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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

## In this issue



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**Date of Preparation:** January 2012

REB12-0002

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- patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis N.B. The individual Rebif 22 µg presentations are not indicated in the treatment of single clinical events suggestive of multiple sclerosis
- patients with relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years.

Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Initiate under supervision of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection. Recommended dose: Weeks 1 and 2: 8.8 µg three times per week (TIW); weeks 3 and 4: 22 µg TIW: week 5 onwards: 44 µg TIW (22 µg TIW can be used if patients cannot tolerate higher dose, but only in treatment of relapsing multiple sclerosis). RebiDose pre-filled pen is for single use and should only be used following adequate training of the patient and/or carer. Follow the instructions provided in the package leaflet.Rebif solution for injection in cartridge is for multidose use and should only be used with the RebiSmart autoinjector device following adequate training of the patient and/or carer. Follow the instructions provided with the RebiSmart device. Limited published data suggest that the safety profile in adolescents aged 12-16 years receiving Rebif 22 TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24 h afterwards, an antipyretic analgesic is advised to decrease flu-like symptoms.Evaluate patients at least every second year of the treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, or to any of the excipients; treatment initiation in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6 – 12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. If overdose occurs, hospitalise patient and give supportive treatment. **Side effects** In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. Very common: flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. Common: injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia, severe elevations of transaminase. Serious side effects include: injection site necrosis, hepatic failure, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, suicide attempt, Stevens-Johnson syndrome, dyspnoea, retinal vascular disorders. Consult the Summary of Product Characteristics for more information relating to side effects. **Legal category** POM Price Rebif 8.8 µg and 22 µg: 6 (0.2 ml) + 6 (0.5 ml) syringes - £552.19 Rebif 22 µg: 12 syringes (0.5 ml) - £613.52 Rebif 44 µg: 12 syringes (0.5 ml) - £813.21 Rebif 8.8 µg and 22 µg: 6 (0.2 ml) + 6 (0.5 ml) pens - £552.19 Rebif 22 µg: 12 pens (0.5 ml) - £613.52 Rebif 44 µg: 12 pens (0.5 ml) - £813.21 Rebif 8.8 µg/0.1 ml and 22 µg/0.25 ml: 2 cartridges – £406.61 Rebif 22 µg/0.5 ml: 4 cartridges – £613.52 Rebif 44 µg/0.5 ml: 4 cartridges – £813.21 For prices in Ireland, consult distributors Allphar Services Ltd. **Marketing Authorisation Holder and Numbers:** Merck Serono Europe Ltd, 56 Marsh Wall, London, E14 9TP; EU/1/98/063/007; 003 ; 006 ; 017; 013 ; 016 ; 010 ; 008 ; 009 **For further information contact: UK:** Merck Serono Ltd, Bedfont Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono, 4045 Kingswood Road, Citywest Business Campus, Dublin 24. Tel: 01 4687590
**Date of Preparation:** December 2011.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. In the Republic of Ireland information can be found at www.imb.ie. Adverse events should also be reported to Merck Serono Limited – Tel: +44(0)20 8818 7373 or email: medinfo.uk@merckserono.net.

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There was a time when the diagnosis of an inherited neuropathy relied on clinical features, neurophysiology and a keen knowledge of their classification. However, in recent years the use of genetic tests has transformed this field as Houlden et al reveal in their excellent review. In this article they not only describe the variety of genes that underlie these different inherited neuropathies but also give practical advice as to the batting order of tests based on the type of inheritance and other relevant factors. They also discuss how this field will evolve with next generation sequencing, and if you do not know what that means, then do read this review!

Terje Lømo delivers a wonderful account of long term potentiation (LTP) starting with his discovery of this back in 1966. He goes on to describe the synaptic processes underlying it and what this process means for learning and memory, and how this can be maladaptive in some clinical situations. This is yet another stimulating and revealing contribution in our series on Leading Norwegian Neurosciences Discoveries and is probably the best account of LTP that I have ever read!

Alastair Compston and Alasdair Coles take us through their final three papers in their selection of the Top Ten papers in Multiple Sclerosis. Their selection includes pivotal studies on immunotherapy; diagnostic criteria and the use of MRI. As with their whole series, their commentaries take us through the importance of the studies which they impart with a great sense of history and personality as they reveal details of the lives of those who undertook such work.

Anthony David and Tim Nicholson describe the approach to the patient with severe medically unexplained neuro-disability. They frame their discussion in the form of the case of a person with severe disability despite an array of normal tests, and describe how common such cases are; how rarely they go on to develop some clear organic major neurological problem; and how they can be helped by inpatient care from neuropsychiatrists. This is another fabulous contribution to the series on Clinical Dilemmas in Neuropsychiatry edited by Alan Carson and Jon Stone.

Joanna Coghill discusses the use of botulinum toxin in the management of childhood spasticity. She highlights that there is limited clinical trial data to support its use, but also makes the point that it can be very beneficial in certain specific instances.

Rhian Raftopoulos and Anand Trip treat us to a lovely review on optical coherence tomography (OCT) and how it has been used, especially in the context of ocular disease and optic neuritis. The authors explain the way in which OCT can give detailed anatomical data on the integrity of the retina and optic nerve fibres as they emerge and form the optic nerve and how this information can then be used, not only in confirming diagnoses, but also as a biomarker of axonal loss. Whilst traditionally being used in the context of optic neuritis in MS, it is now being looked at in ever increasing numbers of conditions including chronic neurodegenerative disorders of the CNS such as Alzheimer's and Parkinson's Disease.

Pooja Dassan tells us of a new ebrain project that seeks to teach at a distance and which has now been successfully completed, despite governments cuts in funding the project.

We have our usual reviews and a brand new MS supplement. Enjoy! ◆

*Roger Barker, Co-Editor.*

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

# Gilenya. Now recommended by NICE.

## It's time for a more comfortable conversation when interferon fails

NICE has now recommended Gilenya, the first once-daily capsule, for patients with highly active relapsing remitting multiple sclerosis if they have an unchanged or increased relapse rate or ongoing severe relapses when compared with the previous year despite treatment with interferon-beta.[1]

Abbreviated Prescribing Information: GILENYA® (fingolimod)
Important note: Before prescribing, consult Summary of Product Characteristics (SmPC).
Presentation: Hard capsule containing 0.5 mg fingolimod (as hydrochloride).
Indications: Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:
- Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as: those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.
Dosage: Adults: Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. One 0.5 mg capsule to be taken orally once daily. Patients can switch directly from beta interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia. Use with caution in patients aged 65 years and over. Safety and efficacy of Gilenya in children up to 18 years has not been established. No dose adjustments required in patients with mild to severe renal impairment or mild to moderate hepatic impairment. Exercise caution in patients with mild to moderate hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh class C). Use with caution in patients with diabetes mellitus due to an increased risk of macular oedema.
Contraindications: Known immunodeficiency syndrome, patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis), known active malignancies, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), hypersensitivity to the active substance or to any of the excipients.
Warnings/Precautions: Bradyarrhythmia: Initiation of treatment results in a transient decrease in heart rate which may be associated with atrioventricular conduction delays. Observe all patients for 6 hours for bradycardia. In the event of bradyarrhythmia-related symptoms, initiate appropriate clinical management and observe until symptoms resolve. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Gilenya has not been studied in patients with sitting heart rate <55 beats per minute, second degree or higher AV block, sick-sinus syndrome, ischaemic cardiac disease, congestive heart failure, significant cardiovascular disease, a history of syncope or those taking beta blockers. Seek advice from a cardiologist before initiation of treatment in these patients. Gilenya should not be co-administered with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Exercise caution at treatment initiation in patients receiving beta blockers, or other substances which may decrease heart rate (e.g. verapamil, digoxin, anticholinesteratic agents or pilocarpine) due to possible additive effects. Avoid medicinal products that may prolong QTc interval. Infections: Reduction of the lymphocyte count to 20-30% of baseline values occurs with Gilenya. Perform a complete blood count (CBC) at baseline and periodically during treatment, and in case of signs of infection, stop Gilenya until recovery if absolute lymphocyte count <0.2x10⁹/L is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing Gilenya. Gilenya may increase the risk of infections. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. Macular oedema: Macular oedema with or without visual symptoms has been reported in patients taking Gilenya. Perform an ophthalmological evaluation 3-4 months after Gilenya initiation. Evaluate the fundus, including the macula in patients reporting visual disturbances. Perform ophthalmological evaluation prior to initiating therapy and periodically thereafter in patients with diabetes mellitus or a history of uveitis. Discontinue Gilenya if a patient develops macular oedema. Liver function: Do not use Gilenya in patients with severe pre-existing hepatic

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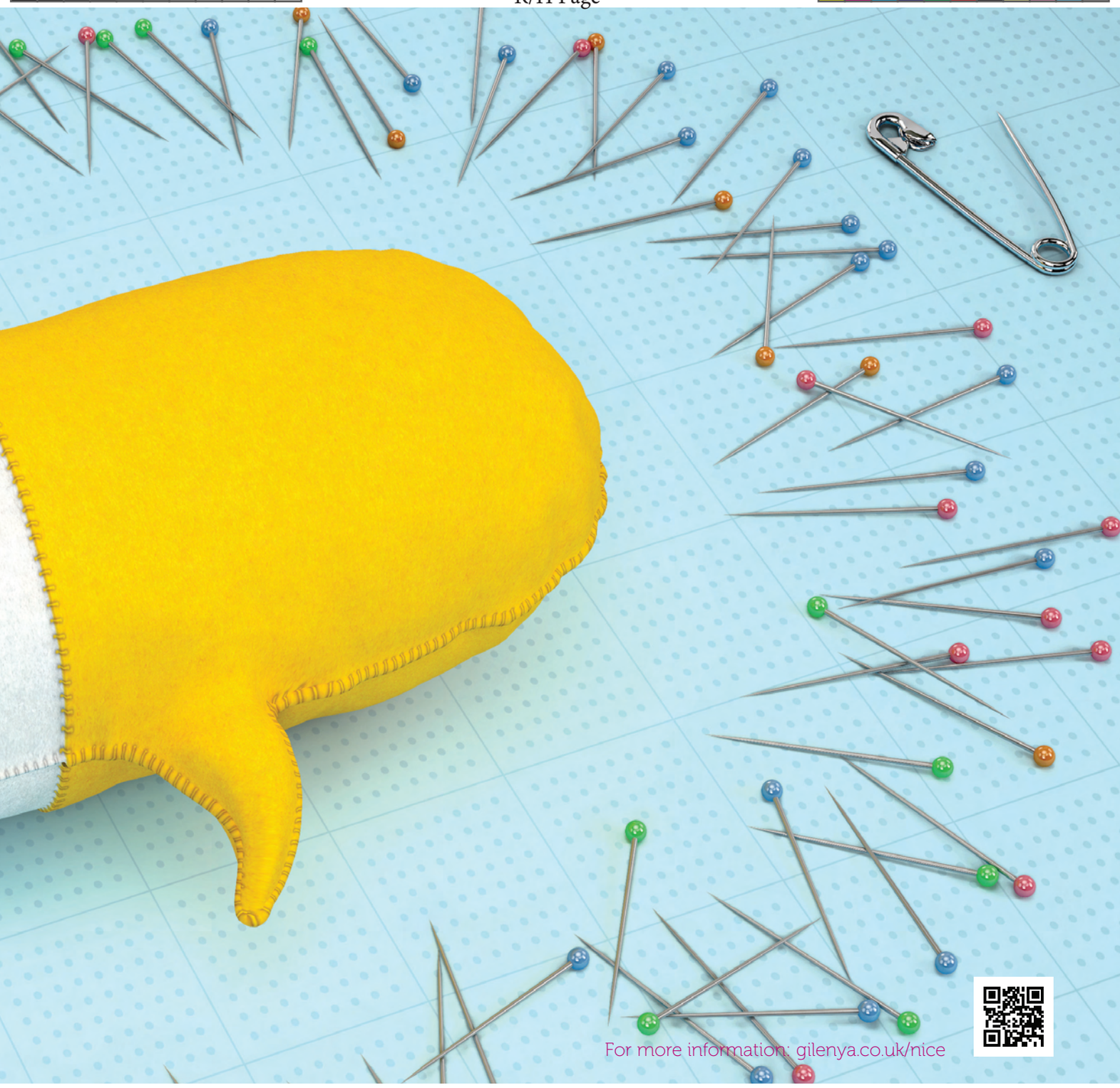


injury (Child-Pugh class C). Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before initiation of Gilenya. Monitor liver transaminases at months 1, 3, 6, 9 and 12 and periodically thereafter. Institute more frequent monitoring if transaminases rise above 5 times the ULN, including serum bilirubin and alkaline phosphatase (ALP) measurement. Stop Gilenya treatment with repeated confirmation of liver transaminases above 5 times the ULN and only re-commence once liver transaminase values have normalised. Patients with symptoms of hepatic dysfunction should have liver enzymes checked and discontinue Gilenya if significant liver injury is confirmed. Resume Gilenya only if another cause of liver injury is determined and if the benefits of therapy outweigh the risks. Exercise caution with Gilenya use in patients with a history of significant liver disease. Serological testing: Peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes. Blood pressure effects: Gilenya can cause a mild increase in blood pressure. Monitor blood pressure regularly during Gilenya treatment. Respiratory effects: Use Gilenya with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease due to minor reductions in values for forced expiratory volume (FEV1) and diffusion capacity for carbon monoxide (DLCO). Prior immunosuppressant treatment: No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya assuming any immune effects (e.g. neutropenia) have resolved. Exercise caution when switching patients from natalizumab to Gilenya owing to the long half life of natalizumab and concomitant immune effects. Stopping therapy: Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the discontinuation of Gilenya due to possible additive effects on the immune system.

Interactions: Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects. Exercise caution when switching patients from long-acting therapies with immune effects, e.g. natalizumab or mitoxantrone. No increased rate of infection was seen with concomitant treatment of relapses with a short course of corticosteroids. Vaccination may be less effective during and for up to 2 months after Gilenya treatment. Avoid use of live attenuated vaccines due to infection risk. Due to additive effects on heart rate, exercise caution when initiating Gilenya in patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers like verapamil or diltiazem, digoxin, anticholinesteratic agents or pilocarpine. Caution is indicated with substances that may inhibit CYP3A4. Co-administration of fingolimod with ketoconazole increases fingolimod exposure. No interaction has been observed with oral contraceptives when co-administered with fingolimod.

Fertility, pregnancy and lactation: There is potential for serious risk to the fetus with Gilenya. A negative pregnancy test is required before initiation of Gilenya. Female patients must use effective contraception during treatment with Gilenya and for 2 months after discontinuation. Discontinue Gilenya if a patient becomes pregnant. Fingolimod is excreted into breast milk. Women receiving Gilenya should not breast feed. Fingolimod is not associated with a risk of reduced fertility.

