingly difficult to find resources for the management of the effects of the SCI and the rehabilitation of the patient in both the acute stage and in the long term. Consequently, the devastatingly wide range of medical effects and the psychological, social, emotional, financial, vocational, environmental and economic consequences are inadequately managed. Such inadequacy of management has implications for quality of outcomes, quality of life of patients and family members as well as implications for the cost to treat complications, the methods of prevention of which have been known for over six decades.

Effects and special characteristics of spinal cord injuries

A SCI causes widespread physiological impairments, medical and non medical problems. The functioning of the various systems of the body depends on reflex activity of the spinal cord segments distal to the lesion as well as on the intrinsic properties of the systems themselves. Changes in levels of reflex activity of the spinal cord occurs throughout the patient's life with unpredictable changes in the functioning of systems of the body. Continuing change of function invariably occurs during the transition between spinal shock and full return of reflex activity, hence the need for close monitoring and constant recalibration of management of the various systems of the body throughout the first few months following injury.

The sensory loss below the injury presents diagnostic challenges to the clinician. Conventional symptoms and signs of pathology are absent. This can result in a delay of diagnosis, usually with unpleasant consequences.

Each system malfunction is a source of one or more disabilities and a potential source of a wide range of complications of varying severity. Impairment of bladder function for example, can result in urinary incontinence, embarrassment and loss of confidence, bladder infections, pyelonephritis, calculi, hydronephrosis and renal failure.

In the acute stage complications such as hypoxia, hypotension and sepsis can cause further neurological deterioration or lack of recovery.

When a complication develops, the absence of higher co-ordinating and moderating functions of the brain over the spinal cord segments below the injury usually result in multiple and/or cascading intersystem effects that are rarely seen in other conditions. These are seldom easy to diagnose and manage. For example, an anal fissure, while painless in a tetraplegic or high paraplegic patient, can nevertheless cause autonomic dysreflexia and/or excess spasticity which in turn may cause a fall and fracture of a long bone. Alternatively or concomitantly if excess spasticity involves the pelvic floor muscles it can result in urinary infection, urinary retention, autonomic dysreflexia and possibly a cerebral haemorrhage. Almost all complications following SCI are preventable or can be minimised. Many are iatrogenic due to unfamiliarity with the pathophysiology of the spinal man/woman. The non-medical effects of spinal cord injury are equally devastating to patients and family members.

Fortunately, the incidence of spinal cord injuries is the lowest of all major trauma. The incidence in the UK ranges between 10-15 per million head of population per year. A district general hospital serving a population of 250,000 is likely to receive fewer than four newly injured patients per year. Unfortunately this small incidence limits the expertise required by a wide range of disciplines outside spinal injury centres.

Aims of the management of the spinal injury

The ultimate goals of management are to ensure maximum neurological recovery and independence, a pain free flexible spine, safe functioning of the various systems of the body with minimal or no inconvenience to patients and prevention or minimisation of complications. It is equally important to enable patients to regain assertiveness, take control of their own lives, re-engage in activities of their choice and whenever possible compete in some spheres of life. The importance of education of patients and ongoing support to maintain health and independence following discharge cannot be overemphasised.

Factors influencing management of the SCI

The majority of those who manage SCI patients in the acute phase have concerns about the biomechanical instability (BI) at the fracture site, further displacement and damage to neural tissues. Many strongly believe that canal encroachment and cord compression can prevent neurological recovery or indeed cause neurological deterioration. The injured cord with cellular and cell membrane disturbances, loss of auto regulatory functions and disruption of blood brain barrier is physiologically unstable.[1] It cannot protect itself from complications outside the spinal canal such as hypoxia, hypotension, hypertension, sepsis and hypothermia. These complications can potentially be as damaging to neural tissues through the physiological instability (PI) of the injured cord as the potential mechanical damage from the BI of the injured column.

Prognostic indicators of recovery

The neurological findings at 48-72 hours from injury are essential in predicting neurological recovery. Over 80% of tetraparetic patients who present in the first 72 hours from injury with any distal movement, however little and patchy (Frankel C, see Table to right), and over 70% of patients who present 48-72 hours from injury with no motor power but with preservation of pin prick sensation down to S3 (Frankel B) will recover to walk again[2,3,4] if they have not been harmed by the treatment. Patients with complete cord injury (Frankel A) and pin prick sensation in the zone of partial preservation will recover significantly and have useful motor power in these myotomes.[5] A neurological level higher than the bony level of fracture is another good prognostic indicator of zonal recovery.[5]

Traumatic biomechanical instability of the spinal column

The degree of BI is usually based on radiological investigations at the time of the presentation of the patient. It is perhaps worthwhile noting that most vertebral fractures heal within 6-12 weeks from injury when biomechanical stability (BS) is restored. Ligamentous injuries, however, can take much longer to heal. BI is therefore time related. During active physiological conservative management (APCM) containment of the BI is safely maintained in recumbency for 4-6 weeks followed by bracing during mobilisation for a further six weeks. The great majority of injuries become biomechanically stable and pain free. There is no evidence to suggest that surgical stabilisation enhances the speed of healing or achieves stability earlier than with APCM.

Admittedly the incidence of kyphotic deformities is lower following surgical stabilisation than following APCM, however the greatest majority of these kyphotic deformities are painless. The discrepancy between deformity and pain has been known for some time.[6] A painless kyphotic deformity enhances wheelchair bound patients' independence and is certainly, much preferable to a stiff straight neck or back following surgery.

Traumatic spinal canal encroachment

Some of the first case reports to suggest that traumatic canal encroachment as demonstrated by computerised tomography does not correlate with the degree of neurological impairment, does not prevent neurological recovery and does not result in neurological deterioration were published by El Masri et al in 1992.[7,8] The same conclusions were made by reviewing the outcome of conservative treatment of 50 consecutive patients with between 10% to 90% canal encroachment in Frankel C, D and E groups; patients in Frankel C&D group recovered ambulation and none of the patients deteriorated neurologically or otherwise.[9] Other groups have since published similar findings.[10,11,12] There is no evidence to suggest that surgical decompression achieves better or earlier neurological recovery than APCM in humans with incomplete cord or cauda equina injury. There is no evidence to suggest that surgical decompression is beneficial to humans with complete traumatic cord or cauda equina injury.

Traumatic spinal cord compression

In humans cord compression does not appear to prevent neurological recovery in patients with traumatic incomplete cord injuries.[13,6,14] Since the installation of the MRI scanner in our institution we have been monitoring (both prospectively and retrospectively) the neurological progress of conservatively managed patients with cord compression. The preliminary results indicate that the same clinical prognostic indicators of recovery apply whether there is cord compression or not.

Some advocate, however, early surgical decompression within four hours of injury. This is based on experimental findings in rodents, cats and dogs with 20-60 million years of evolution behind humans. Translation from the laboratory animal to the clinical situation requires caution.[23] Surgical decompression does not seem to be beneficial in either the laboratory animal or humans when the severity of the initial impact force is beyond a certain magnitude, as recovery will not occur.[15,16,17]

Natural history of complete and incomplete cord injuries

Fewer than 10% of patients initially with clinically complete spinal cord injuries (Frankel grade A, "FA") improve to make a significant recovery to ambulate.[18] Many more however, recover cord functions in one to four myotomal distributions below the level of the injury or improve to FB & FC.

Although increasingly since the 1980s anterior surgical decompression and arthrodesis have become established practice based on suggestions that surgery resulted in motor zonal improvement; to date there is no evidence that surgery provides added value. A series of 53 consecutive patients with complete traumatic tetraplegia, admitted to one centre within two days of injury, demonstrated that similar results can be achieved without surgical decompression or arthrodesis.[5]

Patients with incomplete cord injuries make significant neurological recovery irrespective of the degree of canal stenosis, canal encroachment, malalignment or cord compression[3,6,9,14] provided both the BI of the spinal

1. 'Complete' (A).
This means that the lesion was found to be complete, both motor and sensory, below the segmental level marked. If there was an alteration of level but the lesion remained complete below the new level, then the arrow would point up or down the 'complete' column.

2. 'Sensory only' (B)
This implies that there was some sensation present below the level of lesion but that the motor paralysis was complete below that level. This column does not apply when there is a slight discrepancy between the motor and sensory level but does apply to sacral sparing.

3. 'Motor Useless' (C)
This implies that there was some motor power present below the lesion but it was of no practical use to the patient.

4. 'Motor Useful' (D)
This implies that there was useful motor power below the level of the lesion. Patients in this group could move the lower limbs and many could walk, with or without aids.

5. 'Recovery' (E)
This implies that the patient was free of neurological symptoms, i.e no weakness, no sensory loss, no sphincter disturbance. Abnormal reflexes may have been present.

column and the PI of the spinal cord are well maintained. See case report and Figures 1-11 on the following page.

Although almost every patient is given a choice between conservative and surgical management the majority (85%) of patients with SCI in our institution are treated with APCM irrespective of malalignment, the degree of canal encroachment and the degree of cord compression.

Early mobilisation

Early mobilisation is advantageous to neurologically intact patients with stable fractures or following surgical stabilisation in unstable fractures. These patients can be discharged ambulating soon after surgery.

