

# ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

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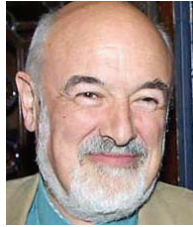
Job No. 0110/AZL/501/049

## Professors Chris and Uta Frith win the European Latsis Prize 2009 for The Human Brain – The Human Mind

Professors Chris and Uta Frith of UCL (University College London), UK and Aarhus University, Denmark have been awarded the European Latsis Prize for their contribution to understanding the human mind and brain.

The European Latsis Prize is valued at 100,000 Swiss francs (€66,000). The prize is funded by the Geneva-based Latsis Foundation and awarded by the European Science Foundation to an individual or a research group who, in the opinion of their peers, has made the greatest contribution to a particular field of European research.

"It's exciting to be awarded this prize and particularly to receive it together, recognising our work individually and as a team" said Chris Frith. "Our collaboration shows that not only is it valuable to cross disciplines, but it is also valuable to cross national boundaries. Europe is uniquely rich in the variation you can find in expertise and



Chris Frith



Uta Frith

approaches. In every country there is something worth borrowing or learning about in relation to knowledge and skills."

The work of Chris and Uta Frith has shaped the way researchers and clinicians think about mind and brain and various socio-cognitive deficits. The prize is awarded to them as a couple and they

were nominated as such. Both Uta and Chris Frith see their marital and academic partnership as the strongest formative influence on their careers.

Uta Frith comments "I think we are a prime example of the benefits of the kind of interpersonal and cross-cultural cooperation that we are now studying explicitly with our Danish colleagues at Aarhus University. We have always discussed each other's research and more recently our constant hidden collaboration has become visible to others as we now tend to publish together."

Chris Frith continues, "If I had not met Uta my research career would have been very different. It has been important to us that, until very recently, we have always worked in different institutions and in different topics. As a result my research has been fertilised by the different approaches and topics that engaged Uta."

## Nominations for 'Life After Stroke' Award



The Life After Stroke Awards - Nominations are open now until 26 February 2010. For more information E. helen.chapman@stroke.org.uk or see [www.stroke.org.uk](http://www.stroke.org.uk)

## Epilepsy charity delights in top award for Earl Howe

Earl Howe has championed the cause of people with epilepsy for 25 years and recently his work for the National Society for Epilepsy (NSE), was recognised with a top award. Westminster played host to the 7th DODS Charity Champion Awards in which Members of Parliament are voted for by other Parliamentarians in recognition of their consistent hard work, commitment and achievement on behalf of voluntary causes and issues. Earl Howe, the President of NSE was nominated by the charity in the health champion category and was delighted to win the award. He also chairs the All Party Parliamentary Group on Epilepsy.



He said, "I'm very proud of my involvement with NSE. It's a wonderful organisation. For many years epilepsy was an unsung condition but it has recently come out of the shadows, not least thanks to NSE's work in pioneering diagnostic techniques and its state-of-the-art research."

Bridget Gardiner, NSE's director of fundraising and marketing, said, "Earl Howe is a deserved winner of this award. We are privileged to have him as our President and thank him for his loyal support and hard work during the last 25 years."

## Heraldry Award for the Association of British Neurologists

The Association of British Neurologists was recently awarded the 2009 "Corporate Heraldry Award" by the UK Heraldry Society. This award is made annually to a corporate body which makes best use of its armorial bearings in the opinion of a panel of judges. The ABN beat several other entrants for the award, and was commended for the widespread use made of its relatively new arms which were granted during 2007. Dr Colin Mumford, Consultant Neurologist in Edinburgh, and Dr Chris Butler, Lecturer in Neurology at the University of Oxford, received the illuminated certificate on behalf of the ABN at a formal dinner held in The Apothecaries' Hall in London.



## New Medals awarded at the World Congress of Neurology

At the recent World Congress the WFN awarded two new medals for the first time. One was for Achievement in Neurology and the other for Services to International Neurology. The former was presented to Professor Roger Rosenberg of the Southwestern Medical School, University of Texas Medical Center in Dallas, US; the latter to Professor Noshir H Wadia from India. Also during the World Congress the WFN held the Annual General Meeting of its Council of Delegates. One item of business on the agenda was the election of new officers and a Trustee.

Professor Vladimir Hachinski from London, Ontario in Canada was chosen to be the new President of the WFN for a 4-year term from 1st January 2010, succeeding Dr Johan Aarli; Professor Werner Hacke from Heidelberg, Germany was elected as First Vice-President; Dr Raad Shakir, Consultant Neurologist from Charing Cross Hospital, London was re-elected unopposed as Secretary-Treasurer General for a further 4 years from 1st January 2011; and Professor Wolfgang Grisold from Vienna, Austria became an Elected Trustee to serve for a 3-year period.

## New President for the British Neuro-Oncology Society

Consultant Neurosurgeon Mr Charles Davis (Lancashire Teaching Hospitals NHS Foundation Trust, UK) is the newly-elected President of the British Neuro-Oncology Society (BNOS) and will continue in this role for the next two years. Charles assisted in the

preparation of the IBTA's recent booklet on "The First Documented, Modern-Day Brain Tumour Surgery for a Glioma" by kindly allowing them to reprint his own article on the subject (co-written with Mr Robert Bradford, also a British neurosurgeon) in the booklet.

In his article, Marios Hadjivassiliou introduces us to the idea of Primary Autoimmune Cerebellar Ataxia (PACA) – a disorder characterised by a slowly progressive cerebellar syndrome, typically beginning later in life often in association with other autoimmune disorders. He brings the evidence together in favour of this theory from a range of sources.

Jacqui Calvin and Sarah Hogg in the second of our review articles detail the investigations that may help in cases of suspected inborn errors of metabolism. Often such cases are stumbled across by me by accident, but Jacqui and Sarah give us a fantastically useful schema by which to approach such problems, with some impressive Tables to digest.

Charlie Stagg gives us a fascinating account on the possible role of transcranial stimulation for recovery in patients with CNS damage. This approach involves both Transcranial Magnetic Stimulation (TMS) as well as transcranial Direct Current Stimulation (tDCS) which has the advantage of being easier to use and administer. The way these two approaches differ is clearly delineated along with how they may be useful in the acute and chronic setting of stroke, when “inter-hemispheric balance” is abnormal. However, which hemisphere should be in receipt of the stimulation is not clear nor how long the effects last after its administration. All in all, though, this article is very stimulating!!

Single fibre EMG (sfEMG) is a technique often used in the investigation of neuromuscular disorders. We are therefore fortunate to have one of the pioneers of this technique, Erik Stalberg to take us through the history of its development and use and the wider applications of this technique. This is another excellent contribution to our Neurophysiology series edited by Andy Michell.

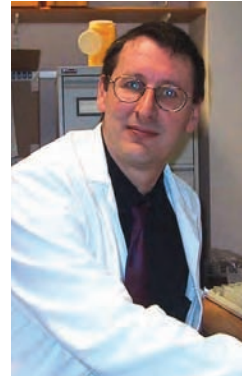
In the research series edited by Boyd Ghosh, the National Institute for Health Research (NIHR) and the Wellcome Trust become the topics for discussion especially with respect to individual researchers in Neurology. Dr John Williams, in his section, lays out how the Wellcome Trust supports research throughout the career of clinical scientists, which is both helpful and encouraging. Dr David Cox, in his excellent review of this area, highlights the different levels of faculty membership and the way in which the NIHR can support research positions. As he concludes “it is a key part of NIHR’s remit to embed research as part of the NHS culture and ethos”, which is reassuring given how much more we hear about audit trails, lengths of stay and waiting list times!

Jonathan Pollock discusses the investigation, presentation and treatment of lesions arising in and around the pituitary. This lavishly illustrated account is a very helpful distillation of clinical wisdom and highlights the usefulness of multi-disciplinary teams to manage these types of lesions.

We have our usual conference, book and journal reviews – with the latter being bigger and better than before courtesy of Mike Zandi and his energetic efforts!

Finally we have an excellent, extensive MS supplement edited by our very own Alasdair Coles, which seeks to summarise the major papers of the year in this field as well as award ACNR prizes to articles and findings that he feels merit them!

So Happy New Year and we hope you continue to enjoy ACNR. ♦



*Roger Barker, Co-Editor.*

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



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Published by Whitehouse Publishing,  
1 The Lynch, Mere, Wiltshire, BA12 6DQ.  
Publisher: Rachael Hansford  
E. rachael@acnr.co.uk

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PRINTED BY  
Manson Group Ltd. Tel. 01727 848 440

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Cover picture: Mouse Purkinje (brain) cells (40x)  
– Alan Opsahl, Pfizer, Inc, Groton, Connecticut, United States.  
Image of Distinction from the Nikon Small World 2009 Competition.

## Job Vacancies

### Clinical Neurology Fellow,

Myasthenia Team, Oxford. Enquiries can be emailed to Dr Jackie Palace at [Jacqueline.palace@clneuro.ox.ac.uk](mailto:Jacqueline.palace@clneuro.ox.ac.uk)

### Clinical Lecturer in Stroke Medicine,

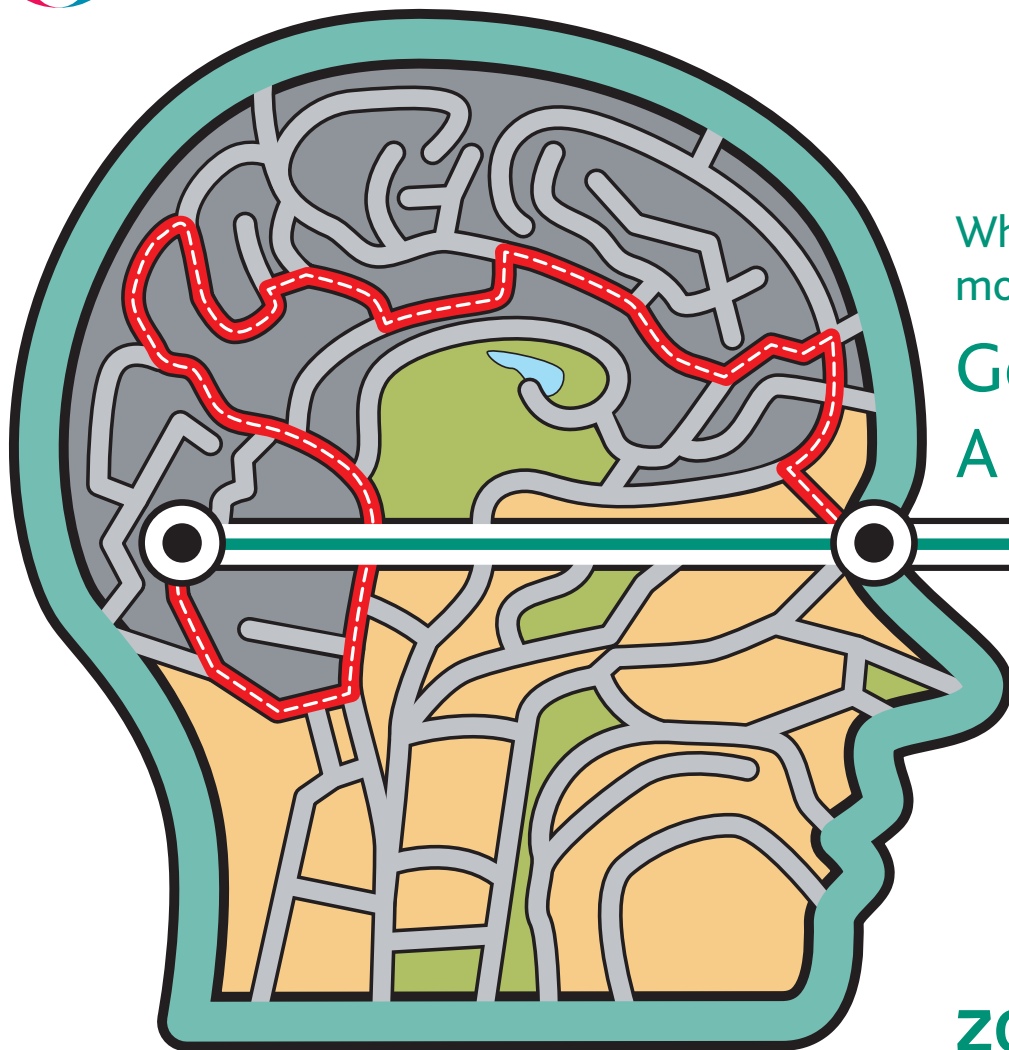
University of East Anglia. Please contact Dr P K Myint on [PHYO.MYINT@nnuh.nhs.uk](mailto:PHYO.MYINT@nnuh.nhs.uk) for more information, quoting ref ATR

### Locum Consultant Neurologist,

Royal Free Hospital, London. All enquiries should go to Dr Lionel Ginsberg, [Lionel.Ginsberg@royalfree.nhs.uk](mailto:Lionel.Ginsberg@royalfree.nhs.uk) or Dr Charlie Davie, [c.davie@medsch.ucl.ac.uk](mailto:c.davie@medsch.ucl.ac.uk)

### Research Fellow in Movement Disorder Neurology,

National Parkinson Foundation Centre of Excellence for Parkinson's Disease, Derby Hospitals NHS Foundation Trust and University of Nottingham. For an informal discussion please contact Dr Nin Bajaj on 01332 254 890/0115 924 9924 ex 66815 or via [nin.bajaj@nuh.nhs.uk](mailto:nin.bajaj@nuh.nhs.uk)



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prior stone formation, a family history of nephrolithiasis and hypercalcaemia. Evaluate and monitor serum bicarbonate levels in patients who have: underlying conditions which might increase the risk of metabolic acidosis; increased risk of adverse consequences of metabolic acidosis; symptoms suggestive of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing the dose, discontinuing or alkali treatment. Use with caution in patients treated with carbonic anhydrase inhibitors, e.g. topiramate. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration and avoid excessive temperatures. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Zonegran 100 mg capsules contain E110. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. **Drug Interactions:** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. **Side effects:** The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Adverse reactions associated with Zonegran in clinical studies and post-marketing surveillance: Very common effects ( $\geq 1/10$ ): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence,

diplopia, decreased bicarbonate. Common effects ( $\geq 1/100$ ,  $< 1/10$ ): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Uncommon ( $\geq 1/1000$ ,  $< 1/100$ ): pneumonia, urinary tract infection, hypokalaemia, anger, aggression, suicidal ideation, suicidal attempt, convulsion, vomiting, cholecystitis, cholelithiasis, calculus urinary. For very rare side effects see SmPC. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged  $\geq 65$  years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. **Legal Category:** POM. **Basic UK NHS cost:** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. **Irish price to wholesaler:** Zonegran 25 mg: packs of 14 €10.95, Zonegran 50 mg: packs of 56 €58.07, Zonegran 100 mg: packs of 56 €77.59. **Marketing authorisation numbers:** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. **Date of preparation:** July 2009.

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Date of Preparation: July 2009

ZON-UK2299a

# Primary Autoimmune Cerebellar Ataxia (PACA)



**Dr Marios Hadjivassiliou**

is a Consultant Neurologist and Honorary Reader in Neurology (University of Sheffield) at the Department of Neurology, Royal Hallamshire Hospital, Sheffield. His main research interests are the neurological manifestations of gluten sensitivity, the ataxias, axonal neuropathies and neurological vasculitis. He has been running the Sheffield ataxia clinic for 13 years.

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Unlike autoimmune diseases that have a clear target organ or clear target cell specificity (e.g. pancreatic islet cells in type 1 diabetes, thyroid in Hashimoto's thyroiditis, melanocytes in vitiligo), in autoimmune diseases affecting the CNS the concept of target specificity is perhaps less well appreciated because the brain is often viewed (mainly by non-neurologists) as one "organ". The brain however, is made up by such a diverse collection of cells and systems that it is probably more appropriate to think of it as a collection of well integrated but nonetheless multiple "organs".

The cerebellum, in particular, is one of the largest, oldest and most structurally conserved structures in the vertebrate nervous system with a remarkable homogeneity across species.<sup>1</sup> Despite its name (cerebellum – Latin for little brain), its structure and complexity suggest that its role within the central nervous system matches in importance, that of the cerebral cortex. It has a limited number of morphologically well-defined classes of cells with Purkinje cells perhaps being the most important of all. They certainly constitute the most important efferent element of the cerebellum, reflected by the fact that each can accommodate up to 160,000 synapses. This is the largest number of synapses seen in any neuron of the mammalian brain. Purkinje cells are often the target of immune mediated insults such as those seen in the context of paraneoplastic cerebellar degeneration. This disease is characterised diagnostically by a number of specific antibodies against different Purkinje cell antigens, pathologically by loss of Purkinje cells, and clinically by a rapidly progressive ataxia.<sup>2</sup> The cerebellum can also be an immune target in the context of other diseases such as post infectious cerebellitis<sup>3</sup> and gluten sensitivity (gluten ataxia).<sup>4</sup>

In addition to these specific entities where autoimmunity is triggered by another disease (cancer, infection, gluten ingestion) there is evidence to suggest that the cerebellum can be an organ specific autoimmune disease,<sup>5</sup> hence the proposed term of Primary Autoimmune Cerebellar Ataxia (PACA). This term implies no obvious trigger factor for the development of immune mediated damage to the cerebellum. The evidence in support of PACA comes from a number of observations:

Firstly, the Human Lymphocyte Antigen (HLA) type DQ2 is significantly overrepresented in patients with idiopathic sporadic ataxia (74% vs 35% in the healthy population). The prevalence of this HLA type in patients with genetically characterised ataxias is no different to the one found in the healthy population.<sup>5</sup> The HLA DQ2 has been shown to have a strong

association with autoimmune diseases, such as coeliac disease, gluten ataxia, type 1 diabetes mellitus, Stiff-Person syndrome (SPS), autoimmune thyroid disease and autoimmune polyendocrine syndromes.<sup>6,10</sup> One interpretation of this observation is that at least some cases of idiopathic sporadic ataxias have an autoimmune basis.

Secondly, it has been shown that there is a significantly higher prevalence of one or more autoimmune diseases in patients with idiopathic sporadic ataxia when compared to the general population and to patients with genetic ataxias (47%, 3% and 5% respectively).<sup>5</sup> Other autoimmune diseases encountered in the context of idiopathic sporadic ataxia include thyroid (usually Hashimoto's disease but also thyrotoxicosis), type 1 diabetes, primary biliary cirrhosis, vitiligo, pernicious anaemia, Sjogren's syndrome, alopecia, but also autoimmune diseases involving the nervous system and muscle such as Isaac's syndrome, polymyositis and SPS (unpublished observation).

Thirdly, it has been shown that cerebellar antibodies can be present in at least 60% of patients with idiopathic sporadic ataxia in contrast to 5% in patients with genetic ataxias.<sup>5</sup> Four different staining patterns were observed in this study, three of which resembled those seen in patients with gluten ataxia (cytoplasmic with processes, cytoplasmic alone, nuclear) and the fourth showing staining of the granular layer of the cerebellum. Further characterisation of such antibodies may prove to be helpful in the diagnosis of PACA. This is very important because PACA may well account for a substantial number of patients with idiopathic sporadic ataxia. Idiopathic sporadic ataxia accounts for 24% of all ataxias attending a specialised ataxia clinic run by the author at the Royal Hallamshire Hospital, Sheffield UK (see Table 1).

Finally, studies have shown that idiopathic sporadic cerebellar ataxia is consistently associated with a high prevalence of glutamic acid decarboxylase antibodies (anti-GAD).<sup>11</sup> These antibodies are a marker of multiple autoimmunity. They were first identified in type 1 diabetes,<sup>12</sup> and subsequently found in patients with SPS.<sup>13</sup> Evidence for anti-GAD antibodies being a marker of multiple autoimmunity comes from the observation that one or more additional autoimmune disorders are present in 60% of anti-GAD positive patients with SPS versus 6% in anti-GAD negative patients.<sup>14</sup> Similarly, patients with anti-GAD antibodies and IDDM have a higher prevalence of autoimmune thyroiditis than anti-GAD negative ones.<sup>15</sup> Thus the findings of a high prevalence of anti-GAD antibodies in patients with idiopathic sporadic



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**Table 1: Cause of ataxia in 640 patients with progressive ataxia attending the ataxia clinic, Royal Hallamshire Hospital, Sheffield, UK.**

<b>Total number of patients assessed</b>			<b>640</b>
<b>familial ataxia</b>			<b>124/640 (19%)</b>
autosomal dominant inheritance	90/124	(73%)	
autosomal recessive inheritance	34/124	(20%)	
genetic characterisation	49/124	(40%)	
(15 SCA6, 13 EA2, 8 FA, 4 SCA2, 2 SCA8, 1 SCA3, 1 SCA1, 1 SCA7, 1 SCA28, 1FAP, 1FBD, 1GSS)			
<b>sporadic ataxia</b>			<b>516/640 (81%)</b>
idiopathic sporadic	154/516	(30%)	
gluten ataxia	113/516	(22%)	
clinically probable MSA-C	87/516	(17%)	
genetic diagnosis	76/516	(15%)	
(28 FA, 12 mitochondrial cytopathy, 8 SCA6, 7 EA2, 7 cerebellar dysgenesis/congenital, 3 Cockayne syndrome, 2 SCA 2, 2 CTX, 1 SCA7, 1 Tay-Sachs, 1 Krabbe's, 1 AOA 2, 1 XP, 1 AHGH, 1 FX)			
alcohol related	65/516	(13%)	
paraneoplastic ataxia	18/516	(3%)	
anti-GAD associated ataxia	8/516	(2%)	
opsoclonus-myoclonus	8/516	(2%)	
<b>idiopathic sporadic out of total</b>			<b>154/640 (24%)</b>
<b>total presumed genetic (124+76)</b>			<b>200/640 (31%)</b>
SCA=spinocerebellar ataxia, FA=Friedreich's ataxia, EA=episodic ataxia, FAP=familial amyloid polyneuropathy, FBD=familial british dementia, MSA-C=cerebellar variant of Multiple System Atrophy, CTX=Cerebrotendinous xanthomatosis, AOA=ataxia oculomotor apraxia, XP=xeroderma pigmentosum, AHGH=ataxia with hypogonadotrophic hypogonadism, GSS=Gerstmann-Straussler-Scheinker syndrome, FX=Fragele X syndrome.			

ataxia who often have an additional autoimmune disease may signify that the ataxia in these cases is due to autoimmunity.

The autoimmune mechanism by which the cerebellum is damaged in the context of autoimmunity remains unclear. In paraneoplastic cerebellar degeneration, a number of well characterised antibodies (e.g. anti-Yo in association with ovarian cancer) appear to be reactive with both tumour and Purkinje cell antigens ultimately resulting in the loss of Purkinje cells and the development of ataxia. Nobody has so far been able to convincingly induce ataxia in an animal model, using serum from patients with paraneoplastic cerebellar degeneration. Thus a pathogenic role of such antibodies in the paraneoplastic cerebellar degeneration remains doubtful. In the case of gluten ataxia, antigliadin antibodies have been shown to cross react with Purkinje cell epitopes. Sera from patients with gluten ataxia have been shown to possess additional antibodies (e.g. transglutaminase antibodies) that react with cerebellar tissue.<sup>16</sup> Support for an antibody mediated pathogenesis in this type of immune mediated ataxia comes from work demonstrating induction of ataxia in a mouse model using serum from patients with gluten ataxia.<sup>17</sup> Another study has demonstrated that ataxia associated with anti-GAD antibodies may be the direct consequence of antibody-mediated neuronal dysfunction, but the precise characterisation of the antibody involved is lacking.<sup>18</sup> This antibody(s) may be unrelated to GAD antibodies. All the evidence however, suggests that the cerebellum and Purkinje cells in particular, are good immunological targets.