Undesirable effects: Very common (≥1/10); Influenza viral infections, headache, cough, diarrhoea, increased alanine transaminase (ALT), back pain. Common (≥1/100 to <1/10); herpes viral infections, bronchitis, sinusitis, gastroenteritis, tinea infections, lymphopenia, leucopenia, depression, dizziness, parasthesia, migraine, blurred vision, eye pain, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, asthenia, increased gamma-glutamyl transferase (GGT), increased hepatic enzymes, abnormal liver function test, increased blood triglycerides, decreased weight. Uncommon (≥1/1,000 to <1/100); pneumonia, macular oedema, decreased neutrophil count.

Packs and price: Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50. Blister packs containing 28 x 0.5 mg hard capsules: £1470.

Legal classification: POM

Marketing Authorisation Holder: Novartis Europharm Ltd, Wimblehurst Rd, Horsham, W Sussex, RH12 5AB, UK.

Marketing Authorisation Numbers: 7 x 0.5 mg hard capsules: EU/1/11/677/001, 28 x 0.5 mg hard capsules: EU/1/11/677/005

Date of last revision of prescribing information: January 2012

Full Prescribing Information available from: Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Surrey, GU16 7SR. Tel: (01276) 692255 Fax: (01276) 692508.

Reference:
1. Fingolimod FAD March 2012

Adverse events should be reported. Reporting forms and information can be found at yellowcard.mhra.gov.uk Adverse events should also be reported to Novartis (01276) 698370

Date of preparation: March 2012 Code: FIN12-CO36b

GILENYA™ (fingolimod) 0.5 mg

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## EFNS Fellowship winners 2012

Congratulations to the winners of the EFNS 2012 Fellowships.

Olena Fartushna from Ukraine was selected for her project: *Cerebral ischaemia measured using MRI spectroscopy* (cerebral ischaemia study) which she will carry out at the Acute Stroke research unit, Western Infirmary, Glasgow, UK chaired by Prof Kennedy Lees.

Olena Fartushna

Andrei Ivashynka from Belarus was selected for his project: *The long-term follow-up study of the first epileptic seizure risk factors in two large cohorts of alcohol use patients* which he will carry out at the Department of Neurology and Rehabilitation, University of Piemonte, Novarra, Italy chaired by Prof Roberto Cantello.

Andrei Ivashynka

Cristina Laza from Romania was selected for her project: *Sonographic monitoring of the optic nerve in patients with increased intracranial pressure* which she will carry out at the Department of Neurology, Justus-Liebig-University Giessen, Germany chaired by Prof Manfred Kaps.

Cristina Laza

Isabel Parees-Moreno from Spain was selected for her project: *Self agency in functional movement disorders* which she will carry out at the the Sobell Department of Motor Neurosciences and Movement Disorders, Queen Square, London, UK chaired by Prof Linda Greensmith.

Isabel Parees-Moreno

Cristina Muntean from Romania was selected for her project: *Prospective study of patients with non-anti MAG DADS neuropathy as a possible variant of CIDP* which she will carry out at the National Reference Center for Neuromuscular Diseases Hospital Pitié-Salpêtrière, Paris, France chaired by Prof Jean-Marc Léger.

Cristina Muntean

Aliona Nacu from Moldova was selected for her project: *Clinical, electro-physiological and immunological assessment of pharmacoresistant Myasthenia Gravis* which she will carry out at the Department of Neurology, Haukeland University Hospital, Bergen, Norway chaired by Prof. Ole-Bjørn Tysnes.

Aliona Nacu

Maria Nazarova from Russia was selected for her project: *Investigation of the effect of action observation and motor imagery on the cortical excitability in healthy subjects: combination of navigated transcranial magnetic stimulation and EEG* which she will carry out at the HUSLab, Helsinki University Hospital, Finland chaired by Dr. Jyrki Mäkelä.

Maria Nazarova

***More information about the 2012 winners is available at: www.efns.org***

## European Academy of Rehabilitation Announces New Annual Prize

The European Academy of Rehabilitation has created an annual prize. The prize is 1200 Euros plus up to 450 Euros for registration, travelling and accommodation when the prize is presented. A submission should be on a rehabilitation, physical medicine or medico-social topic relating to the (re-)integration or persons with disabilities. It should be the work of a doctor or health professional employed in a Physical and Rehabilitation Department of a country which has an official delegate in the Physical and Rehabilitation Medicine Section of European Union of Medical Specialists. (www.euro-prm.org). Candidates should submit their work by 31st July 2012 at the latest.

***For more information about this prize see: www.bsrm.co.uk/***

# Advances in the Genetics of Peripheral Nerve Disorders

***Amelie Pandraud, BSc MSc***

studied Brain, Behaviour and Cognitive Science at the University of Michigan, and then moved to London where she obtained an MSc in Clinical Neuroscience at the Institute of Neurology, University College London, Queen Square. Currently a PhD student at the Institute of Neurology, investigating the genetics of peripheral neuropathies, particularly Charcot-Marie-Tooth Disease.

***Yo-Tsen Liu, MD***

is Lecturer at the National Yang-Ming University School of Medicine, Taipei, Taiwan and a neurologist at Taipei Veterans General Hospital, Taiwan and has developed particular interests in peripheral neuropathies and cerebellar ataxias. She is currently carrying out a PhD at UCL Institute of Neurology. Her research project is to look for the mutated genes in a cohort of patients with severe ataxia and peripheral neuropathy by employing the techniques of next generation sequencing and to look at the functional consequences of these genes.

***Henry Houlden, MRCP, PhD***

is Professor of Neurology and Neurogenetics, Institute of Neurology, whose clinical and research interest is genetics, mainly when applied to inherited neurological disorders such as Charcot Marie Tooth disease, inherited ataxia, spastic paraplegia and other movement disorders. He is also interested in the identification of genetic risk factors through genome wide studies in multiple system atrophy (MSA), Inclusion Body Myositis (IBM), stroke and intracranial aneurysms as well as the development of next generation technologies for research and diagnostics.

***Correspondence to:***
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MRC Centre for Neuromuscular Diseases and the Department of Molecular Neurosciences,
UCL Institute of Neurology,
Queen Square,
London, WC1N 3BG, UK.

Inherited disorders of the peripheral nerve may be classified into those in which the neuropathy is the main feature, and those in which it is part of a more generalised disorder. The advent of novel sequencing technologies has started to revolutionise the screening of known genes and allowed the identification of numerous genes to be newly associated with neuropathies, including Charcot-Marie-Tooth disease (CMT), distal hereditary motor neuropathy (dHMN), hereditary sensory and autonomic neuropathy (HSAN) and hereditary neuralgic amyotrophy (HNA). Indeed, the past two years have seen a significant shift from traditional Sanger sequencing to next-generation sequencing (NGS) methods including whole-genome sequencing, exome sequencing and customized gene panels. As a result, the number of peripheral neuropathy-related genes has nearly doubled in the past few years and continues to rise. This review will provide an update on the genetics of the inherited neuropathies and the implications of NGS to both research and diagnostic services.

**Charcot-Marie-Tooth Disease, hereditary sensory and autonomic neuropathy, distal hereditary motor neuropathy and hereditary neuralgic amyotrophy**

CMT, otherwise known as hereditary motor and sensory neuropathy (HMSN) is a heterogeneous group of diseases, both clinically and genetically. Patients typically exhibit wasting and weakness of distal muscles, reduced reflexes, foot deformities (pes cavus), sensory loss and walking difficulties. CMT is the most common inherited neuromuscular disease, with a prevalence of approximately 1 in 2500, with some variation between populations.[1] In the era prior to the identification of the chromosome 17 duplication including the *peripheral myelin protein 22* (*PMP22*) gene in CMT patients in the 1990s,[2,3,4,5] CMT was categorised primarily according to neurophysiological studies and peripheral nerve pathology.[6] Patients with upper limb motor nerve conduction velocities (NCVs) under 38m/s are classified as CMT1, or demyelinating CMT, and patients with NCVs greater than 38m/s as CMT2, or axonal CMT. An evermore recognised intermediate form describes patients with both axonal and demyelinating features and NCVs between 25 and 45 m/s.[7] The advances made in the genetics of neuropathies in the past two decades have further subdivided CMT according to pattern of inheritance and over 40 causative genes or loci.[6] Autosomal recessive (AR) forms of CMT1 are referred to as CMT4. CMT3 (also called congenital hypomyelinating neuropathy (CHN) or Dejerine-Sottas disease (DSD)) is sometimes used to classify children with a severe demyelinating or hypomyelinating neuropathy usually associated with de novo dominant mutations in *PMP22*, *myelin protein zero (MPZ)* or *early growth response 2 (EGR2)*.[8]

Genes involved in CMT encode proteins with increasingly diverse roles, including myelin structural components, transcription factors needed for gene regulation, protein synthesis, axonal transport, endocytosis and protein sorting, mitochondrial fusion and fission, and ion channels. Metabolic enzymes have also been implicated in CMT: mutations in *PRPS1* have been associated with hereditary peripheral neuropathy with hearing loss and optic neuropathy (CMTX5), opening up the possibility of treating this CMT subtype with antimetabolite therapy.[9]

HSAN is caused by the degeneration of sensory and autonomic neurons. Patients often present with sensory loss and ulcerative mutilations. Autonomic involvement is more likely in AR forms, while motor problems tend to be associated with AD forms of HSAN. AR forms usually have earlier onset. HSAN is categorised into five subtypes according to age of onset, inheritance and phenotype. The 12 genes implicated in HSAN thus far encode proteins with roles in sphingolipid metabolism, DNA methylation, endoplasmic reticulum tubulation, membrane excitability, cytoskeletal organisation, axonal guidance during development and vesicular transport.[10] In contrast, dHMN, also known as distal spinal muscular atrophy (dSMA) predominantly involves motor nerves although some degree of sensory problems may be observed. dHMN is classified into seven subtypes; both AD and AR inheritance have been described. Functions of proteins implicated in dHMN include chaperones, protein synthesis, RNA and DNA unwinding, axonal transport, ion channels and metallation of copper enzymes.[11]

**Novel findings in the genetics of peripheral neuropathies**

The list of genes implicated in inherited peripheral neuropathies is constantly growing. Tables 1, 2 and 3 summarise the genetic subtypes and associated phenotypes in CMT, HSAN and dHMN.

In addition to the identification of new genes, unexpected mutations in previously known peripheral neuropathy genes have been discovered. An alternatively sized duplication upstream of *PMP22* was detected in a CMT patient; the duplication did not encompass *PMP22* and therefore would have been

**Table 1. Classification of CharcotMarieTooth**

| Subtype | Gene/Locus | Phenotype |
|---|---|---|
| **CMT1** | | |
| ADCMT1 | | |
| CMT1 | *PMP22* (Duplication 17p) | Classic CMT1 |
| | *PMP22* (point mutation) | CMT1/DSN/CHN/HNPP |
| HNPP | *PMP22* (Deletion 17p) | |
| CMT1B | *MPZ* | CMT1/CMT2/ICMT/DSN/CHN |
| CMT1C | *LITAF (SIMPLE)* | CMT1 |
| CMT1D | *EGR2* | CMT1/DSN/CHN |
| CMT1E | *MPZ* | (CMT1B) |
| CMT1F | *NEFL* | (CMT 2E) |
| Other | *MFN2* | (CMT 2A) |
| | *PRX* | (CMT4F) |
| | *SOX10* | CMT1/CHN/WaardenburgHirschsprung disease |
| ARCMT1 (CMT4) | | |
| CMT4A | *GDAP1* | severe CMT1/CMT2/DSN/possible vocal cord and diaphragm paralysis/rare AD families |
| CMT4B1 | *MTMR2* | severe CMT1/facial weakness/bulbar palsy |
| CMT4B2 | *MTMR13 (SBF2)* | severe CMT1/glaucoma |
| CMT4C | *SH3TC2 (KIAA1985)* | severe CMT1/scoliosis |
| CMT4D | *NDRG1* | severe CMT1/gypsy/deafness/tongue atrophy |
| CMT4E | *EGR2* | (CMT1D) |
| CMT4F | *PRX* | CMT1 with more sensory involvement/rare AD families |
| CMT4H | *FGD4* | CMT1 |
| CMT4J | *FIG4* | CMT1 |
| CCFDN | *CTDP1* | CMT1/gypsy/cataracts/dysmorphic features |
| HMSN Russe | *HK1* | severe CMT1/early onset/possible proximal weakness/Russe families |
| Other | *PMP22* | Classic CMT1/DSN/CHN/HNPP |
| | *MPZ* | CMT1/CMT2/ICMT/DSN/CHN |
| **CMT2** | | |
| ADCMT2 | | |
| CMT2A | *MFN2* | CMT2/more progressive/optic atrophy/tremor |
| CMT2A | *KIF1B* | CMT2/usually severe/optic atrophy |
| CMT2B | *RAB7* | CMT2 with predominant sensory involvement and sensory complications |
| CMT2C | *TRPV4* | CMT2/dHMN(Congenital SMA)/Scapuloperoneal SMA/respiratory involvement/ arthrogryposis, laryngomalacia, and vocal cord paresis |
| CMT2D | *GARS* | CMT2 with predominant hand wasting/dHMNV |
| CMT2E | *NEFL* | CMT1/CMT2/ICMT/usually early onset and severe/rare AR families |
| CMT2F | *HSP27 (HSPB1)* | CMT2/dHMNII |
| CMT2G | 12q12q13.3 | CMT2 |
| CMT2H | *GDAP1* | (CMT4A) |
| CMT2I | *MPZ* | (CMT1B) |
| CMT2J | *MPZ* | (CMT1B) |
| CMT2K | *GDAP1* | (CMT4A) |
| CMT2L | *HSP22 (HSPB8)* | CMT2/dHMNII |
| CMT2M | *DNM2* | (DICMTB) |
| CMT2N | *YARS* | (DICMTC) |
| ADCMT2 | | |
| ARCMT2A | *LMNA* | CMT2 with proximal involvement/rapid progression/muscular dystrophy/cardiomyopathy/lipodystrophy |
| ARCMT2B | *MED25 (ARC92; ACID1)* | CMT2 |
| ARCMT2C | *GDAP1* | CMT1/CMT2/usually early onset and severe/possible vocal cord and diaphragm paralysis/rare AD families |
| Other | *NEFL* | (CMT2E) |
| | *MFN2* | (CMT2A) |
| **Xlinked CMT** | | |
| CMTX1 | *GJB1 (Cx32)* | CMT1/CMT2/ICMT, male MCVs < female MCVs |
| CMTX5 | *PRPS1* | severe CMT2 with deafness and optic atrophy |
| **Dominant intermediate CMT (DICMT)** | | |
| DICMTA | 10q24.125.1 | CMT2 |
| DICMTB | *DNM2* | CMT1/CMT2 |
| DICMTC | *YARS* | CMT1/CMT2 |
| DICMTD | *MPZ* | (CMT1B) |
| Other | *NEFL* | (CMT2E) |
| | *MFN2* | (CMT2A) |
| **Hereditary neuralgic amyotrophy (HNA)** | | |
| HNA | *SEPT9* | Recurrent neuralgic amyotrophy |