Patients with paralysis, general physiological impairment and multisystem malfunction do not benefit from early mobilisation, which indeed may be counter productive. Early mobilisation of patients is associated with a reduction of vital capacity[19] and a potential drop of oxygen saturation and / or postural hypotension. Individually or in combination these may further impair cord functions. Early mobilisation does not result in early completion of rehabilitation nor earlier discharge of patients with SCI.[1,6,7]

Indications for surgery at the Robert Jones and Agnes Hunt Orthopaedic Hospital

Until credible evidence demonstrates superiority of outcome with one method of treatment of the injured spine over the other, patients should be encouraged to make an informed choice between the various methods of management, assuming that the patient will receive treatment in an institution that can provide equally good APCM and surgical management. Certain groups of patients are likely to benefit from surgery and should be encouraged to consider the option. Neurologically intact patients with physiologically stable cord but unstable injured spine are less at risk from physiological deterioration than the neurologically impaired, do not require intensive prolonged treatment and rehabilitation, and can be discharged a few days following surgery. The uncontrolled epileptic, the mentally challenged and patients who are unable to comply with bed rest are safer following surgical stabilisation than with conservative management. Patients with biomechanical instability from pure ligamentous injuries without bony injury are at risk of developing late painful deformities and indeed may benefit from early surgery. Patients who exhibit signs of neurological deterioration with evidence of further neurological compression of neural tissues on MRI may benefit from surgical decompression.

Systems of management

The simultaneous management of the spinal injury and all its effects by a group of coherently managed multidisciplinary professional experts familiar with the patho-physiology of the SCI patient and proficient at treating all aspects of paralysis under one roof remains the safest, most efficient and most cost effective system of provision of service to these patients.[6] Irrespective of the method of treatment of the spine, patients with spinal injuries have less complications when treated comprehensively in SCI centres than when their management is fragmented.[6,7,20,21] The attention of health economists to this small group of patients which is perceived as expensive to treat is long overdue. It is essential to determine the monetary and human costs of management and compare these between the integrated system of management in specialised centres and the fragmented system of management that is increasingly prevailing.

Conclusions

The favourable neurological outcome of TSCI with APCM has been known for over four decades.[18]

A significant majority of patients who present with sensory sparing with or without motor sparing within the first 72 hours of injury will recover good motor power to ambulate irrespective of the degree of canal stenosis, encroachment, malalignment or cord compression and without surgical, pharmacological, biological or other intervention. Surgery to the injured human spine usually in isolation from the multitude of needs of the patient has become the Current Standard of Care without credible evidence of proof of superiority of outcomes (neurological or otherwise). Although the possibility of benefit from very early surgery in rodents, cats and dogs cannot be ruled out, the outcomes of early surgery in both the laboratory animal and in humans are still debatable.[22] Furthermore, translation from the laboratory to the clinical situation requires caution.[23]

I believe that it is appropriate to revisit both the science scientific and clinical evidence that led to the change of management of TSCI from APCM to surgical management, given the lack of credible evidence that surgery provides better outcomes and/or is not without risks and considering that the good outcomes of APCM are well established and predictable.

It is equally necessary to stop the fragmentation of treatment and to manage patients in adequately resourced specialised centres, capable of offering informed choice to patients, equally good surgical management when indicated by the patient or required, together with APCM of the spinal cord injury and all its effects in an integrated and effective manner. These centres should also be capable of conducting multicentre quality research, to address the real needs of patients with spinal cord injury as well as the various controversies in their management. ◆

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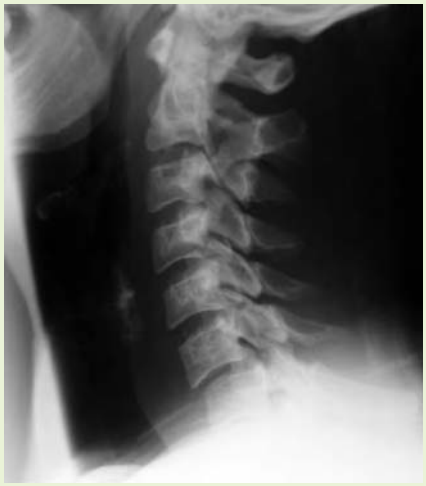
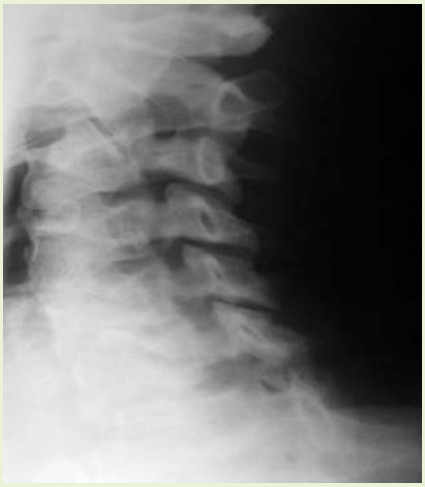
CASE REPORT

This 44-year-old lady sustained a fall in 1992 resulting in Frankel C tetraparesis from a C6/7 unilateral facet dislocation. She presented with weakness in both hands, profound paresis in both lower limbs and paralysis in the right ankle and foot. She was admitted the day of injury. Her motor score was 66/100 according to the ASIA scale. The dislocation was not reduced and the alignment was not restored. She was treated with six weeks of bed rest and APCM followed by six weeks in a Minerva cast. On discharge home (eight weeks following the accident) she had regained most of the motor power and was walking with two crutches for balance. She discarded the crutches four weeks later having recovered full motor power and good sphincter functions. She continues to enjoy a pain free full range of movement, unsupported ambulation and is able to run 17 years following the accident with unrelieved cord compression.





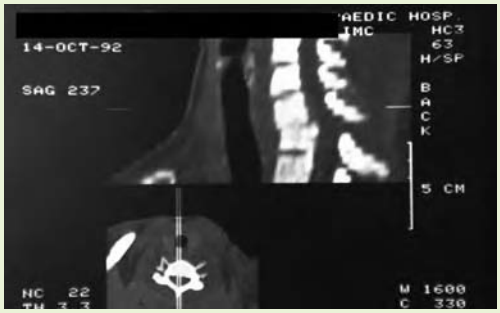


Figure 1 (left): Lateral Xray revealing Unilateral Dislocation C6/C7.

Figure 2 (middle): Oblique Xrays confirming the unilateral dislocation.

Figure 3 (right): Lateral CT confirming the malalignment and the canal encroachment.

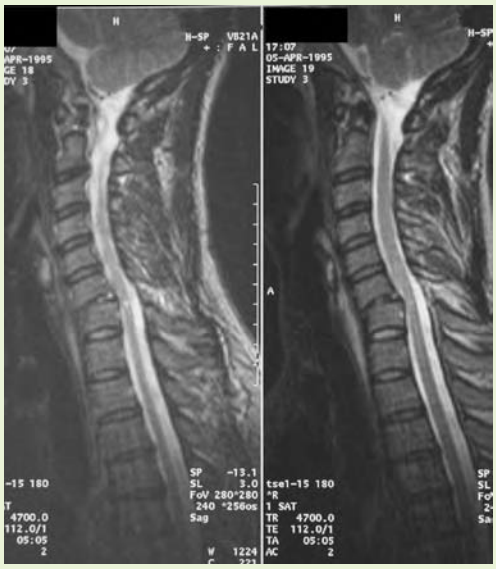
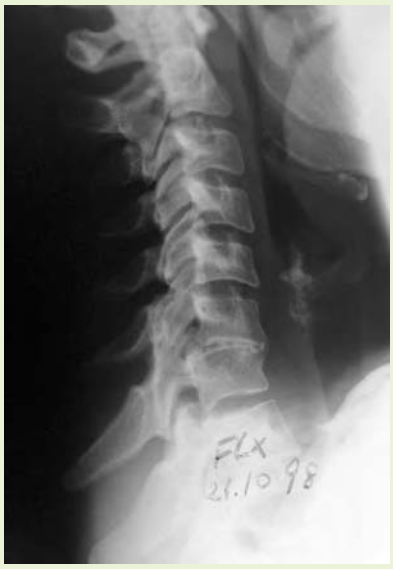
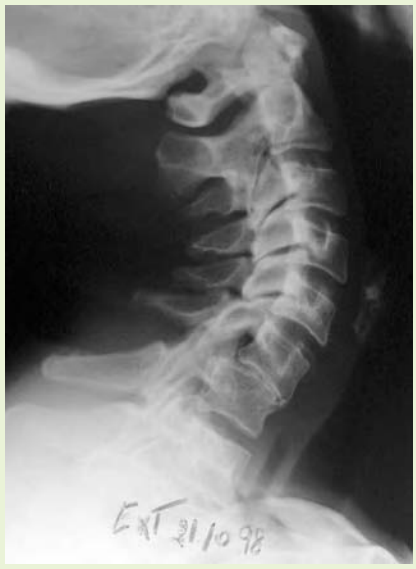
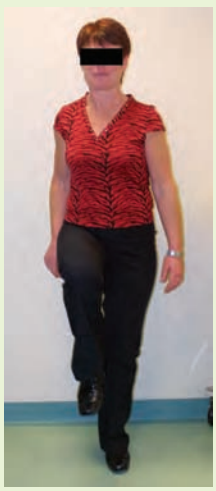


Figure 4: Lateral MRI 3 years later confirms ongoing thecal and cord compression.

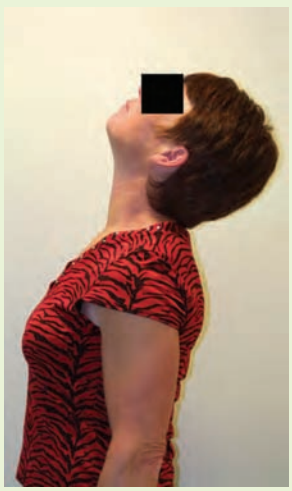


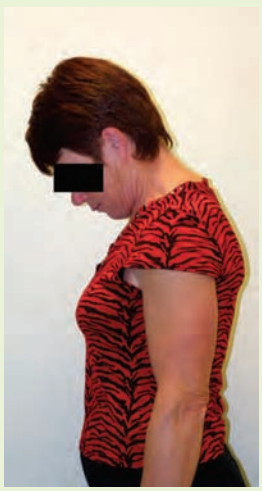


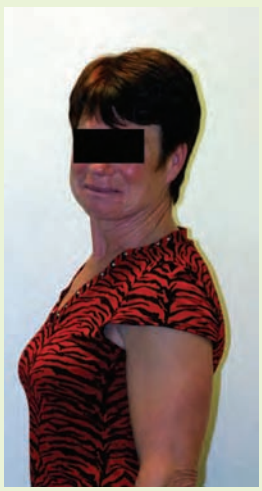
Figures 5 & 6: Lateral Flexion and Extension Xrays confirming restored stability in the dislocated position.