The next step in unravelling and consolidating PACA as a disease entity is a trial of immunosuppression as a means of treatment. Assessment of the value of immunosuppression in these patients will be challenging. Monitoring of treatment response may prove very difficult because of the variable and mostly slowly progressive nature of the disorder and the crude nature of ataxia rating scales. There is emerging evidence however, that MR spectroscopy of the cerebellum may well be an important and accurate tool in monitoring disease.<sup>19</sup> Whilst the final common pathological outcome in PACA, as in other cerebellar ataxias, is the irreversible loss of Purkinje cells, evidence derived from treatment of other immune mediated ataxias suggests that early intervention may not only stabilise the ataxia but could also salvage malfunctioning cells as evident by the demonstration of improvement of the ataxia.<sup>20</sup>

Case identification in PACA is also problematic. As the HLA DQ2 is found in up to 35% of healthy individuals, this test alone cannot serve as the only marker of patients with autoimmune ataxia. Indeed out of the 154 patients with idiopathic sporadic ataxia (Table 1) 54 would have had the HLA DQ2 by chance. The presence of additional autoimmune diseases in either the patient or their first degree relatives may be another helpful pointer. Ultimately characterisation of the cerebellar antibodies in patients with idiopathic sporadic ataxia may prove to be a very useful marker for those cases that may be

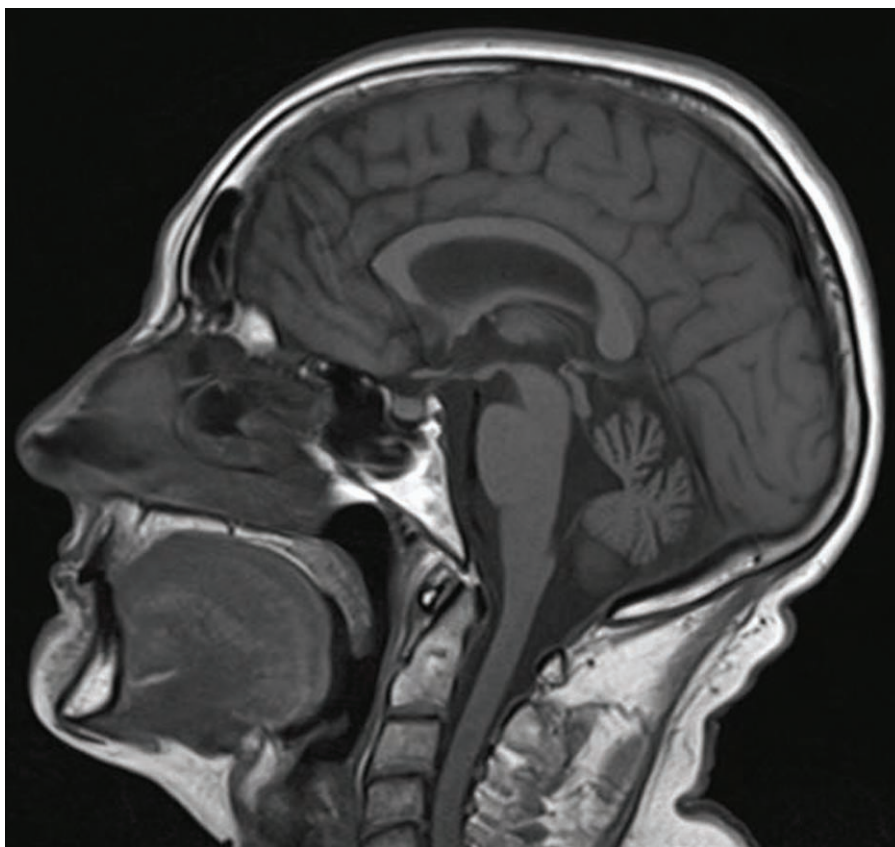


Figure 1: MR imaging demonstrating cerebellar atrophy in a patient with slowly progressive ataxia due to PACA. This patient presented in 1999 at the age of 51. She has the HLA DQ2 and at presentation apart from the ataxia she was positive for thyroid peroxidase antibodies but had normal TSH. She developed hypothyroidism 2 years later. She developed insulin dependent diabetes mellitus 5 years after the onset of the ataxia. Finally she was recently found to have low vitamin B12 with positive parietal antibodies in keeping with pernicious anaemia.

amenable to immunomodulatory therapy.

The clinical characteristics of such patients may also assist in case identification and in some cases distinguish them from other causes of ataxia. Patients with PACA tend to develop ataxia in their early 50s. The ataxia in general tends to be slowly progressive but in a few cases there may be a rather acute onset (a picture not dissimilar to that often seen at presentation in paraneoplastic cerebellar degeneration). Subsequently, however such patients follow a much more benign course. In fact some of these patients may have originally been diagnosed as having post infectious cerebellitis, the difference being that they continue to progress rather than improve, in contrast to patients with post-infectious cerebellitis.<sup>21</sup> Additional autoimmune diseases may be already present or may manifest subsequent to the development of the ataxia (Figure 1). Patients with PACA almost always have cerebellar atrophy on MRI but the severity of atrophy depends on disease duration.<sup>5</sup> These patients are also easily distinguished from patients with cerebellar variant of Multiple System Atrophy (MSA) by the absence of autonomic involvement and the slower progression.

The next logical step in consolidating this disease entity is an adequately-powered study comparing immunosuppressive treatment with placebo. The results of such a study will not only clarify and consolidate the concept of PACA but will hopefully offer hope for a substantial number of patients with progressive sporadic "idiopathic" ataxia. ♦

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# Biochemical Investigation for Inborn Errors of Metabolism in Adults Presenting With Neurological Disorders



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Inborn errors of metabolism (IEM) constitute a diverse group of genetic disorders characterised by defects in biochemical pathways. Many have a predominantly neurological phenotype reflecting accumulation of neurotoxic metabolites and/or a deficiency of substrates critical for normal neurological development and function. Whilst classically presenting in childhood, late onset variants of these disorders are increasingly recognised in adults, either as a true mild phenotype which presents in later life or because the symptoms in childhood were not sufficiently severe to merit investigation. Accurate diagnosis of these disorders is of particular importance given the expanding therapeutic options available<sup>1</sup> and the inherent genetic implications for the patient and their family. Whilst an in depth review of specific disorders is beyond the scope of this article, we aim to provide an overview of IEM presenting with adult-onset neurological disease, focussing upon a practical approach to biochemical investigation and diagnosis.

#### Adult-onset IEM

Adult-onset IEM together with the broad neurological phenotypes are detailed in Table 1. In reviewing the literature we have excluded metabolic myopathies and reports where neurological disease developed during childhood or where the age of onset is not clear. We have listed the different neurological features reported in each disorder, although many patients will not have a "full house", particularly where the disorder is mild. Further information on the individual disorders is available via the website 'Online Mendelian Inheritance in Man' ([www.ncbi.nlm.nih.gov/](http://www.ncbi.nlm.nih.gov/)).

#### When to consider an IEM

Many of the biochemical tests for these disorders are complex and expensive and so extensive biochemical screening is not practical. It can be difficult to identify which patients with neurological disease need investigation; we list below some features which may be suggestive of an IEM.

- Progressive neurological disease and/or disparate neurological signs; e.g. psychiatric and cerebellar disease with cognitive decline in metachromatic leukodystrophy.
- Neurological disease together with systemic features: e.g. hepatosplenomegaly in storage disorders, disordered liver function tests in Wilson disease, adrenal insufficiency in X-linked adrenoleukodystrophy.
- Combinations of various movement disorders
- Abnormal fundus examination; e.g. cherry red spot
- Episodic illness or fluctuating symptoms; particularly where it is out of proportion to the insult

and/or precipitated by intercurrent illness, protein load, or occurring post partum.

- Aberrant response to drugs; valproate may exacerbate urea cycle disorders and multiple drugs precipitate attacks in the acute porphyrias.

The history can provide important evidence; with hindsight there may have been subtle problems in childhood and elucidating the developmental and schooling history of the patient can be fruitful. As with all genetic conditions, the family history may provide important information, although the majority of IEM are autosomal recessive and often present as sporadic cases. Evidence of familial consanguinity should be sought. X-linked conditions in which females may be affected due to skewed X-linked inactivation (lyonisation) can cause diagnostic difficulty, and are discussed in more detail below.

In addition, brain imaging and neurophysiological studies may provide useful information, but are beyond the scope of this review.

#### Biochemical Tests

Routine biochemistry and haematology tests may provide clues (e.g. creatine kinase in mitochondrial disorders) but must be interpreted in conjunction with the clinical picture as these tests are non-specific.

Table 2 lists the first-line biochemical tests useful in the investigation of suspected IEM. These include markers of intermediary metabolism (e.g. organic and amino acids, orotate and acylcarnitines), peroxisomal function (very long chain fatty acids, pristanate and phytanate), bile acid biosynthesis (cholestanol) and lysosomal function (enzymes and storage compounds). Further information on the clinical and technical aspects of these tests is available in biochemical textbooks.<sup>23</sup> It is recommended that clinicians contact their local specialist metabolic laboratory for advice on appropriate tests, sample type and timing, pitfalls and interpretation of results. Further confirmatory tests will usually be required, such as fibroblast enzyme measurement or mutation analysis.

It should be noted that in patients with episodic illness it is crucial to obtain samples for metabolic investigations during an acute attack as the biochemistry may be normal when they are asymptomatic. A negative result during an acute attack makes a diagnosis of an underlying IEM unlikely.

#### Investigation of specific disorders

##### Lysosomal storage diseases

In patients with suspected mucopolysaccharidoses urine glycosaminoglycans (GAGs) provide a simple first-line investigation. It is important to examine the

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aspiration pneumonia and/or potentially fatal respiratory disease after treatment with Botulinum Toxin Type A/B have been reported. There is an increased risk of side effects in patients with underlying neuromuscular disease and swallowing disorders. Close medical supervision is advised in patients with neuromuscular disorders or history of dysphagia and aspiration. Seeking medical attention for respiratory difficulties, choking or any new or worsening dysphagia is advised. Dysphagia has been reported following injection to sites other than the cervical musculature. Dosage units are specific to Botulinum Toxin Type B only and are not relevant to preparations of Botulinum Toxin Type A. **Drug interactions** No specific interaction studies. Effect of co-administration with other botulinum toxin types is unknown. Co-administration of Botulinum Toxin Type B and aminoglycosides or agents interfering with neuromuscular transmission (e.g. curare-like compounds) should be considered with caution. **Side effects** Adverse reactions reported with Botulinum Toxin Type B (toxin-naïve and toxin-responsive) are: Very common ( $\geq 1/10$ ) dry mouth, dysphagia, headache and injection site pain. Common ( $\geq 1/100$  to  $< 1/10$ ) worsening of torticollis (from baseline), torticollis, taste perversion, voice alteration, dyspepsia, myasthenia, blurred vision, neck pain, dysphonia and injection site pain. Electrophysiological jitter, which is not associated with clinical weakness or other electrophysiological abnormalities, may be experienced in some distant muscles. There have been post marketing reports of exaggerated muscle weakness, dysphagia, dyspnoea, aspiration, pneumonia with fatal outcome in some cases, abnormal accommodation, ptosis, vomiting, constipation, flu-like symptoms, and asthenia. **Shelf-life:** 3 years. **Special precautions for storage** 2°C - 8°C. May be stored below 25°C for up to 3 months, without being refrigerated again. Do not freeze. Protect from light. For storage conditions of the diluted medicinal product, see SPC. **Legal Category** POM. **Basic UK NHS cost** Botulinum Toxin Type B 0.5ml vial £111.20,

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NEURO-UK2143d  
Date of Preparation October 2009

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pattern of GAGs in the urine (GAG typing) rather than relying on quantitative screening tests. Apart from urine GAGS there are few simple biochemical tests available for the diagnosis of lysosomal storage diseases. Urine oligosaccharide screening lacks sensitivity in detection of mild late onset forms so for the majority of lysosomal storage diseases white cell enzymes are indicated. In most circumstances normal enzyme activities reliably exclude storage disease. One notable exception is the identification of females with (X-linked) Fabry disease, as normal enzyme activity does not exclude the diagnosis. Measurement of the storage compound (globotriaosylceramide) in urine also lacks sensitivity (noted particularly in the cardiac variant),<sup>4</sup> making diagnosis difficult where no family mutation has been identified. 'Pseudodeficiency' of several lysosomal enzymes complicates interpretation of low results. There is a high frequency of arylsulphatase A pseudodeficiency in most ethnic groups (carrier rate ~1 in 7)<sup>5</sup> complicating the diagnosis of metachromatic leukodystrophy and necessitating confirmatory mutation analysis in patients with deficient enzyme activities.

### Peroxisomal disorders

The most common adult-onset peroxisomal disorders are Refsum disease and X-linked adrenoleukodystrophy, identified biochemically by raised phytanate and very long chain fatty acids respectively. However, only ~85% of female carriers of adrenoleukodystrophy have abnormal plasma concentrations. It should be borne in mind that markedly different phenotypes of adrenoleukodystrophy can occur in one family.<sup>6</sup> 2-methyl-CoA racemase deficiency provides an example of a recently described adult-onset IEM.<sup>7</sup> The clinical features are similar to Refsum disease and characterised biochemically by high concentrations of plasma pristanate. Clinical features reported included peripheral neuropathy, pigmentary retinopathy and seizures. Acute and subacute presentations occur precipitated by rapid weight loss, pregnancy or fever.

### Mitochondrial disorders

Mitochondrial diseases are notoriously difficult to diagnose given the large number of disorders described; they are multi-system disorders presenting at any age, with any mode of inheritance. Simple biochemical tests for mitochondrial disease are limited; the measurement of lactate in plasma and CSF is useful but normal results do not exclude mitochondrial disease, although a normal CSF result in a fitting patient is reassuring. Biochemistry may reveal renal tubular dysfunction, muscle disease and/or endocrine abnormalities. However, diagnosis usually relies on muscle biopsy (histology and respiratory chain enzymes) and genetic studies.<sup>8</sup>

### Urea cycle disorders

Urea cycle disorders may present with acute episodic illness, the diagnosis of which may be overlooked if samples (ammonia, plasma amino acids, and urine orotate) are not collected during an attack. This group of disorders highlights

the need for ammonia estimation in any adult with unexplained encephalopathy.

### Organic acidurias

Organic acidurias typically present in childhood, however some disorders may not be diagnosed until adulthood, including glutaric aciduria type 1, propionic aciduria, L-2-hydroxyglutaric aciduria and 4-hydroxybutyric aciduria. Although there are reports of adult diagnoses of the latter two conditions, presentation was in childhood with symptoms including learning difficulties and ataxia. A limited number of true adult-onset organic acidurias have been reported. A recent example is 3-methylglutaconic aciduria type 1, previously described in a small number of children with a variety of phenotypes. The adult patients described presented with a cerebellar syndrome and cognitive decline,<sup>9,10</sup> which may prove to represent the true phenotype. Investigation is straightforward requiring urine organic acids as the first-line test; acylcarnitines may be useful in certain conditions.

### Cerebral glucose transport

Recently, adult-onset cases of GLUT1 deficiency have been reported, presenting with paroxysmal exercise-induced dyskinesia with and without epilepsy. The fasting CSF/plasma glucose ratio is subnormal but not to the extent seen in the early onset disorder.<sup>11</sup>

### IEM presenting in childhood with abnormal adult neurology

Although we have concentrated on disorders presenting in adults there are a number of early presenting disorders with long term survival. These may have eluded diagnosis because the patient was not investigated, the tests were not readily available or the condition has been described relatively recently. Two examples are the cerebral creatine deficiency syndromes (CCDS) and congenital disorders of glycosylation (CDG).

CCDS comprise guanidinoacetate methyltransferase (GAMT) deficiency, X-linked creatine transporter defect and arginine:glycine amidinotransferase (AGAT) deficiency, all resulting in cerebral creatine deficiency. AGAT and GAMT deficiencies may respond to treatment with creatine. The common features are mental retardation, speech delay and epilepsy which usually begin in infancy, although the condition may not be diagnosed until much later.<sup>12,13</sup> Measurement of creatine and guanidinoacetate in urine and plasma aids diagnosis of these conditions without resort to magnetic resonance spectroscopy.<sup>14</sup>

CDG disorders result in multi-systemic disease and should be considered in adults with a long-standing history of retinitis pigmentosa, seizures, stable ataxia and kyphoscoliosis.<sup>15</sup> The diagnosis may be made by analysis of transferrin glycoforms.

### Summary

The possibility of an underlying IEM should be considered in any patient with unexplained neurological disease. A wide range of biochemical tests are available with the aim of reaching a

working diagnosis. Confirmation usually requires fibroblasts and/or genetic testing. Given the rarity of individual IEM, the many disorders described and the difficulties of identifying mild cases it is likely that late-onset forms are underdiagnosed. In theory mild cases of any IEM could present at a late stage and the list of adult-onset diseases will undoubtedly grow. ♦

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**Table 1: Neurological features in adult onset IEM.**

	Leukoencephalopathy	Spastic paraparesis	Cerebellar Disease	Cognitive decline	Movement disorder	Epilepsy	Acute encephalopathy	Stroke & Stroke-like episodes	Peripheral neuropathy	Psychiatric disease	Other features
<b>Lysosomal Disorders</b>											
Fabry disease							X	X	X		Angiokeratomas, cardiomyopathy, renal disease. X-linked: females affected. Stroke may be the presenting feature
Galactosialidosis			X	X	X	X					Cherry red spot may be present, corneal clouding, angiokeratomas, short stature
Gaucher disease (type III)		X	X		X	X					Horizontal supranuclear ophthalmoplegia, hepatosplenomegaly, bone pain, thrombocytopenia, anaemia
GM1 Gangliosidosis	X	X	X	X	X						Cherry red spot may be present
GM2 Gangliosidosis (Tay Sachs & Sandhoff)	X	X	X		X			X	X		Cherry red spot may be present. May mimic motor neurone disease
Krabbe disease	X	X	X	X				X			
β-Mannosidosis				X				X	X		Angiokeratomas, deafness, dysmorphic features
Metachromatic leukodystrophy	X	X	X	X	X	X		X	X		Optic atrophy
Neuronal ceroid lipofuscinosis type 1			X	X	X				X		Progress to cerebral ataxia, visual loss. Other types described, but not diagnosed biochemically
Niemann-Pick type C		X	X	X	X				X		Vertical supranuclear ophthalmoplegia, hepatosplenomegaly
Sanfilippo syndrome (mucopolysaccharidosis type III)				X					X		Mild dysmorphic features (facial coarsening)
Sialidosis type I			X		X	X					Cherry red spot, visual loss
<b>Peroxisomal disorders</b>											
Adrenoleukodystrophy / Adrenomyeloneuropathy	X	X		X		X		X	X		X-linked. Adults mostly present with adrenomyeloneuropathy. Males may have adrenal insufficiency
2-Methyl-CoA racemase deficiency		X		X	X	X			X		Retinitis pigmentosa
Refsum disease			X	X					X		Retinitis pigmentosa
Steinert carrier protein X deficiency	X				X						Phenotype uncertain (n = 1)
<b>Mitochondrial disorders</b>											
Mitochondrial disorders	X		X		X	X		X	X		Variable phenotypes, often multi-system disease, e.g. sensorineural hearing loss, optic atrophy, retinitis pigmentosa, myopathy
Coenzyme Q10 deficiency			X								Phenotype in adult-onset unclear
Pyruvate dehydrogenase deficiency			X		X				X		Phenotype in adult-onset unclear
<b>Amino Acid Disorders</b>											
Cobalamin C defect	X	X							X	X	Combined degeneration of spinal cord, retinitis pigmentosa, optic atrophy, thromboembolic events
Classical homocystinuria					X	X		X	X		Osteoporosis, thromboembolic events, lens dislocation, marfanoid habitus
Hartnup disorder			X							X	Pellagra-like photosensitive dermatosis
Maple syrup urine disease			X				X				Episodic attacks precipitated by metabolic stress eg catabolism (fasting, intercurrent illness)
Methylene tetrahydrofolate reductase deficiency	X	X	X				X	X	X	X	Subacute degeneration of spinal cord, thromboembolic events
Urea cycle disorders: OTC, citrullinaemia I & II, NAGS, CPS, LPI, HHH						X	X	X		X	Acute attacks triggered by protein load eg catabolism (intercurrent illness), diet. OTC is X-linked
Urea cycle disorders: arginase deficiency		X	X		X	X					Often diagnosed with cerebral palsy
<b>Organic Acid Disorders</b>											
Glutaric aciduria type 1	X		X	X	X	X					Macrocephaly, subdural haematomas
3-Methylglutaconic aciduria type 1	X			X							
Multiple acyl-CoA dehydrogenase deficiency							X				Episodic attacks precipitated by metabolic stress eg catabolism (fasting, intercurrent illness), myopathy
<b>Fatty Acid Oxidation Disorders</b>											
Medium chain acyl-CoA dehydrogenase deficiency							X				Hypoketotic hypoglycaemia. Episodic attacks precipitated by metabolic stress eg catabolism (fasting, intercurrent illness)
<b>Carbohydrate Disorders</b>											
GLUT1					X	X					Confusion/lethargy triggered by fasting
<b>Purine Disorders</b>											
Lesch-Nyhan neurological variant		X			X						X-linked, gout and/or renal calculi, attention deficit, variable mental retardation
<b>Lipid Disorders</b>											
Ataxia with vitamin E deficiency		X	X								Retinitis pigmentosa
Ceroid lipofuscinosis	X	X	X		X	X			X	X	Juvenile cataracts, xanthomas, diarrhoea, mental retardation
<b>Neurotransmitter defects</b>											
GTP cyclohydrolase deficiency					X						Autosomal dominant dopamine-responsive dystonia with diurnal fluctuations in symptoms
<b>Porphyria</b>											
Acute intermittent porphyria						X	X		X	X	Abdominal pain, dysautonomia, hyponatraemia
<b>Metal Disorders</b>											
Haemochromatosis			X		X					X	Hepatic & endocrine disease, arthritis
Neuroferritinopathy		X		X	X						
Wilson disease				X	X	X	X		X	X	Kayser-Fleischer rings, hepatic disease

Abbreviations: CPS – carbamoylphosphate synthetase, HHH – hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome, LPI – lysinuric protein intolerance, NAGS – N-acetylglutamate synthetase, OTC – ornithine transcarbamoylase

**Table 2: Metabolic biochemical investigation for IEM.**

IEM	Biochemical Investigations	Notes
<b>Lysosomal Disorders</b>		
Fabry disease, GM <sub>1</sub> gangliosidosis, Krabbe disease, β-mannosidosis, metachromatic leukodystrophy, neuronal ceroid lipofuscinosis type 1, Sandhoff, Tay Sachs	Lysosomal enzymes	Usually requires white cells (whole blood), some available on plasma/dried blood spots. Check with local laboratory for details
Galactosialidosis	White cell enzyme & urine sialic acid	
Gaucher disease	Chitotriosidase & white cell enzyme	Chitotriosidase markedly elevated (benign chitotriosidase deficiency occurs in ~6%)
Niemann-Pick type C	Chitotriosidase & fibroblast studies	Fibroblast filipin staining & cholesterol esterification. Chitotriosidase mildly elevated
Sanfilippo syndrome (MPS III)	Urine glycosaminoglycans (including typing)	Enzyme analysis required to distinguish subtypes
Sialidosis type 1	Urine sialic acid	
<b>Peroxisomal disorders</b>		
X-ALD, AMN, 2-methyl-CoA racemase deficiency, Refsum disease, sterol carrier protein X deficiency	Plasma VLCFA, phytanate and pristanate	~15% female carriers of X-ALD have normal VLCFA
<b>Mitochondrial disorders</b>		
Mitochondrial disorders	CSF & plasma lactate, respiratory chain enzyme activities in muscle	Lactate & respiratory chain enzymes may be normal
MERRF, MELAS, NARP	Common mitochondrial point mutations	
Pyruvate dehydrogenase deficiency	Enzyme in muscle / fibroblasts	
Coenzyme Q10 deficiency	White cell coenzyme Q10	Consider if abnormal respiratory chain enzymes
<b>Amino Acid Disorders</b>		
Urea cycle disorders (OTC, citrullinaemia I & II, NAGS, CPS, LPI, arginase, HHH)	Plasma ammonia & amino acids, urine amino acids & orotate	Allopurinol loading tests to identify carriers of OTC are not particularly sensitive or specific. <sup>16</sup>
Hartnup disorder	Urine amino acids	
Homocysteine defects (CblC defect, classical homocystinuria, MTHFR deficiency)	Plasma total homocysteine & amino acids (methionine), & urine methylmalonate	MTHFR thermolabile variant is not a cause. B12 & folate usually normal in classical homocystinuria & CblC defect
Maple syrup urine disease	Plasma amino acids & urine organic acids	May be normal between acute attacks
<b>Organic Acid Disorders</b>		
Glutaric aciduria type 1	Urine organic acids & acylcarnitines	Normal results described in the literature – consider fibroblast enzyme assay
Multiple acyl-CoA dehydrogenase deficiency	Urine organic acids & acylcarnitines	Results may be normal between attacks
3-Methylglutaconic aciduria type 1	Urine organic acids	Beware various subtypes of 3-methylglutaconic aciduria
<b>Fatty Acid Oxidation Disorders</b>		
Medium chain acyl-CoA dehydrogenase deficiency	Acylcarnitines & urine organic acids	Positive dipstick for ketones does not exclude
<b>Carbohydrate Disorders</b>		
GLUT1	Paired fasting CSF & plasma glucose	Collect blood prior to lumbar puncture. In adult onset cases ratio may not be <0.4
<b>Purine Disorders</b>		
Lesch-Nyhan neurologic variant	Serum & urine urate, red cell / fibroblast HPRT	HPRT activity very variable (0-50%)
<b>Lipid Disorders</b>		
Cerebrotendinous xanthomatosis	Plasma cholestanol	Serum cholesterol may be normal
Ataxia with vitamin E deficiency	Plasma vitamin E	Protect sample from light
<b>Neurotransmitter defects</b>		
GTP cyclohydrolase deficiency	CSF neurotransmitters	Special collection tubes and snap freeze
<b>Porphyria</b>		
Acute intermittent porphyria	Urine porphobilinogen	Protect sample from light. To exclude collect urine during an acute attack
<b>Metal Disorders</b>		
Haemochromatosis	Transferrin saturation	C282Y common mutation, low penetrance
Neuroferritinopathy	Serum ferritin	Increased by acute phase response
Wilson disease	24 h urine copper	Consider penicillamine challenge

Abbreviations: AMN – adrenomyeloneuropathy, CblC – cobalamin C, CPS – carbamoylphosphate synthetase, HHH – hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome, HPRT – hypoxanthine guanine phosphoribosyl transferase, LPI – lysinuric protein intolerance, MPS – mucopolysaccharidosis, MTHFR – methylene tetrahydrofolate reductase, NAGS – N-acetylglutamate synthetase, OTC – ornithine transcarbamoylase, X-ALD – X-linked adrenoleukodystrophy, VLCFA – very long chain fatty acids.