AD, autosomal dominant; AR, autosomal recessive; CHN, congenital hypomyelinating neuropathy; DSN, Dejerine Sottas neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; MCV, motor conduction velocity

**Table 2. Classification of hereditary sensory and autonomic neuropathies**

| Subtype | Inheritance | Gene/Locus | Phenotype |
|---|---|---|---|
| HSAN I | AD | *SPTLC1* | pansensory loss/lancinating pain /variable distal motor involvement/acromutilation /adolescence onset |
| | AD | *SPTLC2* | pansensory loss/lancinating pain /variable distal motor involvement/acromutilation/adult onset |
| | AD | *ATL1* | severe distal sensory loss and amyotrophy in lower limbs/ trophic skin and nail changes /acromutilation/adult onset |
| HSAB1B | AD | 3p22p24 | cough/gastrooesophageal reflux/rare/adult onset |
| HSANI with dementia and hearing loss | AD | *DNMT1* | loss of all somatosensory modalities/lancinating pain/acromutilations/ sensorineuronal hearing loss/dementia/adult onset |
| CMT2B | AD | *RAB7* | sensorimotor with sensory complications/loss of nociception |
| HSAN II | AR | *HSN2(WNK1)* | loss of pain, temperature and touch sensation/mutilations in hands and feet/acropathy/ congenital or early childhood onset/severe |
| | AR | *FAM134B* | impaired nociception/progressive mutilating ulceration of hands and feet/osteomyelitis/ childhood onset |
| | AR | *KIF1A* | impaired position and vibration senses/acromutilations/minor distal weakness/childhood to adolescence onset |
| HSAN III | AR | *IKBKAP* | no response to painful stimuli and temperature changes/RileyDay syndrome/predominantly autonomic with vasomotor instability and hyperhidrosis/absence fungiform papillae of the tongue/congenital |
| HSAN IV | AR | *NTRK1* | congenital insensitivity to pain with anhydrosis(CIPA)/episodic fever/skin and corneal lesions/ joint deformities/mental retardation/unmyelinated fibres mainly affected |
| HSAN V | AR | *NTRK1* | congenital insensitivity to pain with mild anhydrosis/no mental retardation/mainly small myelinated fibres affected |
| | AR | *NGFB* | congenital insensitivity to pain/severe loss of deep pain perception/minimal autonomic/ painless fractures, joint deformities/no mental retardation/mainly unmyelinated fibres affected |
| HSAN with spastic paraplegia | AR | *CCT5* | loss of all somatosensory modalities/acromutilation/spastic paraplegia |
| Channelopathy associated insensitivity to pain | AR | *SCN9A* | congenital insensitivity to pain/Erythromelalgia |

missed by traditional diagnostic methods. The duplicated segment likely contains a regulatory region affecting *PMP22* expression.[12] In fact, distal enhancers upstream of *PMP22* have recently been identified.[13] A shorter, 800kb duplication encompassing *PMP22* was found in a patient with demyelinating CMT.[14] Copy number variants (CNVs) in the *PMP22* region arising from new mechanisms involving non-recurrent rearrangements have also been associated with HNPP and CMT1A.[15]

Besides the chromosome 17 duplication and whole gene deletions of *GJB1*,[16,17,18] CNVs were not thought to be extensively involved in the aetiology of CMT.[14] Recently however, a duplication of the *MPZ* gene was found to cause CMT. This finding suggests that CNVs may indeed play a role in CMT.[19]

A synonymous change activating a cryptic splice site in *MPZ* was found in a patient with DSD.[20] Silent nucleotide changes are usually ignored in the analysis of sequencing data. Additional precautions will now need to be taken when categorising such variants as non-pathogenic. Similarly, mutations in the un-translated region upstream of *gap junction beta-1 (GJB1)* thought to affect splicing have been found in X-linked CMT.[21,22]

These unexpected findings raise the possibility of novel mechanisms of disease and suggest that new considerations need to be taken into account when interpreting results both in diagnostic and research settings.

## Expanding genotype-phenotype correlations

The identification of new peripheral neuropathy genes and new mutations in known peripheral neuropathy genes is leading to increasingly complex genotype-phenotype correlations. *Mitochondrial DNA polymerase γ (POLG1)* mutations were found in a patient with AR axonal CMT associated with tremor and ataxia; however, this patient showed no features commonly associated with mitochondrial disease.[23] Similarly, *ATP7A* mutations, which typically cause severe Menkes disease or occipital horn syndrome,[24] were found in a patient with X-linked dHMN and no copper deficiency.[25] Mutations in *Atlastin-1 (ATL1)* were described in a patient with HSAN Type 126; this gene is also associated with early onset hereditary spastic paraplegia SPG3A.[27] The genetic basis of a syndrome including AR early onset spastic ataxia and peripheral neuropathy has recently been attributed to mutations in *AFG3L2* using exome sequencing.[28] AD-inherited mutations in this gene are usually associated with spinocerebellar ataxia type 28 (SCA28).[29] This new clinical syndrome had overlapping features of both AD SCA28 and AR hereditary spastic paraplegia type 7, both of which are frequently associated with peripheral neuropathy. Interestingly, both diseases are due to mutations in genes encoding subunits of a particular class of mitochondrial proteases; although these two proteins interact, they lead to strikingly different phenotypes when dysfunctional (Figure 1). This finding also illustrates how NGS can be effective in determining the cause of a complex neuropathy syndrome.[28]

The causative genes responsible for complex forms of CMT were also recently described; these may represent new syndromes. Mutations in *Fibulin-5 (FBLN5)*, encoding a constituent of the extracellular matrix needed for elastic fibre assembly were found in a case of AD CMT. Mutations were subsequently identified in other CMT families with hyperelastic skin, and in patients with age-related macular degeneration, most of whom had a mild to severe peripheral neuropathy.[30] *DNA (cytosine-5-)-methyltransferase 1 (DNMT1)* mutations were associated with both central and peripheral neurodegeneration in one form of hereditary sensory and autonomic neuropathy with dementia and hearing loss.[31] Sporadic or AD intermediate CMT associated with focal segmental glomerulosclerosis (FSGS) was found to be caused by mutations in the *inverted formin, FH2 and WH2 domain containing (INF2)* gene, encoding a protein known to interact with other proteins essential for myelination and myelin maintenance.[32] The association of these genes with such complex phenotypes will help provide new insights into peripheral nerve function.

**Table 3. Classification of distal hereditary motor neuropathies**

| Subtype | Inheritance | Gene/Locus | Phenotype |
|---|---|---|---|
| dHMN I | AD | *HSPB8*<br>*HSPB1*<br>*GARS* | Juvenile onset |
| dHMN II | AD | *HSPB8*<br>*HSPB1*<br>*HSPB3*<br>*BSCL2* | Adult onset typical dHMN/CMT2L<br>Adult onset typical dHMN/CMT2F |
| dHMN III | AR | *11q13* | Early onset/slowly progressive |
| dHMN IV | AR | *11q13* | Juvenile onset/diaphragmatic involvement |
| dHMN VA | AR | *GARS* | Upper limb onset dHMN, slowly progressive/CMT2D |
| dHMN VB | AD | *BSCL2* | Upper limb onset dHMN, possible spasticity in lower limbs/Silver syndrome(SPG 17) |
| dHMN VI | AR | *GHMBP2* | SMARD1/infantile onset respiratory distress |
| dHMN VII | AD | *TRPV4*<br>*DCTN1* | Adult onset/vocal cord paralysis<br>Adult onset/vocal cord paralysis/facial weakness |
| dHMN and pyramidal features | AD | *SETX*<br>*BSCL2* | HMN/ALS4 /early onset/pyramidal signs |
| dHMNJ | AR | 9p21.1p12 | Juvenile onset/pyramidal signs/originating in the Jerash region of Jordan |
| Congenital distal SMA | AD | *TRPV4* | distal weakness at birth/CMT2/congenital SMA/scapuloperoneal SMA/ arthrogryposis/vocal cord paresis |
| Xlinked dHMN | Xlinked | *ATP7A* | distal onset wasting and weakness |

HSPB8 (HSP22); HSPB1 (HSP27); AD, autosomal dominant; AR, autosomal recessive; ALS, amyotrophic lateral sclerosis; SMA, spinal muscular atrophy; SMARD1, spinal muscle atrophy with respiratory distress type 1

### Frequency of genetic subtypes and diagnostic guidelines

In the European/UK and US population, the AD forms of CMT1 and CMT2 are more common and represent about 90% of CMT patients; however, approximately 40% of CMT patients exhibit AR inheritance in populations with high rates of consanguineous marriage such as the region of the Mediterranean basin.[6] The most frequent subtypes of CMT include CMT1A (55% of CMT and 66.8% of CMT1), CMT1X (15.2% of CMT and 18.4% of CMT1), HNPP (9.1% of CMT), CMT1B (8.5% of CMT and 10.4% of CMT1) and CMT2A (4% of CMT and 21.9% of CMT2), while other subtypes account for less than 1% of all CMT.[33-37] *SH3 domain and tetratricopeptide repeats 2 (SH3TC2)* mutations accounted for most of the AR CMT cases (42.9% of CMT4).[35] Similar frequencies were obtained in a cohort of CMT patients in Norway, where the most common subtypes were CMT1A followed by CMT1X, CMT2A and CMT1B.[38] *Serine palmitoyltransferase, long chain base subunit 1 (SPTLC1)* mutations account for the majority of AD HSAN cases.[39]

Considering the number of genes found to be associated with CMT, a diagnostic algorithm encompassing the patient's ethnic background, neurophysiology, pattern of inheritance, and any outstanding features should prove to be extremely useful to clinicians and should help focus the genetic tests to be performed. The use of these algorithms has enabled 70% of CMT patients to receive a genetic diagnosis.[33] Because over half of CMT2 cases remain genetically unexplained[39] fewer patients with CMT2 receive a genetic diagnosis compared to CMT1. Pinpointing the disease-causing gene is essential from the clinician and patient's perspective for improved diagnosis and counselling, as well as for understanding the pathomechanisms underlying the neuropathy and developing targeted treatments.[6,40] A genetic diagnosis also helps avoid unnecessary tests and inappropriate therapy trials.[8]

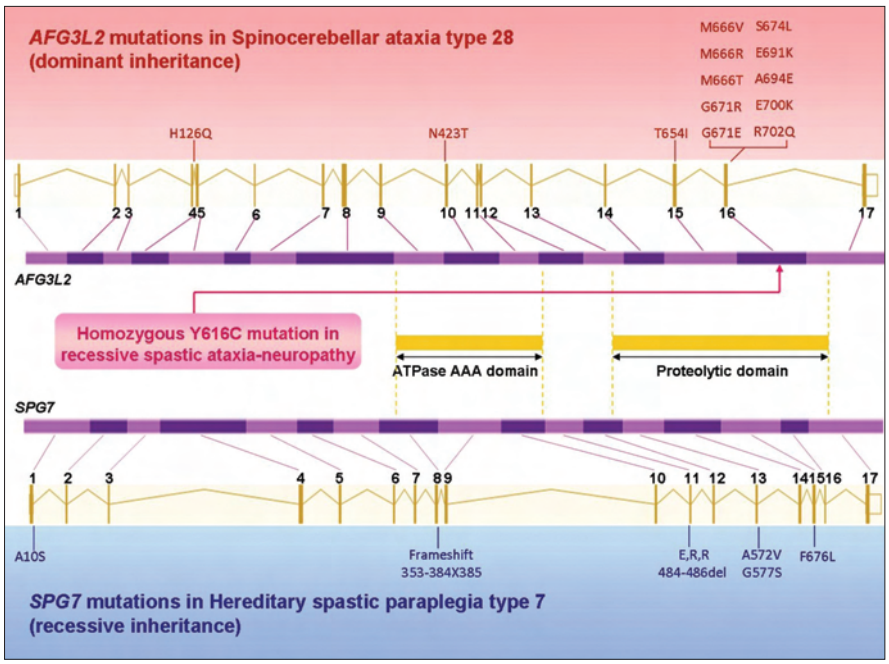


Figure 1: Recessive mutations in *AFG3L2* associated with a new syndrome characterized by early onset spastic ataxia and peripheral neuropathy with overlapping features of both AD SCA28 and AR Hereditary Spastic Paraplegia type 7.