Figures 7 & 8: Demonstrating ability to stand unsupported on one leg at a time.

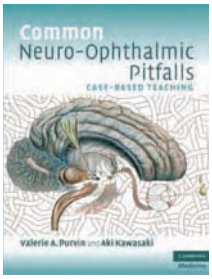






Figures 9, 10 & 11: Demonstrating unrestricted painless range of movement of the cervical spine.

Common Neuro-Ophthalmic Pitfalls: Case based teaching



Authors: VA Purvin, A Kawasaki
Published by: Cambridge University Press, 2009
Price: £45.00
ISBN: 978-0521713269

Reviewed by:
Parashkev Nachev, Institute of Neurology, London, UK.

The existence of medical textbooks is a mystery. The pain of having to read them gives way, in time, to the pain of having to write them, with no interval of pleasure to compensate for the suffering of either. And yet publishers continue to push them out, to gather dust in libraries that these days differ from internet cafes only in lacking the food and drink it is the sole remaining function of librarians to prohibit. Sadomasochism is the only explanation for this bizarre state of affairs, for the pain rarely leaves anything behind but its memory: ask yourself what percentage of your clinical knowledge came from textbooks. Five per cent? Perhaps only if you are a pathologist.

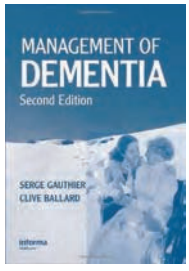
That it need not be so is better illustrated by Purvin and Kawasaki's latest book, "Common Neuro-Ophthalmic Pitfalls", than by any medical book I have come across for many years. Note this is not a medical textbook, in the conventional sense. It does not, like conventional textbooks, pointlessly and infuriatingly supply the reader with innumerable facts he would never be reading the book if he did not know already, such as that Huntington's disease is dominantly inherited or an extensor plantar response is indicative of an upper motor neuron lesion. It does not dwell at interminable length on the "classical" features of a syndrome, which occur only on the almost fictional occasions the diagnosis is never in doubt and no guidance of any kind is required. It does not enumerate a legion of drug trials notable only for their failure or their impending redundancy, usually a fact by the time the book is published. And it does not tell us about any new genes.

No, it focuses not on describing the centres of variation of each clinical entity but on describing the boundaries between them: their more or less intricate contours, lines of uncertainty or sharp demarcation, landmarks defining points of unexpected continuity or deflection. In short, it gives us the tools not to characterise a population but to place a specific case in one category or another: what clinical medicine is all about.

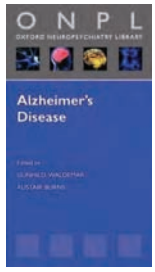
Of course, kinds of misclassification can themselves belong to one category or another, so here we have them elegantly partitioned into contrasts such as orbital disease vs neurologic disease, congenital anomalies vs acquired disease, abnormal radiology with normal physiology, and so on. Each category is illustrated by a series of cases followed by a cogent discussion of which specific set of features allows one to make the classification correctly. For example, we are given the distinction between glaucomatous and non-glaucomatous optic atrophy, between migrainous and retinal photopsias, papilloedema and pseudopapilloedema, ocular ischaemic syndrome and corneal disorders, congenital and acquired sixth nerve palsies, and countless others. Refreshingly, the critical features in each distinction mostly emerge from the history or examination, not some sophisticated test only a tertiary centre could access, and the approach to making the distinctions is clearly laid out and, where possible, given its physiological or pathological explanation. In short, the reader has all he needs to perform - clinically - just as the authors would in his place.

Why do we not have more books like this? Partly, it is because it is so much harder to write them – even in simple information theoretic terms defining the boundaries of a multivariate distribution is much harder than just giving the parameters of some approximation of it. But I suspect it is also because textbooks are usually written not by clinicians but by academics, who naturally like to simplify and generalise: capturing the meaning of life in one line is the academic's wet dream. If a more clinically minded authorship were to take over the climate might alter. But clinicians are, sadly, mostly too busy doing what they do.

Management of Dementia (2nd edition)
Alzheimer's Disease (Oxford Neuropsychiatry Library)



Editors: S Gauthier, C Ballard
Published by: Informa Healthcare, 2009
ISBN: 978-1841846675
Price: £100.00.



Editors: G Waldemar, A Burns
Published by: Oxford University Press, 2009
ISBN: 978-0199569854
Price: £5.99

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

The continuing importance of dementia in neurological practice is emphasised by these two short books.

Gauthier & Ballard's book on management of dementia was originally published in 2001, with Simon Lovestone as a co-author. The new edition has a broad sweep, appropriate to the advances in the field, covering diagnosis, management of behavioural and sleep problems, genetic issues, biomarkers, pharmacotherapy and care issues. The format is to start each chapter with a question or questions typically heard from patients or relatives in the clinical setting, which gives the text an immediacy perhaps lacking in other tomes. Information is presented in easily digestible chunks, and is generally well referenced, although one wonders whether all sections have in fact been rewritten since the first edition (see, for example, structural imaging on p67). The size discrepancy between the chapters on "Diagnosis" (11 pages) and "Behavioural disturbances" (25 pages) is perhaps no more than a reflection of the authors interests. The book finishes with a variety of assessment scales (perhaps odd that the popular Addenbrooke's Cognitive Examination didn't make it into this section), and some unannotated algorithms/flowcharts, one of which seems to advocate cholinesterase inhibitor (ChEI) drug holidays in deteriorating patients (p158). Anyone involved in assessing or managing people with dementia will want to have access to a copy of this book.

Waldemar & Burns's book fits easily into an inside pocket, and could be negotiated by the determined reader in an afternoon. In addition to the expected chapters (e.g. diagnosis, epidemiology, pathophysiology, treatment of cognitive and behavioural features of AD), there are also some less common, but nonetheless welcome, pieces, for example on supporting patients and carers, safety issues, and diagnostic disclosure. In the latter I was surprised to read that "All laws have an opt out clause" (p52); perhaps this may be true in France, the domicile of the authors, but in the enlightened UK even "guidance" on dementia is, apparently, obligatory rather than optional (i.e. NICE/SCIE). David Wilkinson's chapter explains in the clearest possible terms (p58) why the NICE approach of relying on MMSE to measure efficacy of ChEI in a relentlessly progressive disease is misguided, and incidentally argues against the use of ChEI drug holidays (p62-63). Minor criticisms might be levelled at the book (e.g. delirium does not seem to feature amongst causes of "fluctuating confusional states", p5), but nonetheless this is a tremendous short introduction to the subject of AD, or a stimulating refresher for those requiring an update.

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

To list your event in this diary, email brief details to John Gustar at editorial@acnr.co.uk by 8th April, 2010

2010

March

Brain Injury Conference: Moving Forward
2 March, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Acupuncture Evening Workshops Treating the Foot & Ankle Region
4 March, 2010; London, UK
www.physiouk.co.uk

Insight Workshop
5-6 March, 2010; Gatwick Airport, London, UK
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

The International Brain Injury Association's 8th World Congress on Brain Injury
10-14 March, 2010; Washington, D.C., USA
E. congress@internationalbrain.org
www.internationalbrain.org

Understanding Brain Injury
12 March, 2010; Ely, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Posture & Balance in Neurological Conditions – Upper Limb Assistant Staff
15 March, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Recognising Post Traumatic Stress
7 March, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

British Institute of Radiology: Spring Open Day
17 March, 2010; London, UK
E. British_Institute_of_Radiology@mail.vresp.com

NCYPE Open Day
17 March, 2010; Lingfield, UK
T. 01342 832243
E. openday@ncype.org.uk

End of Life Care in Neurological Patients
18 March, 2010; Cardiff, UK
T. 01872 225552
E. info@redpublish.co.uk
www.redpublish.co.uk/courses

1st International Congress on Epilepsy, Brain & Mind
17-20 March, 2009; Prague, Czech Republic
T. 42 0 284 001 444
E. epilepsy2010@guarant.cz

Neuromusculo-skeletal Assessment and Treatment Course: Back to Basics with Andrea Hemingway: The Spine
20-21 March, 2010; Manchester, UK
www.physiouk.co.uk

6th World Congress for NeuroRehabilitation
21-25 March, 2010; Vienna, Austria
E. christian.linzbauer@medacad.org
www.wcnr2010.org

20th Annual Rotman Research Institute Conference – The Frontal Lobes
22-26 March, 2010; Toronto, ON, Canada
T. 416 785 2500 ext. 2363
E. pferreira@baycrest.org

International Symposium on Disturbances of Cerebral Function Induced by Food and Water Contaminants
23-25 March, 2010; Valencia, Spain
E. catedrasg@cac.es
www.fundacioncac.es/catedrasg

Management of Spasticity in MS
24 March, 2010; Glasgow, UK
T. 01462 476704
E. education@mstrust.org.uk
www.mstrust.org.uk/studydays

BIRT – Brain injury rehabilitation – a heady mix?
24 March, 2010; Glasgow, UK
T. 0141 404 6060
E. Wilma.whyle@thedtgroup.org

11th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy
24-27 March, 2010; Geneva, Switzerland
E. jharbison@siumed.edu / ahamilton@siumed.edu