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avoided. **Pregnancy and Lactation:** Effects of pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used during breast-feeding. **Undesirable Effects:** Frequency of adverse reactions from placebo controlled clinical trials in Parkinson's disease includes; Very Common ( $\geq 1/10$ ) – nausea, dizziness, dyskinesia, hypotension and somnolence. Common ( $\geq 1/100$  to  $< 1/10$ ) – insomnia, hallucinations, amnesia, behavioural symptoms of impulse control disorders and compulsions, restlessness, visual disturbance including vision blurred and visual acuity reduced, headache, constipation, vomiting, weight decrease, abnormal dreams, confusion and peripheral oedema. Hypotension may occur at the beginning of treatment, especially if Mirapexin is titrated too fast. Especially at high doses seen in Parkinson's disease, signs of pathological gambling, increased libido and hypersexuality have been reported, generally reversible upon reduction of dose or treatment discontinuation. See SPCs for other undesirable effects. **Pack sizes and NHS price:** 30 tablets: 0.26mg (**0.375mg**) £28.65; 0.52mg (**0.75mg**) £57.30; 1.05mg (**1.5mg**) £114.60; 2.1mg (**3mg**) £229.20; 3.15mg (**4.5mg**) £343.80. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. **MA Numbers:** EU/1/97/051/014 (0.26mg (**0.375mg**)); EU/1/97/051/017 (0.52mg (**0.75mg**)); EU/1/97/051/020 (1.05mg (**1.5mg**)); EU/1/97/051/023 (2.1mg (**3mg**)); EU/1/97/051/026 (3.15mg (**4.5mg**)). Prescribers should consult the Summary of Product Characteristics for full prescribing information. Prepared in October 2009. Further information is available from Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, Berkshire RG12 8YS.

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# How Single Fibre EMG Moved Into Clinical Routine



## Prof Erik Stålberg

developed SFEMG and a number of other EMG methods such as Macro EMG, Scanning EMG, Multi-MUP analysis. Quantitative EMG analysis in EMG for the understanding of pathophysiology in nerve and muscle disorders is his main research interest.

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## History

In the late 1950s, conventional EMG had been proven to be a useful complement in the evaluation of patients with neuromuscular disorders. The method had then been tested in some laboratories for a decade. At this time Dr Jan Ekstedt and myself were introduced to research in the Dept of Pharmacology, Uppsala. Our mentor, Prof Bárány, suggested to us to study fatigue of skeletal muscle. Could this be reduced pharmacologically in the same way as the heart muscle can be strengthened? For that we needed techniques to measure fatigue. Trials with mechanical force measurements with strain gauges in combination with various recordings of electrical muscle activity, electromyography (EMG), were the basic methods to be used. With insufficient information from these routine methods, we concentrated on the improvements of the EMG methods and tried surface EMG, wire electrodes and conventional concentric needle EMG. Inspired by multielectrode studies by Buchthal and collaborators,<sup>1</sup> we started to construct multielectrodes, but smaller and more selective than those previously used. This ended with various multielectrodes with the recording wires sized 25µm in diameter, that is smaller than a normal muscle fibre, exposed in a side-port close to the tip of a small cannula. We recorded brief signals, the nature of which finally, after experiments with ischaemia, curare, simulations, special electrode configurations, were proven to represent activity from single muscle fibers. This resulted in two PhD theses, one on the recording method itself and the description of the jitter phenomenon<sup>2</sup> and one the measurements of propagation velocity and "fatigue" in single muscle fibres.<sup>3</sup> Without substantial work on the original project on fatigue we left the institution and moved to the clinical side, Ekstedt to neurology, and I to clinical neurophysiology. I now had the chance to test this new method in patients, and successively implement it for routine use.

## What do we measure

The method of single fibre EMG is much more selective than conventional EMG. There are two parameters that have a clinical application. One is the assessment of fibre concentration within a motor unit, a parameter called Fibre Density (FD). The background is that muscle fibres, innervated by the same neuron with connected axon, are randomly distributed within an area of 5-15 mm, and separated from each other by about 200µm. In cases of reinnervation the surviving motor unit will innervate denervated neighboring muscle fibres. This so called collateral reinnervation

results in a change in organisation of the muscle fibres that now occur in small or large groups together. On biopsies this is observed as so called fibre type grouping. Also in myopathies, the organisation is different from normal due to splitting, degeneration-regeneration. This parameter is a good complement to the conventional EMG when the picture is difficult to interpret.

The other parameter is the neuromuscular jitter. This is, in the individual motor end-pate, the variability of the trans-synaptic time for a nerve pulse to activate a muscle fibre. This particular parameter is the most important contribution from SFEMG.

## Screening the usefulness of SFEMG in various neurological disorders

The early steps in the development were to test the method in a variety of nerve and muscle disorders. It was clear that the jitter parameter was directly applicable in the diagnosis of myasthenia gravis, MG, and other disorders with disturbed neuromuscular transmission. It also contributed to the understanding of reinnervation dynamics and has found a place in the neurogenic diseases. In myopathies, special new aspects have evolved particularly in the field of channelopathies (myotonic disorders). The results have been published in a large number of publications.<sup>4,5</sup> The interested reader is referred to a monograph on SFEMG<sup>6</sup> with a new edition under preparation (Stålberg, Trontelj, Sanders, 2010).

## Technical improvements

The jitter is based on measuring time variability of the order of four to a few hundred µsec, normally below 50µsec. Initially, the electrodes and amplifiers were home built, and the measuring devices were dependent on separate timers for short time intervals (Figure 1). Since the wide testing of the SFEMG in various pathological conditions successively showed the clinical usefulness, commercial electrodes became available and all high level EMG equipment now have inbuilt software for jitter analysis and other software based on the results from SFEMG studies (Figure 2). The technique to obtain single fibre potentials takes some training and manual skill. It has therefore been of utmost importance that the online signal analysis can be made with user friendly software.

## Applications and Present indications

The jitter parameter is the most sensitive physiological test of neuromuscular transmission.<sup>4</sup> It is possible to detect even subclinical disturbance, i.e. before the patient has symptoms in that mus-



Figure 1: The author and his engineer (1977) in front of their assembled EMG recording system. Large, multi-knobbed and very flexible equipment connected to a separate computer.

cle. The method has therefore become a routine method in many laboratories all over the world, and is recommended to be used when the repetitive nerve stimulation (RNS) test is negative. It should be stated that increased jitter is not equal to MG, but indicates disturbed neuromuscular transmission. One such situation is during ongoing reinnervation. The sensitivity in MG has been tested by many authors. The largest study is published by Sanders and collaborators.<sup>7</sup> They find a correlation to severity of the MG. In 503 MG patients, the sensitivity of SFEMG was 97% in ocular MG if two muscles are studied and 99% in generalised. They have also shown that the degree of jitter follows the clinical situation and that the method can be used in monitoring over time.

Usually SFEMG recording is performed under slight voluntary activation of the muscle. Some investigators prefer to use stimulation SFEMG. Here a monopolar electrode is inserted in the muscle as stimulating cathode and the individual endplates are studied.<sup>8</sup> The advantage is that no patient cooperation is necessary (small children, unconscious patients, patients with movement disorders). In addition, the neuromuscular junction can be studied during different stimulation frequencies, one way to differentiate presynaptic from postsynaptic defects. Stimulation SFEMG has been used in the study of congenital myasthenic syndromes.<sup>9</sup> Stimulation is performed with a small needle electrode near the facial nerve, and recording is performed in the frontalis or orbicularis oculi muscle.

The fibre density, FD, parameter is used to evaluate the organisation of the motor unit, as a sensitive indicator of abnormality, neurogenic or myogenic. No special measuring software is necessary. FD measurements can be performed in all EMG equipment where the sweep can be triggered. This is often a parameter that is included in the complete SFEMG study. The SFEMG indications can be briefly summarised as follows:

#### **Jitter**

Neuromuscular transmission disorders  
diagnosis,  
distribution between muscles,  
monitoring.

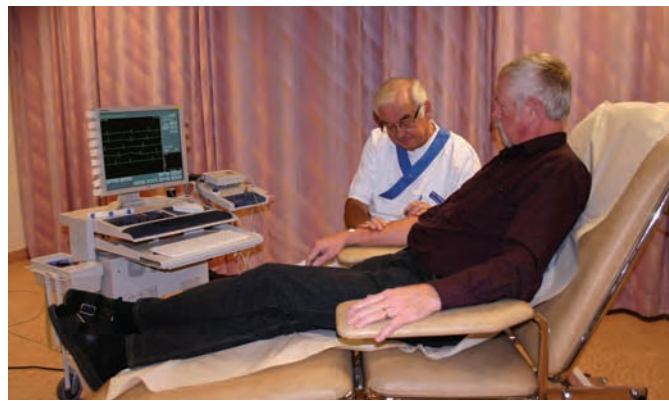


Figure 2: The author and an engineer (2009) from the Dept of Clinical Neurophysiology using modern EMG equipment, developed in the Department (by S Stålberg and the staff, and by Dantek A/S, Copenhagen, Denmark). Note the size reduction of this compact, multi purpose EMG equipment for routine use with inbuilt computer connected to a laboratory network.

Reinnervation dynamics (larger jitter in the phase of ongoing reinnervation, larger jitter in active than in chronic myositis).

#### **FD**

Reinnervation

Degree of involvement.

Complement to EMG when results are uncertain.

Myopathy

When conventional EMG is uncertain.

#### **Special indications**

For spike triggering (motor unit counting, Macro EMG, Scanning EMG), Firing rate of individual motor units.

#### **New developments**

Over the last 10 years, the use of re-sterilised products has been discouraged or abandoned due to potential risk of prion infections. The SFEMG electrodes can be used for hundreds of investigations if properly maintained, but are too expensive for single use. Therefore there has been a great interest in alternatives with disposable electrodes. One such alternative is the conventional concentric electrode used with special filter settings on the amplifiers. A small facial needle electrode seems to be a reasonable replacement.<sup>10</sup> Reference values have been established in a few individual laboratories (for summary see reference 11) indicating that the jitter values for concentric recordings are about 3-5µsec lower than those published from a multicenter study with regular SFEMG.<sup>12</sup> This new possibility is therefore accessible for all electromyographers, since the electrode has the same low price as other disposable electrodes. Great care should be taken during recording and interpretation, and some more work is necessary to define some details of the technique.

#### **Summary**

- The principles of SFEMG should be known by all electromyographers, since the single fibre action potentials are the basic components of the motor unit potentials. The jitter seen in SFEMG can also be observed in the motor unit potentials as variability in its shape at consecutive discharges. Thus, this should be interpreted as an indicator of disturbed neuromuscular transmission, a useful observation from conventional EMG.

- SFEMG should be applied in patients with suspicion of neuromuscular disturbance, particularly when RNS has been negative.
- SFEMG can be used to assess the dynamics of neurogenic and myogenic disease. An increased jitter indicates active reinnervation after denervation that has taken place during the last 3-6 months.
- The electromyographer may also use SFEMG in situations when conventional EMG has given uncertain results. The additional information may then help understand the condition better.
- SFEMG can be performed in all muscles where conventional EMG can be performed.
- Small children, unconscious patients can be studied by using stimulation SFEMG.

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# Transcranial Stimulation as a Potential Therapeutic Intervention in Chronic Stroke



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## Background

There are records of electrical currents being used for the relief of various neurological and psychiatric disorders for approximately two millennia. Techniques have developed from the use of torpedo electric fish in the days of Galen and Pliny the Elder to the transcranial stimulation techniques in use today: Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS).

TMS elicits excitability changes in the underlying cortex via production of large, rapidly modulating magnetic pulses within a coil placed on the scalp to induce current in the underlying tissue. tDCS involves passing very small currents in the order of a few milliamps through the skull via two large electrodes placed on the scalp. Typically, tDCS currents are passed continuously for between 10 and 20 minutes. Although both techniques have an important potential role in clinical studies, tDCS has a number of practical advantages as a prospective rehabilitation tool in that it is well tolerated, relatively easy to administer and portable. In addition, although the neurophysiological effects of tDCS and TMS are similar, their mechanisms of action are at a cortical level, and therefore their potential effects in patients, are likely to be distinct. For these reasons this review will concentrate mainly on tDCS; for a wider review of the potential of TMS in the stroke population see Hummel & Cohen (2006).<sup>1</sup>

The effects of tDCS are polarity dependent. Anodal stimulation, when the current is flowing from the active electrode over the motor cortex to the reference, is facilitatory whereas cathodal stimulation, where the current flow is in the other direction, is inhibitory.<sup>2</sup> The effects on cortical excitability outlast the stimulation period by up to 90 minutes, dependent on the duration of the stimulation applied. Because of the potential of tDCS to robustly modulate cortical excitability the technique is attracting interest as a potential tool for neurorehabilitation, particularly in the context of chronic stroke.

Neuroimaging studies suggest that patients with impairments of their hand function after stroke demonstrate increased activity in the motor areas within the intact hemisphere when moving their paretic hand compared with con-

trols.<sup>3</sup> This contralesional activity is greatest in patients who have made a poor recovery; patients who have made a good recovery show a more lateralised activity pattern closer to that of healthy controls.<sup>4</sup> In addition, poorly recovered patients exhibit abnormally high levels of inter-hemispheric inhibition between the two motor cortices,<sup>5</sup> suggesting that the intact hemisphere may be exerting a pathological level of inhibition on the stroke-damaged hemisphere. This idea of an "inter-hemispheric imbalance" between the two motor cortices has prompted the use of transcranial stimulation in these patients to try and "rebalance" the hemispheres, either by facilitating the affected hemisphere, or inhibiting or down-regulating the unaffected hemisphere.

Both these approaches have been shown to improve motor function in the affected hand in a clinically relevant task,<sup>6,7</sup> and a recent study has demonstrated that tDCS is capable of shifting the inter-hemispheric balance of motor-related activation in healthy controls,<sup>8</sup> suggesting this "rebalancing" as a putative mechanism for observed behavioural improvements. However, the functional improvements in patients were short-lived, lasting less than one hour before the patients' performance returned to baseline.

For this reason, there remain a number of questions to be answered before transcranial stimulation paradigms can be used as adjuncts to rehabilitation in clinical practice: in particular whether the duration of effects of stimulation can be increased; whether this model of inter-hemispheric imbalance holds true for the wider clinical population and whether the magnitude of the effects would be increased if stimulation was applied in the acute or sub-acute period.

## Duration of after-effects

An increasing body of evidence suggests that tDCS modulates both the GABA and glutamatergic systems.<sup>9,10,11</sup> This observation raises the possibility that synaptic modulation occurs with tDCS, and as a result that longer-term modifications in cortical excitability, and consequently behaviour, may be possible if the correct stimulation parameters are used. There is evidence from the animal literature to suggest that in neocortical slice preparations, repeated stimulation sessions are

often required to elicit long-lasting excitability changes.<sup>12</sup> Although the stimulation parameters used in these studies are clearly far removed from those used in humans, a recent study in healthy controls has suggested that the use of repeated stimulation sessions may be a powerful approach. Reis and colleagues investigated the effects of five daily sessions of tDCS paired with a visuo-motor learning task, and demonstrated residual improvements in task performance with tDCS which outlasted the stimulation period by more than 90 days.<sup>13</sup> Similar effects have yet to be established in the chronic stroke population, but this study suggests the potential of such an approach.

### Inter-hemispheric Imbalance

A number of studies have demonstrated that down-regulating the unaffected hemisphere using either tDCS or TMS leads to improvements in motor function in patients.<sup>1</sup> However, it is important to note that the patients included in these studies were highly selected for their relatively good recovery and small, sub-cortical strokes. In patients with more extensive or cortical strokes, or in those who have not made such a good recovery, there is increasing evidence that the activity within the unaffected hemisphere may be playing a helpful, rather than a pathological, role.<sup>14,15,16</sup> If transcranial stimulation is to be used as an aid to rehabilitation, then the question of how best to target stimulation must be addressed for the wider population of patients. An algorithm has been proposed based on baseline MRI and neurophysiological characteristics to differentiate between patients who might benefit from therapy targeted to their affected hemisphere and those who might

benefit from approaches designed to increase activity in the unaffected hemisphere.<sup>17</sup> This differentiation will become of primary importance if transcranial stimulation approaches become more widely used.

### Acute and sub-acute settings

It seems an attractive idea that, if transcranial stimulation can modulate behaviour in the chronic phase of stroke recovery, then it may have even more powerful effects in improving behaviour in the days or weeks following the stroke, when the brain is undergoing massive adaptation and reorganisation. Caution has been applied in this approach for two major reasons: a concern over potential behavioural effects and fears over the safety of the intervention.

In healthy controls the effects of tDCS depend on the background activity of the cortex. If anodal, facilitatory tDCS is applied synchronously with a motor task subjects' performance of that task improves.<sup>18</sup> However, if the stimulation is applied before the task, performance is unchanged.<sup>19</sup> The concept of the effects of a stimulation paradigm being dependent on prior activity within the cortex is in line with the theory of homeostatic plasticity, a regulatory mechanism postulated to stabilise neuronal activity within a useful dynamic range.<sup>20,21</sup> Homeostatic theory might therefore suggest that the effects of transcranial stimulation will differ between patients with concurrent cortical reorganisation and chronic patients. However, in contrast, a therapeutic trial of facilitatory, 3Hz rTMS for 10 days in the acute period, combined with rehabilitation, led to improvements over and above the control condition for a year after stimula-

tion,<sup>22,23</sup> suggesting that beneficial effects can be achieved with stimulation in the acute phase. Similar effects of tDCS in the acute phase have not been demonstrated, but a large, multi-centre trial is currently underway to investigate the potential of the technique in this setting (<http://clinicaltrials.gov/ct2/show/NCT00909714>).

As with the use of transcranial stimulation in any setting, potential safety has been a concern. Both tDCS and TMS have the potential to induce seizures, although they are now extremely rare as subjects at an increased risk of seizures are excluded from studies.<sup>24</sup> However, in a population where cortical excitability is already increased, seizure risk may also be increased, especially if repeated sessions or high doses of stimulation are used. A number of TMS studies have been performed in the acute and sub-acute phases of stroke, none of which reported any adverse events,<sup>24</sup> suggesting that, for selected patients at least, the procedure is safe. However, as with any novel intervention, adverse event reporting must continue to occur and it will be some time before a full safety profile can be determined.

### Summary & Conclusions

Transcranial stimulation paradigms are well-tolerated by patients and induce clinically relevant, albeit short-lived, behavioural improvements. Because of these promising effects in proof-of-principle studies the full potential of transcranial stimulation as a rehabilitation intervention is currently being actively explored by research groups world-wide. It is to be hoped that the results from these studies will allow a more complete understanding of the possible role of transcranial stimulation in

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# Neurological Aspects of Sellar and Parasellar Tumours



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## Introduction

Pathology in the sellar and parasellar regions accounts for several disabling and distinctive neurological syndromes characterised by visual failure and upper cranial neuropathies. These features have a major impact on functional outcome and can be more intrusive for the patient than the commonly associated endocrine morbidity.

Recent advances in this field include the emphasis on multidisciplinary team (MDT) working, skull base endoscopy and stereotactic radiation therapy. This paper summarises the presentation, treatment and prognosis of sellar and parasellar lesions with particular reference to their neurological presentation and outcome.

## The optic nerves and chiasm

Sellar and parasellar lesions commonly cause loss of visual acuity and visual field defects. Visual acuity tends to be progressively impaired in chiasmal or optic nerve compression; ultimately optic atrophy from chronic compression occurs with associated disc cupping and pallor on ophthalmoscopy. The patterns of visual field defect caused by parasellar lesions have been of diagnostic value for well over a century, since visual field perimetry pre-dated X-ray as a diagnostic tool.<sup>1</sup> Visual fields still provide valuable information about visual function and a means of measuring the progress and outcome of treatment.

## Clinical Assessment

### Visual acuity and fields

Visual acuity is best measured with the LogMAR charts now standard in eye clinics. These have several advantages over the historically familiar Snellen chart, though the test is more time consuming. The scale is linear with equal increments of difficulty between the lines of characters, there are the same numbers of letters on each line, and the notation is a single figure which lends itself to statistical analysis. This is especially helpful for comparison of pre and postoperative patient groups.

Beside confrontational testing of the four quadrants of each eye with a red target can be useful for screening for field defects. Formal assessment requires the use of a binocular Esterman program (10dB stimulus intensity) on the Humphrey visual field analyser. It is important to establish whether patients with visual field defects are driving and advise them according to the criteria specified by law. In the UK the Driver and Vehicle Licencing Agency (DVLA) sets the requirements for safe driving, outlined in Table 1.<sup>2</sup>

## Features of visual impairment

Symmetrical chiasmal compression from an enlarging sellar lesion produces an upper temporal quadrantanopia progressing to a complete temporal hemianopia. Whilst an early upper quadrantic defect (Figure 1) from impaired inferior retinal fibres in the inferior chiasm often goes unnoticed, symptoms from a bitemporal hemianopia may cause involuntary collision with objects, sometimes when driving. The hemi-fields

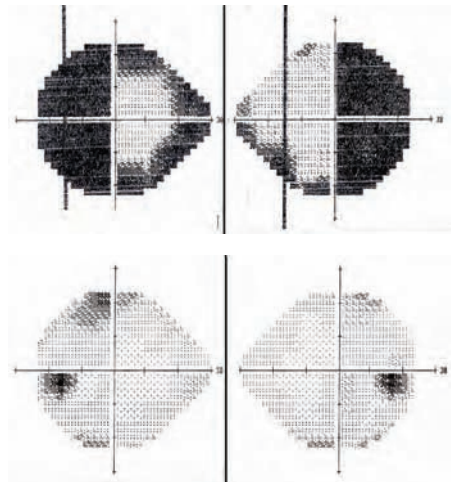


Figure 1a and 1b: Humphrey visual fields pre and postoperative.

affected are blank not black. The site of the lesion and the degree of pre or post-fixation of the chiasm with reference to the pituitary stalk, determine the scale of the defect. Preferential impairment of the inferior temporal quadrants implies superior chiasmal compression. Asymmetric lesions such as the case of neurosarcoidosis demonstrated in Figure 2 produce asymmetric field defects.

Other visual symptoms may develop because of dissociation of the two visual fields from lack of overlapping information, known as the hemi-slide phenomenon. This causes 'slippage' - the breaking up of a line of text when reading, or 'post-fixational blindness' which occurs when focussing on an object causes those behind it to disappear. This produces difficulty threading a needle, or the tendency to cut one's fork with the knife.<sup>3</sup>

The rate of deterioration of visual impairment may suggest the pathology. In pituitary apoplexy deterioration may develop over hours or even minutes. Malignant lesions may produce subacute deterioration whilst benign pathology such as

**Table 1 : DVLA guidelines with reference to visual fields and diplopia**

	<b>Group 1 (motor car ; motorcycle)</b>	<b>Group 2 (HGVs ; buses)</b>
<b>Visual field impairment</b>	Driving must cease unless confirmed able to meet recommended national guidelines:  The minimum field of vision for safe driving is defined as “a field of at least 120° on the horizontal measured using a target equivalent to the white Goldmann III4e settings. In addition, there should be no significant defect in the binocular field which encroaches within 20° of fixation above or below the horizontal meridian”	Normal binocular field of vision is required, i.e., any area of defect in a single eye is totally compensated for by the field of the other eye.
<b>Diplopia</b>	Cease driving on diagnosis. Resume driving on confirmation to the Licensing Authority that the diplopia is controlled by glasses or by a patch which the licence holder undertakes to wear while driving. (If patching, must meet additional requirements for monocularity). Exceptionally a stable uncorrected diplopia of 6 months' duration or more may be compatible with driving if there is consultant support indicating satisfactory functional adaptation.	Permanent refusal or revocation if insuperable diplopia. Patching is not acceptable.

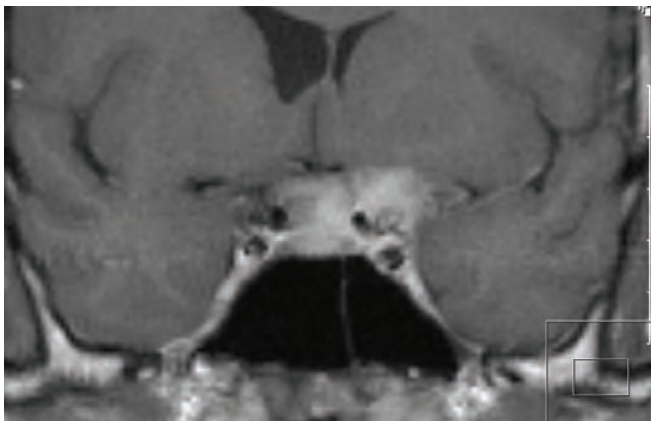


Figure 2: Coronal T1W + contrast. Neurosarcoidosis.

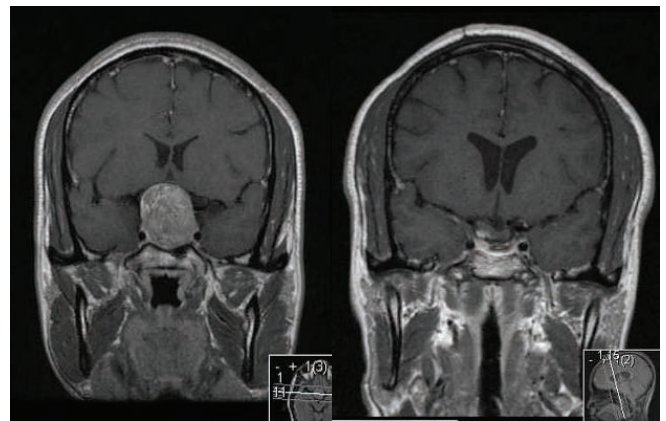


Figure 3a and b: Coronal MRI T1+Contrast. Pituitary adenoma pre and postoperative.

pituitary adenoma or meningioma may cause slow or imperceptible deterioration. Positive visual symptoms such as flashes of light can result from focal demyelination at the site of compression of the optic apparatus.<sup>3</sup>

#### External ocular movements

The III, IV and VI cranial nerves lie in the parasellar region. Careful examination is required to assess the integrity of these nerves. Eye movements are normally tested in a H-pattern. Movement of the globe in the horizontal plane is achieved by the medial rectus (adduction) and lateral rectus (abduction) muscles. The fully abducted globe enables isolation of superior rectus (elevation) and inferior rectus (depression) muscle action due to the anatomical location of the tendons of these muscles. Similarly, the adducted globe enables the superior oblique (depression) and inferior oblique (elevation) muscle function to be isolated.