If the nerve conduction studies indicate demyelination and the phenotype is that of classic CMT with AD inheritance, the chromosome 17 duplication should be tested first. If there is no male-to-male inheritance, *GJB1* should be screened; if there is male-to-male transmission, *MPZ* should be tested, followed by *PMP22*, and finally the less common genes including *EGR2*, *lipopolysaccharide-induced TNF factor (LITAF)* and *neurofilament light (N-FL)* subunit.[6,41]

If the neuropathy is AD and axonal with a classic CMT2 phenotype, *GJB1* should be screened if there is no male-to-male inheritance, as well as *MFN2*, especially if the disease is severe with childhood-onset and/or optic atrophy is present. The next genes to be screened in AD axonal neuropathies with a classical phenotype are *MPZ* (especially for late-onset CMT2), followed by *N-FL*, *alanyl-tRNA synthetase (AARS)*, *ganglioside-induced differentiation-associated protein 1 (GDAP1)*

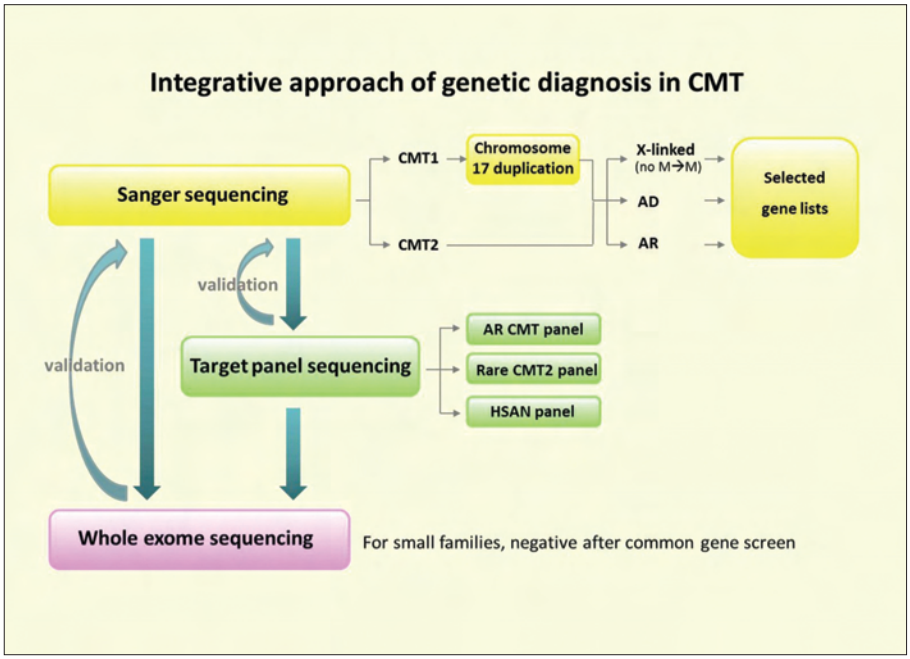


Figure 2: Flow diagram of CMT diagnostics incorporating Next-Generation Sequencing

*and transient receptor potential cation channel, subfamily V, member 4 (TRPV4)*.[6]

If the patient presents with AD CMT2 with strong sensory involvement, *SPTLC1* should be screened, followed by *RAB7*. If on the contrary, the neuropathy is AD CMT2 with motor predominance, *Berardinelli-Seip congenital lipodystrophy 2 (BSCL2)* and *glycyl-tRNA synthetase (GARS)* should be tested in patients where the upper limbs are mostly affected, and *heat shock protein beta-1 (HSPB1)*, *heat shock protein beta-8 (HPSB8)*, *BSCL2* and *TRPV4* should be screened in this order for lower-limb predominance.[6,34] The overlap between CMT, HSAN and HMN further complicates diagnosis; for example, mutations in two genes associated with either HSAN or CMT can cause a similar phenotype, and mutations in one gene can be implicated in both dHMN and axonal CMT.[39]

Selecting which genes to screen in AR CMT will depend on the particular phenotype and ethnic background of the patient.[6]

Genes to be tested in dHMN cases should be prioritised according to inheritance. In AD cases, phenotypic features such as upper versus lower limb onset, vocal cord palsy and pyramidal signs may be used to focus genetic testing.[11]

## Genetic modifiers of disease

Recent years have seen increased interest in identifying potential genetic modifiers of various diseases including hereditary neuropathies. Indeed, the high intra- and inter-familial variability in disease severity typical of CMT1A and of many other subtypes of CMT, HSAN and dHMN renders it difficult for clinicians to advise patients on the way their disease is likely to progress and how severely their children may be affected. A recent study has found that the mRNA levels of certain lipid metabolism genes in the skin biopsies of CMT1A patients could account for 47% of the variance in disease severity.[42] The identification of such genetic modifiers will help provide a more accurate disease prognosis, and will likely help understand the disease pathways.

## Next-generation sequencing in peripheral neuropathies

Non-Sanger-based sequencing technologies are revolutionising gene discovery and diagnostics for Mendelian and complex diseases. Although traditional 'first-generation' Sanger-sequencing and linkage studies are likely to remain important tools in genetic research, we are progressively moving to the era of next-generation sequencing (NGS), which encompasses whole-genome sequencing, exome sequencing and targeted re-sequencing of regions of interest.

All NGS technologies involve preparation and fragmentation of a DNA library, amplification of the library and massively-parallel sequencing of amplicons. The principal differences between these technologies are the enrichment method used and the length of DNA fragments which can be read depending on the sequencing chemistry used. The Roche 454 pyrosequencing™, Illumina/Solexa™ Genome Analyzer, Invitrogen Ion Torrent™ and Applied Biosystems SOLID™ system are popular sequencing platforms used in NGS.[43,44]

High-throughput and cost-efficient sequencing are distinguishing features of next-generation techniques. Other advances include the ability to sequence many bases using 1-2ug of DNA and the ability to investigate disease genes in small families. Next-generation technologies are essential to utilise in heterogeneous disorders such as the inherited peripheral neuropathies. For example, whole-genome sequencing has been used to identify a mutation in a known CMT gene, *SH3TC2*, in a patient with AR CMT. The authors argue that whole-genome sequencing may be useful in the diagnostic setting for highly penetrant, heterogeneous diseases such as CMT.[45] Exome sequencing, which involves target enrichment and high-throughput re-sequencing of the coding and intronic boundary regions of the genome, was successfully used to identify the causative mutation in a novel gene, *dynein cytoplasmic 1 heavy chain 1 (DYNC1H1)* in a case of axonal CMT.[46] Exome sequencing was also used as a comprehensive diagnostic screen in a CMT patient, leading to the identification of a mutation in a known CMT gene, *GJB1*.[47] Exome sequencing is not only suitable for detecting rare disease-causing variants, but also potential risk factors in protein-coding regions. Moreover, this technique allows causative genes to be found in small families or isolated individuals in whom positional cloning or linkage is not feasible.[48]

Targeted re-sequencing using customised gene panels is also becoming increasingly popular as it allows researchers to focus on particular areas of interest. This type of NGS is especially well-suited to the diagnostic setting as it involves less data handling and a quicker turnaround time. Panels can be designed for specific diseases or phenotypes, and may include a few genes to hundreds of genes depending on the platform used. The Illumina MiSeq and the Invitrogen Ion Torrent™ are especially suited to such purposes.

Currently, diagnosis by Sanger-sequencing is slow and expensive, and is often not available for many subtypes of inherited neuropathies. Testing of rarer genes is often restricted to the research setting.[6] These NGS techniques will undoubtedly change the face of medical diagnostics, including which genes are prioritised for testing[49] (Figure 2). Diagnosis of genetically heterogeneous diseases such as inherited neuropathies will become faster and will allow for simultaneous testing of many genes. Although most NGS are currently too expensive to be used routinely, they are quickly becoming more affordable.[47] NGS will not only facilitate the identification of new genes, but may also be a tool for finding modifiers of disease severity. Before these techniques are integrated into the clinical setting, extensive knowledge in both molecular biology techniques and bioinformatics will be needed.[44]

While these NGS methods are more cost-efficient and less time-consuming, it is not advisable to use them routinely without restraint. Unnecessary testing is one of the dangers associated with NGS; genetic testing should be focused and guided by diagnostic algorithms.[8,34,50,51] The most common genes should still be tested first, according to inheritance pattern and phenotype[47] as mutations in 1 of 4 genes, *PMP22*, *MFN2*, *MPZ*, or *GJB1* accounted for over 90% of 527 patients with a known genetic diagnosis of CMT in a recent study by Saporta and colleagues.[35]

### Challenges in Next-Generation-Sequencing and diagnostics

Searching for new genes is an exciting endeavour, but the analysis of the large datasets produced by whole-genome and exome sequencing can be daunting. Although a functional candidate gene approach is advisable, CMT-associated genes are not always nerve-specific and are generally ubiquitously expressed. Recently identified genes have been involved in pathways never previously described to cause inherited neuropathies. It is therefore far from trivial to prepare a list of candidate genes when searching for new causative genes, especially for CMT. Even with these caveats we predict that over the next 18 months, diagnostic exome sequencing will become available in the UK.

Once the list of candidate genes has been reduced to a manageable number, one is still faced with the difficult task of assessing the pathogenicity of the variants. A recent survey of loss-of-function mutations in coding genes has estimated that a single genome from a "healthy" human contains approximately 100 loss-of-function variants.[52] This is evident in NGS studies, which produce long lists of potentially pathogenic variants of unknown significance. Whole-genome sequencing studies uncover a high number of variants in coding regions, including in many genes known to cause CMT.[53] This issue also applies to traditional Sanger-sequencing methods. Variants previously thought to be pathogenic in CMT patients have later been reclassified as polymorphisms, and vice-versa. Segregation of the mutation in families, frequency in controls, conservation between species and functional studies may help sort through variants.[6,54 55] Comprehensive online databases of known variants associated with particular diseases will also be valuable. Good genotype-phenotype studies will also assist clinicians and researchers in interpreting the variants.[53] ◆

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# Long-Term Potentiation (LTP) – normal and abnormal aspects

Leading Norwegian discoveries in neurology and neurolscience are presented in a series of short articles in ACNR, initiated by the journal. All the selected discoveries have links to ongoing research projects in leading groups. They span from clinical to more basic topics. The discoveries are all relevant for clinicians evaluating and treating patients with brain and nervous system disease. Neuroscience with a clinical focus has been a priority for Norwegian research. Further expansion is planned in cooperation between the universities, the university hospitals, the Research Council of Norway, and the Norwegian Brain Council. Although the discoveries in this series are presented as Norwegian, they all appear in an international context. They represent small pieces fitting into the bigger puzzle, but contribute in elucidating mechanisms for brain and neuromuscular function, thus laying foundations for improved treatment of human disease.

***Terje Lømo,***

MD, PhD, is professor emeritus at the Institute of Basic Medical Sciences, University of Oslo, Norway. He discovered long-term potentiation (LTP) in 1966 and with Tim Bliss did the first systematic study of LTP. He has also studied mechanisms related to nerve-muscle interactions, including the formation of neuromuscular junctions. He has provided compelling evidence that impulse activity controls contractile and non-junctional membrane properties of skeletal muscle fibres, not putative trophic factors as was generally accepted in the 1960's and 70's.

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The phenomenon that we now call long-term potentiation (LTP) was first observed in 1966.[1] Using electrophysiological methods, I was studying the perforant path input to the dentate gyrus in anaesthetised rabbits for my PhD in Per Andersen's laboratory at the University of Oslo. Stimulating the perforant path with repetitive trains of stimuli at 10-20Hz, I, like others before me,[2] saw a marked potentiation of monosynaptic granule cell responses during the stimulation. But I also saw that the potentiation could last for hours after the last stimulus train. Thus, brief stimulation of afferent axons had caused a persistent increase in the efficiency of synaptic transmission, a sign of synaptic plasticity that others had looked for in vain.[3]

The observation led to a separate project with Tim Bliss when Bliss came to Oslo in 1968 as a postdoc to work with Andersen. Bliss was primarily interested in mechanisms that might underlie learning and memory and had heard from Andersen about my results. Over the next year, and in between much else, we did the first systematic study of LTP using the perforant input to the dentate gyrus.

**Some properties of LTP**

This study[4] revealed some basic features of LTP. First, bursts of presynaptic impulses led to a persistent increase in the efficacy of synaptic transmission. Second, the increase built up gradually with repeated bursts until saturation. Third, the potentiation was specific to tetanised cells as nearby control pathways were unaffected. Fourth, the population spike, representing number of discharging granule cells, was often larger than expected from the potentiated field EPSP, suggesting an additional increase in postsynaptic excitability, later termed EPSP-to-spike (E-S) potentiation. Other basic features were shown later, for example cooperativity and associativity, meaning, respectively, that for LTP to occur, an input must be above a certain strength or if weak, that a stronger input to the same neuron must be active at about the same time.[5]

Choice of induction protocol is important. So-called theta burst stimulation (TBS), consisting of high frequency bursts of stimuli, often only four stimuli per burst repeated at theta frequency (~5Hz), is often more effective than conventional tetanic stimulations. A protocol that induces LTP in the adult animal may cause long-term depression (LTD) at an early developmental stage[6] and some protocols induce LTD rather than LTP.

The duration of LTP is critical for a role in learning and memory. Today LTP is divided into two main forms, an early form (E-LTP) lasting no more than a few hours and a late form (L-LTP) that is gene expression and protein synthesis dependent and lasts perhaps a life time.[7] In addition, there is a short-term form (STP) lasting up to about one hour.

For several years, most neuroscientists showed little interest in LTP. Interest then exploded after three important discoveries; that LTP could be induced in slices of the hippocampus maintained *in vitro*[8] and that it depended on activation of NMDA receptors[9] and an increase in intracellular levels of $Ca^{2+}$.[10]

**Mechanisms underlying LTP**

At most synapses LTP is induced and expressed postsynaptically. NMDA receptors (NMDARs) are required for the induction of LTP, AMPA receptors (AMPARs), PKMζ (an isoform of PKC), and brain-derived neurotrophic factor (BDNF) for the expression of many forms of LTP, particularly L-LTP.

*NMDARs* are located in the postsynaptic membrane on dendritic spines. They are opened by glutamate released from active excitatory presynaptic terminals if, and only if, the postsynaptic membrane is depolarised above a threshold at about the same time. Above this threshold, the altered electric field across the postsynaptic membrane causes ejection of $Mg^{2+}$ ions from their blocking position in the NMDAR channel. $Ca^{2+}$ enters the cell and activates several postsynaptic signaling pathways with the end result that more AMPA receptors (AMPARs) become inserted into the postsynaptic membrane and the synapse becomes more efficient (potentiated).

*AMPARs* sit in the same postsynaptic membrane as the NMDARs. They are immediately opened by glutamate from the presynaptic terminal, ensuring fast transmission independently of NMDARs. Therefore, blocking NMDARs may not affect 'normal' fast transmission. While an open NMDAR can add to the EPSP generated by opened AMPARs, the essential function of the NMDAR is to control the efficiency of the synapse, that is its plasticity, by controlling $Ca^{2+}$ influx and, consequently, the number or conductance of AMPARs in the postsynaptic membrane.

*PKMζ* operates in postsynaptic dendritic spines. When inhibited, L-LTP and several forms of natural memory are erased, even when the inhibitor is briefly applied days, or even weeks or months after the

remembered event. Molecular mechanisms underlying this remarkable phenomenon have now been clarified in some detail.[11] Briefly, it requires transport from the nucleus to dendritic spines of a mRNA encoding constitutively active PKMζ, which remains untranslated in the spines until induction of LTP by NMDAR activation. Local translation then occurs, which together with other signaling events result in persistent PKMζ activity, insertion of AMPA receptors into the postsynaptic membrane, and potentiation of the synapse. Thus, long-term maintenance of LTP and memory requires continuously active PKMζ. Blocking PKMζ activity even briefly, interrupts local feedback circuits that are necessary for persistent PKMζ activity. The synapse reverts to a basal un-potentiated state and LTP and associated memories are erased, leaving affected pathways otherwise intact and ready for new induction of LTP and learning.

*BDNF* LTP-producing activity causes release of BDNF from presynaptic terminals. BDNF then binds to TrkB receptors on dendritic spines which is necessary in many cases for persistent activation of PKMζ and L-LTP expression.

*Presynaptic mechanisms.* One exception to postsynaptic induction and expression is the dentate granule cell-CA3 pyramidal cell synapse, where LTP results from increased transmitter release independently of NMDAR activation.[12] Whether increased glutamate release contributes to postsynaptically expressed LTP at other synapses has been much debated. If so, a retrograde signal from post- to presynaptic structures would be required. Candidate signaling molecules exist, for example arachidonic acid and nitrous oxide, but unequivocal evidence has been difficult to obtain. Nevertheless, evidence for increased presynaptic release exists,[13,14] but perhaps only for E-LTP, which is not blocked by inhibition of postsynaptic PKMζ.