Epilepsy as a long term condition: improving health services for children in the South-East
25 March, 2010; Lingfield, UK
T. 01342 832243
E. communications@ncype.org.uk

Acupuncture Evening Workshops Treating the Neck & Shoulder Region
25 March, 2010; London, UK
www.physiouk.co.uk

The Series 2010: An integrated approach to restoring function & relieving pain
25 March, 2010; London, UK
www.physiouk.co.uk

Normal Gait
25 March, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

International Congress on Epilepsy, Brain and Mind
18-20 March, 2010; Prague, Czech Republic
www.epilepsy-brain-mind2010.eu

3rd National Childhood and Adolescent Addictions
25-26 March, 2010; London, UK
E. anne.haylock@markallengroup.com

Neurological Infectious Diseases Course
25-26 March, 2010; Liverpool, UK
T. 0151 5295461
www.liv.ac.uk/neuroidcourse

European Association of Neurosurgical Societies Annual Meeting (EANS 2010)
25-27 March, 2010; Groningen, Netherlands
T. 41 229 080 488
E. eans2010@kenes.com

Spring School 2010: Axon-Glia Biology in Health and Disease
29-31 March 2010; Cambridge, UK
T. +44 (0)1223 331174
E. Trish Jansen: pj214@cam.ac.uk
www.brc.cam.ac.uk
https://webservices.admin.cam.ac.uk/cgi-bin/booking/xbbi/index.cgi

British Neuropsychological Society Spring Meeting
30-31 March, 2010; London, UK
E. dana.samson@nottingham.ac.uk

Partnerships in Care, Brain Injury Services Conference
31 March, 2010; Cheshunt, UK
T. 01255 871 017
E. scoburn@partnershipsincare.co.uk
www.partnershipsincare.co.uk/bis

April

Evolving MS Services
9 April, 2010; Wyboston Lakes, UK
T. 0208 438 0809
E. pcrossman@mssociety.org.uk

63rd Annual Meeting of the American Academy of Neurology
9-16 April, 2010; Honolulu, HI
www.aan.com

62nd Annual Meeting of the American Academy of Neurology
10-17 April, 2010; Toronto, Canada
E. memberservices@aan.com
www.aan.com

Foundation Acupuncture Course
16-18 April & 11-13 June 2010; London, UK
www.physiouk.co.uk

Guillain-Barré Syndrome Support Group Annual Conference
17 April, 2010; London, UK
T. 01529 304615
E. admin@gbs.org.uk

Know Your Blood Pressure Awareness Day
17 April, 2010; London, UK
T. 01604 687720
E. helen.chapman@stroke.org.uk
www.stroke.org.uk

6th European Conference on Comparative Neurobiology
22-24 April, 2010; Valencia, Spain
www.fundacioncac.es/catedrasg

International Conference on Neurology and Neurorehabilitation
23 April, 2010; Goa, India
E. mohamed.sakel@ekht.nhs.uk
www.icnr2010.org

Hyperacute Ischaemic Stroke: multidisciplinary discussion; how do we achieve state-of-the-art 24/7 management?
23 April, 2010; London, UK
E. sellarannie@hotmail.com

6th European Conference on Comparative Neurobiology (ECCN6)
22-24 April, 2010; Valencia, Spain
E. catedrasg@cac.es
www.eccn6valencia.es

Acupuncture Evening Workshops Treating the Elbow & Forearm Region
22 April, 2010; London, UK
www.physiouk.co.uk

Cognitive Assessment: Test Selection, Administration and Interpretation
23 April, 2010; Ely, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

MA Healthcare 4th Schizophrenia Conference
29-30 April, 2010; London, UK
T. 020 7501 6762
www.mahealthcareevents.co.uk

May

The 15th Euroacademia Multidisciplinaria Neurotraumatologica Congress
7-9 May, 2010; Antalya, Turkey.
E. aguven@symcon.com.tr

International Child Neurology Congress 2010 - ICNC 2010
7-10 May, 2010; Cairo, Egypt
E. mohamed@icnc2010.com
www.icnc2010.com

OZC - Cognitive Assessment and Rehabilitation
11 May, 2010; Ely, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Association of British Neurologists Annual Meeting
11-14 May 2010; Bournemouth, UK
T. 020 7405 4060
E. info@theabn.org

MA Healthcare 5th Neuroscience Conference: Epilepsy
12 May, 2010; London, UK
T. 020 7501 6762
www.mahealthcareevents.co.uk

Neuroscience: Epilepsy Conference
12 May, 2010; London, UK
E. anne.haylock@markallengroup.com

14th International Neuroscience and Biopsychiatry Conference "Stress and Behavior"
16-20 May, 2010; St. Petersburg, Russian Federation

Thoracic Outlet Syndrome: Assessment, Differential Diagnosis & Hands-On Treatment
15 May, 2010; Manchester, UK
www.physiouk.co.uk

Brain Injury Awareness Week
17-23 May, 2010; Nationwide
E. Catherine.portman@thedtgroup.org

Management of Spasticity in MS
18 May, 2010; London, UK
T. 01462 476704
E. education@mstrust.org.uk
www.mstrust.org.uk/studydays

2nd Clinical Skills in Eating Disorders Conference
20-21 May, 2010; Croatia
E. anne.haylock@markallengroup.com

3rd International Epilepsy Colloquium: Surgery of Extratemporal Lobe Epilepsy
19-22 May, 2010; Cleveland, OH, USA
T. 216 983 1239 / 800 274 8263
E. medcme@case.edu

RCN Congress and Exhibition
25 May, 2010; Bournemouth, UK
www.rcn.org.uk/congress

Parkinson's Disease Consultants Masterclass
26-28 May, 2010; Bedruthan Steps, UK
T. 01872 225552
E. info@redpublish.co.uk
www.redpublish.co.uk/courses

International Symposium on Usher Syndrome and Related Diseases
27-29 May, 2010; Valencia, Spain
E. catedrasg@cac.es
www.fundacioncac.es/catedrasg

Second World Parkinson Congress

Conference details: 28 September-1 October, 2010; Glasgow, UK. Ted Dawson, MD, PhD – WPC 2010 Program Chair.

PREVIEW

The second World Parkinson Congress, also known as the WPC 2010, is expected to once again unite the global Parkinson's community in September in Glasgow offering a unique experience for researchers, clinicians, allied health professionals, people with Parkinson's, carers, and policy makers. Under the leadership of Co-Chairs Stanley Fahn and Andrew Lees, the 77 Congress committee members from 17 countries are helping the WPC take shape as the hottest meeting to attend this year for people interested in Parkinson's disease.

The WPC 2010 follows the success of the first WPC which took place in 2006 in Washington, DC. Based on the success of that meeting, along with the feedback we are receiving from the community and current registration numbers, we expect more than 3,000 delegates from over 50 countries to participate in this high-level, inspirational meeting. A variety of sessions ranging from plenary talks that bring members across the spectrum of Parkinson's together in large settings as well as medium sized lecture halls and workshops offered in small settings are designed to allow for cross-pollination of the audience and better exchange of ideas.

The programme has been carefully put together over the past year by 38 people representing academia, the clinical management of Parkinson's and those who experience the reality of living with this condition. The aim has been to profile and highlight the latest and seminal issues in Parkinson's today. Topics on gene and cellular therapy will run alongside sessions on neuroprotection, clinical trials, physical therapy, and care delivery to name a few. The provisional programme can be viewed and downloaded on the WPC website at www.worldpdcongress.org.

WPC 2010 is one of the only global conferences in all fields of health that actually brings the full range of people, including those living with the illness, together. This provides a unique opportunity for a global exchange of ideas between all the stakeholders.

A European researcher attending the WPC 2006 said that he brought a number of his junior researchers along with him to the meeting and that it was the first time many of them had actually met a person living with Parkinson's. He said it was a meaningful experience for his staff and something they would carry home long afterward. For researchers, the value of seeing, hearing and talking to people living with Parkinson's is too often underestimated and many feel the interaction generates a sense of focus, renewed passion and often new ideas.

The WPC 2010 currently has 132 Organisational Partners from 36 countries which helps ensure the delegate body is diverse and representative of the global Parkinson's community. These partners represent professional and patient organisations and within the UK alone include such groups as our lead partner: Parkinson's UK, British Geriatrics Society Movement Disorders Section, AGILE: Chartered Physiotherapists Working with Older People, The Cure Parkinson's Trust, British and Irish Neurologists' Movement Disorders Group, British Association of Neuroscience Nurses, and the Parkinson's Disease Nurse Specialist Association.

The exhibit hall will offer a chance to meet with representatives of companies and patient voluntary organisations from around the world. This time the poster display will not simply extend to highlighting the science of Parkinson's. There will also be a section for posters from those who experience life with Parkinson's and to illustrate the ways they have faced up to it. Many people with Parkinson's do not want to be perceived as merely "patients" but as a resource in their own right, whether this be in helping others the with the condition or contributing to the research agenda itself. The posters will be a way of making some truly inspiring initiatives more conspicuous so that they can be used by others.

A selected number of outstanding poster presenters will be invited to speak about their work each morning to a large audience. This opportunity will open the door for junior researchers or those working on late-breaking research to take centre stage in front of some of the most influential neuroscientists and renowned Parkinson's authorities on the planet. Submission deadline for both scientific and living with Parkinson's posters is Monday 12 April 2010.

The Renewal Room at the Congress is designed to demonstrate activities that can be done to help alleviate the challenges of living with Parkinson's and will include short programs such as yoga, dance, laughter therapy, clay therapy, singing and more. In addition to this room, the WPC 2010 will introduce a new space for delegates called the Rest & Regeneration Room. This room will offer a quiet space for delegates to rest, relax, rehydrate and even get a short massage. The WPC 2010 is a high-level meeting with a programme that can exhaust even the most experienced conference attendee. We aim to keep everyone healthy and fit while they are learning about Parkinson's!