#### Management

The management of sellar and parasellar lesions is dependent upon the pathology of the lesion. MRI scanning is very useful at determining the likely disease process.

#### Pituitary adenoma

Transsphenoidal surgery has an important role in the management of pituitary adenomas (Figure 3). The conventional transnasal transsphenoidal approach is undertaken via a submucosal tunnel adjacent to the nasal septum. The sphenoid sinus is opened enabling access to the pituitary fossa. The adenoma can usually be distinguished from the underlying gland by its soft, friable consistency. 72% of patients with macroadenomas had visual field defects with 58% having bitemporal hemi-

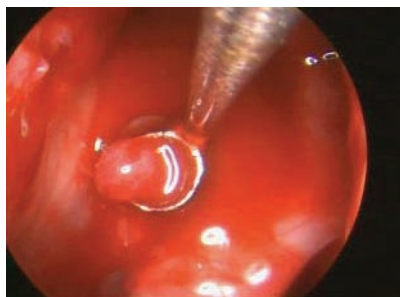


Figure 4 Endoscopic transsphenoidal view of removal of pituitary adenoma.

anopia and 8% a unilateral quadrantanopia in Ebersold's series.<sup>4</sup> The capsule of a pituitary adenoma compresses but does not invade the optic chiasm facilitating postoperative visual recovery (Figure 1). Of 289 patients reported by Mortini with impairments of fields or acuity, over 90% improved following surgery with 40.5% returning to normal at early follow-up.<sup>5</sup> Vision improved in 74.6% of Ebersold's patients at a median follow up of 73.4 months.<sup>4</sup> In Dekkers' cases, assessment at three months postoperatively showed 30% of patients had normalisation of visual fields and a further 60% had improved. Thereafter 36% showed further improvement in visual fields in the interval between three months and one year.<sup>6</sup> Data appear less favourable when assessing the prevalence of field defects in a population of previously operated adenoma patients. 162 patients (84%) out of 192 revision surgery patients had a residual visual defect.<sup>7</sup>

Skull base endoscopy for pituitary adenoma has gained rapid acceptance. This modification of the transsphenoidal route was developed by Jho in the USA and Cappabianca in Europe.<sup>8,9</sup> Direct transnasal access to the sphenoid sinus is achieved without a submucosal tunnel. The endoscope provides a wider angle of view than that afforded by the microscope (Figure 4). No differences in neurological outcome are yet evident between transsphenoidal microsurgery and an endoscopic approach but the enhanced view of the optic apparatus possible with the endoscope suggests that outcome might improve for more adherent and inaccessible lesions. Intra-operative MRI is likely to be a useful adjunct to achieving maximal resection in centres with this facility.<sup>10</sup>

Non-surgical treatment is successful in selected cases of macroadenoma with visual impairment, notably in prolactinoma where dopamine agonists

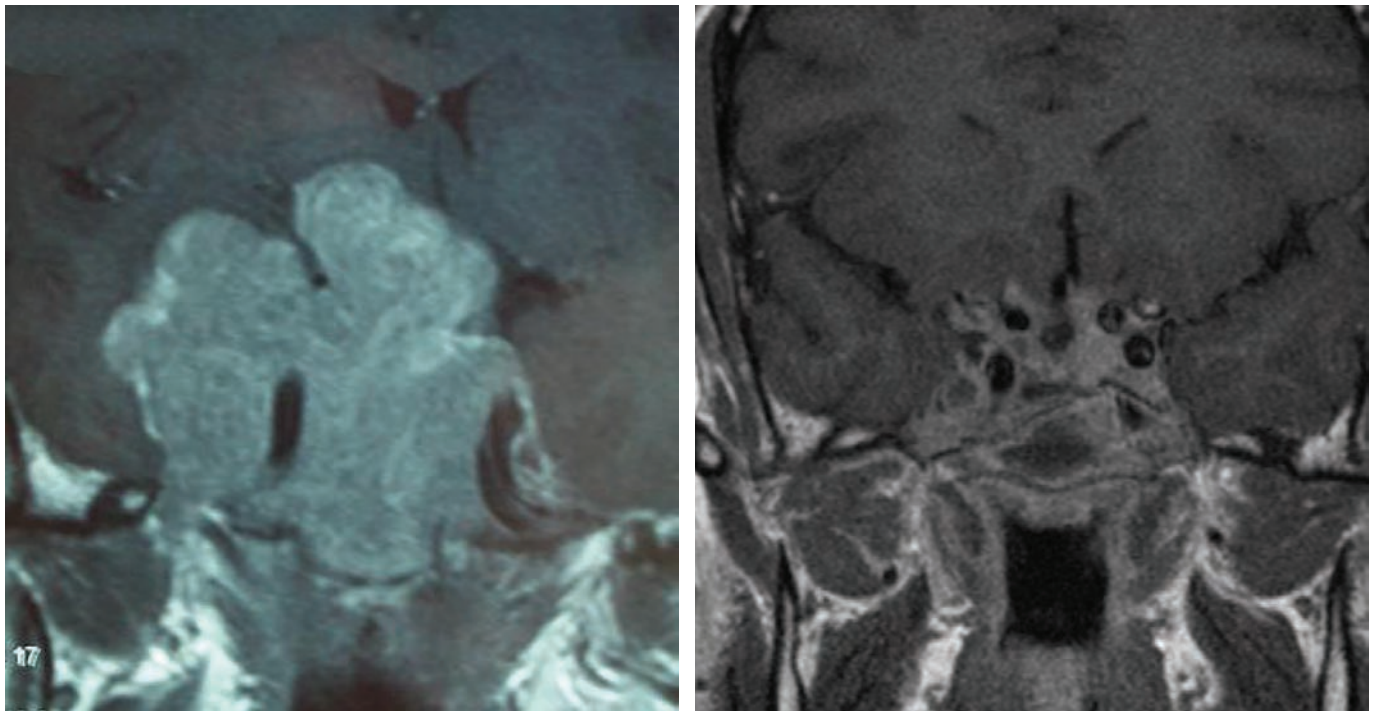


Figure 5a left: Coronal MRI T1+Contrast. Prolactinoma at presentation with a dense bitemporal hemianopia and prolactin level of 950 000 mIU/L. Figure 5b right: Same lesion after 7 months of treatment with Cabergoline.

(e.g. Cabergoline) produce visual improvement in addition to radiological shrinkage in 70% of cases (Figure 5).<sup>11</sup> Medical therapy is the treatment of choice in prolactinoma even with large tumours and those producing significant visual symptoms. Surgery can be reserved for drug-resistant cases or for cases of spontaneous cerebrospinal fluid rhinorrhoea which is an occasional complication of this treatment.

Surgical removal remains the mainstay of therapy for non-functioning macroadenomas. The somatostatin analogue Octreotide produced visual improvement in a series of non-prolactinoma patients but the significant side effects of these drugs make surgery much more successful by comparison.<sup>12</sup>

Conventional 3-D conformal radiotherapy

(RT) is effective at reducing the recurrence rate after surgery. Breen reported that 87.5% of tumours were controlled at 10 years.<sup>13</sup> This is at the expense of complications, most notably a high incidence of new pituitary hormone deficits which increases over time.<sup>14</sup> A 2.5% incidence of second brain tumours at 20 years has been reported.<sup>15</sup> Optic neuropathy following radiotherapy is rare and is related to the dose received by the optic apparatus.<sup>16</sup>

Stereotactic radiosurgery (SRS) provides an alternative to conventional RT. The radiation dose is administered via a multi-field source such as the Gamma Knife, or a shaped beam LINAC system. Both modalities aim to deliver a very high dose to a highly conformal field reducing collateral damage. Advantages over

conventional RT include the theoretical possibility that the higher radiation dose might improve control of growth rate and the potential to spare normal functioning pituitary gland from subsequent hypopituitarism. Seventy-eight cases of residual or recurrent adenoma treated with SRS using the gamma knife were described by Petrovich.<sup>17</sup> Only 4% of 52 patients with normal pre-treatment hormone function developed hypopituitarism, but follow-up was limited to a mean of 41 months. Reduction or stability of tumour volume was achieved in all the non-functioning adenomas.

For tumours that lie in very close proximity to the optic apparatus, SRS may cause radiation-induced visual impairment. To minimise the injury to such “organs at risk” a hypo-fractionat-

**Table 2: Summary of management of pituitary apoplexy**

<b>Clinical features</b>	Acute onset neurological symptoms and signs e.g. bitemporal field defect, possible diplopia or ptosis in a patient with haemorrhage or necrosis in a surgically proven pituitary adenoma. <sup>41</sup> Hypopituitarism present in 74%. <sup>22</sup>
<b>Investigations</b>	
Radiology	<b>CT Brain.</b> Expanded sella with haemorrhage. Possible associated SAH <b>MRI Brain.</b> More sensitive for diagnosis than CT. <sup>20</sup>
Endocrine assessment	Cortisol measurement prior to commencing Hydrocortisone - 9am measurement if possible. Subsequent short synacthen test or ITT, TSH; Free T4; LH; FSH; prolactin; IGF-1; testosterone / oestradiol. <sup>20</sup>
Visual assessment	Visual acuity; Clinical field assessment; Humphrey visual fields if well enough.
<b>Treatment</b>	Resuscitation: Correct hypotension and hypoxia; i.v. steroid therapy; other endocrine replacement where indicated.
	Consider transphenoidal surgery in presence of significant or progressive visual failure with or without visual motor deficit. Emergency surgery rarely required.
	Consider conservative management in moderate visual impairment if stable or improving, or when symptoms limited to visual motor deficits.
<b>Late management</b>	Endocrine re-assessment after the acute phase + hormone replacement where indicated
	MRI at 3 months in all cases. Some tumours may involute. <sup>20</sup>
	Consider late surgery in conservatively managed cases with residual symptoms or tumour; possible role for radiotherapy.



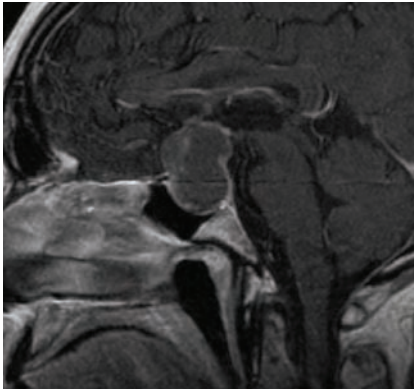


Figure 6: Sagittal T1W MRI + contrast. Pituitary Apoplexy presenting with sudden onset of bitemporal field defect, impaired acuity and partial right third nerve palsy.

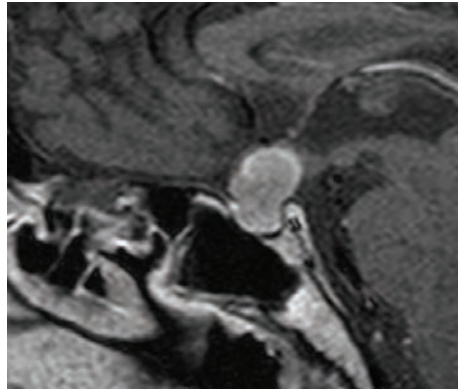


Figure 7: Sagittal T1W MRI + contrast. Rathke's cleft cyst.

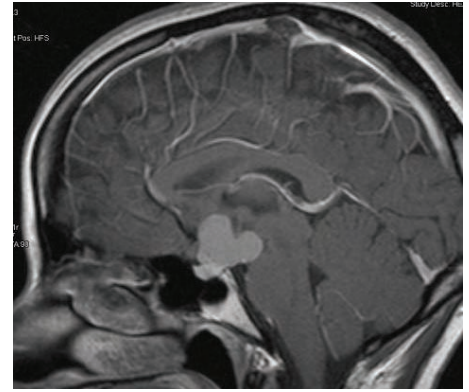


Figure 8: Sagittal T1W MRI + contrast. Craniopharyngioma.

ed regime of stereotactic radiotherapy using a re-locatable frame is gaining credence.

Best current practice is to optimise surgical resection with a view to avoiding adjuvant radiotherapy. Postoperative MRI and endocrine assessment is then performed to plan treatment of any residual tumour and to detect asymptomatic recurrence during long-term follow-up in the multi-disciplinary clinic.

**Pituitary apoplexy** (Figure 6 and Table 2) is a rare but clinically important subgroup of pituitary adenoma, comprising 2.9% of McFadzean's series.<sup>18</sup> Pituitary apoplexy is a syndrome of haemorrhage or infarction within a pituitary adenoma and usually presents acutely, although a subacute presentation is sometimes seen and the diagnosis may be made in retrospect. The symptoms overlap with those of subarachnoid haemorrhage, which may be present in severe cases.<sup>19</sup> At presentation the responsible pituitary adenoma is unsuspected in the majority of patients. Precipitating factors such as major illness, surgery, conditions that impair or acutely enhance blood flow to the gland, dynamic endocrine testing and coagulation abnormalities have been noted in 40% of patients.<sup>20,21</sup>

Surgery should always be considered since

field defects and diplopia are both disabling conditions and swift relief of elevated intracapsular pressure should minimise them. However, authors differ in their emphasis on surgical management. Semple et al. recommend emergency surgery when there is deteriorating vision, sudden onset of blindness, or diminished level of consciousness.<sup>22</sup> Surgery within the first week may yield better outcomes than surgery at a later time point.<sup>23,24</sup> Other authors report successful non-surgical treatment in selected cases.<sup>20,25</sup> Indeed, visual motor deficits have a favourable outcome, whether treated conservatively or with surgery.<sup>22</sup> As with elective adenomas, patients rendered blind by the condition do poorly even with an operation.<sup>22</sup> In the absence of any clinical trials, this author recommends urgent decompression in a patient with significant or progressive visual impairment with or without a visual motor deficit.

**Rathke's cleft cyst** (Figure 7) is a common abnormality arising from remnants of the craniopharyngeal duct. It is non-neoplastic but cystic enlargement can occur, causing visual and endocrine symptoms.<sup>26</sup> As with adenoma, the cyst compresses the visual apparatus without invasion or adherence, and surgical removal, usually via a transsphenoidal route, is associated

with a favourable visual outcome. El-Mahdy found that visual acuity recovered in 66.6% of eyes and field defects recovered in 68% of eyes.<sup>26</sup> Belleci reported complete recovery of vision in seven patients. Favourable results are also seen in simple or arachnoid cysts of the pituitary region.<sup>27</sup>

**Craniopharyngioma** (Figure 8) is an epithelial tumour derived from Rathke's pouch epithelium. Presentation with impaired visual acuity, frequently in association with features of hypopituitarism, is common.<sup>28</sup> Although non-malignant, the lesion has an intimate relationship with surrounding structures. The surgical approach is governed by the radiological appearances. Cyst drainage may be appropriate but is often associated with symptom recurrence and disease progression. Total, or subtotal resection, may be achieved by a transsphenoidal route but frequently a transcranial exposure is required.

In most series, microsurgical removal produces improvements in vision, but the morbidity in the post-operative cohort remains significant. Children tend to have a worse visual prognosis than adults. 39% of Abrams surgical series of 31 children had visual symptoms at presentation. 10% had acuity of less than 20/200 prior to

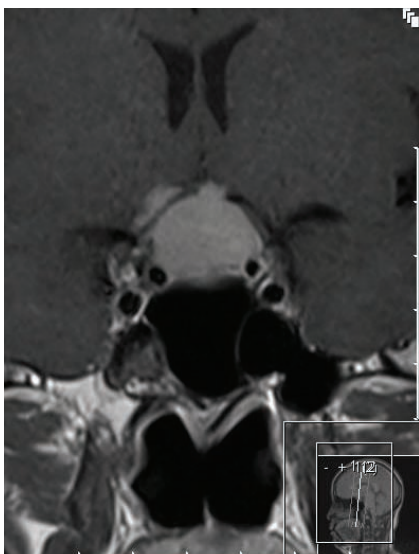


Figure 9: Coronal T1W MRI + contrast. Tuberculum sellae meningioma.

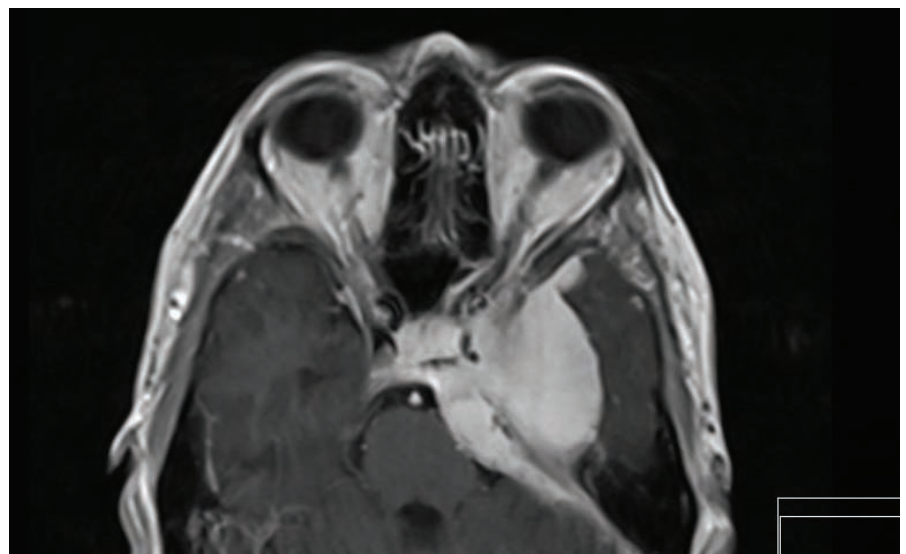


Figure 10: Axial T1W MRI + contrast. Extensive cavernous sinus meningioma with middle fossa and posterior fossa extension. 20y of left-sided visual failure, proptosis and intermittent left sided facial numbness.

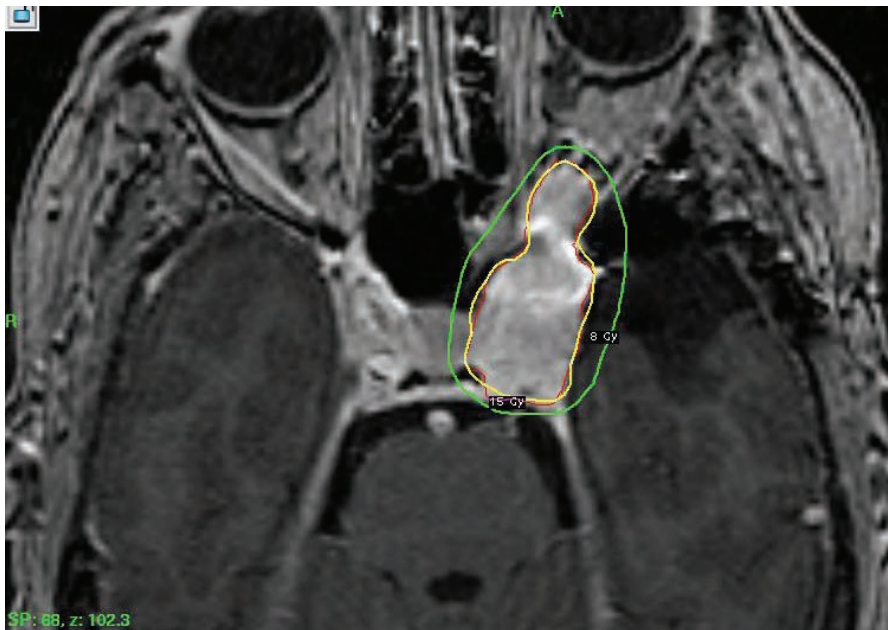


Figure 11: Radiosurgical plan for Gamma Knife treatment of cavernous sinus meningioma.

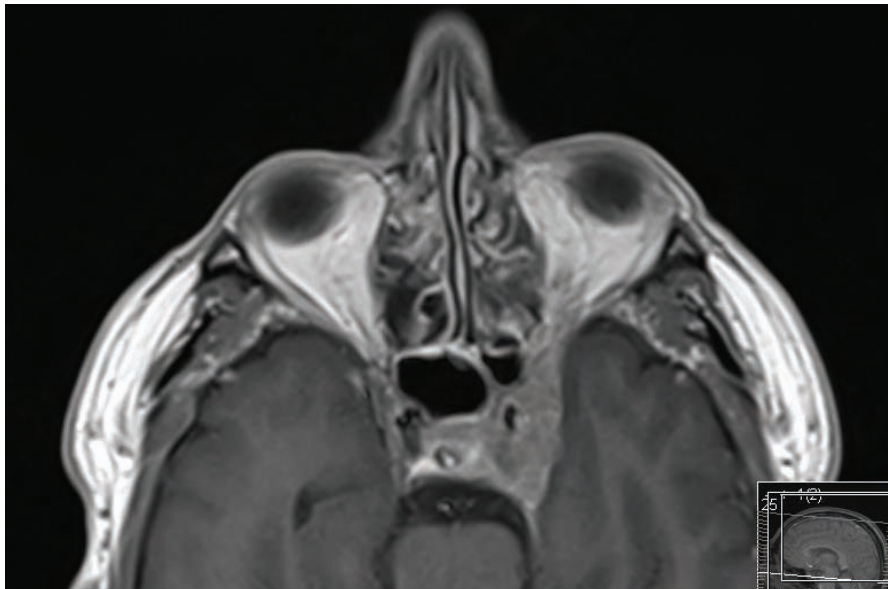


Figure 12: T1W MRI + contrast. Proptosis and left cavernous sinus lung metastasis with intraorbital extension.

surgery and this group increased to 26% following surgery, when 81% of eyes showed evidence of optic atrophy.<sup>29</sup> In a series of adults and children, 93% of patients had impairment of visual fields at presentation with post-operative improvement in 87%.<sup>28</sup> Yasargil noted visual improvement in 60% of cases.<sup>30</sup> Associated endocrine deficits are common at presentation and rarely improve after surgery. In addition, hyperphagia and weight gain due to hypothalamic dysfunction occur in 44% of cases and short-term memory impairment occurs in 5.8% of patients.<sup>28</sup> Radiotherapy is commonly used as an adjuvant therapy when residual disease is present.

**Meningioma** (Figure 9) of the suprasellar region commonly presents with impaired visual acuity, external ocular movement dysfunction,

ptosis and sometimes, pituitary dysfunction. The arachnoid plane around the optic nerves is often breached by tumour with direct involvement of the pial network of neural blood vessels. In advanced cases the optic nerves may be completely encased by tumour.<sup>31</sup> Microsurgical removal therefore presents significant risk to the vascularity of the nerves, and removal only produced improvement in visual acuity in 18% of Margalit's series. Visual acuity deteriorated in 20% and remained stable in 62% of cases.<sup>31</sup> Care is required in selecting the operative approach for sellar region meningiomas; good access to the plane between the optic apparatus and the tumour is imperative and this usually requires a subfrontal or pterional craniotomy. Extradural optic nerve decompression has been pro-

posed to optimise visual outcome.<sup>32</sup> Although total resection is the main objective of surgery, sub-total resection may be the best that can be achieved for extensive tumours. Stereotactic radiosurgery or radiotherapy is an appropriate postoperative treatment option in patients with residual or recurrent disease.

### The cavernous sinus region

The pattern of neurological symptoms from tumours of the cavernous sinus (CS) is different to those confined to the midline. Diplopia or ptosis may result from impairment of oculomotor, trochlear or abducent nerve function, and sensory loss in the upper two divisions of the trigeminal nerve territory can occur. The mandibular nerve is usually spared because of its inferior course via the foramen ovale. Facial pain, sometimes diagnosed as trigeminal neuralgia, can be a feature. Diplopia is a disabling condition that precludes driving and impacts significantly on quality of life (Table 1).