*Structural changes at synapses undergoing LTP.* Insertion of AMPARs into the the postsynaptic membrane implies structural changes and such changes have now been demonstrated.[15] Within minutes of LTP induction some postsynaptic spines on hippocampal CA1 pyramidal cells of mature rats start growing displaying increased levels of mRNAs and polyribosomes that could assist in the translation of PKMζ-mRNA into constitutively active PKMζ.

**Is LTP necessary for learning?**

From recent evidence the answer very likely is yes, despite contrary arguments.[16] In one set of experiments,[17] a conditioned eye-blink response was elicited by combining a tone (CS) with electrical stimulation of the supraorbital nerve (UC). In the hippocampus, one electrode was implanted to stimulate Schaffer collaterals, another electrode to record stimulus-evoked monosynaptic field EPSPs of CA1 pyramidal cells, and, finally, a cannula to infuse ZIP, an inhibitor of PKMζ, into CA1. During learning (paired CS and UC stimulations) the eye-blink response to CS alone gradually increased. Remarkably, the field EPSP evoked by single constant stimuli to the Schaffer collaterals also gradually increased, as if the collaterals had been tetanised to induce LTP. Infusion of active ZIP immediately suppressed both the naturally induced LTP and the learned conditioned response, whereas an inactive scrambled ZIP did not. Stimulation-induced LTP before learning also disrupted subsequent natural learning, presumably because the synapses needed for such learning had become saturated and could not be potentiated any further. However, after erasure by ZIP, both LTP and natural learning could again be obtained.

In other experiments,[18] a constant repetitive light stimulus over many days evoked a gradually increasing field response, called stimulus-specific response potentiation (SRP), a natural analog of LTP, in lamina 4 of the visual cortex of mice. Furthermore, tetanic stimulation of thalamocortical fibres to the same cortical region induced LTP there. The authors then show that stimulation-induced LTP suppressed subsequent naturally-induced SRP, since the relevant synapses also in this case likely had been saturated. And again local infusion of ZIP erased both LTP and natural SRP. Interestingly, LTP potentiated the response to different types of visual stimuli, whereas SRP potentiated only the response to the visual stimulus used for training. Apparently, artificial LTP is indiscriminate (global) in that it affects synapses belonging to many different circuits, whereas natural SRP is specific in that it affects only those synapses that belong to the circuit(s) formed to serve the new responsiveness.

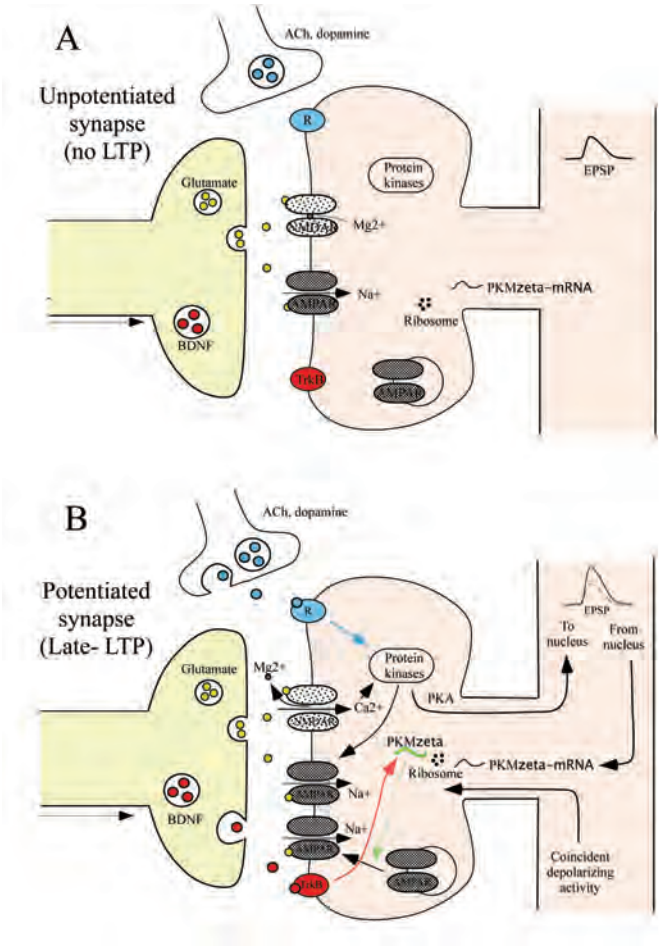


Figure 1:
A much simplified scheme of transmission at unpotentiated (A) and potentiated (B) synapses.

A. A weak afferent input releases presynaptic glutamate, which binds to and opens postsynaptic AMPAR-channels to evoke EPSPs and fast transmission. Glutamate also binds to NMDARs but $Mg^{2+}$ ions block their channels.

B. A strong afferent input or a weak input that coincides with a strong input elsewhere on the cell depolarises the postsynaptic membrane sufficiently to force $Mg^{2+}$ ions out and allow glutamate to open the channel. $Ca^{2+}$ ions enter and cause activation of CaMKII, PKA, and PKMζ (green) and other protein kinases. Kinase activity potentiates AMPAR-dependent EPSPs by increasing AMPA channel conductance and causing insertion of more AMPARs into the postsynaptic membrane. Such insertion requires PKMζ, translated from PKMζ-mRNA at local ribosomes. The process is enhanced by PKA-dependent signaling to the nucleus, up-regulation of PKMζ-mRNA expression, and transport of PKMζ-mRNA to the spine, where translated PKMζ maintains L-LTP by becoming autonomously and persistently active.

Co-release of BDNF from presynaptic terminals 'tags' the synapse for potentiation by binding to TrkB receptors, a necessary event for the formation of constitutively active PKMζ. Induction of L-LTP also induces expression of postsynaptic BDNF, which together with PKMζ serve as plasticity related proteins (PRPs) to promote the protein synthesis and structural changes underlying L-LTP, which includes insertion of AMPARS. Such PRPs will be 'captured' at tagged synapses only and thereby restricted to the synapses engaged in a particular learning or memory task.

Other inputs converge and release modulatory transmitters such as dopamine and acetylcholine (ACh) depending on sensory inputs related to novelty, attention, motivation, reward, or punishment. Under their influence, E-LTP induced by a weak input can be transformed into L-LTP.

Not shown in this figure is the E-LTP that fails to persist because the input is either too weak or is unassisted by coincident modulatory or other inputs. Early-LTP lasts at most a few hours, is independent of protein synthesis, is not blocked by inhibition of PKMζ and therefore independent of insertion of AMPARs into the postsynaptic membrane. Instead, it appears to be primarily accounted for by increased presynaptic transmitter release.

Unlike declarative memories (memories of events, places, what has been seen or heard), procedural learning, like learning to ride a bicycle, is independent of the hippocampus. Instead, it requires the motor cortex where synapses of horizontally running fibres display LTP as rats learn new motor skills.[19] Importantly, both types of long-term memories are erased when ZIP, the inhibitor of PKMζ, is infused into either the hippocampus or the motor cortex[20].

Results such as these and the lack of convincing examples of learning without LTP in a vast literature make it seem obvious that LTP in one of its many forms is necessary for learning.

**LTP in humans**

Mammals are evolutionarily related, have similarly organised brains, and must be able to learn, remember, and acquire skills to survive in unpredictable and changing environments. Hence, one would expect LTP to be at least as important in humans as in other mammals. Recent work on humans confirms this expectation (see review 21. Examples are (1) LTP, similar to that observed in animal models, can be induced in slices from parts of the temporal lobe or hippocampus removed during surgery for epilepsy,[22] (2) transcranial magnetic stimulation (TMS) when paired with peripheral nerve stimulation, induces increased motor cortex responsiveness indicative of underlying LTP, [23] (3) electrical stimulation of peripheral nociceptive fibres that induce LTP in ascending pain pathways in animal models also induce LTP-like responses in humans as indicated by subjective pain scores.[24]

**Modulators of LTP**

*Dopamine* is one of many substances that nerve terminals release to modulate the functions of neuronal networks. Sensory inputs related to reward, punishment, or novelty can drive bursts of impulse activity in dopaminergic neurons in the brainstem and thus enhance dopamine release in target structures. In the hippocampus, infusion of dopamine receptor antagonists or genetic deletions of dopamine receptors impair not only long-term memories of locations related to reward or punishment but also the production of L-LTP. Conversely, dopamine agonists rescue both LTP and natural learning after dopamine depletion (see review 25). Hence, LTP appears necessary for this type of learning to take place.

*Acetylcholine* is another modulator affecting cognitive functions and LTP. Recent work shows that stimulation of cholinergic fibres from the septum facilitates LTP at hippocampal Schaffer collateral-CA1 pyramidal cell synapses by activating acetylcholine receptors on CA1 postsynaptic spines.[26,27] The mechanisms are complex involving muscarinic or nicotinic receptors with effects that depend on the temporal order and time intervals of cholinergic input and Schaffer collateral activation. Interestingly, phasic ACh release in CA1 of anaesthetised rats is highly correlated with spontaneous or induced theta oscillations, suggesting that coincident ACh release and theta oscillations promote neural plasticity and thereby learning and memory.[28]

*Insulin-like growth factor II (IGF-II)* has recently emerged as an enhancer of LTP and memory retention.[29] It is highly expressed in the hippocampus and its expression decreases with age. In rats trained to remember fear-conditioning stimuli or to avoid places where they receive foot shocks, IGF-II expression in hippocampus is markedly but transiently enhanced during the 2nd day after the training. Bilateral hippocampal injection of anti-sense oligonucleotides blocks both the enhanced IGF-II expression and the memory of the shock, whereas injection of recombinant IGF-II enhances the memory and ensures its maintenance when tested three weeks later. In addition, IGF-II transforms E-LTP induced by weak high frequency stimulation into L-LTP.

Understanding how modulators of synaptic plasticity affect LTP should help in linking subjective states, such as thinking, motivation, expectation, anxiety, fear, and addiction, to concrete brain processes, and in finding remedies when such states become abnormal.

**Clinical implications of maladaptive LTP**

*Pain memories.* LTP is likely to contribute to the chronic pain states that can develop after acute injuries to peripheral nerves or tissues. In the spinal cord, both high and low frequency stimulation of nociceptive fibres in peripheral nerves produce LTP at the synapses that these fibres form with 2nd order sensory neurons in the superficial dorsal horn.[30] Experimental nerve damage or tissue inflammation evokes similar afferent impulse patterns in nociceptive fibres and have similar long-lasting effects at the same synapses. Such central changes may not only amplify primary hyperalgesia but also be responsible for secondary hyperalgesia, allodynia and spontaneous pain.[31] Spinal LTP is NMDA receptor-dependent, and relies on insertion of new AMPA receptors in the postsynaptic membrane. Moreover, inhibition of PKMζ in the spinal cord erases both the L-LTP and the persistent pain evoked by peripheral injury.[32] The anterior cingulate cortex (ACC) is a major cortical target for impulses in nociceptive fibres. Here also NMDA and AMPA receptor-dependent LTP occurs at glutamatergic synapses in animal models of hyperpathic pain. And again, local inhibition of PKMζ markedly reduces both pain behaviour and LTP.

*Stress memories.* Stress affects cognitive and emotional behaviours, as expected from the expression of stress hormones and their receptors in neurons of the hippocampus and amygdala, two regions that play important roles in such behaviours and display prominent LTPs. But the response to stress is opposite in dorsal and ventral regions. In dorsal CA1, where spatial and cognitive functions and efferent projections to the cortex predominate, stress or corticosteroids markedly suppress LTP and impair cognitive functions. In ventral CA1, on the other hand, where emotional functions and connections with the amygdala and hypothalamus predominate, stress and corticosteroids enhance LTP and potentiate emotional responses.[33]

Early-life stress is of particular interest because it affects brain development and can have adverse effects later in adult life and on offsprings. Rat pups exposed to one postnatal week of disrupted maternal care display enhanced corticotropin releasing hormone (CRH) expression in hippocampal neurons together with dendritic atrophy, impaired LTP, and poor memory performance as adults.[34] Remarkably, all these effects are counteracted by CRH receptor (CRHR) antagonists applied after the early-stress period, evidently by acting directly on CRHRs in the hippocampus. Mice with conditionally knocked out CRHR1s in glutamatergic forebrain neurons (cortex, hippocampus, amygdala) display reduced anxiety in behavioural tests and reduced LTP in the basolateral amygdala.[35]

*Drug memories.* The mesocorticolimbic system includes projections from the ventral tegmental area (VT) through nucleus accumbens (NAc) to prefrontal or anterior cingulate cortex. It handles inputs that lead to expectations of reward, memories of rewarding inputs, and associations with environmental cues of forthcoming rewards as in Pavlovian conditioning.[36] Cues that predict rewards (positive reinforcers) induce phasic firing and LTP in glutamatergic synapses onto DA neurons in VT and NAc. Drugs of abuse, such as cocaine, similarly activate the mesocorticolimbic system resulting in AMPA receptor-mediated LTP. In rats, this LTP lasts up to two weeks after forced injections of cocaine but up to three months after cocaine self-administration, suggesting that voluntary intake further promotes learning and results in a drug memory that facilitates reinstatement of drug-seeking behaviour after periods of abstinence.[37] As in the hippocampus where LTP and learning require continuously active PKMζ, blockage of PKMζ in NAc by ZIP erases memories of places that rats prefer after conditioning with morphine or cocaine injec-

*Understanding how modulators of synaptic plasticity affect LTP should help in linking subjective states, such as thinking, motivation, expectation, anxiety, fear, and addiction, to concrete brain processes, and in finding remedies when such states become abnormal*

tions, an erasure that is prevented by blockage of AMPA receptor endocytosis.[38] Thus, Late-LTP in Nac may contribute to the formation of circuits that store memories of the reward and that can be reactivated later by appropriate cues to cause relapse even after long periods of abstinence. Ethanol, another substance of abuse with serious societal consequences, similarly affects the mesocorticolimbic system by promoting $Ca^{2+}$ influx in dopamine neurons and LTP of NMDA receptor-mediated transmission at glutamatergic synapses with DA neurons in VT.[39]

Findings such as these are likely to facilitate the development of drugs and procedures for treating chronic pain, stress or drug abuse. By suppressing or blocking LTP in the relevant neuronal circuits one might erase the memories that lead to maladaptive behaviours. Already, local anaesthetics are used with good effect as a supplement to general anaesthesia during major surgeries to block LTP-inducing afferent impulse activity.