A person with Parkinson's who attended the WPC 2006 told us afterward that the meeting gave him his first experience to meet and interact with scientists who were working on finding a cure. He said this interaction gave him hope knowing that there were such smart people dedicating their lives to curing Parkinson's, something he had lived with for a number of years.

The aim of WPC 2010 is to bring the world of Parkinson's together in one place. What better way to kick-start dialogue, innovation and partnership? The cure for Parkinson's will ultimately be accelerated through working together as a team. WPC 2010 brings that team together. The whole team!

This meeting is one that should not be missed! We hope you will join us in Glasgow in September. ◆

Glasgow, Scotland, UK
28 September – 1 October, 2010

Join more than 3,000 international clinicians, researchers, allied health care professionals, and people living with Parkinson's at this global Congress. This novel meeting, supported by more than 132 Organisational Partners from 36 countries, has representatives from all areas of the Parkinson's community creating unique opportunities for collaboration and innovation in science, care and advocacy.

Important Dates:

5 January 2010 – Registration opens
12 April 2010 – Abstracts submission closes
30 June 2010 – Reduced rate registration ends

Learn more at www.worldpdcongress.org

2010

Third Advanced Parkinson's Disease Masterclass

30th April 2010, Hilton Birmingham Metropole
This course is open to all previous graduates from the Parkinson's Disease Classic or SpR Masterclasses, Mentors & Speakers. Final Places available to others with an interest in PD.
The course will advance understanding of Parkinson's disease and related movement disorders through taught sessions.
Full course programme, application form – www.redpublish.co.uk/courses/advanced-masterclass/

Implementing the End of Life Care Strategy in Neurological Patients

18th March 2010, Hilton Hotel, Cardiff – Keynote Speaker: Baroness Ilora Finlay
Full course programme, application form – www.redpublish.co.uk/courses/end-of-life-care-in-neurology/

Parkinson's Disease Consultants Masterclass

Module One 26th-28th May 2010, Bedruthan Steps, Cornwall (FULL)
Module Two 24th-26th November 2010, Hilton Bath City, Bath
(Continuation from Module One)
NB Both modules must be completed
Full course programme, application form – www.redpublish.co.uk/courses/classic-masterclass/

Parkinson's Disease SpR Masterclass

28th June – 2nd July 2010, Mithian, Cornwall (FULL)
Full course programme, application form – www.redpublish.co.uk/courses/spr-masterclass/

2011

Parkinson's Disease Consultants Masterclass

Module One 25th – 27th May 2011, Cornwall
Module Two 23rd – 25th November 2011 (location tbc)
(Continuation from Module One)
NB Both modules must be completed

Parkinson's Disease SpR Masterclass

27th June – 1st July, Cornwall 2011 (date and location tbc)

Contact information for all:
RED Publishing Ltd • Tel: 01872 225552 • Fax: 01872 225554
Web: www.redpublish.co.uk/courses • Email: info@redpublish.co.uk

UCL

UCL INSTITUTE OF NEUROLOGY
in association with the
National Hospital for Neurology and Neurosurgery,
Queen Square, London WC1

Queen Square Advanced Short Courses

to include interactive patient sessions and lectures by international experts

17th-21st May 2010

Sleep	(17 May)
Dementia	(18 May)
Movement Disorders	(19 May)
Deep Brain Stimulation (morning only)	(20 May)
Palliative Care (afternoon only)	(20 May)
Stroke	(21 May)

Course fees
£850 for the whole week
(which includes a copy of the Queen Square Text Book on General Neurology)
OR
£250 per day

For further details please contact:
The Education Unit
UCL Institute of Neurology
National Hospital for Neurology and Neurosurgery
Queen Square, London WC1N 3BG
Tel: 020 7692 2346 Fax: 020 7692 2345
Email: J.Reynolds@ion.ucl.ac.uk
www.ion.ucl.ac.uk

The UCL Institute of Neurology promotes teaching and research of the highest quality in neurology and the neurosciences

1st Oxford Integrated Neurology Course (OINC)

Conference details: 30 June-2 July, 2010; Oxford University, Oxford, UK.

PREVIEW

We would like to announce the first 'Oxford Integrated Neurology' Course. This is a new course, running from 30 June-2 July 2010, and this year St Anne's College will host us, with a formal dinner at Trinity College. It is aimed at neurology trainees and consultants and will offer three days of talks, covering a wide range of topics. You may ask yourself if there really is a need for another neurology course, but we hope that we have something a bit different to offer. The aim of the course is to combine talks about everyday clinical scenarios with more neuroscience related topics and their integration into clinical life. We will address 'old chestnuts', such as whether 'vertebro-basilar insufficiency' really exists, and we will fuse common clinical dilemmas (what does it really take to make a diagnosis of motor neuron disease?), with related neuroscience updates (what are the genetics of motor neuron disease?). Some of these topics may not have a right or wrong answer, but we hope that this will encourage a lively exchange between speakers and delegates. We certainly have been able to attract a

number of highly acclaimed speakers and to encourage discussion, we are limiting places to 50 (first come, first served).

We hope that the course will offer trainees the opportunity to hear inspirational experts speak, and to get a variety of views on a range of neurological topics. For consultants, we hope that the course will offer an update, refresher and discussion forum. In addition to hearing about current neurology, we also hope that delegates will enjoy the historic atmosphere of Oxford, once home to Thomas Willis, William Osler and Charles Sherrington among others. You will live and dine in College, and there will be a "cultural extra" on the Friday afternoon after the course – as well as the opportunity to pursue some typical Oxford summer activities, such as punting.

We hope that this course will offer a unique combination of clinical neurology and neuroscience. We are already looking forward to this event and hope you will join us. ◆

For further information,
please contact Anne Taylor.
Email: anne.taylor@clneuro.ox.ac.uk
Telephone: 01865 231912
Fax: 01865 231914

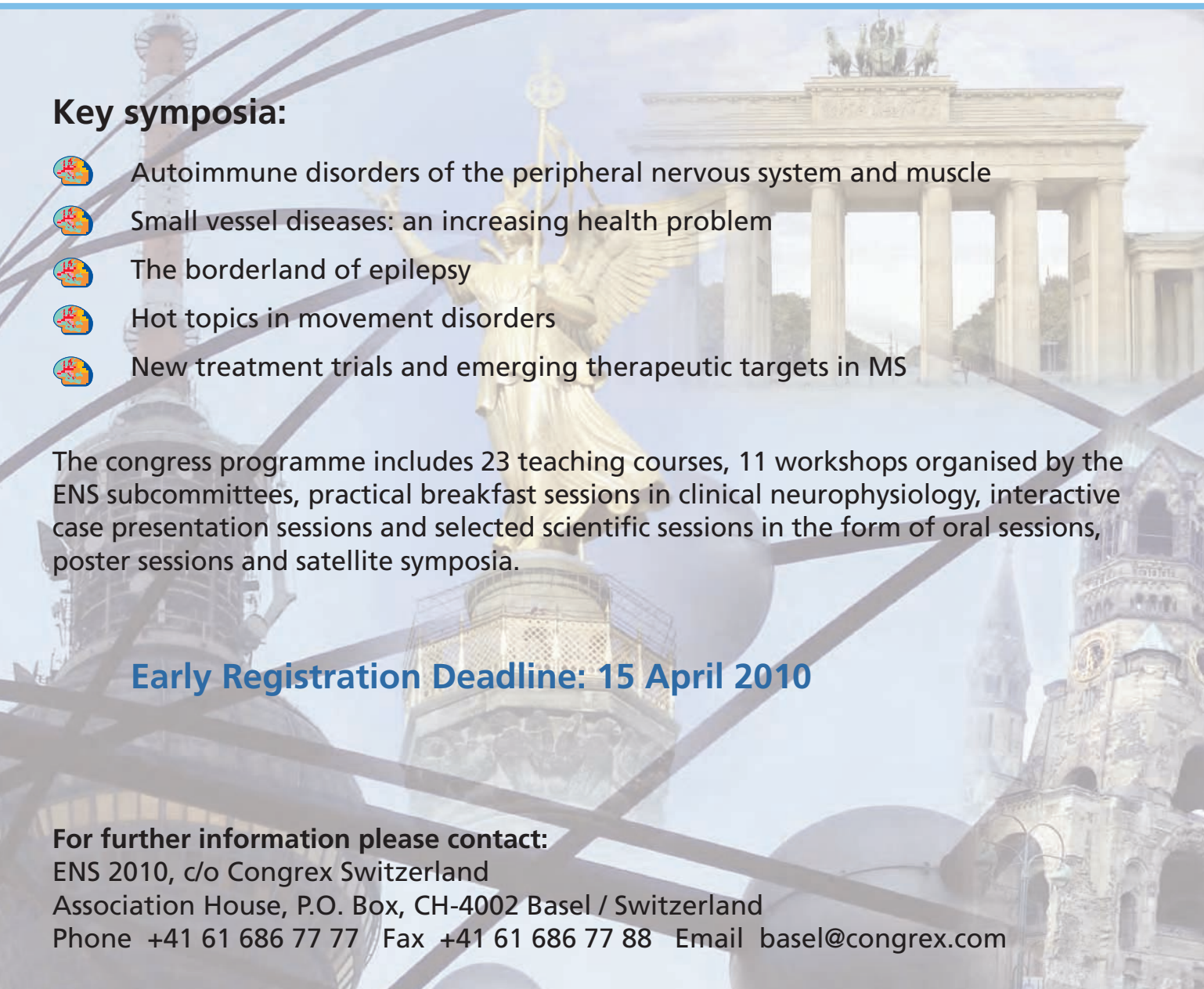
Organising Committee:
Professor Chris Kennard,
Drs Ursula Schulz & Martin Turner,
Oxford University
Department of Clinical Neurology

Twentieth Meeting of the
European Neurological Society

19 – 23 June 2010

Berlin, Germany

Neurology: Learning, knowledge, progress and the future



Key symposia:

- Autoimmune disorders of the peripheral nervous system and muscle
- Small vessel diseases: an increasing health problem
- The borderland of epilepsy
- Hot topics in movement disorders
- New treatment trials and emerging therapeutic targets in MS

The congress programme includes 23 teaching courses, 11 workshops organised by the ENS subcommittees, practical breakfast sessions in clinical neurophysiology, interactive case presentation sessions and selected scientific sessions in the form of oral sessions, poster sessions and satellite symposia.