Pituitary adenomas often show extensive radiological CS involvement with little or no CS neurological deficit. The prolactinoma in Figure 5a produced a dense bitemporal hemianopia but no other cranial nerve symptoms. Yokoyama described 10 similar patients with no CS neurological symptoms.<sup>33</sup> This type of CS involvement does not predict an adverse prognosis for the tumour, and the most likely explanation for this pattern of growth may be weakness of the medial CS wall, rather than increased tumour aggressiveness.<sup>33</sup>

Cavernous sinus meningiomas have a high incidence of CS neurological deficits (figure 10). 23.5% of nerves III, IV and VI showed a deficit in 39 preoperative patients reported by O'Sullivan et al.<sup>34</sup> Associated visual failure and proptosis is common; 57% of Litre's series had reduced acuity and 30% had exophthalmos.<sup>35</sup> 39% of cases had impaired visual acuity in Abdel Aziz's series.<sup>36</sup>

Microsurgery to this region has been pioneered by Dolenc, using extensive extradural drilling to achieve exposure of the neurovascular contents.<sup>37</sup> Despite this, neurological outcome from surgery remains very disappointing, chiefly because of the intimate association of the cranial nerves with the tumour.<sup>38,39</sup> Seven out of 10 patients with normal preoperative oculomotor function developed a significant new permanent deficit, and only 2 of the 17 patients with preoperative dysfunction improved.<sup>34</sup>

Conservative management in the first instance is therefore a preferable option for CS meningiomas with minimal symptoms. Skull base meningiomas as a group are generally more benign in behaviour than their convexity counterparts,<sup>40</sup> and serial scanning can be performed whilst monitoring symptoms. This is also an attractive location for the use of SRS or SRT (Figure 11). Meningiomas treated in this way show good rates of tumour control with minimal neurovascular morbidity albeit without extended follow-up to date.<sup>35,36</sup>

Metastases to the skull base may present in

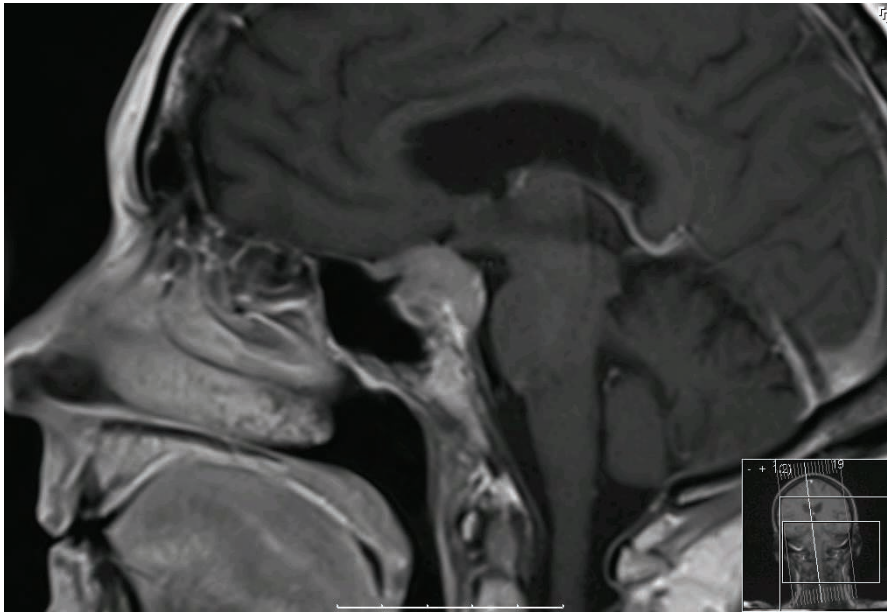


Figure 13: Sagittal T1W MRI + contrast. Sellar region metastasis; multiple myeloma.

the sellar and cavernous sinus regions (Figures 12 and 13). Symptom progression with multiple cranial nerve deficits is often rapid. Stereotactic radiosurgery may be an appropriate treatment option in such patients.

### Summary

Decision making for parasellar tumours of all types requires careful clinical, radiological and endocrine assessment. This is effectively undertaken in the context of the pituitary or skull base MDT where the required skills are available.

Surgery is an important treatment modality for parasellar tumours, especially for pituitary adenomas, where the visual prognosis following surgery is usually good. Craniopharyngioma can be cured by surgery but is associated with a guarded visual prognosis. Meningiomas exhibit complex relationships with the cranial nerves, therefore observation or incomplete resection with adjuvant treatments including SRS or SRT may be favoured. ♦

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# The Research Series

In this issue of the research series, we have addressed the topic that worries potential (and established) academics the most – funding. We have two articles from the biggest grant making agencies in the UK. John Williams is head of clinical activities at the Wellcome Trust. He has succinctly spelt out the range of grants available to clinicians at every stage of their career, from undergraduate to international researcher. In doing so, he has given us a road map to follow if we wish to travel towards academic independence and beyond.

Our second article is written by David Cox, deputy director of the Research Faculty at the National Institute of Health Research (NIHR).

The NIHR is only three years old, but it has already had an enormous impact on researchers and research alike. David has mapped out a framework for NIHR activity, which stretches from establishing an infrastructure for research in the NHS to the mentoring of trainees. Along the way he has explained the NIHR's philosophy and detailed what they look for in those all important grant applications! I hope that these articles go some way towards allaying your fears and provide you with the information you need to pursue or continue your academic aspirations. ♦

Boyd Ghosh, *Series Editor.*



## 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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### 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

## Researchers Find Some Wellcome Support



### Dr John Williams

Dr John Williams trained initially as a neuroscientist at the National Institute for Medical Research, London. Postdoctoral training followed at Stanford and Duke. In 1998 he changed direction and embarked on a career in science administration when he joined the Wellcome Trust. He has held a number of roles within the organisation. He is currently Head of Clinical Activities and Head of Neuroscience and Mental Health.

The Wellcome trust is a large charitable organisation founded by Sir Henry Wellcome to advance medical research. As part of this goal, we seek to encourage clinicians to carry out medical research. We endeavour to provide schemes at every stage of a clinician's career to facilitate this (Figure 1).

### Medical students

We believe that it is never too early to encourage an enquiring mind. We provide elective grants to enable students to carry out research at recognised research centres. Students apply through their medical school and if successful are given funding for no less than four weeks.

### Graduate students

At any stage of their career, from medical student to newly qualified CCST, Wellcome aims to encourage and support clinicians to carry out research towards a PhD. This is usually achieved in one of two ways. Clinicians can apply for a personal research fellowship, where a grant is allocated to them for their research at a particular centre. This is the usual method of funding which most people are familiar with. The best vehicle for this is as part of an academic clinical fellowship, academic foundation programme or an MB/PhD programme.<sup>1,2</sup> These programmes provide the researchers with time and funding so that they can develop their research question before applying for a research training fellowship.

The second method involves applying directly to a Wellcome research centre for a 3-4 year PhD programme. One of the problems of personal fellowships is that they often rely on a chance encounter between a keen student and a suitable supervisor. In a Wellcome research programme, students work at an internationally recognised centre and will have the assurance that they have the very best opportunities for their research. Students are deliberately recruited in cohorts to foster a team spirit. Successful applicants select their supervisor themselves and are encouraged to think "outside the box" when deciding their field of research. While different centres vary, most have a slightly lengthened course between three and four years and some have an initial "immersion" experience to provide students with as much exposure to different fields as possible early on.

In both scenarios, we look for people who have established at an early stage that they have an enquiring mind and have the potential to carry out research. We would be looking for people who have carried out research in special study modules or electives and gained distinctions and prizes during their degree. They would normally have graduated with honours and obtained prestigious jobs with academic institutions during their career.

### Post doctoral level

There are competing priorities for clinicians at this stage. They must develop their clinical skills, in

order to obtain their specialist qualifications, but at the same time remain competitive in their chosen field of research. We have a number of schemes to help researchers manage these different priorities.

For those who have carried out an MB/PhD, there is the MB/PhD post-doctoral programme. This gives the opportunity to have a graduated entry to clinical work. Fellows are funded for 100% research for a year or two and then typically 50% and 25% in subsequent years. Funding is sometimes available to pay for a research assistant to continue with research while the clinician is receiving their clinical training.

Researchers in specialist clinical training would usually apply for a clinical lecturer post. This is an NIHR funded post, described by Chris Butler in the last issue. It allows applicants to develop ideas for the next stage of their research and to acquire pilot data for their next substantial application for funds. These posts do not usually carry any money for consumables. Wellcome, through the Academy of Medical Sciences, provides grants for £30,000 to help with research costs.

### Clinician scientist

The clinician scientist stage is a concept developed from a report by Sir John Savill<sup>3</sup> for the academy of medical sciences. This report highlighted the difficulty faced by clinicians trying to gain clinical and research independence. Clinician scientist awards, which are available through a range of different funders, enable fellows to carry out up to 40% clinical work in order for them to qualify for their CCST. The award available from Wellcome is for a period of five years and includes funds for research assistants and larger items of equipment. Applicants for this stage should have already shown promise in their early research career, with at least one substantial first-authored paper in an influential journal. These awards are designed to enable clinicians to complete their higher clinical training to CCST. If clinicians only have a year to go before completion of CCST, then we have a truncated version called an intermediate fellowship. This is for a period of up to four years.

### Post clinician scientist

Researchers who have graduated through the clinician scientist stage have received the very best training and will have achieved independence in both clinical and academic fields. They are usually highly sought after for tenured posts in academic departments or substantive NHS posts with ring-fenced research time. However academics who are not tenured or in NHS posts can apply for senior research fellowships. These are highly prestigious personal fellowships for five years with funds allocated for research expenses and assistants. These fellowships can be renewed for a further five years on the understanding that the department funds 50% of the applicants salary.

Academic clinicians can also apply for project or programme grants. A project grant is aimed at those at clinician scientist stage and higher and can be sought by an individual or a group of researchers. They are intend-

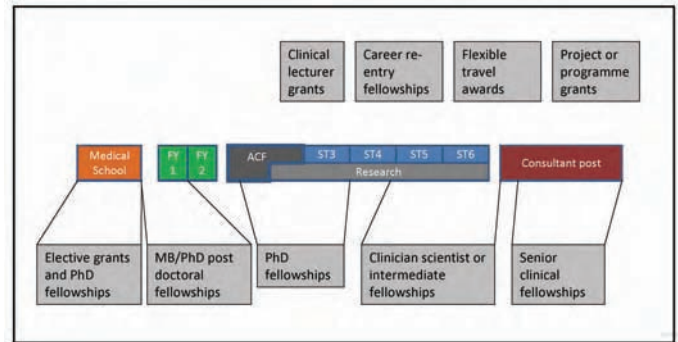


Figure 1: A summary of grants available throughout a clinician's career. Fellowships for particular stages are detailed below and grants available at a number of different points are shown above. FY is foundation year; ACF academic clinical fellowship; ST specialist trainee. Details of all the awards are in the article or at <http://www.wellcome.ac.uk/Funding/Biomedical-science/index.htm>

ed to facilitate investigation in a particular area. The larger programme grant is intended to provide independence to the academic. It enables them to pursue lines of enquiry as they occur without needing to frequently apply for more funds and is therefore intended for only the most experienced individuals with a strong track record of research success.

### Other grants

To enable researchers who have taken a career break of a few years to return to an academic career, Wellcome provide career re-entry fellowships. This is tenable for two to four years and includes funds for training and research consumables.

Flexible travel awards are available to clinicians to obtain experience or skills in fields outside their own. This may be in an emerging aspect of their own field or an interdisciplinary subject. Funds cover travel and research consumables as well as course fees if appropriate. ♦

### References and further reading

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2. Dr Geraint Fuller "Doing research in the post MMC world" ACNR 2009;9(4):33-4 available at [http://www.acnr.co.uk/SO09/ACNRSO09\\_research.pdf](http://www.acnr.co.uk/SO09/ACNRSO09_research.pdf)
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Details of grants are available at the Wellcome Trust website on <http://www.wellcome.ac.uk/Funding/Biomedical-science/index.htm>

# Embedding Research in the NHS Culture



### Dr David Cox

is Deputy Director – Research Faculty, in the Research & Development Directorate of the Department of Health. He joined the Department in October 2008 after working in a variety of research management roles at the MRC. Before that he spent a decade as a neuroscientist.

### The historical perspective

The National Institute for Health Research (NIHR) was established in April 2006 to carry forward the vision, mission and goals outlined in the Government's health research strategy for England: Best Research for Best Health.<sup>1</sup> NIHR's remit is to create a health research system in which the NHS supports outstanding individuals, working in world class facilities, conducting leading edge research focused on the needs of patients and the public.

In order to achieve this, the Institute has developed a health research system that is integrated with the nation's health system, and is based on four main work elements (Figure 1):

1. NIHR Faculty: supporting the individuals carrying out and participating in research
2. NIHR Research: funding research that aims to improve NHS health and social care services
3. NIHR Infrastructure: providing the support and facilities for a thriving research environment
4. NIHR Systems: working with partners to

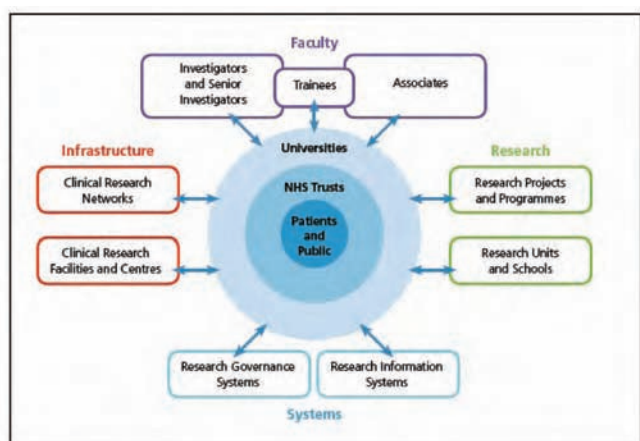


Figure 1: The four main work strands of the National Institute for Health Research (NIHR).

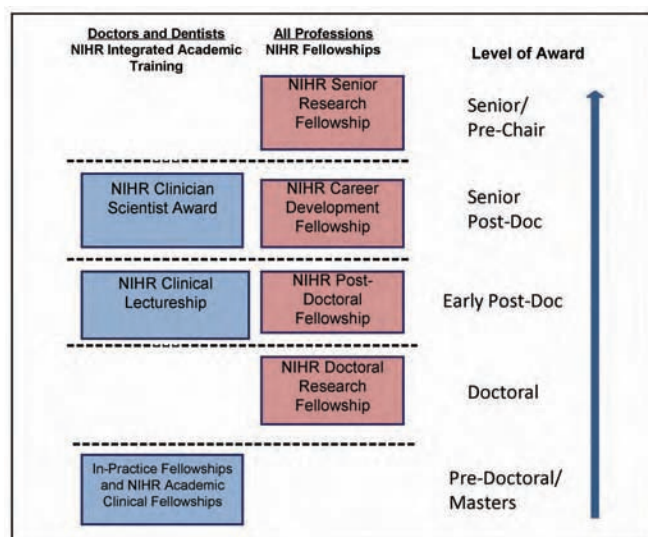


Figure 2: NIHR Research Career Pathways.

strengthen research governance, and to streamline the procedures underpinning research. NIHR infrastructure and systems facilitate research and research led outcomes in the UK. They work in the background to ensure that research is streamlined and efficient. For example,

1. NIHR was a leading organisation behind the inception of the Integrated Research Application System (IRAS) which is a one-stop portal for providing the information needed to secure ethical and other approvals for research.
2. The NIHR Clinical Research Networks are facilitating the participation of patients and health professionals in clinical trials, in part through allocation of funding for service support for research; and
3. The NIHR coordinated system for gaining NHS permissions (NIHR CSP) facilitates multicentre trials by reducing duplication in the NHS review process.

We believe that Infrastructure and Systems are pivotal to the research community in the UK. However, this article concentrates on the aspects of NIHR which are of more direct concern to individual researchers in Neurology, namely NIHR Faculty and Research.

### NIHR Faculty

The aim of the NIHR Faculty is to create a vibrant community of outstanding individuals exchanging ideas about research and innovation that will improve health and well-being. All members of the research community whose salary is supported, at least in part, by the

NIHR or Department of Health Policy Research Programme (PRP) and who are employed or are students in the NHS or a UK University, are eligible to join the NIHR Faculty.

The Faculty is made up of three main categories of members: Trainees, who undertake research training and career development funded by NIHR; Associates who support research programmes led by others; and Investigators who are independent researchers conducting NIHR research programmes. Investigators are eligible to apply for the position of NIHR Senior Investigator. This is a prestigious position, achieved through tough competitions that are run annually. Each award is accompanied by a \$15,000 personal discretionary research fund. Senior investigators form an NIHR college, which provides leadership to the NIHR Faculty.

The Faculty aims to support members in several ways:

1. Funding training and career development
2. Implementing research capacity building programmes
3. Offering mentoring and outreach support for NIHR Trainees
4. Supporting the development of present and future leaders of clinical and applied health research
5. Running events such as conferences, meetings and summer schools
6. Sponsoring collaborative working through the NIHR Portal
7. Working with partners to create better information about career paths and opportunities.

The NIHR has been developing research career pathways and building research capacity across the health care professions. Each year, the NIHR allocates and fully funds 250 Academic Clinical Fellowships (ACFs) and 100 Clinical Lectureships (CLs) within the integrated academic training pathway for doctors and dentists. We have been working with the Chief Nursing Officer and the Chief Scientific Officer to create a similar clinical academic pathway for those seeking to combine research and clinical careers in nursing, midwifery, the allied health professions, and healthcare science.

We also have a series of personal training awards, open to all health professions, that cover the whole range of career stages from doctoral training to senior fellowship. The NIHR's schemes of most interest to neurologists are set out on Figure 2.

Neurologists will typically enter on a research career path through NIHR in two ways. Firstly, they can apply through a Deanery for an ACF, which enables trainees to combine pre-doctoral research training in protected time, with continuing specialty training. Many ACFs will then go on to a 3 year Doctoral Research Fellowship (which might be supported by a number of research funders and is called by some a Clinical Research Training Fellowship) before returning to another joint research/clinical training post at post-doctoral, CL level. The most promising researchers then go on to a Clinician Scientist Award. The ACF and CL posts have already been discussed in detail by Geraint Fuller and Chris Butler in previous issues of ACNR. However, award of an ACF should put the individual neurologist into a strong position when applying for a personal doctoral fellowship, either through NIHR or another grant making body.

NIHR Fellowship Scheme (These are Personal Awards and apply to ALL professions)			
Name of award	Level	Who for (all professions)	Brief details at 2009
Doctoral Research Fellowship	Doctoral	To register or already registered for PhD for less than 12 months	3 yr FT salary or PT(75%,60% 4 or 5 yr) + research costs. Also training and development costs
Postdoctoral Research Fellowship	Early Post-Doc	Less than 3 years Post Doctoral experience	3 yr FT salary or PT(75%,60% 4 or 5 yr) + research costs. Also training and development costs
Career Development Fellowship	Senior Post-Doc	Less than 7 years Post Doctoral experience	3 yr FT salary or PT(75%,60% 4 or 5 yr) + research costs. Also training and development costs
Senior Research Fellowship	Pre-chair	With strong research track record	5yr FT salary or PT (75%,60%) + research costs. Also training and development costs
NIHR Integrated Academic Training (Integrating clinical training with research)			
Name of award	Level	Who for (Doctors, Dentists)	Brief details at 2009
Academic Clinical Fellowship	Pre-Doctoral	For Doctors + Dentists in speciality training	25% time spent in research salary costs. Max 3 yrs (or 4 for GP's)
Clinical Lectureship	Post-Doctoral	For those in speciality training, and qualified GPs, after gaining PhD	50% time spent in research. Max 4 years. Ends at CCT
Clinician Scientist	Senior Post-Doctoral	Registrars/GP/Dentists with PhD and reasonable research track record	5 years FT salary plus research costs (can be PT 75% or 60%)

Figure 3: NIHR research funding applicable to Neurologists.

**Box 1: Characteristics of successful grant applications:**

- Proposals will be more successful if they address important research areas for the NHS, producing results likely to generate significant (and quantifiable) benefit for NHS patients within 3-5 years of the end of the funding period.
- Proposals should have clearly articulated, relevant and engaging aims and objectives, each addressed by research strands whose methods are described in sufficient detail to enable the Selection Panel to judge their quality and feasibility.
- Proposals should be presented in a logical and coherent way, using appropriate sub-headings and keeping the use of jargon, abbreviations and acronyms to a minimum.
- Proposals should outline appropriate arrangements for patient and public involvement in research design, participation and evaluation stages.
- Proposals should clearly and realistically identify the major scientific, technical or organisational challenges associated with any research and outline how these challenges can be addressed.
- Proposals need to offer excellent value for money, where the requested resources are clearly justified and commensurate with the type and scale of the work proposed.
- Research team members should offer the necessary breadth and depth in all the methodological expertise required to deliver the proposed programme of work.
- For programme grants, research teams should have an excellent track record in applied health research, as indicated by publication output, previous research funding, and impact on health service practice and policy.

**Common reasons for unsuccessful applications:**

- They contain work that does not meet NIHR's stated definitions of applied health research or fail to demonstrate patient benefit within the relatively near future.
- A lack of appropriate multidisciplinary involvement in the research team, particularly the failure to include relevant experts in statistics, health economics, health service research etc. as applicants or, at the very least, named collaborators.
- Some lack sufficient depth of detail of the research methods, making it impossible to judge whether the proposed research is appropriately designed and feasible.

Alternatively, doctors or other health professionals with prior research experience who wish to concentrate on research can follow the personal fellowship route. This starts at the Doctoral Research Fellowship but can be entered at any stage (see figure 3). These fellowships cover salary and research costs. They are designed to allow career progression for trainees through increasing levels of independence until they are established as independent investigators. Fellowship proposals are investigator-led and there is no upper limit set for research costs, although the interviewing board scrutinises costs closely.

NIHR does not just offer financial support. Each year, the NIHR runs a major conference for NIHR trainees. These and other events are focused on different groups of members within the Faculty and, depending on the audience, cover research, training and more general policy issues. Faculty Trainees on the integrated academic training pathway are also offered mentoring, which is coordinated through the Academy of Medical Sciences and is a key part of our support for trainees. This will be discussed in more detail in the next issue of ACNR by the Academy themselves.

**NIHR Research**

NIHR funds a wide range of research via a number of different programmes. These are all listed in detail on the NIHR website given at the end. However, we have detailed some of those most relevant for neurologists involved in research.

Programme Grants for Applied Research are prestigious awards of up to £2m over a period of three to five years, directed towards leading researchers with impressive track-records of achievement in applied health research. Each programme funds a series of related projects, which form a coherent theme in an area of priority or need for the NHS.

The Research for Patient Benefit (RfPB) Programme is a national programme for high quality investigator-led research addressing issues of importance to the NHS. It funds research into everyday practice in the health service. Health service staff identify and develop proposals with appropriate academic input. All proposals must show evidence from systematic reviews to ensure patient safety and value for money.

The Invention for Innovation (i4i) Programme helps accelerate take-up of proven new treatments and devices by the NHS. The programme incorporates the Challenge Fund for Innovation, which promotes and accelerates knowledge transfer and innovation between the NIHR and the NHS.

The Research for Innovation, Speculation and Creativity (RISC)

Programme provides small, discrete grants for new speculative and radical health research proposals that could lead to a step change in the care and management of patients. RISC awards are intended particularly for speculative, novel proposals that are unlikely to gain support via traditional peer review processes.

The Health Technology Assessment (HTA) programme funds research to provide healthcare professionals, NHS managers, public and patients with the latest information on costs, effectiveness and impact of new developments in health technology. It commissions investigator-led clinical trials investigating issues of direct relevance to clinical practice in the NHS; primary research on the effectiveness of new technology through Technology Assessment Reviews for the National Institute for Health and Clinical Excellence (NICE); and clinical trials of importance to the NHS coordinated by the newly established NIHR Clinical Research Networks.

All applications are rigorously peer reviewed. NIHR only funds high quality peer-reviewed research clearly focused on creating benefit for patients in the NHS and those receiving social care services. Applications for research funding are more likely to be successful if they can demonstrate clear patient benefit, lead to efficiencies within the NHS, and involve patients and the public in the design and evaluation stages. Box 1 outlines key criteria for successful applications and common failings.

The NIHR has achieved a great deal in three years, as our latest progress report shows. The systems we have put in place are not just for academics working in university research departments. We are keen to support NHS clinicians – specialist consultants, hospital doctors, nurses, GPs and other health professionals. It is a key part of NIHR's remit to embed research as part of the NHS culture and ethos. Only then will we see continuous improvement in clinical practice – new solutions, better treatments, and ultimately healthier and happier patients. ♦

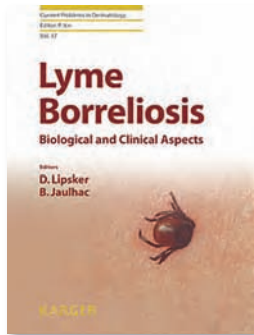
**Further Information**

1. Best research for best health – a new national health research strategy. Published by the department of health January 2006 available at: [www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4127127](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4127127)

Information about fellowships is available at: [www.nihrtcc.nhs.uk/](http://www.nihrtcc.nhs.uk/)  
More information about NIHR and its work can be found at [www.nihr.ac.uk](http://www.nihr.ac.uk)

# Lyme Borreliosis: Biological and Clinical Aspects

(Current Problems in Dermatology volume 37)



Editors: Lipsker D, Jaulhac B  
 Published by: Karger, 2009  
 ISBN: 978 3 8055 9114 0  
 Price: €153.50.

Reviewed by:  
 Nick Gutowski, Exeter.

This conveniently sized book is from the 'Current Problems in Dermatology' series. Cutaneous manifestations are the most frequent signs of Lyme disease. Despite the series title the book deals with all aspects of Lyme borreliosis, contributors come from the fields of microbiology, infectious diseases, neurology, rheumatology, internal medicine and dermatology. The book editors are from Strasbourg and the contributing chapter authors are from Continental Europe, therefore there is a European slant to the content, but adequate coverage of North American Lyme borreliosis. Lyme infection can easily be acquired outside the UK and then present to UK clinicians, therefore it is important to be aware of significant differences in disease expression between North American and European Lyme. There are also differences in manifestations between children and adults. There is one predominant species in North America and at least 4 pathological species in Europe, transmission to the host from the tick is not immediate but depends on the species (slower in North America) and does not always result in illness. Lyme borreliosis only occurs in the northern hemisphere.