*Alzheimer's disease (AD).* In this disease, cognitive decline is associated with impaired cholinergic function that is also involved in the production of LTP. β-amyloid peptide (Aβ), a toxic break-down product in Alzheimer's disease, strongly suppresses AChR-dependent LTP.[40] Accumulations of PKMζ occur in neurofibrillary tangles in limbic and medial temporal lobe structures in autopsy material from demented but not non-demented elderly individuals.[41] Given that LTP production requires active PKMζ at appropriate neuronal sites, this finding further suggests that dysfunctional LTP and memory loss are linked.

## Concluding remarks

This review is based on the premise that neuronal circuits and impulse traffic along them determine an individual's behaviour. Building appropriate circuits then becomes critical for brain development, as does changing circuits throughout life to allow learning. remembering, and acquiring skills. To build and change circuits, synapses must be plastic, and LTP is one means to ensure such plasticity.

Any major neurological or psychiatric illness seems likely to reflect faulty circuits in the brain. Hence they are probably caused by or accompanied by altered synaptic plasticity. Abnormal LTP production is a sign of many dysfunctional states of the brain. Development of drugs that interfere with LTP production, such as inhibitors of PKMζ, stress hormone analogs or their antagonists, and that can ameliorate abnormal behaviour in animal models, point towards helpful therapies in the future. However, the danger of overuse and side effects from targeted and non-targeted tissues, is real, as amply illustrated by drugs already in use. Evidently, the beneficial effects of many psychoactive drugs, such as anti-depressants, are mainly placebo effects.[42] Placebo effects demonstrate that positive expectations and motivations play important roles in the treatment of many brain-related disorders, effects that involve synaptic plasticity, including LTP. Perhaps the best way forward is to combine positive expectation and motivations with training, as in various forms of cognitive therapy, together with judicious use of appropriate drugs to allow new and more appropriate behaviours to be learnt and old and inappropriate ones unlearnt. Such treatment likely targets the relevant circuits better than drugs alone. ◆

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# Top Ten Papers in Multiple Sclerosis
## The Beginning of the End?

In the last of our articles on the Top Ten papers in multiple sclerosis, we show how three papers in the 1980s greatly increased diagnostic precision and demonstrated that multiple sclerosis was treatable.

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**1981: the first evidence showing that multiple sclerosis is treatable. The end of the beginning?**

*Jacobs L, O'Malley J, Freeman A, Ekes R. Intrathecal interferon reduces exacerbations of multiple sclerosis. Science 1981;214:1026-8.*

'There is evidence that multiple sclerosis is caused (at least partially) by a viral infection of the central nervous system that acts as a 'trigger' for repeated exacerbations of neurologic symptoms characteristic of the disease. Interferon is a naturally occurring biologic product with potent antiviral activities. It does not cross the blood-brain barrier in significant quantity when administered systemically, but can be safely administered intrathecally'. So opens Larry Jacobs' landmark paper on the use of interferon as a treatment of multiple sclerosis.

There are many problems with this paper. Its premise, that viral infections are the remedial cause of multiple sclerosis, is probably incorrect; its analysis is flawed; and, rightly, it met with considerable controversy. However, the paper deserves selection as a landmark because it introduced an intervention that does, to a degree, suppress disease activity in multiple sclerosis; and, in Larry Jacobs, it introduced one pioneer of the 'DMTs' (disease modifying therapies). But this was not the first study of interferons in multiple sclerosis; although not acknowledged in the paper, Verveken had used interferon-beta IM in three patients with "chronic progressive multiple sclerosis"[1] and Fog tested interferon-alpha SC in six patients with similar disease-type.[2] Neither observed any benefit.

The 'interferons' had been identified in 1975 by Isaacs and Lindenmann as products that interfere with viruses (Isaacs 1975). Human interferon could be made with difficulty in the laboratory by 'superinduction' of human fibroblasts, and purified by affinity chromatography, to generate a 'natural' interferon, so-called to distinguish it from the subsequent recombinant interferons. One such laboratory was the Roswell Park Memorial Institute (now Roswell Park Cancer Institute) in Buffalo, New York. From this unit came the first evidence that interferons can ameliorate chronic active hepatitis and kill tumour cells in vitro, both in 1979.[3,4] At around that time, Larry Jacobs arrived as a young neurologist in Buffalo from his residency at Mount Sinai, to work at the Dent Neurologic Institute. With colleagues he initially contemplated using interferon from the Roswell Park Memorial Institute to treat amyotrophic lateral sclerosis, but their attention soon turned to multiple sclerosis.

Verveken suggested that interferon failed because it does not cross the blood-brain-barrier, and suggested that administration should be intrathecal. Larry Jacobs took up this suggestion, no doubt aware that a group at Roswell Park were using intrathecal interferon to treat meningeal leukaemia.[5] His study group consisted of 20 patients, four with relapsing-remitting disease, four with relapsing-progressive disease and 12 who were 'stable with residua'. Ten received natural interferon-beta by lumbar puncture, twice a week for four weeks then monthly for five months. Ten patients were used as unblinded controls. Patients were followed up for over a year. At the end of the study, two the interferon-treated patients had experienced four relapses, compared to ten relapses from six controls: for the first time, there was a hint that relapse rate in multiple sclerosis might be modified.

Jacobs' paper deserved some of the criticism that followed, for instance from Charles Berry from University of California, San Francisco.[6] There are simple arithmetical errors in the tables and the primary outcome is not statistically significant, as was erroneously claimed. Jacobs' reliance on a change in relapse rate before and after treatment is potentially distorted by regression to mean. And, most oddly to modern readers, there is no explanation for the death of one patient receiving interferon in the first month of the study, other than to say it was unrelated to treatment.

However, the data were encouraging and more studies, led by Jacobs, followed. He went on to produce a much more rigorous trial, including placebo-injection lumbar punctures, in 69 patients with relapsing-remitting disease[7] and did show a definite effect. However, a few years later a trial of natural interferon-beta had to be stopped early because it exacerbated rather than ameliorated multiple sclerosis disease activity.[8] There was a sense of growing concern over the need for intrathecal injections and the biological variability of human-derived interferon. Thereafter, interferons derived from recombinant technology were given systemically. Still there were problems. Recombinant interferon-alpha was shown to have no efficacy in 1986[9] and recombinant interferon-gamma (Immuneron, Biogen) provoked relapses.[10]

Larry Jacobs was undeterred. He set up the Multiple Sclerosis Collaborative Research Group to test Biogen's recombinant interferon-beta 1a. He designed a large trial, with some innovative features, which eventually led to a product licence for Avonex in 1996 in the US and in the EU from 1997. But he was pipped to the post by Ken Johnson, another key figure in the interferon story. With Berlex laboratories, Johnson had managed to

get another recombinant, interferon-beta 1b (Betaseron), licensed in 1993.[11,12]

In 1998, Larry Jacobs became the first holder of the Irvin and Rosemary Smith Chair in Neurology at Buffalo School of Medicine and Biomedical Sciences, which had been established through a $1.5 million endowment by Biogen. He died in 2001, aged 63.

The introduction of the interferons as disease-modifying treatments of multiple sclerosis brought many benefits to people affected by the disease other than a modest reduction in disease activity and an uncertain effect on the long term course of the disease; not the least by drawing the attention of the pharmaceutical companies to the potential marketplace for novel therapies, and also by requiring an infrastructure of neurological and nursing support, that improved the generic care of people affected by multiple sclerosis.

### 1983: a step towards increased diagnostic accuracy

*Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. 1983. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13(3):227-31.*

The first attempt at systematic criteria for the diagnosis of multiple sclerosis came from Allison and Millar (1954) who classified the disease as early (few physical signs but a recent history of remitting symptoms); probable (soon changed to early probable or latent: no reasonable doubt about the diagnosis); possible (findings suggesting the diagnosis and no other cause found but the history static or progressive and with insufficient evidence for scattered lesions); and discarded.[13,14]

However, then as now, neurologists have not felt the need to be constrained by criteria when making the diagnosis of multiple sclerosis. As Charles Poser wrote in 1965, "many clinicians thus insist that there is, in arriving at any diagnosis, and certainly in diagnosing MS, an intangible, unpredictable, highly personal and almost mystic diagnostic item frequently referred to as the 'feel' or the 'smell' of the patient, and which can best be characterised by the almost classical, pontifical pronouncement: "Don't ask me why I think that this patient has MS, I just know!". [15]

Poser was not impressed. In his huge multiple sclerosis practice, he frequently encountered misdiagnosis, against which he battled all his life. He died in November 2010, at the age of 86. After escaping Nazi-occupied Belgium with his family, he grew up in New York City and attended George Washington High School and City College. After returning from Army service in World War II, he trained at the New York Neurological Institute under Dr. H. Houston Merrit.

Poser's motivation to introduce diagnostic criteria for multiple sclerosis was to improve research, in particular the quality of epidemiological studies. He set out his stall in a classic paper in 1965.[15] He asked 190 neurologists in 53 countries to read 30 case records and decide if they had 'probable', 'possible' or 'unlikely' multiple sclerosis. In fact, the cases had all come to post mortem and included 25 with pathologically proven multiple sclerosis, three cases with other conditions mimicking multiple sclerosis and in two cases, MS coexisting with other conditions. 108 neurologists replied (only two from England, Dr Acheson from Oxford and Dr Garland from Leeds). There was a consistent 2/3 diagnostic accuracy, across the board of geography and experience (except that the Swedes and those trained in Sweden, were less confident in making a diagnosis of 'probable' multiple sclerosis). Somewhat embarrassingly, people regarded as multiple sclerosis experts performed rather worse than general neurologists. However, between individual diagnosticians, there was a great deal of variety. So Poser analysed symptoms and signs that neurologists find helpful in making the diagnosis of multiple sclerosis, both in negative and positive terms, from which he derived a rather complex scoring system to refine the clinician's suspicion of multiple sclerosis. Immediately he recognised that his scoring system could be fooled by non-multiple sclerosis conditions such as brainstem glioma, so he mandated at least two years since the onset of symptoms before the diagnosis of multiple sclerosis could be made.

Ultimately, Poser's scoring system was just too complex and it never took off. In the US, neurologists continued to use the Schumacher 1965 criteria; however this focused just on the "probable" group and did not incorporate the growing literature on paraclinical tests or imaging.[16] In the UK, the McDonald and Halliday (1977) criteria gained favour, as they recognised the value of, for instance evoked potentials.[17] Poser was not satisfied, so he set out in 1982 to come up with comprehensive diagnostic criteria for research: "The main reason for establishing these criteria is to restrict therapeutic trials and other research protocols to patients with definite MS; the category of probable is designed for the purpose of prospectively evaluating new diagnostic methods" So, Poser gathered at Washington the luminaries of multiple sclerosis, including George Ebers, Ian MacDonald and Donald Paty. They proposed four categories of multiple sclerosis: "clinically definite, laboratory-supported definite, clinically probable and laboratory-supported probable". At last 'paraclinical' evidence of a lesion could be substituted for clinical evidence. For instance, typical abnormalities on CT or 'NMR' imaging, evoked potentials and induced hyperthermia (the 'hot bath test'). So, laboratory-supported definite multiple sclerosis could be diagnosed after one attack only, with paraclinical evidence of a subsequent new lesion affected (for instance a CEP that becomes abnormal) AND oligoclonal bands. Clinically probable required two attacks with clinical evidence of one lesion, or one attack and clinical or paraclinical evidence of two separate lesions, separated in time. Laboratory supported probable required two attacks and oligoclonal bands.

Poser's criteria lasted nearly two decades until replaced by the 2001 McDonald criteria, which were themselves modified in 2005 and, most recently, in 2010.[18,20] Much of Poser's thinking remains. But he did not agree with the elevation in importance of MRI; "one of the big problems I see now is the numbers of patients who have minimal symptoms, and maybe some abnormal MRI findings, who have been treated for MS for years and who have never had it. I see people like this every week in my office".[21] Of critical importance for the writers of the new McDonald is the ability to make the diagnosis of multiple sclerosis as early as possible, to allow the introduction of therapy. So, the absolute requirement for a second clinical (or paraclinical) attack has been dropped; instead any new MRI disease activity after a clinically isolated syndrome now fulfils the criteria to diagnose multiple sclerosis. This process has reached its apotheosis under the 2010 criteria, which it is proposed that evidence of dissemination in time can be derived from a single MRI scan during a clinically isolated syndrome; if it shows the simultaneous presence of asymptomatic gadolinium-enhancing lesions and non enhancing lesions at any time.

### 1988: surrogate markers in life for disease activity in multiple sclerosis

*Miller DH, Rudge P, Johnson G, Kendall BE, Macmanus DG, Moseley IF, Barnes D, McDonald WI. Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. Brain 1988;111: 927-39.*

Magnetic resonance imaging of the brain has become an invaluable technique for the diagnosis and management of people with multiple sclerosis, as well as into research of its pathogenesis and treatment. The paper we have selected is not the first study of multiple sclerosis using MRI. But it is, in our view, the first MRI study to bring new understanding of the pathogenesis of multiple sclerosis.

In 1973 a paper appeared in Nature, having been previously rejected as of insufficient general interest by the editor, entitled "Image formation by induced local interaction; examples employing magnetic resonance".[22] The author was Paul Lauterbur, a chemist at the State University of New York at Stony Brook. Peter Mansfield, a physicist from Nottingham University, systematically solved the many problems of transforming this observation to a medical imaging system and produced, in 1976, the first "nuclear magnetic resonance" image of a human part (a cross-section of the finger)[23]. Thus arrived the definitive method for studying human tissue structure and func-

tion in health and disease, for which the two received the Nobel Prize for Physiology or Medicine in 2003.

MRI was first explored in multiple sclerosis through a collaboration between the Hammersmith Hospital in London and the Central Research Laboratories, Thorn-EMI Ltd in Hayes, Middlesex. Their Lancet report from 1981 exudes excitement at the vastly improved ability to visualise multiple sclerosis lesions compared to computed tomography. The new technique "demonstrates abnormalities in MS on a scale not previously seen except at necropsy although the specificity of these abnormalities is uncertain at present"[24]. Other investigators soon picked up on the technique, and early work confirmed and extended its role in supplementing clinical evidence for the diagnosis of multiple sclerosis.