Early Registration Deadline: 15 April 2010

For further information please contact:
ENS 2010, c/o Congrex Switzerland
Association House, P.O. Box, CH-4002 Basel / Switzerland
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www.ensinfo.org

Pills for Multiple Sclerosis

Throughout 2009, multiple sclerosis conferences were dominated by presentations, and gossip, about three big trials. And here they are, finally served up in one multiple sclerosis bonanza issue of the *New England Journal of Medicine*! These are serious trials, likely to be highly cited in the multiple sclerosis literature, and to be repeatedly lauded as "launching a new dawn in multiple sclerosis treatment" or something like that.

So what are these drugs? You may already know fingolimod as "FTY720", an unlicensed drug that has been around the scientific and transplantation literature for a while. It acts in an entirely novel way. It antagonises the sphingosine-1-phosphate type 1 receptor on lymphocytes, which react by withdrawing the receptor from their cell surface. Normally, these receptors are needed for lymphocytes to get their cue to leave the comfort of the lymph node and do their stuff in the wide world. So fingolimod stops them leaving the lymph nodes and there is effective peripheral lymphocyte depletion. Very unusually for a drug in multiple sclerosis, fingolimod crosses the blood-brain barrier. There is reasonable animal data that it may have neuroprotective effects, but these have not been demonstrated in humans yet. Cladribine is an old drug; it received FDA approval in the 1980s for treatment of hairy cell leukaemia. It is phosphorylated to a toxic nucleotide CdATP, which accumulates and causes DNA strand breaks, inhibition of DNA synthesis, and cell death. The selectivity of its action on lymphocytes arises from the accident that these cells have a high ratio of deoxycytidine kinase to 5′-nucleotidase. So, cladribine leads to prolonged T and B cell lymphopenia.

- The big news, of course, is that both drugs are given as tablets. This is an important advance in convenience for people with multiple sclerosis. This is particularly true of cladribine, which is so potent that as few as eight tablets a year appears to be effective! For the obsessive, I have tabulated the details of the trials below. Here are just a few thoughts.
- On the whole, the FDA likes to see two phase 3 trials of a multiple sclerosis drug. So, the fact that there are two for fingolimod but only one for cladribine probably means that fingolimod is ahead in the race to get to market. (Indeed when Merck tried to submit cladribine for licensing to the FDA last year, they were politely turned down, for undeclared reasons).
- In each trial, the drug has a useful impact on relapse rate, greater than would be expected for interferon-beta. But the key efficacy outcome in multiple sclerosis trials is disability and, strictly speaking, neither drug has shown any greater efficacy than interferon-beta on disability. This is because cladribine has only been tested against placebo, and in the fingolimod-interferon head-to-head (TRANFORMS) there was actually no statistically significant difference in disability measures. I don't want to be churlish here.... the greater impact on relapse rate than interferon may translate into greater efficacy against disability for

Table: Antibody targets and associated conditions

STUDY NAME	TRANSFORMS	FREEDOMS	CLARITY
Study drug arms	Fingolimod 1.25 mg daily	Fingolimod 1.25 mg daily	Cladribine 3.5mg/kg daily for 8-20 days a year
	Fingolimod 0.5 mg daily	Fingolimod 0.5 mg daily	Cladribine 5.25 mg/kg daily for 8-20 days a year
Comparator	Avonex	Placebo	Placebo
Trial duration	12 months	24 months	96 weeks
N	1292	1272	1326
(N completed study)	1153	1033	1184
Inclusion criteria	RRMS EDSS 0-5.5, 1 relapse in last year; may or may not have had previous disease-modifying therapy	RRMS EDSS 0-5.5, 1 relapse in last year	RRMS EDSS 0-5.5, 1 relapse in last year, may or may not have had previous disease-modifying therapy
Annualised relapse rate reduction	38-52% reduction versus interferon	54-60 % reduction versus placebo	54-58 % reduction versus placebo
Annualised relapse rate	0.2 and 0.16 (fingolimod) versus 0.33, interferon p<0.001	0.18 and 0.16 (fingolimod) versus 0.4 placebo, p<0.001	0.14 and 0.15 versus 0.33 placebo, p<0.001
% patients with confirmed disability accumulation over 3 months	6.7 % and 5.9 % versus 7.9 % p=0.5 **NOT SIGNIFICANT**	17.7 % and 16.6 % versus 24.1 % **p = 0.01 and 0.03**.	14.7 % and 15.1 % versus 20.6 % on placebo, **p = 0.02 and 0.03**
Worrying AEs	**INFECTION:** 2 deaths (herpes simplex encephalitis and disseminated primary varicella) on fingolimod; also CANCER: 2 breast cancers in each of the fingolimod groups. 5 basal cell carcinomas and 3 melanomas in the fingolimod groups versus 1 basal cell carcinoma and 1 squamous cell carcinoma in the interferon group.	**CANCER:** 1 breast cancer in the fingolimod groups versus 3 in the placebo group. 5 basal cell carcinomas and 1 melanoma in the fingolimod groups versus 3 basal cell carcinomas and 1 melanoma in the placebo group.	**INFECTION:** neutropenia seen in 3 patients on cladribine and 1 case of exacerbation of latent tuberculosis. 3 cases of primary varicella **CANCER:** 3 cases in study in cladribine groups (melanoma, pancreas and ovary) with one emerging after study period (choriocarcinoma).
Less worrying AEs	also non-fatal herpesvirus, macular oedema, AV block, hypertension	also non-fatal herpesvirus, macular oedema, AV block, hypertension	Herpes zoster in 20 patients on cladribine, none on placebo

these drugs.... and a discernible difference in disability might emerge from longer follow-up of the TRANSFORMS patients...

- The duration of these trials is a big issue. The fingolimod-interferon head-to-head was only 12 months, which is nothing in the life of a patient with multiple sclerosis. Just as short duration compromises power for efficacy outcomes, so too does it impair our ability to understand the safety issues. And it becomes very difficult to spot dose effects. In both trials, two doses were tested, but to my mind it is not clear yet which is preferable.
- These drugs are not as safe as interferon-beta. There is a "signal" that both slightly increase the risk of cancer and infection, especially by herpes and varicella viruses. It is hard to be definite about these risks, as these are low frequency events in all the trials and there is plenty of "noise"; for instance, the skin cancer signal in TRANSFORMS is not really replicated in the FREEDOMS trial.

A glib conclusion might be the ubiquitous "more research needed". And certainly that is true: hopefully we will get to hear the long-term follow-up of these trial patients for one. But, it is very easy to say these things...and forget these are seriously large and expensive trials that have already consumed literally hundreds of millions of dollars, and dominated investigator resources at hundreds of sites around the world. I am beginning to come round to thinking that there ought to be another way of testing drugs. Perhaps both drugs could be licensed as probationary drugs for a few thousand patients and then a full license reconsidered in a few years time? Like learner plates?

– Alasdair Coles

Cohen JA, et al.; the TRANSFORMS Study Group. Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis. NEJM – 2010 Feb 4;362(5):402-415.
Kappos L, et al.; the FREEDOMS Study Group. A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis. NEJM – 2010 Feb 4;362(5):387-401.
Giovannoni G, et al.; the CLARITY Study Group. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. NEJM – 2010 Feb 4;362(5):416-426.

ALS: of mice and miR-206

Amyotrophic lateral sclerosis (ALS) kills over 1200 people each year in the UK and remains incurable. Around 10% of cases are familial. Much of what we understand about disease pathogenesis has come from models based on mutations of superoxide dismutase 1 (SOD1), which account for about 20% of familial ALS (FALS). In the December 11th issue of Science, Williams and a team led by Eric Olson in Dallas, Texas, describe how they have used the G93A SOD1 mouse model to implicate a specific micro-RNA, miR-206, in disease progression and survival, and have suggested that this may be a therapeutic target. Using a battery of transgenic overexpressing and knockout mice they show that miR-206 is significantly overexpressed in G93A mice, coincident with onset of an ALS phenotype. MiR-206 appears to be involved in muscle reinnervation following denervation, a possibly compensatory sequence of events also seen in ALS patients. These findings are interesting in the light of recent advances in ALS research, which have implicated RNA-processing agents, in particular TDP-43 and FUS. TDP-43 is the hallmark protein of pathological inclusions in ALS, and mutant isoforms of TDP-43 and FUS account for around 8% of familial ALS (reviewed by Lagier-Tourenne and Cleveland 2009). Intriguingly, both proteins have been implicated in mi-RNA biogenesis as they interact with the Drosha complex (Gregory et al 2004).

Micro-RNAs are short RNA sequences ~22 nucleotides in length. Rather than coding for protein, they target complementary sequences on other RNA molecules, usually inhibiting their translation by binding to the upstream 3'-untranslated region. Mi-RNAs have diverse cellular roles through modulation of gene expression. Genes encoding mi-RNAs are therefore not 'junk' DNA as previously thought. Furthermore, mi-RNAs have been implicated in cancers, and aberrant mi-RNA pathways may contribute to the pathogenesis of various neurodegenerative diseases, including frontotemporal dementia, Parkinson's disease, Alzheimer's disease and Huntington's disease (reviewed by Hebert and Strooper, 2009).