The book is in two parts, the first part has six chapters and makes up the bulk of the book, 154 pages. The first five chapters cover in depth all aspects of Lyme and are entitled: *Borrelia burgdorferi* sensu lato diversity and pathogenicity; Life cycle and transmission of *Borrelia burgdorferi*; Epidemiology; Clinical manifestations and diagnosis of Lyme borreliosis; and Treatment and prevention of Lyme disease. The final sixth chapter in the first section 'Other tick borne diseases in Europe' lists these diseases. I found this chapter a little hard going, particularly the classification of all Rickettsioses.

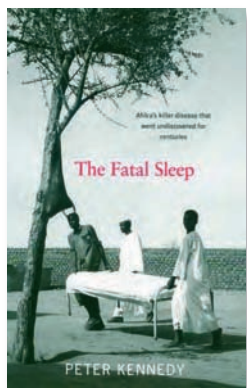
The second part of the book provides six short and very help-

ful discussion chapters on frequently asked questions about Lyme borreliosis. These are entitled: What should one do in case of a tick bite?; When is the best time to order a western blot and how should it be interpreted?; Is serological follow-up useful for patients with cutaneous Lyme borreliosis?; How do I manage tick bites and Lyme borreliosis in pregnant women?; What should be done in case of persistent symptoms after adequate antibiotic treatment for Lyme disease? (this latter question is a most vexing problem and assuming the diagnosis of Lyme is correct and there is no active infection, repeated courses of antibiotics are not recommended but emotional support and symptomatic treatment is indicated); and the final chapter: What are the indications for lumbar puncture in patients with Lyme disease?

Each book chapter has a helpful representative abstract at the beginning and is well referenced, inevitably there will be some newer references that are not quoted (I noticed one recent UK epidemiological study was absent) but reference coverage generally is good. There is some duplication in content between chapters but I found this helpful to reinforce points. It allows each chapter in some respects to be read as a 'stand alone', but see below regarding neuroborreliosis. There is a section of 8 colour figures, some composite, in the Clinical manifestations and diagnosis of Lyme borreliosis chapter, including borrelial lymphocytoma and acrodermatitis chronica atrophicans.

Overall the book is very readable and provides detailed information on Lyme borreliosis and can be considered as a reference of current knowledge. Those who want to read exclusively about neuroborreliosis will have to look through several chapters to extract all the information, inevitably there is some variation between information in each chapter. ♦

## The Fatal Sleep



Author: Kennedy P.  
 Published by: Luath Press Ltd, 2007.  
 ISBN: 978 1 9052 2267 4  
 Price: £20.00

Reviewed by:  
 Professor Tom Solomon,  
 Chair of Neurological Science and  
 Head of the Brain Infections Group,  
 University of Liverpool, UK.

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

Not for gentle slumber. It is not often that I take more than a year to write a book review, but this is no reflection on the book; if anything, it is the opposite. I had hoped Peter Kennedy's popular science book on African trypanosomiasis, *The Fatal Sleep*, would be good bedtime reading, expecting to read a chapter or two, and nod off into gentle slumber. But in fact the opposite was the case. After just a few pages I realised this was no bed-time book, and if I wasn't careful I would be gripped, and ruin the whole week. So I tucked it away, saving it for a holiday, when I could really enjoy it. And a rainy week in Edinburgh provided just such an occasion. Part autobiography, part historical novel, part travelogue, part encyclopaedia, part discursive thesis, *The Fatal Sleep* has a little bit of everything, and as such it is a great read. Mind you, given the subject matter, it would be hard for it to be otherwise. Sleeping sickness is one of those fascinating neurological infections that surely captures the imagination of every medical student: a slowly progressive parasitic disease, caused by the bite of a tsetse fly, that is invariably fatal if untreated, where the treatment seems to kill almost as many as it cures; a parasite where ecology, climate, economic, and political conditions contrive to make control almost impossible; a disease where even the name of the parasite itself, *Trypanosoma brucei* gambiense or rhodesiense, conjures up images of Scottish tropical medicine pioneer Sir David Bruce hacking his way through the jungles of the Gambia and Rhodesia to determine its cause; how could this be anything other than a fascinating condition?

In this book Kennedy draws us into his passion for this disease, and indeed for all of Africa itself. Describing first his medical student days at University College London, with the likes of Sir Lancelot Spratt, Kennedy describes the chance encounters that led

to his visits to Africa, and ultimately his involvement with trypanosomiasis; he describes with great accuracy his observations of patients, the need for better control of the vector and animal reservoirs, the challenges faced in establishing a mouse model, and how he hopes these will help with the development of new treatments. Kennedy makes compelling arguments about the need for further work in this area; with one third of Africa held captive by the tsetse fly, with few advances in diagnosis and treatment over the last century, and a treatment for neuroinvasive disease which kills a staggering one in twenty of those who receive it, few would argue with the fact that this is a neglected tropical disease. Thankfully with funding from the Bill and Melinda Gates Foundation, and heroic efforts from clinicians and scientists working in Africa, and support from *Medicine Sans Frontieres* things are beginning to move in the right direction, but there is a great deal to do.

Occasionally the book is a little idiosyncratic, but if anything this adds to the appeal: I am not sure I wanted to know the population of Tororo in Uganda, to the last man (402,621 – for those that do want to know!); but I particularly enjoyed Kennedy's "what on earth am I doing here?" moments, which all those who have worked in the tropics will recognise. In the foreword Kennedy worries whether lay readers will understand all the intricacies of the science. He needn't be concerned; even if they don't understand every word, they will certainly grasp the main messages. As for medical readers I think they will be delighted, charmed, horrified and fascinated in equal measure. And even if the book does nothing more than raise awareness among medics of this terrible problem, it will have achieved a great deal. ♦



To list your event in this diary, email brief details to John Gustar at [editorial@acnr.co.uk](mailto:editorial@acnr.co.uk) by 8th February, 2010.

# 2010

## JANUARY

### Development of the human neocortex

5-7 January 2010, Oxford, UK  
E. [g.j.clowry@ncl.ac.uk](mailto:g.j.clowry@ncl.ac.uk),  
[www.anatsoc.org.uk/events/  
event\\_details.php?id=115](http://www.anatsoc.org.uk/events/event_details.php?id=115)

**Clinical Reasoning courses with Linda Exelby**  
9-10 January, 2010; Kettering, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**Neuromusculo-skeletal Assessment and Treatment Course: Back to Basics with Andrea Hemingway: The Upper Limb**  
9-10 Jan, 2010; Manchester, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**Neurodynamic Assessment & Treatment of the Upper Limb Evening Workshops**  
12 & 19 January; Rochdale, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**Cognitive Rehabilitation Workshop**  
15-16 January, 2010; Gatwick Airport, London, UK  
E. [enquiries@braintretraining.co.uk](mailto:enquiries@braintretraining.co.uk)  
[www.braintretraining.co.uk](http://www.braintretraining.co.uk)

**Acupuncture Evening Workshop: Treating the Lumbar Spine and Hip Region**  
21 January, 2010; London, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**RCN Forensic Nursing Conference**  
21 January, 2010; London, UK  
[www.rcn.org.uk/events](http://www.rcn.org.uk/events)

**Preview of Critical Care Ward**  
21 January, 2010; South Newton, UK  
T. 01722 741801  
E. [marketing@glensidemanager.co.uk](mailto:marketing@glensidemanager.co.uk)

**Effective Exercise Prescription for Neck Pain Evening Lecture with Shaun O'Leary**  
21 Jan, 2010; London, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**Advances in Chronic Pain Management**  
21-22 January, 2010; London, UK  
T. 020 7501 6768,  
E. [lisa.freeman@markallengroup.com](mailto:lisa.freeman@markallengroup.com)

**7th British Skull Base Society Meeting**  
21-22 January, 2010; Sheffield, UK  
T. +44 (0)7808 716121  
E. [aynsley.pix@bbsraun.com](mailto:aynsley.pix@bbsraun.com)  
[www.aesculap-academia.co.uk](http://www.aesculap-academia.co.uk)

**Acupuncture Evening Workshops Treating the Lumbar Spine and Hip Region**  
21 January, 2010; London, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**3rd European Neurological Conference on Clinical Practices: Neurovascular and Neurodegenerative Diseases**  
22-24 January, 2010; Bucharest, Romania  
T. 33 0 153 644 489,  
E. [alexandra.quetard@discovery-cascade.com](mailto:alexandra.quetard@discovery-cascade.com)

**RCN Rheumatology Conference**  
25 January, 2010; Brighton, UK  
[www.rcn.org.uk/events](http://www.rcn.org.uk/events)

**International Symposium on Protein Phosphorylation in Neurodegenerative Diseases**  
28-30 January 2010; Valencia, Spain  
E. [catedrasg@cac.es](mailto:catedrasg@cac.es)  
[www.fundacioncac.es/catedrasg](http://www.fundacioncac.es/catedrasg)

**OZC – Phototherapy**  
29 January, 2010; Ely, UK  
T. 01353 652173  
E. [Rachel.everett@ozc.nhs.uk](mailto:Rachel.everett@ozc.nhs.uk)

**How to do Cognitive Rehabilitation**  
30 January, 2010; Gatwick Airport, London, UK  
E. [enquiries@braintretraining.co.uk](mailto:enquiries@braintretraining.co.uk)  
[www.braintretraining.co.uk](http://www.braintretraining.co.uk)

## FEBRUARY

**NCYPE Training Day**  
1 February, 2010; Lingfield, UKL  
T. 01342832243  
E. [info@ncype.org.uk](mailto:info@ncype.org.uk)

**The Society for Research in Rehabilitation Winter Meeting 2010**  
2 February, 2010; Salford, UK  
T. 0161 2957012/14  
E. [cpdunit-fhsc@salford.ac.uk](mailto:cpdunit-fhsc@salford.ac.uk) or  
[srr\\_secretary@srr.org.uk](mailto:srr_secretary@srr.org.uk)

**Chronic Pain Management**  
3 February, 2010; Derby, UK  
T. 01332 254679  
[www.ncore.org.uk](http://www.ncore.org.uk)

**Neurological Futures: Speculation, Value and Promissory Hope in the Bioeconomy**  
5-6 February, 2010; Oxford, England  
E. [ENSN@lse.ac.uk](mailto:ENSN@lse.ac.uk)

**Stroke Training Weekend**  
5-7 February, 2010; London, UK  
E. [Robert.simister@uclh.nhs.uk](mailto:Robert.simister@uclh.nhs.uk)

**Gunn Intramuscular Stimulation Part 2 Course with James Pinkney**  
5-7 February, 2010; Bookham, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**OZC – Mood Assessment and Rehabilitation**  
7 February, 2010; Ely, UK  
T. 01353 652173  
E. [Rachel.everett@ozc.nhs.uk](mailto:Rachel.everett@ozc.nhs.uk)

**CBT**  
10 February, 2010; Derby, UK  
T. 01332 254679  
[www.ncore.org.uk](http://www.ncore.org.uk)

**The Leeds National Demonstration Centre in Rehabilitation Annual Day Conference**  
10 February, 2010; Leeds, UK  
T. 0113 3055086,  
F. 0113 3055081  
E. [adele.archer@nhs.net](mailto:adele.archer@nhs.net)

**Exploring Gait as it relates to Posture & Balance for Qualified Therapists**  
10 February, 2010; Derby, UK  
T. 01332 254679  
[www.ncore.org.uk](http://www.ncore.org.uk)

**Acupuncture Evening Workshops Treating the Knee Region**  
11 February, 2010; London, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**12th National Dementias Conference**  
18-19 February, 2010; London, UK  
E. [conferences@markallengroup.co.uk](mailto:conferences@markallengroup.co.uk)

**RCN Outpatients Conference and Exhibition**  
20 February, 2010; London, UK  
[www.rcn.org.uk/events](http://www.rcn.org.uk/events)

**Neuromusculo-skeletal Assessment and Treatment Course: Back to Basics with Andrea Hemingway: The Lower Limb**  
20-21 February, 2010; Manchester, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**NCYPE Conference Commissioning Epilepsy Services**  
23 February, 2010; London, UKL  
T. 0207 9723049  
E. [tom.loader@itc-team.org.uk](mailto:tom.loader@itc-team.org.uk)

**EDDP 2010 International Conference on Early Disease Detection and Prevention**  
25-28 February, 2010; Munich, Germany  
[www.paragon-conventions.com/eddp2010](http://www.paragon-conventions.com/eddp2010)

### Long-term (Neurological) End of Life Care Conference

25 February, 2010; London, UK  
Mr Mark Baker,  
T: 0208 780 4500 ext 5010,  
E. [mbaker@rhn.org.uk](mailto:mbaker@rhn.org.uk)  
[www.rhn.org.uk/institute](http://www.rhn.org.uk/institute)

**RCN Education Conference**  
26-27 February, 2010; Blackpool, UK  
[www.rcn.org.uk/events](http://www.rcn.org.uk/events)

**3rd International Congress on Gait & Mental Function**  
26-28 February, 2010; Washington, USA  
E. [gait@kenes.com](mailto:gait@kenes.com)  
[www.kenes.com/gait](http://www.kenes.com/gait)

## MARCH

**Brain Injury Conference: Moving Forward**  
2 March, 2010; Derby, UK  
T. 01332 254679  
[www.ncore.org.uk](http://www.ncore.org.uk)

**Acupuncture Evening Workshops Treating the Foot & Ankle Region**  
4 March, 2010; London, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**Insight Workshop**  
5-6 March, 2010; Gatwick Airport, London, UK  
E. [enquiries@braintretraining.co.uk](mailto:enquiries@braintretraining.co.uk)  
[www.braintretraining.co.uk](http://www.braintretraining.co.uk)

**Recognising Post Traumatic Stress**  
7 March, 2010; Derby, UK  
T. 01332 254679  
[www.ncore.org.uk](http://www.ncore.org.uk)

**The International Brain Injury Association's 8th World Congress on Brain Injury**  
10-14 March, 2010; Washington, DC, USA  
E. [congress@internationalbrain.org](mailto:congress@internationalbrain.org)  
[www.internationalbrain.org](http://www.internationalbrain.org)

**Understanding Brain Injury**  
12 March, 2010; Ely, UK  
T. 01353 652173  
E. [Rachel.everett@ozc.nhs.uk](mailto: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](http://www.ncore.org.uk)

**NCYPE Open Day**  
17 March, 2010; Lingfield, UK  
T. 01342 832243  
E. [openday@ncype.org.uk](mailto:openday@ncype.org.uk)

**1st International Congress on Epilepsy, Brain & Mind**  
17-20 March, 2009; Prague, Czech Republic  
Marcela Rajtorova,  
T. 42 0 284 001 444,  
E. [epilepsy2010@guarant.cz](mailto:epilepsy2010@guarant.cz)

**End of Life Care in Neurological Patients**  
18 March, 2010; Cardiff, UK  
T. 01872 225552  
E. [info@redpublish.co.uk](mailto:info@redpublish.co.uk)  
[www.redpublish.co.uk/courses](http://www.redpublish.co.uk/courses)

**International Congress on Epilepsy, Brain and Mind**  
18-20 March, 2010; Prague, Czech Republic  
[www.epilepsy-brain-mind2010.eu](http://www.epilepsy-brain-mind2010.eu)

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

**6th World Congress for NeuroRehabilitation**  
21-25 March, 2010; Vienna, Austria  
E. [christian.linzbauer@medacad.org](mailto:christian.linzbauer@medacad.org)  
[www.wcnr2010.org](http://www.wcnr2010.org)

**20th Annual Rotman Research Institute Conference – The Frontal Lobes**  
22-26 March, 2010; Toronto, ON, Canada  
Paula Ferreira,  
T. 416 785 2500 ext. 2363,  
E. [pferreira@baycrest.org](mailto: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](mailto:catedrasg@cac.es),  
[www.fundacioncac.es/catedrasg](http://www.fundacioncac.es/catedrasg)

**Management of Spasticity in MS**  
24 March, 2010; Glasgow, UK  
T. 01462 476704  
E. [education@mstrust.org.uk](mailto:education@mstrust.org.uk)  
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**11th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy**  
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**Spring School 2010: Axon-Glia Biology in Health and Disease**  
29-31 March 2010; Cambridge, UK  
T. +44 (0)1223 331174  
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**British Neuropsychological Society Spring Meeting**  
30-31 March, 2010; London, UK  
E. [dana.samson@nottingham.ac.uk](mailto: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](mailto:scoburn@partnershipsincare.co.uk)  
[www.partnershipsincare.co.uk/bis](http://www.partnershipsincare.co.uk/bis)

## APRIL

**Evolving MS Services**  
9 April, 2010; Wyboston Lakes, UK  
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E. [pcrossman@mssociety.org.uk](mailto:pcrossman@mssociety.org.uk)

**62nd Annual Meeting of the American Academy of Neurology**  
10-17 April, 2010; Toronto, Canada  
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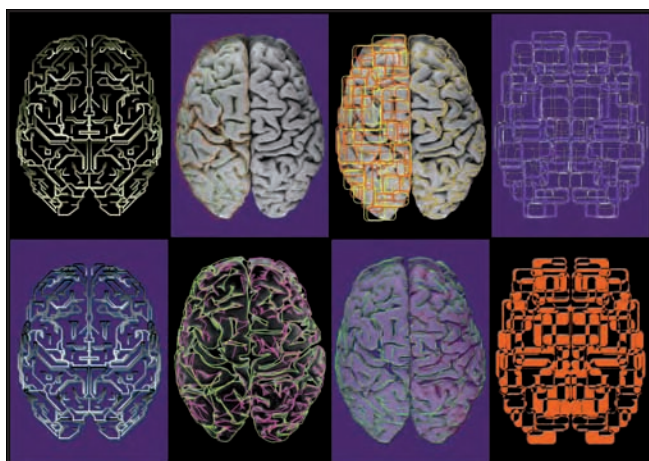
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# Practical Cognition Course

**Conference details:** 8-9 October, 2009; Newcastle, UK. **Reviewed by:** Dr Christine Albertyn, Neurology Trainee, Dublin, Ireland.

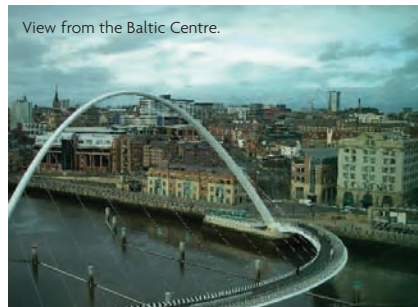
Consultants and trainees in neurology, neuropsychology, rehabilitation medicine, psychiatry and age-related psychiatry convened in the "Venice of the North" (Newcastle, that is!) for the second two-day course on Practical Cognition. The core aim was to develop skills and knowledge of the cognitive assessment and relate this to the patient.

The format of the course was intimate, with just over 30 attendees, which allowed for a relaxed and friendly atmosphere, encouraging questions and responses from all.

Prof Tim Griffiths set the tone in his introductory remarks: the course begins and ends with the patient, emphasising that a neuropsychological examination is a cost-effective, sensitive and specific way of diagnosing many neurodegenerative diseases and other brain disorders. The main topics covered in the course were movement and cognition, parietal lobe disorders and visual disorders. Each topic was introduced through a series of interactive case reports, including video footage, of a patient that may realistically be seen in the clinic or ward.

Dr Andrew Larner runs a cognitive neurology clinic in Liverpool and spoke about the bedside tests of cognition. He pointed out the potential shortfalls of the Mini-Mental State Exam (MMSE), in particular the lack of frontal lobe testing. The Revised Addenbrooke's Cognitive Examination (ACE-R) was discussed and by applying evidence-based medicine, he explained how this test may be best used, keeping in mind the sensitivity and specificity at various cut-off points.

Dr Tom Kelly, neuropsychologist, explained his role in practice and touched on the discrepancy between how neurologists view psycholo-



gy, in terms of localisation (i.e. frontal lobe) and how psychologists are trained in terms of function, (i.e. concentration). After a whistle-stop tour of the vast armour of tests, the delegates had a practice run of constructing and recalling the Rey Complex figure (not an easy task!). He emphasised the value of observing a patient performing the various tests, as this is as informative as the final score. He therefore hopes that the era of computer-administrated testing is still a distant one.

A personal highlight of the course was the session dedicated to cognition and movement. Six case reports vividly highlighted features that may be seen in the context of movement disorders, ranging from cortico-basal degeneration to Huntington's chorea. Prof David Burn is a movement disorder specialist and gave an excellent review of movement disorders and the associated neuropsychological features that can aid in diagnosis. His practical approach and tips were pearls of wisdom! The evening concluded on a high note with dinner at a restaurant on the top floor of the Baltic arts centre with a beautiful view of the Quayside.

The next morning, the parietal lobe disorders were practically illustrated through cases

of neglect, visual agnosia and simultaneous agnosia. The expert lecture was given by Prof Masud Husain, Consultant Neurologist at UCL. He classified the disorders of attention and elaborated on the localising value of certain forms of inattention. The dorsal and ventral visual streams were also discussed with the aid of MRI, helping attendees define anatomical landmarks. He showed interesting experiments demonstrating how neglect can vary with the number of competing stimuli and briefly touched on the fascinating research being done in impulse control disorders in Parkinson's disease.

The final session was on visual disorders, covering areas such as cortical blindness and blindsight. The expert lecture was given by Prof Geraint Rees, director of the Institute for Cognitive Neuroscience at UCL. His fascinating account of the visual pathways was a tour de force of understanding the visual brain. He touched on optical illusions, how we recognise faces and on the advances and limitations of functional imaging. He has certainly challenged me to see my sight in a different way, beyond the "anatomy of the visual pathway" of my student days!

The course was sponsored by the Guarantors of Brain and was structured to begin and end with the patient. The vivid examples made the learning points easy to remember. The core aim of developing skills and knowledge of the cognitive assessment and relating this to the patient was certainly met. It would be of value to all professionals in the area of neurology, psychiatry, age-related medicine and psychology. It not only equipped me, but left me inspired and excited to apply my new-found knowledge at the bedside! ♦

# Developments in Acquired Brain Injury

**Conference details:** 11 November, 2009; London, UK. **Reviewed by:** Dr Judith Allanson, Consultant in Neuro-rehabilitation at Addenbrookes Hospital, Cambridge, UK.

The United Kingdom Acquired Brain Injury Forum (UKABIF) Conference held on 11 November was deemed a huge success by delegates, speakers and sponsors. The two hundred delegates included brain injury survivors and their families, a range of professionals from health and social services, representatives from the independent sector, case managers, Headway professionals and legal professionals. The event aimed to update attendees in areas ranging from nerve recovery to developments in rehabilitation assessments and therapies, outcome measures and changes in the law. The conference ended with a presen-

tation from Professor Keith Willett, National Director of Trauma Care.

The conference was treated to full and entertaining Plenary lecture from Professor Micky Selzer, Professor of Neurology and Director, Temple University School of Medicine, USA. He presented an excellent and comprehensive overview of developmental and regenerative neuroscience using examples from work on the lamprey where locomotion can recover well after cord section. He presented MRI studies, where individual nerve fibre pathway integrity after injury and during regeneration has been visualised and

explained how findings suggest that regeneration is not the same process as development. He summarised some of the well established mammalian research which has described differences between nerve recovery in the peripheral and central nervous systems.

There were pertinent clinical examples, with rather sobering facts that have emerged from study of the US military. 19% of US service members were found to have suffered at least a mild TBI. Professor Selzer explained that a blast injury was a relatively new form of brain injury caused by blast waves which travel at 26,400 feet/sec creating alternating extremes

of low and high pressure which can induce brain oedema, burst blood vessels, and can lead to air emboli, and cavitations. He made the interesting point that rest of body was more protected by Kevlar.

Sandra Stark, Consultant Therapist in Neurorehabilitation, Walkergate Park Centre for Neurorehabilitation and Neuropsychiatry, then, very clearly painted the complex picture of the many and rapid changes in therapy and service development that have occurred recently. She explained that a range of drivers to change have influenced practice and service development within Neurorehabilitation in the last few years. These include national reviews such as the Darzi report; changes in how services are commissioned by PCTs and SHAs such as World Class Commissioning and the Transformation of Community Services; the evolution of different ways of working such as the development of integrated care pathways; generic rehabilitation therapists; delivery of treatment closer to home; as well as the development of new ways of offering therapy.

We were reassured that most patients had embraced new technological solutions such as conference calls for consultation and advice, and the use of commercially available user/computer interface games such as the "Wii". In addition we were reassured that there was good reason for strength training and exercise making a comeback as myths of these exacerbating spasticity have generally been dispelled, albeit mostly in studies on treatment of people with stroke rather than other less focal forms of ABI. The use of constraint induced therapy and mirror therapy was elegantly reviewed with the impression that they have proved useful in most groups of stroke patients studied.

After coffee, Professor Anthony B Ward, from North Staffordshire Rehabilitation Centre, University Hospital of North Staffordshire, Stoke on Trent, developed the theme of new developments, describing the role of Rehabilitation physicians who now undertake a specific training as laid out in the updated curriculum of the RCP. He explained that rehabilitation was a process concerned with the promotion of physical and cognitive functioning, activities (including behaviour), participation (including quality of life) and modifying personal and environmental factors. He reminded us of the recent papers which illustrate the benefits of acute rehabilitation units, which can concentrate therapy – (which in turn can be associated with shorter hospital stays and improved outcomes); create an effective learning environment and with the right skill mix of staff optimise patients' physical and social functioning.

Several measures of dependency and outcome were presented showing how these have been used to increase efficiency of units where they have been able to adjust staffing levels according to need. One of the trends is the increased use of the Goal Attainment Rating Scale for outcome measurement which may be used as part of service evaluation in the future.