Enthusiasm for the technique soon spread beyond the academic world. The first commercial MR scanner in Europe (from Picker Ltd.) was installed in 1983 at the University of Manchester Medical School. In the same year, the Multiple Sclerosis Society of Great Britain and Northern Ireland funded the first MRI scanner in the world to be solely dedicated to multiple sclerosis research, at the National Hospital for Neurology and Neurosurgery at Queen Square, London. Ian McDonald led the group and their early work emphasised the number of "silent lesions" visible on MRI scans at presentation in multiple sclerosis and in clinically isolated syndromes.[25]

The paper we have chosen comes from Ian McDonald's group. Its importance lies in the insights it gave to the natural history of multiple sclerosis, particularly to the realisation that there is continued disease activity even during periods of clinical stability. The problem that David Miller and colleagues sought to solve was how to judge the age of an individual MRI lesion. They argued that distinguishing between new and old lesions would help in two contexts: first, in the assessment of the patient with a clinically isolated syndrome (where lesions of different age would suggest dissemination in time and hence the probability of multiple sclerosis); and, secondly, in therapeutic trials. They turned to the paramagnetic agent, gadolinium DTPA, which Donald Silberberg's group at the University of Pennsylvania had shown more frequently to demonstrate abnormalities in patients with clinical disease activity than unenhanced scans.[26]

Ten patients with multiple sclerosis were scanned initially, eight of whom were experiencing a relapse at the time. Fifty six contrast enhancing lesions were observed in total compared to none in the two non-relapsing patients. In six of eight patients, an enhancing lesion was seen which was anatomically congruent with the relapse phenotype. A second scan was performed between three and five weeks later in nine of these patients. Of the previous 54 enhancing lesions, only 12 persisted. But 12 new lesions had appeared (including four previous lesions where enhancement extended into previously unaffected brain areas). Six months later, eight patients were rescanned and 15 new lesions were seen on unenhanced scans, of which eight showed enhancement. In passing, the authors note that some enhancing lesions were seen in the cortex, and one enhancing spinal cord lesion is shown.

For the first time, the dynamics of plaque formation could be studied and some of the controversies arising from static pathological studies resolved. The observation that enhancement was seen as the first abnormality in every new lesion which appeared on interval scans placed breakdown of the blood-brain barrier as an initiating event in the evolution of the plaque. David Miller and colleagues suggested that the elevated T1/T2 ratio of enhancing lesions reflected the increased intracellular water associated with acute inflammation; and the low T1/T2 ratio of old non-enhancing lesions might reflect increased extracellular water from leakage of an incompletely repaired blood brain barrier. Cortical plaques, which were known from pathological studies but had not been seen on unenhanced scans, could now be visualised with the use of gadolinium.

For most contemporary readers the big news was the revelation of the frequency of new lesions in people apparently with stable multiple sclerosis. This had several implications. For research, MRI provided a sensitive measure of brain inflammation: Don Paty, at the University of British Columbia in Vancouver, was the first to correlate active lesions with changes in peripheral immune function.[27] But the most obvious conclusion was that gadolinium- enhancing lesions could be used to reduce the duration and cohort sizes of clinical trials.

The findings of this paper were soon ratified. Henry McFarland at the National Institutes of Health (Bethesda) produced a study of six patients with "early, mild, relapsing-remitting multiple sclerosis" scanned monthly for 8-11 months and showed that "numerous enhancing lesions were observed irrespective of clinical activity"; and again suggested that these lesions be used as an outcome measure in clinical trials.[28] ◆

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# Generation of TDP-43 M337V iPSC-derived motoneurones advances ALS research

A huge problem for neurodegeneration researchers is the weakness of the biological "models" available. In vitro systems use either non-neuronal human cells, or neural cells of animal origin, such as primary rat cortical cells. To investigate human disease what we really need is live, human neuronal tissue in a dish. Of course, live human neural tissues have been used by scientists and indeed clinicians, the most notable example being nigral tissue transplants in patients with Parkinson's disease. However, these cells are obtained from human foetuses, an ethically sensitive area. Using neural cells from adults sounds like a great idea except that neurones are post-mitotic, so once they die so does your experiment, and there is the small issue of regularly sourcing fresh, living, human brain tissue - not straightforward. Another approach, as used to clone Dolly the sheep, involves nuclear transfer to a donor egg (somatic cell nuclear transfer, SCNT). However, controversy surrounds this approach because of concerns about human cloning.

One solution to these technical and ethical dilemmas is induced pluripotent stem cell (iPSC) technology, first described in the seminal paper of Takahashi and Yamanaka, 2006. This technique 'reprograms' non-neuronal cells (such as easily-obtained fibroblasts from skin biopsies) to become pluripotent stem cells through the ectopic expression of just four genes (OCT4, SOX2, KLF4 and c-MYC). These cells can then be programmed to become whatever you want, including neurones.

Using this technique Bilican et al have developed iPSC-derived motoneurones. Although this has been done before from a mutant SOD1 source, Bilican et al started with skin biopsies from patients with a known mutation in TDP-43. 90% of ALS is sporadic, 10% familial, and of the latter TDP-43 mutations account for about 5% of families. However, 95% of all ALS cases have TDP-43 inclusions in brains and anterior horns of the spinal cord. Thus, TDP-43 is the single molecule most consistently linked with nearly all ALS, and TDP-43 models of ALS promise to tell us much about the mechanisms of ALS.

Bilican et al took small skin samples from an ALS patient with the M337V mutation in TDP-43 (Sreedharan et al 2008) and controls, converted them to iPSCs and demonstrated genetically and morphologically that they were indeed truly pluripotent. They then set about transforming them into motoneurones using an established set of signalling molecules and confirmed neurophysiologically and biochemically that they had indeed created motoneurones. They then investigated TDP-43 biochemistry and found that while TDP-43 mRNA expression levels were equivalent in mutant and control cells, mutant motoneurones had four-fold higher levels of full-length and pathologically-linked C-terminal fragments of TDP-43. This supports research that suggests that mutant TDP-43 may be inherently more stable and less degradable than wild-type. Although early cell development was not affected, toxicity studies demonstrated that mutant TDP-43 caused an almost three-fold increased risk of cell death. This may be linked to increased vulnerability to PI3K inhibition, an important neuronal signalling pathway.

iPSC technology has come a long way since 2006 and further refinements are occurring to ensure that consensus is reached amongst stem cell scientists Reviewed by . iPSC-derived neural cells means no foetuses, no human cloning and a potentially limitless source of patient-specific neural cells. Further work is ongoing to examine the therapeutic utility of iPSC-derived neural cells, but in the meantime the work of Bilican et al has shown that they are an important addition to the armoury of the neurodegeneration researcher.

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# New problems with an old friend

Lamotrigine has been available for twenty years in the UK and has become a first line medication. Serious side effects are relatively rare, although I have given at least two patients Stevens Johnson syndrome and countless others minor rashes and headaches. The authors searched the FDA adverse event reporting system database and looked for more than a headache; patients had neck stiffness and a fever as well and confirmed leukocytosis in the CSF. Nine AED's were assessed but lamotrigine was consistently associated with aseptic meningitis roughly ten times more often than the other drugs. Moreover, of 15 patients re-challenged with the drug, six (40%) had a recurrence of meningitis.

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**Simms KM Mortpeter C, Avigan M. Lamotrigine and aseptic meningitis. Neurology 2012;78:921-7.**

# What is going on in psychogenic seizures?

Psychogenic non-epileptic seizures (PNES) are seizures which lack the electrical signature of epileptic seizures. They are psychologically driven, which for many neurologists is enough to sit back and diagnose SEP – somebody else's problem. A key characteristic of patients with PNES is an increased susceptibility in a range of measures of dissociation, defined as a disruption of conscious functioning and often seen as a coping strategy, to separate consciousness from a range of stimuli. In this fMRI study, 13 patients with high measures of dissociability were compared to 13 healthy controls. During the fMRI study, subjects were: 1) shown pictures of a highly sentimental nature; 2) asked to undertake the Stroop task, which is susceptible to hypnotic induction; 3) a baseline condition of visual fixation; 4) resting state.

In both groups, tasks 1 and 2 activated hippocampi, left lateral frontal cortex, parahippocampal gyrus and fusiform gyrus. Compared to controls, patients had stronger activations in the anterior and posterior insular cortex, central sulcus, parieto-occipital fissure and anterior and posterior cingulate gyri. There were correlations in activity between some of these: precentral sulcus and anterior insula, and precentral sulcus and posterior insula.

The anterior cingulate is suggested to be important in hypnosis. This area was functionally correlated with inferior frontal gyrus and both were related to dissociative scores on questionnaires. A previous study in functional motor disorders has shown functional correlation between amygdala and SMA during processing of emotional stimuli. The current study also supports and alteration in the dynamic association between emotional and motor areas of the brain.

So the heuristic conclusion is that patients with PNES have a different relationship in their brains between emotional areas and some other areas. But which is chicken and which egg? Might for example a severely traumatic experience, such as childhood sexual abuse, alter functional connectivity? How helpful is it to think in these terms? Should we continue to think and treat patients in terms of a psychodynamic model or should we be making this disorder into an organic disease? I think psychiatry has been here before. And doubtless will again. I await a gene or an antibody for PNES! More likely a spectrum; some people wired to generate this behaviour if exposed to a sufficiently nasty trigger.

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**van der Krujis S, Bodde N, Vaessen M et al. Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures (PNES).**
**JNNP 2012;83:239-47.**

# Old men need not be grumpy – more from SANAD

There are few good quality epidemiological studies in epilepsy. Whilst primarily not an epidemiological study, but a pragmatic study of treatment, SANAD has given us some of the most useful information in guiding treatment decisions. In this analysis, the authors look deeper into their data and give us some prognostic information which will be valuable in clinical practice. They looked only at the focal epilepsy group of around 1600 patients and tried to predict demographic features which predisposed to treatment failure or time to 12 month remission. Obviously, since these patients had received medication and we know that the medication was differentially effective, this had to be included as one variable in their analysis. However, it is the other things that are interesting. With regard to treatment failure, the following

were predictors of an increased risk: female gender; abnormal EEG; having had more than 2 seizures before randomisation; complex partial seizures without secondary generalisation (worse than those with); unlocalised epilepsy, rather than temporal lobe or other better defined focal epilepsies. There was pretty much a linear relationship between age and time to remission, with those over 70 faring best. With regard to reaching 12 month remission, the curve with age was U-shaped, with those under the age of 10 and those over the age of 70 achieving remission most rapidly. Time to remission was greater for men, but their remission rate was slightly higher than for women. A greater numbers of seizures before randomisation and abnormal CT or MRI scan results were adverse prognostic feature. In both analyses, unsurprisingly, attempted treatment with the drug prior to SANAD was an adverse prognostic factor. I have not included the effects of the drugs themselves, which I believe are well-known. Some of this reinforces previous data but stratification will be helpful in guiding patients.

***– Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospital NHS Trust, Bedford.***

**Bonnett L, Turdur Smith C, Smith D et al. Prognostic factors for time to treatment failure and time to 12 months of remission for patients with focal epilepsy: post hoc, subgroup analyses of data from the SANAD trial. Lancet Neurology 2012;11:331-40.**

## Eating the debris of Rett syndrome

The infant's development appears normal. The future is filled with a myriad of exciting milestones and events. Then, rather abruptly between 6 and 18 months, purposeful hand movements disappear along with any verbal communication that previously existed. Development appears to stop and, as with the vast majority of cases, intractable seizures ensue. This, of course, is the story of a child with Rett syndrome.

Since its first description by Andreas Rett in 1966, a number of key discoveries have been made such as the identification of the X-linked gene, often mutated de novo, associated with the disease. This gene, MECP2, encodes a protein that regulates the expression of other genes by binding to methylated DNA, a key modification in terms of the coordinated pattern of gene expression vital for the ongoing development of the nervous system. Much attention has focused on the apparent impaired brain stem noradrenergic and dopaminergic networks, as seen in the Mecp(+/-) and Mecp(-/-) knockout mice. Despite these advances, management in humans remains supportive.

However, a recent report in Nature suggests a novel potential approach to the treatment of Rett syndrome. Derecki et al. describe their experiments using Mecp2-null mice. Building on previous work suggesting the important role that glia may play in pathogenesis, the authors set out to focus on bone marrow derived microglia. Firstly, Derecki et al. subjected the mutant mice to lethal split-dose irradiation followed either by the intravenous administration of syngenic bone marrow from healthy mice or were given autologous cells (i.e. Mecp2 null). Remarkably, those Mecp2-null mice who received wild-type bone marrow appeared to survive significantly longer than those who received autologous cells or those that were left naïve. Furthermore, the transplanted mice receiving wild-type bone marrow regained the body size of their healthy wild-type littermates, no longer exhibited the many features of disease, such as severe involuntary tremors and disordered gait, and the abnormal breathing patterns often seen in Rett syndrome was also significantly improved.

To test the hypothesis that the improvements observed were due to the repopulation of brain microglia derived from wild type bone marrow, the authors repeated the above experiment but this time shielded the brain from the pre-transplant irradiation, preventing brain parenchymal engraftment. As expected, the benefits of transplantation were lost in this scenario suggesting that the improvements seen were due to the replacement of endogenous Mecp2-null microglia with wild type bone-marrow derived cells.

What are these transplanted cells doing that the Mecp2-null microglia cannot? Derecki et al. postulate that the microglia derived from wild type bone marrow mediate their effects through phagocytosis, providing some evidence to support this by comparing the phagocytic capacity of wild type and Mecp2-null cells and also using inhibitors of phagocytosis.

The authors are careful to point out that whilst their findings are striking, the underlying pathological processes in Rett syndrome remain to be fully understood. They suggest a hypothesis that Mecp2-null microglia are defective in carrying out phagocytosis and are unable to clear debris secondary to the normal processes of neuronal cell death which, in an environment where Mrcp-null neurons are already compromised, might exacerbate the functional deficits seen.

Whilst this study provides a feasible potential treatment for a hitherto untreatable genetic disease, we must sound a note of caution. Firstly, the timing of transplantation was critical in that minimal efficacy was seen when Mecp2-null mice were transplanted at an older age when the abnormal signs of disease were well established. Secondly, as we do not fully understand the pathological process, transplantation might not prevent the eventual development of the syndrome, merely delaying its onset. In time, therefore, we may need to consider a trial offering bone marrow transplantation to children (invariably girls as an X-linked disorder) at the onset of abnormal clinical signs, with all the inherent accompanying risks and complications, without the guarantee of a cure.

This study provides a glimmer of hope to those patients with Rett syndrome and their families, in a field with scarce therapies to prevent, delay or reverse the devastating neurological decline invariably seen.

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## Axons: the Achilles heel in ALS

Neurones are generally depicted in textbooks as circular objects (soma) with fur (dendrites) and a single stubby process (axon) with a handful of blobs on the end (boutons). In reality, if a motoneuronal cell body (the largest cell body in the CNS) were the size of a 10 pence piece, the axon would extend up to about 500metres. We simply don't do the axon justice (see Coleman and Freeman, 2010).