Williams et al show that miR-206 may exert its trophic effects by downregulating histone deacetylase 4 (HDAC4) expression and thus increasing fibroblast growth factor binding protein 1 (FGFBP1) expression. Histones are proteins that package DNA, and when acetylated they release the condensed DNA allowing gene transcription to occur. This is regulated by histone acetlytransferases (HATs), and HDACs. Interestingly, histone metabolism has previously been linked with sporadic ALS risk through the genetic association of ELP3 variants. ELP3 is part of the RNA polymerase II complex and is involved in histone acetylation and RNA elongation (Simpson et al, 2008). The therapeutic potential of HDAC inhibitors is also under investigation, and although results have been promising in animal models, clinical study has so far not demonstrated any positive effects (Piepers et al, 2009). The authors state that miR-206 appears to have a 'salutary function in ALS'. It is more accurate to describe the mice as suffering a 'motor neuron phenotype' rather than ALS, which is a human disease. It will of course be important to validate these results in humans. It is also important that similar studies are conducted in other models of ALS, particularly TDP-43 transgenic animals, as SOD1 ALS and SOD1 transgenic models are not characterised by TDP-43 inclusions. Nevertheless, the findings are significant, not only in highlighting another potential mechanism for ALS pathogenesis but also in suggesting a novel therapeutic approach.

– Jemeen Sreedharan, Guy's and St Thomas' NHS Trust, London

Williams AH et al. MicroRNA-206 delays ALS progression and promotes regeneration of neuromuscular synapses in mice. SCIENCE – 2009;326(5959):1549-54.
Lagier-Tourenne C and Cleveland DW. CELL – 2009;136(6):1001-4.
Gregory RI et al. NATURE – 2004;432(7014):235-40.
Hébert SS and De Strooper B. TRENDS NEUROSCI – 2009;32(4):199-206.
Simpson CL et al. HUM MOL GENET – 2008;18(3):472-81.
Piepers S et al. ANN NEUROL – 2009;(2):227-34.

EPILEPSY: here today, gone tomorrow. Back the day after?

So you have started medication for the patient's epilepsy and they are doing well. You have discharged them at the earliest opportunity, under NHS new-to-follow-up rules, patted them on the back and they have left with a jovial: "Hope I never see you again doc". Will you smile benignly or wistfully? Will it be good-bye or more likely, according to this study, *au revoir*? Of the 566 patients entering the study, 85 were excluded, leaving 481 evaluable. Of these 225 did not achieve a one year remission and 256 did. Of the 256, only 154 achieved a sustained remission, for 5 years, just over one third of the original cohort. The five year cumulative relapse rate was 40% and 25% became refractory. A handful of these later became surgical candidates, although it was considered in all the patients. The strongest factor predicting relapse was a higher number of drugs required to achieve a remission; others were the duration of pre-remission epilepsy and the frequency of seizures prior to remission. When we counsel our seizure-free patients about their illness in relation to life choices and particularly their career choices, it would be wise to consider these data.

– Mark Manford, Neurology Unit, Addenbrooke's Hospital, Cambridge, UK.

Schiller Y. Seizure relapse and development of drug resistance following long term seizure remission. ARCHIVES OF NEUROLOGY – 2009;66:1233-39.

Channels under scrutiny

Louis Ptáček at the University of California, San Francisco, and an international team have uncovered a novel inwardly rectifying potassium channel gene, KCNJ18, which encodes Kir2.6, and in the process have identified a possible mechanism for some cases of thyrotoxic hypokalaemic periodic paralysis (TPP). Kir gene mutations have had disease implications before, in Andersen syndrome (periodic paralysis, cardiac arrhythmias, and dysmorphic features, Kir2.1, Ptáček again, Cell, 2001). But this paper showcases a triumph of discovery. The problem with KCNJ18 (Kir2.6) is that it is so similar to KCNJ12 (Kir2.2), with 98-99% homology at the coding region, and as such has been interpreted previously as a polymorphism of KCNJ12.

The find is arrived at beautifully, first by fishing out channels with putative thyroid-response elements in their promoter regions, and then by applying some lateral thinking to PCR to overcome the doppelgänger problem. Then, 6 mutations were found in patients with TPP, but not controls, with varying prevalence in different ethnic groups; the highest at 33% in a group of TPP patients from Brazil, the US and France. The functional studies of each of the mutations are ongoing, but some are shown to alter conductance. The proposed model is that triiodothyronine (T3) enhances transcription of KCNJ18 in order to help stabilise the muscle membrane, which is already affected in a number of ways by thyrotoxicosis – in the cases with a mutant, the rectifying channel is a false friend.

A small study from Barcelona provides some support for the intuitive notion of genetic mutations that, rather than defining a disease, shape the subtleties of phenotype and modulate the details. The paper by Serra et al examines the electrophysiological function of a mutation in CACNA1A found in two members of a large familial hemiplegic migraine family; the pair conspicuous by an absence of face/tongue paraesthesiae or hemiplegia, though visual aura was retained. Such a mutation seems to impair interaction of the channel with vesicle exocytosis machinery, perhaps through the structural alteration in the I-II loop. A proposed model is that such a reticence to engage synaptic machinery may reduce cortical spreading depression, in non-visual cortex areas at least.

– Mike Zandi

Ryan DP, et al. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. CELL – 2010 Jan 8;140(1):88-98.
Serra SA, et al. A mutation in the first intracellular loop of CACNA1A prevents P/Q channel modulation by SNARE proteins and lowers exocytosis. PNAS – 2010;107:1672-7. Epub 2010 Jan 8.

REPAIR: the tale of making new neurons!

The discovery a few years ago that somatic cells could be reprogrammed back into pluripotent stem cells (iPS cells) caused a great deal of excitement, especially when the initial work in mice was extended to human skin cells. The way to do this was surprisingly not that complicated and over the years refinements in the necessary factors have been made along with an increase in the efficiency of the process. Now Vierbuchen et al have gone a stage further by reprogramming murine fibroblasts directly into neurons. The authors argued that committed fibroblasts could be made into neurons by using neural-lineage specific transcription factors of which 19 were chosen for starters. Whilst the possible combinations of 19 different factors to find the right recipe is enormous, the authors discovered that one single factor (Ascl1) was sufficient to induce immature neuronal features and that two additional factors (Brn2 and Mytl1) could turn these cells into mature iN (induced neuronal) cells. These latter cells had all the hallmarks of neurons- they could generate action potentials; they expressed a whole range of neuronal markers and could even make synapses. The iN so generated were interestingly mainly glutamatinergic and thus excitatory with markers of cortical identity- which is rather different to that seen with many other neurons derived from other sources of stem cells which tend to be GABAergic.

So there we have it, three transcription factors seem to be able to drive mouse fibroblasts (including post-natal cells) to functional neurons, and according to this paper the technique seems robust and relatively efficient. If this approach can be readily replicated in other labs in much the same way as was seen for iPS, then there are exciting times ahead. Because, as the authors of this paper conclude "...iN cells could provide a novel and powerful system for studying cellular identity and plasticity, neurological disease modelling, drug discovery and regenerative medicine".

– Roger Barker

Vierbuchen T et al. Direct conversion of fibroblasts to functional neurons by defined factors. NATURE – 2010 [Epub ahead of print].

REHABILITATION: Stroke and Mirrors

Most physiotherapy gyms will have a full-length mirror, often arranged at the end of a set of parallel bars, so that patients beginning to mobilise can monitor their own position and alignment. Although the research base for this intervention is somewhat limited, there is a growing literature on the use of mirrors in upper limb rehabilitation. In the 90's, this became associated with the work of Ramachandran and the use of a "mirror box" in the management of phantom limb pain in upper limb amputees. Although his original study has some significant methodological limitations (in sample size and selection), it gained prominence in the popular scientific literature of the time and prompted debate about the interaction between vision and proprioception as well as the potential for utilising alternative neural pathways as part of the recovery process from neurological disease. This, of course, prompted further investigation.

This meta-analysis of the effectiveness of mirror therapy in upper limb function identifies that research has been performed using mirror therapy in the recovery period following hand surgery as well as amputation, stroke and CRPS. There are only 15 published studies and the majority are methodologically weak. Of the 5 studies looking, specifically, at stroke rehabilitation, there are 27 different outcome measures and 6 different standard functional scales to assess baseline function. All of the studies demonstrated a positive effect on arm function as a result of mirror therapy, but 2 did not have a control group, making it difficult to draw conclusions about the effectiveness or otherwise of mirror therapy.

The authors speculate that the effectiveness of mirror therapy in upper limb rehabilitation may be due to restoration of sensorimotor coupling through augmented sensory feedback. It is known that the primary motor cortex (M1) is modulated by ipsilateral limb movement as well as observation of the contralateral limb and mirror therapy could facilitate this by increasing feedback from an (apparently) active limb on the affected side. Given that mirror therapy is a relatively inexpensive and safe treatment strategy, further supporting evidence from larger methodologically sound studies would be extremely welcome in providing justification for its use in upper limb rehabilitation.

– Lloyd Bradley, Western Sussex Hospitals Trust

***E*zendam D, Bongers RM, Jannick MJA. Systematic review of the effectiveness of mirror therapy in upper extremity function. DISABILITY AND REHABILITATION – 2009; 31(26):2135-49.**

What is in a picture?