We were then given a fascinating update on

the use of combinations of clinical, electrophysiological and imaging techniques that are being employed to further our understanding of the vegetative state, by John Pickard, Professor of Neurosurgery, University of Cambridge at Addenbrookes University Hospitals Trust, Cambridge. One of the changes presented was that thinking has evolved in this area over the last decade and many now feel that consciousness is only achieved when several parts of cortex are functioning together in networks rather than activity in isolated parts of the cortex being sufficient. It was suggested that assessment tools for describing the presentation of people with impaired consciousness such as the WHIM (Wessex Head Injury Matrix), Coma recovery scales and the SMART, were best used by people who were familiar with them as the tools were only useful if used appropriately.

Prof Pickard emphasised that anatomical imaging and pathological findings rarely related well to function or outcome in this group. Recent developments in imaging analysis such as white matter tractography studies have been able to demonstrate significant white matter tract loss after traumatic brain injury. Furthermore, several studies have now described more white matter loss after hypoxic brain injury than after traumatic injury consistent with clinical findings in these groups. Professor Pickard described the use of combinations of assessment; one example being a recent study, where electrophysiological studies coupled with PET, were able to record selective responses to complex spoken language tasks in two patients, who appeared unaware at the time of study but who then emerged from a clinical vegetative state several months later.

Before lunch William Challis, Optua UK, described the development of a new Care Pathway which is aiming to be accessible to injured people, their family and all professionals. Information is expected to be arranged by a stage in the pathway (e.g. in patient rehabilitation) and by geographical location. The hope is that a click on a part of the pathway for a particular location will reveal details of any relevant services available for that person at that stage of their recovery. Challis promised that this structure will be available for all to use from early January 2010. From the "offline" demonstration given on the day this tool promised to be a very useful and long awaited resource. It will however be entirely dependent on the quality of information that is collected/supplied by each service that is included.

After lunch there was no danger of falling asleep listening to Bill Braithwaite QC's lively recall of several fascinating cases. While he emphasised that it remains best to avoid a trial if at all possible, he expertly took us through the recent case of "PETERS v EAST MIDLANDS 3.3.09" which set a precedent for a claimant opting for self-funding and damages in preference to reliance on the statutory obligations of a public authority provided that there was no real risk of double recovery.

Martin John, Chief Executive of the Office of

the Public Guardian then outlined the principles of the mental capacity act (2005) and how its implementation since October 2007 was now being reviewed. Martin John was keen to reassure us that the principles of the MCA were not being re-visited, and that the expectation was to work in partnership with all stakeholders. He thought that changes that were currently being planned would result in a bigger and stronger service which was understood and trusted by its customers.

After tea, Professor Nick Alderman, Clinical Neuro Psychologist, St Andrews Hospital, Northampton described the need for a new neuro-behavioural rating scale to help describe both an individual's progress during rehabilitation and service performance. While emphasising the diversity of impairments displayed by people recovering from injury, he did persuade us of the place for both individual case studies and service level "snap shots of measures of difficulty". He illustrated the process of developing valid, reliable and consistent measures by describing the evolution of a new Neurobehavioural rating scale the SAS-NOS (St Andrew's-Swansea Neurobehavioural Outcome Scale). It remains to be seen how translatable this will be to less specialised neurorehabilitation settings.

The conference ended with a presentation from Professor Keith Willett, National Director of Trauma Care calling for assistance with organising rehabilitation services to facilitate the new trauma delivery plan. This left delegates filled with hope for the future provision of rehabilitation services and UKABIF have offered their assistance with any aspect of this work.

## Conclusions

The organisers should be warmly congratulated for putting together such a successful event. As introduced by its Chair, Professor Mike Barnes; this could be described as "the biggest event in the Brain Injury calendar". The day provided not only an excellent overview of developments in Acquired Brain Injury, but also created an excellent milieu for discussion and liaison between groups who have few opportunities to meet informally. If there was a problem at all it was that some speakers had produced such thorough, detailed overviews, that it was difficult to digest all of the details within the time. (The website does however have links to most of the talks).

Furthermore it was particularly exciting to hear from the trauma Tsar himself. He clearly has head trauma and early involvement of rehabilitation high on his agenda. There now seems to be a real possibility that the pathway to recovery following brain injury may become better defined, more coordinated better signposted and perhaps better understood by central government (although as yet not more adequately funded!).

UKABIF will hold the 2010 Conference at the Hotel Russell, London on Thursday 11th November 2010. Please see [www.ukabif.org.uk](http://www.ukabif.org.uk) for details about the conference and the organisation. ♦

# Dementias 2010

**Conference details:** February, 2010; London, UK. **Reviewed by:** Rebecca Linssen, Editor, British Journal of Hospital Medicine.

PREVIEW

The 12th national conference for all those working with patients suffering from dementia will be taking place in London in February 2010. The 2-day conference, organised in association with the British Journal of Hospital Medicine, will give delegates a review and update on current developments in the dementias; in the fields of research, investigations, clinical care and service and policy issues.

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

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

The first day will begin with a key-note speech from Professor Martin Prince, King's College Hospital London, looking at dementia in a world perspective. Following a range of talks on clinical topics covering areas from management of dementia in primary care to issues around mental capacity and a look at imaging, the day will conclude with a special session including case histories and discussions of alternative treatments.

Professor Cornelius Katona, Professor of Dept Mental Health Sciences, University College London, London, will open the second day of the conference with an overview on the Treatment of behavioural and psychological symptoms. Following talks on Effects of physiotherapy and other treatments on care home residents and Cognitive stimulation, Professor Roy Jones, Director of the Research Institute for the Care of Older People in Bath, will outline drugs which are currently in clinical trials, and look at the potential these may offer for future treatments.

In the afternoon of day two Professor Julian C. Hughes, Consultant in Old Age Psychiatry and Honorary Professor of Philosophy of Ageing, Northumbria Healthcare NHS Foundation Trust, will discuss the Nuffield Council Report which looked at ethical issues

affecting patients with dementia. Dr Elizabeth Sampson, Senior Lecturer in Psychiatric and Supportive Care of the Elderly, Department of Mental Health Sciences, UCL, London will consider the importance of good end of life care for people with dementia. The conference will conclude with a joint session from the speakers and chairmen from the second day in which each details the best paper on dementias which he/she has read in the last year.

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

For further information, or to book a place, go to [www.mahealthcarevents.co.uk](http://www.mahealthcarevents.co.uk) or phone 020 6501 6762.

# Highlights from the 20th International Symposium on ALS/MND

**Conference details:** 8-10 December, 2009, Berlin, Germany. **Reviewed by:** Dr Belinda Cupid, research manager, Motor Neurone Disease (MND) Association.

How close are we to understanding the cause? How can we best support people living with motor neurone disease (MND) and Amyotrophic Lateral Sclerosis (ALS) – the most common form of MND? What is the latest news on drug treatments? These are the key questions I know friends, colleagues and patients with MND will ask me when I talk about the 20th International Symposium on ALS/MND.

Dr Dena Jacobs presented some data showing the expression of one of the key transporters across the blood-brain and blood spinal cord barrier P-glycoprotein (P-gp). Her data provided evidence for the pharmacoresistance of people with MND to new treatments. P-gp commonly removes xenobiotics from the brain and spinal cord. Following poorer than expected results on a SOD1 mouse model of MND of a compound that



showed promise in the wild type, Dr Jacobs from Thomas Jefferson University, Philadelphia investigated the properties of this protein in ALS in more detail. Their hypothesis was that their candidate drug was a substrate for P-gp. Thus as P-gp expression increased with disease, the pharmacokinetics and the therapeutic effect were significantly altered. There is increased expression of P-gp in astrocytes in the spinal cord in symptomatic mice. These changes are not seen in spinal cord neurones or brain astrocytes in either wild type or pre-symptomatic mice.

Crucially, their preliminary data in humans reflected the findings in mice. P-gp levels are higher in the spinal cord of people with MND compared to unaffected controls. They are currently working to confirm their findings.

In contrast to exploring why drugs may not produce the expected results, there were a few reports of promising clinical trials. Watch this space for the results of the promising drug from Knopp Neurosciences Inc. The successful results of their phase 2 study of KNS-760704 were presented and plans for a phase 3 study are underway. It was a similar story for ceftriaxone, where recruitment has begun for a US phase 3 study. Concerns about being able to recruit for a clinical trial of an i.v.-administered drug have been unfounded so far – their recruitment is on track.






In the huge poster session of the symposium – over 330 posters were presented –

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-  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.

**Abstract Submission Deadline: 3 February 2010**

**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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there was a description of another phase 2 trial underway. The results of the selective AMPA antagonist Talampanel are expected in the third quarter of 2010.

One of the sessions that created a real buzz at the meeting was the session on motor neuron biology. Prof Roger Lemon, based at the Institute of Neurology, UCL London made delegates sit up and take notice of the role and relevance of the corticospinal tract (CST) to understanding MND. As suggested in his excellent review of this area (Lemon Annual Review of Neuroscience 2008, 21: 195-218) his first point was that a description of neurones as 'upper' and 'lower' motor neurones is unjustified with modern knowledge of neuroscience and neuroanatomy. The importance of the CST to MND has been illustrated by a number of observations: the loss of fine, finger movement is an early feature of hand dysfunction in MND (an area controlled by CST input) and the motor neurones often spared in MND – the eye muscles and Onuf's nucleus receive no direct CST projections.

Anecdotally, neurologists may observe that their patients led athletic or very physically active lives prior to developing MND. Several years ago, the idea of a link between physical activity and MND became more prominent by reports of a higher than expected incidence of the disease in Italian footballers. In Berlin, we organised a debate entitled 'Is exercise is a predisposing factor in ALS?'. Prof Adriano Chio (from Torino, Italy) and Prof Wokke (from Utrecht, The Netherlands) presented the case for and against respectively. Emerging themes from their entertaining and comprehensive reviews of the epidemiological, pre-clinical and biological research included that exercise may lead to an earlier onset of MND and that more research is required to confirm the motion!

A symposium first was a dedicated session on spirituality for people with MND. Many delegates were inspired and moved by the presentations on meaning in life (as opposed to meaning of life) and case studies on spirituality. Exploring an individual's spirituality

helped people with MND, their families and those supporting them, illustrating the diversity and individual nature of spirituality. A key point in the presentation from Martin Fegg based at Munich University was that the loss of meaning in life is one of the main determinants for a person requesting to end their life. This session continued the ideas presented by Baroness Finlay, a patron of the MND Association, in her inspiring, opening talk of the conference, on palliative care.

She stressed good communication and good listening is essential if health and social care professionals are to help patients who are feeling helpless and hopeless. The one message I took from her presentation was to ask the very simple question 'What can we do to improve today'. Baroness Finlay also urged us to consider children affected by MND. ♦

More information about the 20th International Symposium on ALS/MND is available online at: [www.mndassociation.org/mysymposium](http://www.mndassociation.org/mysymposium).

## 20th Meeting of the European Neurological Society

Conference details: 19-23 June, 2010; Berlin, Germany. Report by: Prof G Said, ENS Executive Committee.

PREVIEW

### Teaching programme:

- 5 Main Symposia
- 23 Teaching Courses covering all important topics in Neurology
- 12 Workshops
- 6 Interactive Case Presentation Sessions
- Practical Sessions in Clinical Neurophysiology

### Early registration deadline:

15 April, 2010

### Abstract submission deadline:

3 February, 2010



Attendance to courses and workshops was a very rewarding aspect of the ENS meeting 2009 in Milan, with rooms completely filled with neurologists in training. Young neurologists are encouraged to apply for ENS support to attend the meeting and especially the teaching programme. Thanks to our programme for neurologists in training, many young neurologists can be invited to attend high quality teaching and scientific sessions.

The teaching programme will continue on Sunday morning and afternoon with courses covering the different neurological subspecialties ranging from neuro-oncology to motor neuron disease and neurorehabilitation. The latter will deal with the treatment of major problems after stroke and spinal cord injury. Practical approaches of current treatments in neurology will be taken care of in the teaching course devoted to tractography in clinical neurology, myasthenia gravis, conscious and unconscious agendas in the brain, painful neuropathies, pitfalls in neurological examination and developments in pathophysiology and treatment of CNS infection.

Practical breakfast sessions on clinical neurophysiology are included this year again with

hands-on sessions on EMG, nerve conduction and reflex studies.

The scientific programme will start on Monday morning with the Presidential Symposium on autoimmune disorders of the peripheral nervous system and muscle chaired by Prof. G. Said from Paris. Four main symposia on small vessel diseases, the borderland of epilepsy, hot topics in movement disorders and new treatment trials and emerging therapeutic targets in MS will also take place during the meeting.

Last but not least, oral and poster presentations with walking tours and interviews with presenters of scientific papers on various topics will illustrate the vitality of neurology in Europe. ♦

*We are looking very much forward to these stimulating sessions.  
European Neurological Society*

For further information, please visit the ENS 2010 website: [www.ensinfo.org](http://www.ensinfo.org)

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## EDITOR'S CHOICE

# What's new in the treatment of Huntington's Disease?

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder characterised by progressive cellular dysfunction and loss in many brain areas, but especially the striatum. As a result much attention has been focused on repairing this area of the brain with transplants of fetal striatal tissue and neurotrophic factors such as CNTF. Two recent papers using these approaches in different ways report some interesting findings. In the first of these Keene et al report the post-mortem findings of a young patient who was grafted with fetal striatal tissue into her affected basal ganglia, two years into the illness, who subsequently died 121 months later. Clinically the patient showed some initial improvement but then developed upper motorneuron signs and had a scan that showed space occupying cysts bilaterally in the putamen, which were examined histologically upon her death from advanced HD rather than any progressive mass effect from these cysts. This post-mortem examination worryingly revealed not only the cysts, but some mass lesions containing a range of neural structures including striatal elements, which is encouraging. The cysts seemed to be lined by GFAP-immunopositive ciliated ependymal cells- which were of donor (XY karyotype) origin in some instances. None of the lesions were mitotically active at the time of death, suggesting that they were not malignant cells but simply cells that had proliferated early on- perhaps in a developmentally normal fashion. Obviously this is a single case report, but it does emphasise that grafting cells into brains is not without risks, some of which are hard to quantify experimentally- making any translation to patients not straightforward.

In contrast, Lee et al report that using adipose stem cells can rescue the cells destined to misbehave and die in HD. This they show in vitro, using conditioned media from the cells, as well as in vivo using both the older excitotoxic striatal lesion model of HD as well as the R6/2 transgenic mouse. In all cases the grafted cells rescue the phenotype to a degree. The proposed mechanism, based on their in vitro data, is that this is mediated by the release of certain important factors from the cells that could reverse some of the known pathogenic mediators in HD cell death. Thus, they propose, as have many others, that stem cells could treat conditions such as HD not by cell replacement but by trophic support. Thus we have two transplant stories, both reporting some benefits but using different approaches with radically different pathological findings!

Whilst this is one approach to treating HD, an alternative strategy involves trying to block the effects of the mutant protein itself. This leads me onto two further papers on HD, the first of which strives to also better explain the pathology in a disorder in which the mutant protein is ubiquitously expressed in the CNS. In this new paper from the group of Lipton and Hayden, they postulate that it relates to the degree of glutamatergic stimulation- in particular the synaptic versus extrasynaptic NMDA receptor. In years gone by before the gene for HD was identified, the disease

was modelled through excitotoxic lesions to the striatum, on the grounds that such lesions selectively affected specific neuronal populations in a way that mimicked that seen pathologically in patients dying from this disease. In this recent article, it is shown using a variety of in vitro approaches as well as the YAC128 mouse model of HD, that the extent to which mutant htt aggregates is different depending on which type of NMDA receptor is activated- synaptic versus nonsynaptic- and involves different pathways. This was explored in the animal model using two different doses of memantine on the grounds that low dose only blocks extrasynaptic NMDA-R whilst high dose also blocks synaptic NMDA-Rs. This latter therapy encourages mutant htt disaggregation which exacerbates the pathological load to the cell and the animal, which was what was seen in this study both histologically and behaviourally. This is a new interesting angle in on the regional pathology of HD as well as highlighting the complexities of trying to treat it with disease modifying therapies, as it is not just what you use, but at what dose!

The final paper explores the use of siRNA to target the mutant htt and by so doing silence it and stop the pathological process. This is a technique that has often been shown to work well in vitro but is harder to use in vivo because of delivery problems and fear of silencing the non-mutant htt. In a recent paper by Drouet et al they have shown using a lentiviral system that mutant htt can be silenced with a beneficial effect, that is seen even after pathology has begun. Furthermore partially silencing the normal htt to a significant extent was not associated with a worsening of HD pathology or obvious changes in the striatum. This is all very encouraging, but does also throw up questions about what normal huntingtin does and the extent to which mutant htt interferes with normal htt function, as has been proposed by Elena Cattaneo et al with respect to BDNF. An effect that may also help explain the regional pathology of HD. All very interesting. – **RAB**

**Keene CD et al.**

**A patient with Huntington's disease and long-surviving fetal neural transplants that developed mass lesions.**

**ACTA NEUROPATHOLOGICA  
2009;117:329-38.**

**Lee ST et al.**

**Slowed progression in models of Huntington Disease by adipose stem cells transplantation.**  
**ANNALS OF NEUROLOGY  
2009;66:671-81.**

**Okamoto SJ et al.**

**Balance between synaptic and extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant huntingtin.**  
**NATURE MEDICINE  
2009;15:1407-13.**

**Drouet V et al.**

**Sustained effects of nonallele-specific Huntingtin silencing.**  
**ANNALS OF NEUROLOGY  
2009;65:276-85.**

## Journal reviewers

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## EPILEPSY: value of a tap on the head

Let's be honest, it is disappointing how little difference the great explosion of new antiepileptic drugs has proven in the search for the only truly useful outcome in epilepsy, that is seizure freedom. Sure, the new drugs are not enzyme inducers (mostly) but then who really cares, that is hardly an insurmountable problem. They have slightly less neuropsychiatric side effects than the old ones but they are hardly free of those problems. But then, virtually all our treatments do the same thing; they alter the relative balance of uppers and downers in the determination of cortical excitability. In truth they are not really anti-epileptic drugs at all, they are seizure control agents. It is perhaps not altogether surprising that whatever knife you use to skin a cat, you end up with a skinned cat (apologies to moggie-loving neurologists everywhere) and that nearly all the drugs (apart from the really awful ones) have very similar seizure control rates and pretty similar adverse event rates. So how can we find something better? One way of doing it is to look at models where we know there is a high risk of developing epilepsy and seeing if we can stop it happening. Of course this is only a minority of cases, but they may prove informative and several acute brain events have such high rates of later epilepsy that it is worth looking at them, such as haemorrhagic stroke, severe head injury and encephalitis. This study used an established model of traumatic brain injury, the fluid percussion model and looked at subtle clinical and electrographic changes in experimental rats. They found that very brief discharges, less than two seconds, which were only detectable on intracranial EEG, were associated with behavioural changes as seen on video, including an increased chance of behavioural arrest, when seen by blinded observers. This short duration of discharge would have been ignored as probably irrelevant in previous studies. The authors then went on to analyse intracranial EEG in 4 patients undergoing presurgical evaluation for their epilepsy and found similar short duration discharges, which were also associated with subtle behavioural changes when their videos were analysed. The argument goes that these brief discharges may be an early sign of epileptogenesis that has previously been ignored and that offers opportunities of a model to interfere with the process and develop drugs that are truly anti-epileptic, rather than anti-seizure. We are desperately in need of a fundamentally new approach to epilepsy control to keep up with the disease-modifying aspirations of our colleagues in Alzheimer's and MS. – **MRAM**

**D'Ambrosio R et al.**

**Functional definition of seizure provides new insight into post-traumatic epileptogenesis.**

**BRAIN**

**2009;132:2805-21.**

## DEMENTIA: carving up behavioural variant FTD

The trouble with dementias is that they are difficult to classify. Like other conditions, they have clinical features, test results, imaging appearances, and histopathological findings. Unfortunately, you end up classifying patients in four completely different ways depending which of these you see as the most important. Behavioural-variant frontotemporal dementia (bvFTD) is a clinically-defined dementia syndrome, which may be more familiar by its colloquial name of 'frontal dementia'. Patients with this condition are 'frontal' - that is, they are apathetic or disinhibited in much the same way as patients with focal frontal lesions. Not surprisingly, then, if a group of bvFTD patients is compared with suitable controls, most atrophy is found in the frontal lobes. However, this group-wise analysis tends to lead to the belief that all bvFTD patients have predominantly frontal atrophy, which is not quite the same thing. Rather than assuming that all patients are the same, the authors of this paper examine the details of the data to see what classification they suggest.

The authors define the distribution of atrophy in each of a group of bvFTD patients, according to twenty-six pre-defined regions of interest,

and use the statistical method of hierarchical cluster analysis; the idea is that the most similar cases are categorised together first, then these groups gradually merge until they form one big group. The analysis doesn't tell you how many subgroups there might be, but it tells you the most meaningful way of dividing the patients into any particular number of groups. Having looked at the results, the authors choose to classify the patients into two groups, each dividing into two subgroups. These turn out to represent patients with frontal-dominant and temporal-dominant atrophy respectively, which in itself is an interesting result: a significant number of patients with 'frontal' dementia have atrophy predominantly in the temporal lobes. Of course, the behavioural features might still be caused by frontal atrophy, even if the temporal atrophy is more severe. Within the temporal-dominant group, there is a small subgroup who have fairly pure temporal atrophy, specific deficits in naming and verbal memory, and mutations in the gene for tau protein. In other respects though, the patient groups defined by the location of atrophy don't differ from each other significantly, in terms of the clinical features, neuropsychological deficits, or underlying pathology. Although the numbers are small, this result is just as important. The relationship between macroscopic atrophy and clinical features in dementia is a subtle one; a stroke destroys cells indiscriminately in the affected area, but degenerative disease affects certain groups of neurones while sparing others, and seems to proceed through functionally-connected distributed networks of cells. This paper's contribution to the classification debate is due as much to what it doesn't find as what it does. – **JK**

**Whitwell JL et al.**

**Distinct anatomical subtypes of the behavioural variant of frontotemporal dementia: a cluster analysis study.**

**BRAIN**

**2009;132(11):2932-2946**

## HEADACHE: allodynia, migraine and mood

This study examined and highlighted the link between migraine, other pain syndromes, cutaneous allodynia, and mood disorders. Cutaneous allodynia is a recognised manifestation of migraine and has been studied clinically and experimentally. It is a manifestation of central sensitisation, and reflects convergence of nociceptive pathways at many levels of the nervous system, including spinal cord, brain stem, thalamus and cortex. The authors found that 60% of migraineurs reported cutaneous allodynia, and this was associated with mood disorders (depression and anxiety), and other pain conditions (irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome). The worse the allodynia, the more likely the co-morbidity. This is a tangled web, and it is likely that there is a mixture of causality and consequence. Chronic pain, and in particular migraine, is associated and worsens depression, and depression is likely to be worse if the pain is more severe. Central up-regulation of nociceptive pathways and central receptor and transmitter modulation may exacerbate or cause mood disorders. Central changes are documented in cerebral reactivity, metabolism and function, and are becoming more clearly understood, and will be important in clarifying these clinical observations. Clinically this is really important. We all need to be aware of the link between mood disturbance and migraine, and that often both may need treatment in migraineurs. This is crucial in making therapeutic choices and in monitoring response, for example in ensuring that treatment with beta-blockers is not worsening depression. Further, in patients with daunting multiple symptomatology of fatigue, pain and low mood, untargeting and treating the migraine may bring great benefit. – **HAL**

**Tietjen G et al.**

**Allodynia in Migraine: Association with Comorbid Pain Conditions.**

**HEADACHE**

**2009;49:1333-44.**

## CONSCIOUSNESS: as night follows day

The recently reported case of a Belgian man with a locked in syndrome who was “missed” for 23 years, suffering in apparent silence while the world moved on around him has been this year’s cause-célèbre in the world of vegetative and minimally aware states. The application of ever more sophisticated scanning techniques in the assessment of those with severe brain injury has changed the way that we conceptualise the disorders of consciousness. Whether you consider that changes in activity within certain parts of the brain in response to stimulation really equate to “consciousness”, the role of the clinician in the proper assessment of these patients at various stages in their recovery should not be understated. The value of a good history, examination and the assimilation of evidence from imaging and neurophysiological modalities underpin proper clinical assessment. Part of this assessment is the longitudinal observation of patients in minimally aware states over time. This small study (5 patients) looked specifically at circadian rhythms in patients in low awareness states. The presence of a sleep-wake cycle is felt to represent the threshold at which the comatose state becomes the vegetative state, which may be an important herald of change. Surface skin temperatures were recorded continuously for three consecutive days. Surface skin temperatures are known to change in a circadian pattern in accordance with environmental and light intensity changes. The degree of cerebral atrophy was also determined for this patient group. Of the 5 patients, only 2 demonstrated circadian patterns of temperature variation. These patients had sustained traumatic brain injuries and demonstrated significantly less cerebral atrophy than the 3 who did not display circadian rhythms (who had all sustained anoxic brain damage). Although the authors freely acknowledge that the study is too small to allow definite conclusions to be drawn, the difference in pattern of circadian rhythms between the traumatic and anoxic brain injury group demonstrates that this may form a valuable addition to the assessment battery in low awareness states. – **LB**

**Bekinschtein T et al.**

**Circadian Rhythms in the Vegetative State.**

**BRAIN INJURY**

**2009; 23(11):915-19.**

## HEADACHE: a measure between auras?

During and after migraine with aura there is cerebral hyperperfusion and hypoperfusion. The situation between attacks has been unclear, with transcranial Doppler giving inconsistent results. This study used semi-automated transcranial Doppler measures to visually evoked responses. In 70 patients with migraine with aura and 40 controls (with migraine without aura or with no migraine), the visual evoked flow rate, a robust measure of functional vasomotor reactivity, was measured. There was a significant difference in vasomotor reactivity interictally, with higher visually evoked flow rate in migraine with aura patients than controls. This change must be considerable as it has been demonstrated in quite small numbers. Of course this is likely to be quantitative, as migraine is so common and migraineurs are not separate from the rest of the population but at one end of a continuum. This work provides a potential tool to monitor and understand therapeutics. – **HAL**

**Wolf ME et al.**

**Changes in functional vasomotor reactivity in migraine with aura.**

**CEPHALALGIA**

**2009;29:1156-64.**

## ENCEPHALITIS: status quo vadis

The latest discovery from Josep Dalmau, of antibodies to GABA receptors, will surprise no-one who has been following the story of neuropil-encephalitis. And the prominent seizures seem to make sense. In a throw-away line in the methods, we see the pecking order of these antigens start to emerge from the fog. Seemingly, a growing bank of 410 sera, from

patients suspected to have a paraneoplastic or autoimmune encephalitis, has been extensively studied for antigen specificities. 357 samples found an antigen – nearly 90%. Of note, 275 were specific for NMDA receptors – that’s a whopping two-thirds of the total collection. 27 were specific to potassium channels, 19 to glutamic acid decarboxylase, 15 to AMPA receptors. The remainder were subjected to a well trodden path of antigen identification, through staining of brain sections, cultured neurons, and decorated human embryonic kidney cells. The focus here is on the clinical features of 15 patients with antibodies that recognise the B1 subunit of the GABA receptor. There are no surprises. The patients were relatively old (range 24 – 75). 7 of the 15 had a tumour, 5 of which had small cell lung cancer. Clinical response to tumour removal or immunotherapy was good in 9 of the 10 treated cases. But where are we going? There is a clear need to fully demonstrate the pathogenicity and origins of these antibodies, and to further develop novel methods of antigen identification – **MZ**

**Lancaster E et al.**

**Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen.**

**LANCET NEUROLOGY**

**2010;9:67-76. Published Online December 3, 2009.**

## NEUROGENESIS: new for old

Adult neurogenesis occurs in two constitutive areas of the adult mammalian brain- the subventricular zone from where the cells migrate out to the olfactory bulb, and the subgranular zone of the hippocampus where they migrate out to form neurons that contribute to the normal circuitry of this structure. The function of these new neurons is not fully resolved, we have postulated that they contribute to pattern separation (Clelland C et al, Science 2009), whilst others have postulated that they mediate other cognitive or affective processes. In this last respect Kitamura et al have recently shown using a combination of approaches “that decreased hippocampal neurogenesis is accompanied by a prolonged hippocampal dependent period of associative fear memory”, whilst enhancing this process with voluntary exercise “sped up the decay rate of HPC dependency of memory, without loss of memory”. They therefore conclude that “the level of hippocampal neurogenesis plays a role in the determination of the HPC-dependent period of memory in adult rodents”. This is of interest, but one of the critical questions that obviously arises is the extent to which this is also true for man, and what this means therapeutically in patients with neurological diseases. In this respect there are two papers that explore this- one looking at the cognitive deficits of cranial irradiation and the other Alzheimer’s disease. In the first study Acharya et al depleted the stem cell/precursor cell pools in the adult brain (especially the hippocampus) using irradiation and then grafted them 2 days later with human embryonic stem cells (hESCs) into the hippocampal complex. These transplanted cells survived and differentiated and appeared to ameliorate some of the cognitive deficits- presumably by replacing the adult neurons that were lost to the irradiation process. In the second study Biscaro et al showed that ABeta immunotherapy not only removed amyloid plaques but promoted the survival and maturation of neurons generated through the normal hippocampal neurogenic pathway. The exact mechanism by which this is achieved is not clear nor is its relationship to the increased angiogenesis that they also report, but it does once more highlight that innate repair processes may be useful in disease recovery, if they can be helped by combining strategies that also involve removing the pathological proteins themselves. – **RAB**

**Kitamura T et al.**

**Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory.**

**Cell – 2009;139:814-27.**

**Acharya MM et al.**

**Rescue of radiation-induced cognitive impairment through cranial transplantation of human embryonic stem cells.**

**PNAS – 2009;106:19150-5.**

**Biscaro B et al.**

**ABeta immunotherapy protects the morphology and survival of adult-born neurons in doubly transgenic APP/PS1 mice.**

**THE JOURNAL OF NEUROSCIENCE – 2009;29:14108-19.**

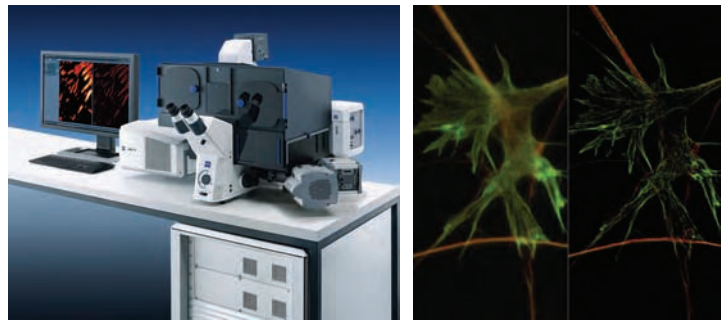
## Carl Zeiss introduces Superresolution Microscope Systems

The Carl Zeiss ELYRA microscope systems introduce two discrete superresolution techniques to optical microscopy for the first time. Structured Illumination Microscopy (SIM), developed by scientists at the University of San Francisco, and Photoactivated Localisation Microscopy (PAL-M) each offer extraordinarily high resolutions that overcome the classical diffraction limit to microscopic resolution.

Compared to conventional microscopy, superresolution images have up to double the resolution in all three spatial directions, down to less than 200 nanometers. The ability to resolve to this level within the living cell opens up original experimental possibilities, especially in cell biology and neurological research.

PAL-M technology offers the highest resolution currently available while the outstanding feature of SR-SIM technology is its high level of flexibility in the choice of dye. This means that both superresolution methods minimise previous limitations in dye selection or user-friendliness and that users no longer need to invest in single extremely specialised and expensive systems.

Three microscope systems are being offered. ELYRA S.1 is the first microscope system to offer SR-SIM technology on a standard microscope stand while ELYRA P.1 offers PAL-M technology commercially for the first time. The ELYRA PS.1 offers both technologies in one system and in combination



Photograph on right: Neuronal growth cone with widefield microscopy (left) and SR-SIM, staining for tubulin (red) and F-actin (green). Specimen: M Fritz and M Bastmeyer, University of Karlsruhe (TH), Germany.

with a laser scanning microscope, meaning that that an object can be successively imaged with LSM, SR-SIM and PAL-M.

For more information [E. micro@zeiss.co.uk](mailto:E.micro@zeiss.co.uk)

## High performance objectives optimised for live cell imaging

Nikon has launched its latest high performance, high numerical aperture (NA) objectives for use in biological applications. Featuring the highest ever NAs for water immersion objectives (1.27 and 1.25), these new objectives employ Nikon's unique, ultra low refractive index nano crystal coat, and are optimised for live cell imaging, providing the highest transmission at a broad range of wavelengths. This results in high contrast image acquisition, with faster image capture times at lower excitation levels, achieving less photobleaching and minimising damage to live cells, allowing longer-term observation. Comprising the CFI Plan Apo IR 60XWI and Lambda S series – CFI Apo 40XWILS, CFI Apo 60XHLAS and CFI Apo LWD 40XWILS, the new objectives feature high optical performance across the widest spectral wavelength with high chromatic corrections for sharp contrast imaging.

Nikon's nano crystal coating technology employs multiple layers of extra low refractive index nano particles that virtually eliminate internal lens element reflections across a wide range of wavelengths extending from the ultraviolet to the near-infrared. It is particularly effective in reducing stray light reflections and flare in high angle (large NA) lenses.

For further information Tel. +44 (0)208 247 1718, [E. info@nikoninstruments.eu](mailto:E.info@nikoninstruments.eu), [www.nikoninstruments.eu/Optics-Objectives](http://www.nikoninstruments.eu/Optics-Objectives)



## Cool camera for high definition

The DS-Fi1c is the latest addition to Nikon's Digital Sight series of cameras. Featuring a high definition cooled colour camera head and the latest optical technology, the DS-Fi1c is ideal for both brightfield and fluorescence applications as well as sensitive samples. An optimal microscopic digital imaging system can be configured for any bioscience or industrial application, from documentation to advanced image processing and analysis.

The DS-Fi1c uses a Peltier cooling mechanism to cool the CCD to 20°C below the ambient temperature. When capturing fluorescence images where long exposures are required, thermal background noise is suppressed, enabling capture of high contrast images. With a high dynamic range, low noise and high frame rate, the DS-Fi1c offers high performance under short and longer exposure times, and is suitable for sensitive samples across a wide variety of applications including fluorescence, brightfield, phase contrast and differential interference contrast (DIC). The high definition 5.0-megapixel CCD produces better fluorescence images.



For further information T. +44 (0)208 247 1718, [E. info@nikoninstruments.eu](mailto:E.info@nikoninstruments.eu), [www.nikoninstruments.eu/Cameras/Digital-Cameras/DS-Fi1c](http://www.nikoninstruments.eu/Cameras/Digital-Cameras/DS-Fi1c)

## Elekta's Extend receives FDA 510(K) clearance

At the 2009 Congress of Neurological Surgeons (CNS) Annual Meeting in New Orleans, Louisiana, Elekta demonstrated how its line of stereotactic solutions expand treatment capabilities and bring new hope for patients presenting serious conditions. Topping the list of innovations is Extend™, a stereotactic treatment programme that lets clinicians apply the power and precision of Gamma Knife® surgery to a broader class of targets, including certain cancers of the head and neck. Including a re-locatable frame and



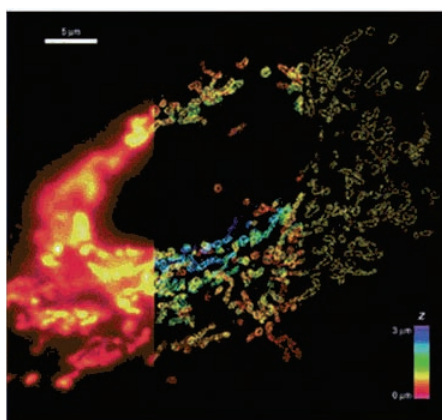
support for fractionated treatments, Extend provides cross functional advantages in both SRS and SRT for both neurosurgeons and radiation oncologists. Extend for Leksell Gamma Knife® Perfexion™ has received 510(k) clearance from the US Food and Drug Administration (FDA) and is now available in the United States.

For more information see [www.elekta.com](http://www.elekta.com)

## N-STORM microscopes will enhance resolution 10-fold

Nikon Corporation has signed a licensing agreement with Harvard University granting Nikon the rights to use the Stochastic Optical Reconstruction Microscopy (STORM) technology. Nikon will manufacture STORM enabled microscopy systems, designed to realise resolution higher than ever before achieved by conventional optical microscopes, and market them with the N-STORM name.

Enabling clearer observation of tissues and cells, STORM technology is an advanced form of optical microscopy – one of the most widely used imaging methods in biomedical research. However, the spatial resolution of optical microscopy, classically limited by the diffraction of light to several hundred nanometres, is substantially larger than typical molecular length scales in cells, leaving many biological investigations beyond the reach of light microscopy. To overcome this limit, a new form of high resolution light microscopy, STORM, was developed. STORM uses photo-switchable fluorescent probes to temporally separate the otherwise spatially overlapping images of individual molecules, allowing the construction of super resolution images. Using this concept,



Comparison of conventional and STORM images of mitochondria in a mammalian cell. The mitochondrial outer membrane protein Tom20 was labelled. (Left panel) Conventional image of the left part of the cell. (Middle panel) 3D STORM image of the middle part of the cell. The z-dimension information is colour-coded according to the colour scale bar. (Right panel) The xy-cross-section of the STORM image of the right part of the cell. Image courtesy of Zhuang Research Group, Department of Chemistry and Chemical Biology, Harvard University, Cambridge MA.

two- and three-dimensional, multicolour fluorescence images of molecular complexes, cells and tissues with a few tens of nanometres resolution have been achieved. This new form of fluorescence microscopy allows molecular interactions in cells and cell-cell interactions in tissues to be imaged at the nanometre scale.

Providing resolution that is 10 times or better than that of conventional optical microscopes, N-STORM is based on the world renowned Nikon Eclipse Ti research inverted microscope. The system incorporates CFI60 objectives featuring high numerical apertures developed using unique optical design, coatings and manufacturing techniques. The N-STORM instrumentation will be capable of multi-spectral two-dimensional and three-dimensional nanoscopy, with lateral resolution to approximately 20nm and axial resolution to approximately 50nm, extending the role of the optical microscope to near molecular level resolution. The N-STORM Super Resolution microscope system will be available in May 2010.

For more information T. +44 (0)208 247 1718,  
E. [info@nikoninstruments.eu](mailto:info@nikoninstruments.eu), [www.nikoninstruments.eu/N-STORM-Super-Resolution](http://www.nikoninstruments.eu/N-STORM-Super-Resolution)

## Molecular scale resolution possible with N-SIM microscopy system

Nikon Corporation has signed an agreement with the University of California, San Francisco Office of Technology Management for Structured Illumination Microscopy (SIM) technology. Under the terms of the agreement, UCSF will license its technology to Nikon to make N-SIM enabled microscopes designed to realise resolution higher than can be achieved by conventional optical microscopes.

Optical microscopes are essential for the clear observation of tissues and cells in life science research. However, if multiple objects such as protein molecules cluster at distances of less than 200nm apart, conventional optical microscopes cannot identify them as single objects, necessitating the use of instrumentation such as electron microscopes. Nikon's super resolution fluorescence microscopy technology greatly exceeds the resolution limits of conventional optical microscopes,



Conventional microscope Mitochondria in a living NIH3T3 cell stained with MitoTracker Red. N-SIM Mitochondria in a living NIH3T3 cell stained with MitoTracker Red. Total magnification: 250x

making it possible to view microstructures and nanostructures of fixed and living cells with molecular-scale resolution.

Nikon's N-SIM microscopy system can produce two times the resolution of conventional optical microscopes by combining SIM technology licensed from UCSF and based on the world renowned Eclipse Ti research inverted microscope with Nikon's legendary CFI Apo TIRF 100x oil objective lens (N.A. 1.49), developed using unique optical technologies and manufacturing techniques. Nikon's official

name for the commercialised system is Super Resolution Microscope N-SIM, and it will be available in May 2010.

For further information contact T. +44 (0)208 247 1718,  
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## Lumenera Corporation appoints Vision Source as distributors

Vision Source, an established company with a record in digital imaging solutions for microscopists, is pleased to announce their exclusive appointment by the Lumenera Corporation to sell and support their range of digital camera systems.

As a global market leader, Lumenera provides an extensive range of high quality digital cameras with unique combinations of speed, resolution and sensitivity to satisfy the demands of today's imaging applications. Lumenera also offers custom design services to OEM partners requiring specialised hardware and software features.

Lumenera's INFINITY USB 2.0 digital cameras offer 1.3 to 32 megapixel resolution and are specifically designed for life science, clinical or industrial applications. Every

camera includes INFINITY ANALYZE software for advanced camera control, image processing, measuring and annotation, as well as INFINITY CAPTURE, an intuitive user interface which includes all of the basic features needed to control your INFINITY camera and capture images.

Vision Source will carry stocks of INFINITY cameras which they will happily demonstrate to potential users.

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## Reinventing cranial fixation with the Neos Cranial Loop™

The NEOS Cranial LOOP™, the latest product from NEOS Surgery® is the first-ever cranial fixation device made entirely of PEEK-OPTIMA®, the advanced biocompatible polymer from Invibio Biomaterial Solutions. NEOS' innovative design harnesses PEEK-OPTIMA's unique combination of mechanical characteristics and performance properties to realise significant surgeon/patient benefits beyond the range of metallic biomaterials. The result of extensive research and development, the Cranial LOOP is a game-changing addition to NEOS' line of innovative cranial fixation devices.

The instrument-free design is made possible by PEEK-OPTIMA material characteristics (including high elastic modulus, high tensile strength, and highly radiolucent CT/MRI imaging without scattering or artifacts) and incorporates a

self-cutting function for removing the non-implantable part of the device. A fast and easy "pull and tighten" action allows the surgeon to control and feel the fixation; a standard bone flap with three Cranial LOOPS can be fixated in less than a minute. The NEOS Cranial LOOP produces fixation strengths similar to those of other standard metallic, non instrument-free fixation devices. Its unique design and materials allow it to perfectly adapt to the epicranial and subcranial shape and curvature.

The benefits and efficacy of the Cranial LOOP have been demonstrated by widespread commercial success across Europe.

*For more information contact NEOS Surgery at T. +34 935 944 726 (Barcelona, Spain), E. [info@neosurgery.com](mailto:info@neosurgery.com), [www.neosurgery.com](http://www.neosurgery.com)*



Neos Surgery Cranial LOOP Fixation.

## Eisai launches once-daily anti-epileptic, Zebinix®

Eisai has launched the once-daily anti-epileptic Zebinix® (eslicarbazepine acetate) in the UK as adjunctive therapy in adults with partial-onset seizures, with or without secondary generalisation. Zebinix (eslicarbazepine acetate) has been developed from the 40-year-old, 'gold standard' treatment, carbamazepine, but with significant changes to avoid formation of the epoxide metabolite associated with neurological side effects.

Pooled analysis of three phase III trials (1,049 adult patients with partial onset seizures; 800mg median daily dose) showed a 35% reduction in seizure frequency and a 36% responder rate for patients achieving at least a 50% reduction in seizure frequency.



Patients who then went on to one-year open label extension studies continued to take eslicarbazepine acetate with retention rates ranging from 68-79% at one year. Side effects were mostly described as mild to moderate and most commonly included dizziness, headache, drowsiness and nausea.

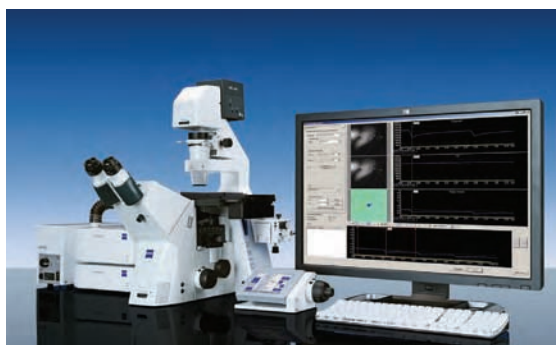
Patients reported improvements in health-related quality of life measures such as 'seizure worry' and 'cognitive function' as well as improvement in the depressive symptoms often reported by patients with poorly controlled epilepsy.

*For more information E. [Imedinfo@eisai.net](mailto:Imedinfo@eisai.net), T. +44 (0)20 8600 1400.*

## Carl Zeiss advances the study of highly dynamic processes within cells

Much of our understanding of the structural organisation of the living cell has come about through recent advances in fluorescence-labelling of target molecules and laser scanning microscopy. With the release of DirectFRAP from Carl Zeiss, scientists can now make similar strides in probing the dynamics of membrane transport and the movement of molecules within the living cell.

FRAP, FLIP, photoactivation, conversion of Dendra, on-off switching of Dronpa and other photomanipulation techniques, use a combination of intense pulses of laser light and widefield epi-fluorescence observation to measure the movement of fluorescent markers within the cell. Fitted to the Carl Zeiss Axio Observer microscope, DirectFRAP overcomes the dynamic compromises inherent in previous systems by eliminating the link between laser intensity and the size of the ROI, allowing simultaneous photo-manipulation across the entire area and first image acquisition in as little as two milliseconds. The precise millisecond control of the laser pulses is



achieved by acousto-optic tuneable filters (AOTFs) and the system is notable for its brilliant image formation at high acquisition rates and a wide observation field in fast experiments.

Flexible diaphragm options enable a high level of flexibility during experiments and DirectFRAP has been designed to be used in combination with other Carl Zeiss imaging systems, such as the Laser TIRF 3 or Cell Observer SD (Spinning Disc). These system combinations permit the observation of processes in a single Z plane and are ideal for the examination of the smallest cell structures. The same

lasers can be used simultaneously for DirectFRAP and Laser TIRF 3 or Cell Observer SD. With all systems, laser pulse control and data acquisition is performed by the ZEISS AxioVision software.

*For further information E. [micro@zeiss.co.uk](mailto:micro@zeiss.co.uk)*

## Branded or generic prescribing in epilepsy?

The Department of Health is currently considering legislation to allow pharmacists to dispense a generic drug against a branded prescription (ie generic substitution) in order to save money.

This is currently out for consultation, but many concerns have been raised about this issue, with particular reference to patients with epilepsy. Indeed, the National Society of Epilepsy has campaigned for an exemption of AED's from any policy of substitution. There is a real concern that patient safety may be compromised.

The potential savings are not likely to be significant enough to justify such draconian measures as it is reported that 84% of prescriptions are written generically and it is estimated that in a further 15% of cases there are clear clinical reasons for a branded prescription.

A potential saving would therefore relate to just 1% of all prescriptions.

In their guidance on the treatment of epilepsy NICE emphasised the importance of concordance and the necessity of involving the patient or carers in the healthcare decisions. The choice of presentation of AED may have an impact on concordance and there is good evidence that poor adherence to prescribed AED regimens is directly related to the incidence of seizures.

For example, Beacon Pharmaceuticals have said that there may be a number of reasons why patient adherence may be better with Episenta (controlled release sodium valproate) than with generic version. Factors such as the dosing interval or the ease of swallowing can have a significant impact on adherence and hence patient outcome.



For more information contact Beacon Pharmaceuticals, T. +44 (0)1892 600930.

## Bassetlaw installs a trio of Siemens systems

Bassetlaw Hospital, part of Doncaster and Bassetlaw Hospitals NHS Foundation Trust, is benefiting from enhanced imaging capabilities and streamlined workflow following the installations of a MAGNETOM® Avanto 1.5 Tesla MRI, Artis zee® Multipurpose and SOMATOM® Sensation CT from Siemens Healthcare.

The Avanto has been installed in Bassetlaw's MRI department for general scanning purposes and to provide diffusion imaging assistance in neurological examinations.

The system's spatial resolution capability has enabled the hospital to offer quick and high quality brain scans in accordance with National Stroke Strategy guidelines. The Avanto's syngo® Native™ application is beginning to be used to carry out scans on patients with severe renal impairments. The application is powered by Siemens' Tim® (Total imaging matrix)



technology, designed to increase flexibility, speed and accuracy in MRI and has enabled staff to carry out renal artery imaging without giving patients contrast CT procedures.

The Artis zee Multipurpose is being used in the X-ray department for a range of procedures. The system's superior image quality means that radiologists are able to rapidly detect and diagnose abnormalities such as tumours. The procedure is also less invasive than a traditional endoscopic examination.

The SOMATOM Sensation multislice scanner has enabled the hospital to streamline workflow and increase patient throughput.

For more information T. 01276 696338, E. [kerry.milton@siemens.com](mailto:kerry.milton@siemens.com), [www.siemens.co.uk/healthcare](http://www.siemens.co.uk/healthcare)

## SonoSite hand-carried ultrasound systems revolutionise orthopaedic surgery

SonoSite's MicroMaxx® and S-Nerve™ hand-carried ultrasound systems have become essential tools for regional anaesthesia at Morrision Hospital in Swansea, especially in orthopaedic surgery where approximately 75 % of the regional blocks in the hospital are performed.

Dr Christian Egeler, Consultant Anaesthetist at Morrision Hospital with a main interest in regional anaesthesia and chronic pain, explained, "We have established a service where one anaesthetist using a SonoSite hand-carried ultrasound system can perform regional blocks for two upper limb surgery lists simultaneously in a day surgical setting. This would clearly be impossible without ultrasound. Regional anaesthesia is far less traumatic for patients than general anaesthesia; they virtually jump off the table and are ready to go home within a few hours of surgery."

Dr Egeler continued, "The MicroMaxx system is flexible with excellent features, and the newer S-Nerve is perfectly suited for nerve block procedures, with just a few simple easy-to-use controls and excellent image quality on a large screen. We often carry the systems between the hospital's main orthopaedic theatre, the burns and plastics complex and the day surgical unit, and we can easily take them on the wards or to A&E when blocks are requested on site. I also use ultrasound for chronic pain relief in my back pain service; these patients need deep injections and, before we had the S-Nerves and the MicroMaxx, it was impossible to look at the back structures using ultrasound."



For more information T. +44 (0)1462 444 800, E [europa@sonosite.com](mailto:europa@sonosite.com) [www.sonosite.com](http://www.sonosite.com)

Zebinix is indicated as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

95% whale

Small change  
Big difference

Introducing new once-daily

**Zebinix**<sup>®</sup>  
eslicarbazepine acetate  
Evolved to add quality to life

**PRESCRIBING  
INFORMATION**  
Zebinix<sup>®</sup> ▽

(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<sub>cr</sub>) (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, hypoaacusis, 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, melana, 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 & C<sup>o</sup>, 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](http://www.yellowcard.gov.uk). Adverse events should also be reported to Eisai Ltd on 0208 600 1400/0845 676 1400 or [Lmedinfo@eisai.net](mailto:Lmedinfo@eisai.net)

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Date of preparation: October 2009  
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