Just occasionally I come across a paper that captures my imagination, even if I struggle to understand the details of what has been done (I am sure my clinical fellows and PhD students would say that this is the "norm"). So it is with a recent paper in PNAS by Hughes et al, who have undertaken a study of the drawings of the great Flemish artist Pieter Bruegel the Elder (1525-1569). The approach they have adopted is stylometry, which is defined as "The use of mathematical and statistical techniques for the analysis of artwork". Thus in this study they have essentially modelled (using a sparse coding model if that helps) some drawings of Bruegel using a novel technique, which then allows them to show that pictures imitating those of Bruegel are just that- not originals. The modelling is all too complex to me, but the paper is a fascinating read in an evolving area which may help art historians probably attribute paintings and drawings. As such, techniques such as this could impact on verification of pieces of art, although in this paper the authors are cautious in making such claims and see their technique as helping, not replacing, those individuals charged with ascribing authorship to paintings and drawings especially those of historical value.

– Roger Barker

Hughes JM et al. Quantification of artistic style through the sparse coding analysis in the drawings of Pieter Bruegel the Elder. PNAS – 2010:107:1279-83.

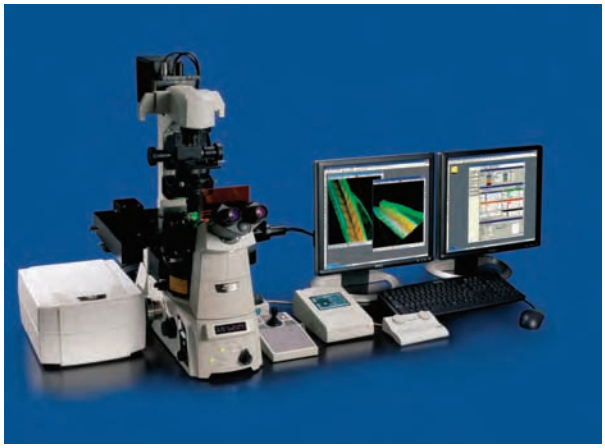
Dynamic live cell and deep tissue imaging

Nikon Instruments has launched its new A1R MP Multiphoton and Confocal microscope system for high speed, high resolution and high sensitivity multiphoton excitation and confocal fluorescence imaging. The A1R MP allows for deeper, faster and sharper imaging, while remaining cell-friendly with fast resonant imaging at up to 420 fps.

This multiphoton imaging system features a high resolution galvanometer scanner and a high speed resonant scanner that is capable of frame rates from 30 fps at 512 X 512 pixels to as fast as 420 fps in band scan mode. New four channel non-descanned multiphoton detectors with higher sensitivity, reduced dark current and broad spectral range allow for real time unmixing of closely spaced probes for deep tissue and accurate, high contrast spectral imaging. This is especially important in multiphoton imaging because of the overlap of emission spectra of probes and autofluorescence, which is often unavoidable when using a single laser line.

"The A1R MP can image deep within a specimen and image at video rates for full frame images or even faster for 32 line band scans," commented Stan Schwartz, vice president, Nikon Instruments, Inc. "This system is particularly well-suited for imaging deep within brain tissue where it is not possible to cut thin sections and keep circuitry intact to study neural phenomenon."

The Nikon A1R MP also features a one click auto-alignment of the infrared femtosecond Ti:sapphire multiphoton excitation laser. This device completely encloses the beam within the instrument from the laser to the objective lens – a huge improvement in operating safety.



Bright, high resolution imaging is provided by the newly introduced Nikon Lambda S (λS) objective series, featuring the highest numerical apertures (NA) for water immersion objectives yet. The CFI APO LWD 40X WI λS objective with NA 1.15 and a working distance of 610 microns incorporates Nikon's new Nano-crystal coat. This unique coat provides high transmissions over an expanded correction range.

For further information see www.nikoninstruments.eu/A1R-MP-Multiphoton-Confocal

Genus Pharmaceuticals - the new name for Britannia

Over the following twelve months the Britannia company name will be changing to Genus Pharmaceuticals. The Britannia company brand will be phased out from all APO-go products and materials and replaced with Genus branding.

Genus Pharmaceuticals Ltd (the UK division of STADA Arzneimittel AG) acquired Forum Bioscience in August 2007, and with it, Britannia, which became consolidated into Genus on 1st October 2007, but continued to operate under the Britannia company brand name until December 2009. The name change completes the integration of Britannia into Genus, and the combined strengths leave a company which can provide a more robust financial platform for future APO-go products, services and accelerated developments so that healthcare professionals and their patients with PD can be better supported.

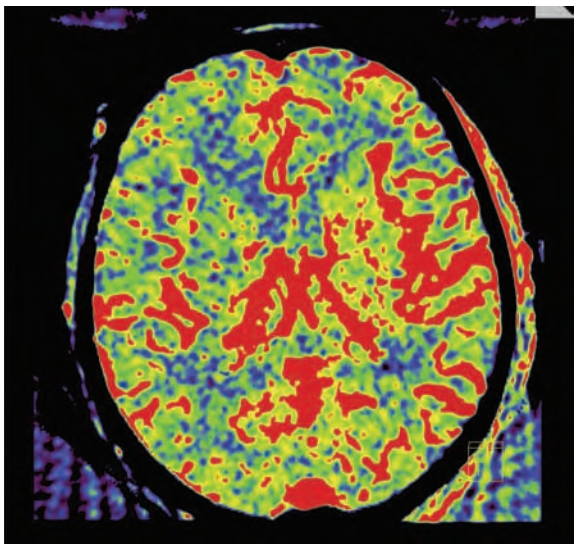
Sarah Woozley, APO-go's Marketing Manager comments, "Although the Britannia name has changed, the dedicated and friendly team who work on APO-go, with their vast experience, remain unchanged. The integration into Genus has enabled us to invest in future research, development and new technologies with the aim of making life simpler for our APO-go customers."

For further information contact Genus Pharmaceuticals Ltd, T. 01635 568400, E. info@genuspharma.com

Faster stroke treatment with new functional imaging application

To shorten the time from diagnosis to treatment in stroke patients, Siemens Healthcare has developed a new software application, which enables the visualisation of parenchymal blood flow during minimally invasive interventions in the brain for the first time. This feature assists the neuroradiologist in the treatment of stroke patients by displaying the condition of the cerebral tissue directly in the angio suite and is available on the Artis zee™ systems.

Minimally invasive techniques for stroke treatment involve guiding a thin catheter through the arteries of the brain to either deliver a drug to dissolve the blood clot or mechanically remove it. By displaying the current condition of the cerebral tissue directly in the angio suite, syngo® Neuro Parenchymal Blood Volume, Interventional Suite (PBV IR) assists in the accurate guidance of the catheter and is equally helpful for tumour biopsy and treatment, tissue embolisation and vasospasm therapy.



Siemens Healthcare has introduced syngo® Neuro Parenchymal Blood Volume, Interventional Suite (PBV IR), which displays cerebral blood flow during interventional procedures.

The PBV information is generated via two C-arm rotations around the patient coupled with a steady state contrast injection. The sophisticated processing algorithms of the system use the resulting data to generate a neurological PBV map, which is available at tableside in less than 40 seconds.

Another benefit of the new software is that it is capable of providing blood volume data for the whole brain, unlike traditional CT acquisition and allows the clinician to review the information from any orientation. syngo Neuro PBV IR uses cone-beam CT technology (syngo® Dyna CT) to acquire the information required for such advanced tissue visualisation.

For further information please visit: www.siemens.co.uk/healthcare or T. 01276 696338.

High NA, long WD, wide FOV objective for neuroscience

Nikon has added the CFI Apo LWD 25X objective to its series of low refractive index, high numerical aperture (NA) objectives for use in biological applications. Employing Nikon's ultra Nano-crystal coat technology, the new objective features high optical performance across the widest spectral wavelength with high chromatic corrections for sharp contrast imaging. This, combined with a high NA, wide field of view and long working distance make it ideal for neuroscience imaging.

Neuroscience and other applications require a large field of view for studying samples such as brain slices and blood vessels. In addition, live specimens such as tissue demand a long working distance. A high NA is extremely important for high resolution imaging of neurons and their axons; furthermore, NAs higher than 1.0 are essential to provide a high axial resolution to go deep into the tissue. Previously, manufacturers have found it difficult to make high performance objectives that combine all these features. Now, designed and optimised specifically for neuroscience and similar applications, the Nikon CFI Apo LWD 25X not only features a wide 22mm field of view and an unrivalled working distance of 2.0 mm, but also an extremely high NA of 1.10. In addition, a 33° approach angle on the lens provides easy access for micromanipulators in electrophysiology applications. An adjustable correction ring, for both non-coverglass and coverglass observations, reduces the effects of light scattering when imaging deep into specimens.

For further information see www.nikoninstruments.eu/products/Optics-Objectives

New website for The Ring Chromosome 20 Foundation

In 2009 the r(20) website recorded a record number of hits from medical professionals and individuals from all four corners of the world including; Japan, Australia, Europe, India as well as North and South America.

In response the updated website www.ring20.org now has multiple translations of key information including French and Spanish, as well as a multilingual essential information CD-Rom, which can also be ordered from the site. There is also the added feature of an online members' message board for people to share and exchange their own personal experiences.

Another important internet development has been the inclusion of video clips showing top medical professionals from all over the world discussing r(20) syndrome, at the first international symposium dedicated to r(20) syndrome which was held at the 28th International Epilepsy Congress in Budapest. This helps individuals and professionals who are not able to travel to see important, up to date information first hand, without the financial or logistical burden of travelling long distances.

For further information, E. info@ring20.org, or T. 01708 403 620.

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** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS 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** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. >1%: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **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. Do not freeze. **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** – March 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: March 2009 C0309/566a

TEVA

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COPAXONE®
(glatiramer acetate)
Standing up to RRMS everyday