So, it is not surprising that the earliest degenerative processes in ALS start in the axon and nerve terminal and extend retrogradely towards the cell body ('dying back' degeneration). This is evidenced by spinal cords from ALS patients and the mutant SOD1 ALS mouse model, which demonstrate distal corticospinal tract (CST) changes suggesting early distal axonal degeneration. Axonal transport also fails early, and mutations in proteins with axonal functions are linked to ALS, including SMN and dynactin. A direct role for TDP-43 (the hallmark protein of pathological inclusions in ALS) in axonal functioning is also emerging. TDP-43 localises with presynaptic vesicles at motoneurone terminals in human spinal cord and can aggregate early in motor axons of ALS patients. Overexpressing TDP-43 disrupts motoneuron axons and neuromuscular junctions (NMJs) in flies, zebrafish and transgenic rodents. TDP-43 also moves into axons following axonal injury.

Kano et al 2012 have added further weight to the dying back hypothesis. They have conducted important studies investigating the time course of axonal inflammation and denervation in peripheral nerves and spinal cords in mutant G93A SOD1 mice. Denervation was assessed by measuring the reappearance of mRNA coding for the acetylcholine receptor foetal gamma subunit in two muscles: the diaphragm and gastrocnemius. Levels of this mRNA were raised when the mice were 55 days old. However, levels of inflammatory markers (including mRNA coding for CD68, a macrophage marker) in the innervating nerves (phrenic and sciatic) were raised much later at 77 days of age. Moreover, histological inflammatory changes were seen in the lumbar spinal cord before the cervical cord.

The data of Kano et al suggests that in ALS a primary neurodegenerative process involving the axon occurs prior to any inflammatory changes. This process begins in the distal axon (as lumbar cord was affected before cervical) and works proximally towards the motoneuronal cell body (further evidence of 'dying back' degeneration). Given that axons may extend to more than a metre and make up over 99.9% by volume of many neuronal subtypes, it is not surprising that axons could be the Achilles heel in ALS. Axonal degeneration is also an early and significant process in both Alzhimer's disease and Parkinson's disease. However, most research in neurodegenerationhas focussed on the cell body. Axonal protection is something we must seriously focus on if we are to prevent the earliest pathological processes in these diseases and may be the most effective way of successfully treating ALS.

***– Jemeen Sreedharan, National Hospital for Neurology and Neurosurgery, Queen Square.***

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Welcome to the eleventh in a series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to write short pieces in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.

# Severe Medically Unexplained Neuro-Disability:

## Should you investigate (again) and is there a cure?

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## Case

Dear Doctor
Please could you see this 48 year old man; I have just taken over his care. He has a 12 year history of "?MS" which began with vertigo, bilateral leg weakness and collapse while working on a building site. He was thoroughly investigated at the time (he has a fat file but a lot is missing) and the results were equivocal. He is mostly confined to a wheelchair and has a catheter in situ. He requires carers to come in twice a day. He complains of blurred vision and has double or even triple vision when you test eye movements. He has backache and is under the local pain team who have him on a transdermal patch. He still complains of dizziness and chest pain when he tries to stand and the cardiologists are investigating him. He also has irritable bowel syndrome and type 2 diabetes. He is rather disgruntled especially with his former employers but not depressed. I was wondering whether it would be useful to have a fresh look at his problems and perhaps carry out some investigations. He had a normal MRI scan of his brain and spine and lumbar puncture two years ago and a neurological opinion was that it was 'functional'. Surely a person wouldn't be as disabled as this purely because of conversion disorder (especially with the incontinence)? Do you think it would be worth repeating these investigations? Is he treatable?

We are now well used to hearing that a large proportion of patients seen in neurology clinics have a 'functional' disorder – or put another way, 30% have symptoms that are not at all or only somewhat explained by neurological disease.[1] This medically unexplained group has higher levels of disability and distress and are in receipt of more disability related state benefits than patients with symptoms explained by neurological disease. A chronic course is not uncommon; for example, Stone and colleagues in Scotland[2] reported the 12 year prognosis of 60 patients with unilateral 'functional' weakness or motor-conversion disorder. Of those followed up, the vast majority reported continuing symptoms and physical limitation; 29% had taken medical retirement. Patients often had other somatic symptoms and in only one did a true neurological disorder emerge. Buried within these common disorders is a subgroup of patients with very severe disabling conditions. A number of case-series have been reported. For example 25 patients referred to liaison psychiatry or neurological disability services in Oxfordshire[3] were selected on the basis of persistent severe disability; over half had a diagnosis of motor-conversion disorders with the rest a diverse group of somatoform disorders and chronic fatigue syndrome. Most were unable to walk, unemployed and receiving disability living allowances. A subgroup of 10 of these patients confined to a wheelchair was studied in further depth.[4] All had a diagnosis of conversion or somatoform disorder, six had a previous history of major depression. Duration of illness was very long, with wheelchair use being on average 8.3 years; most were regarded as incurable. An earlier study from a spinal injury centre[5] painted a rather similar picture. Patients were identified who following their admission were rediagnosed with 'hysterical paraplegia'. However, the authors reported that the response to intensive physically based rehabilitation prognosis was good.

Switching to the primary care setting, a postal survey to general practitioners, surveying a catchment area population in Nottingham found 18 with conversion disorder[6] six of whom were very disabled, bed or wheelchair bound. It was clear that the burden of care for these individuals fell on the general practitioner. The overall prevalence rate works out at 48/100,000.

There seems to be no limit to the extremes of

*The importance of this problem is not just its cost but the fact that there is a solution*

severe medically unexplained pseudo-neurological disability that is attributable to psychological or social rather than neurological dysfunction. Sufferers are often characterised by extreme forms of dependence, convoluted and often deeply unsatisfactory encounters with a whole range of medical specialists and finally, very expensive and extensive care packages, often drawing resources from mental health, physical disabilities and social care. They frequently undergo unnecessary investigation and procedures which are not only costly but also reinforce their medical model of illness, especially when minor abnormalities are found and misinterpreted as aetiologically relevant. Such patients lead severely blighted lives and place an enormous burden on carers and families, not to mention social and health care systems and society as a whole.

Why does this happen? First, there is a lack of a clear diagnostic label – patients with similar clinical presentations acquire such radically different diagnostic labels such as "?MS", catatonia, fibromyalgia, chronic fatigue syndrome/ME and so on. Second, there is no clear professional ownership, leading to patients bouncing from doctor to doctor and incoherent care planning; symptoms and disability cross care pathways leading to 'falling between the stools' of health and social care; acute care, chronic care and rehabilitation. Finally, such patients engender poor therapeutic relationships – added to which are feelings of helplessness among practitioners ('heart sink') and in some instances, strident patient advocacy.

**Other diagnostic labels**

The case referred to above represents another common scenario where patients have an apparent diagnosis of, for example, multiple sclerosis, stroke or Parkinson's disease but where the evidence that they are suffering from that condition is at best tenuous or at worst non-existent. Nevertheless the label persists, perhaps with the collusion of professionals with the view to trying to contain and constrain help-seeking medical presentations and providing a mechanism for the affected individuals to receive some kind of acceptable (i.e. physical) support.

While conversion disorder probably accounts for the majority of these cases there are other diagnostic labels under which such patients may be hiding. The diagnosis of factitious disorder in neurology is controversial. A thorough and persuasive review by Kanaan and Wessely (2010)[7] makes the point that physical disability that might otherwise by called factitious disorder tends to be labelled as hysteria/conversion when there is a predominantly neurological flavour to the presentation. The label of factitious tends to be given where there is other evidence apart from the key symptom that the person has been creating symptoms or perhaps misleading the professionals as to the history of previous treatment or extent of disability. However, these can be subtle and are by no means absent in cases of conversion disorder. Factitious disorder in turn blends in with malingering, especially where litigation is involved or there is pursuit of benefits or compensation.

**Some dilemmas of management**

The case presents two familiar conundrums. The first is, not so much whether to investigate or refer for specialist opinions, but rather when to stop. Reading such a history, albeit brief, it is tempting and indeed justifiable to be thinking that the patient has somatisation disorder – he has a number of medically unexplained symptoms in various systems. He has unexplained severe disability and chronic pain. He also has diabetes, and other conditions of middle age; there is a suspicion of feigned symptoms such as triplopia, perhaps some ongoing dispute or litigation with an employer and possible atypical depression or other psychopathology which may be resistant to treatment. No doubt he is on several different medications so there is also a strong possibility of iatrogenic symptoms. We will not offer specific advice here. A careful review of symptoms, investigations and treatment is essential to obtain a clear picture of what to do in the patient's best interests but this is likely to be time-consuming and to raise as many questions as answers.

However, a degree of restraint is to be commended and this is supported by evidence. In the mid 1960s, Eliot Slater, neuropsychiatrist at Queen Square published a famous paper of a cohort of patients admitted to that hospital and diagnosed with hysteria. Follow-up after several years revealed, according to Slater's controversial interpretation, an exceedingly high incidence of neurological disease, which was at times fatal. This tapped into the universal anxiety in clinicians, especially psychiatrists, that they were missing 'organic' diagnoses. A follow-up of the same kind of patients three decades later provided considerable reassurance on this matter[8] and a meta-analysis of similar follow-up studies confirmed it.[9] The likelihood of new neurological disease emerging which might explain a hysterical or conversion disorder is very small and has been declining for decades, long before the introduction of MRI and CT. Presumably this is due to generally better standards of medicine and diagnostic tools and correspondingly more rigorous reporting of follow-up studies. However, trying to derive a simple 'take home message' from this is dangerous. Clearly it would be wrong to say that clinicians needn't worry about making a proper diagnosis! Rather, if you have gone through the usual steps to make a diagnosis (including taking account of psychiatric and psychosocial factors) trust your judgement and don't feel you have to do 'just one more test' despite the pressure to do so. Patients may contribute to this pressure and may appear to be reassured by a negative result but such reassurance is often short lived and our modern armamentarium is so sensitive that after a certain age, minor changes or variations in normality frequently crop up leading to an inevitable prompt to test further and so on ad infinitum.

The second conundrum raised in the referral is whether the degree of disability goes beyond conversion disorder. There is nothing in this case that might not be explained by conversion disorder. For example, incontinence is often thought to be 'very rare' in conversion disorder since surely there can be no net secondary gain for such a distressing symptom? This is wrong in our experience. Another which goes back to Freud and Charcot is the rarity of 'hysteria' in men. In fact, Dave from Dagenham is as familiar a figure in 2012 as was Anna O from fin de siècle Vienna. The combination of chronic somatoform pain (and its treatment) with motor symptoms is also all too familiar.

**Is it treatable?**

The importance of this problem is not just its cost but the fact that there is a solution. While the prognosis of untreated conversion disorder is poor,[8] there have been several studies[10 13] which have shown dramatic responses to treatment in these patients once the nature of the condition has been recognised and an appropriate management plan put in place. Much has been written about the principles of treatment which often involve an initial physical focussed rehabilitation and physiotherapy approach becoming more psychologically focussed. Multi-disciplinary treatment is recommended in all cases, and treatment of comorbid psychiatric disorders such as major depression forms an integral part of the management. The nature of the setting is often important and placement within a physical rehab unit or neurological hospital appears to maximise engagement and

avoids alienating patients with very strong physical illness attributions. Unfortunately randomised controlled trials in this area are rare.

Our ward in the South London and Maudsley NHS Foundation Trust, the Lishman Unit, has built up considerable experience and expertise managing those with severe medically unexplained disability. Although part of a mental health hospital campus, it is a neuropsychiatric unit and so has a different atmosphere from a regular psychiatric in patient unit. The presence of physiotherapists, in particular, plus the more usual MDT, is critical to the work on the unit. This may be because physiotherapists are able to engage with patients at the level which is most salient to them and they can be guided, sometimes very gradually, to increase movement and mobility while concerns and fears, around increasing fatigue or causing damage to 'nerves', can be addressed. A strong psychiatry presence is nevertheless essential. Partly because untreated depression, anxiety, personality disorders and occasionally psychosis are not rare but perhaps more important are the skills psychiatrists have in dealing with the complex dynamics that often occur with such patients and their families, carers and professional agencies. Robust neurological and other medical knowledge is also invaluable in balancing the need for appropriate use of further investigations and opinions.

Psychological input is also essential; ideally it is eclectic and tailored. Cognitive behavioural therapy (CBT) is highly effective in challenging illness beliefs and assumptions and dealing with emotional modulation of symptoms (see ref 14) but for some, a clear CBT model does not seem to be convincing and other approaches from the purely behavioural to the psychodynamic are appropriate. Finally, patients who have been living the life of a severely disabled person are not able to change quickly and we find that most admissions require at least 12 weeks of treatment.

Units such as this are rare in the UK but not unique. It is essential that experiences in such units can be compared and contrasted and that outcomes measured and presented objectively. Clinical trials are of course the only means to develop truly evidence based interventions and are being planned. ◆

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# Managing Spasticity in Children: Botulinum Toxin

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Cerebral palsy is the commonest cause of childhood physical disability. The prevalence is 2 to 2.5 per 1,000 live births.[1] It is a non-progressive neurological condition resulting from damage to the developing brain. As with stroke in adulthood the brain injury is static, however the clinical manifestations in cerebral palsy vary over time as children grow and develop. It encompasses a range of movement, development and posture difficulties. Spasticity is the dominant impairment in over 80% of children. Spasticity is defined as 'a motor disorder characterised by a velocity-dependent increase in the tonic stretch reflexes (muscle tone)'.[2] It is considered to be the main contributor to reduced longitudinal muscle growth and impaired function in children with cerebral palsy and other neurological disorders associated with spasticity.

The treatment aims for children with cerebral palsy depend on the type and severity of their condition. The management of spasticity involves a multidisciplinary team approach including physiotherapy, orthotic services, orthopaedic surgery and anti-spasmodic drugs. Botulinum toxin is a treatment modality used for children which may potentiate or even delay the need for some of these interventions.

## Mode of action

Botulinum neurotoxin is produced by the gram negative anaerobic bacterium, clostridium botulinum. It is a potent neurotoxin and causes muscle weakness through neuromuscular blockade. Seven types have been identified but only botulinum toxin type A (BtA) is available therapeutically in the UK. BtA is available as Dysport and Botox, with Botox being three times stronger.

## Clinical effects

The clinical effects of botulinum toxin have been recognised since the end of the 19th century. It was first used therapeutically by Alan Scott during the early 1980s for treating strabismus.[4] Its use in cerebral palsy and spasticity came almost a decade later, aiming to improve movement and function.

Botulinum toxin works as a local muscle relaxant and is highly selective for peripheral nerve terminals containing acetylcholine, preventing its release. As a result botulinum toxin causes reduced muscle contraction which reduces dynamic tone. This muscle relaxation enables longitudinal muscle growth. Botulinum toxin is therefore a key treatment option as it is the muscle shortening in cerebral palsy, arising as a consequence of spasticity, which leads to deformity.

## Patient selection

It is important to select the correct group of children for treatment. Botulinum toxin is predominately used for children with cerebral palsy but it is also indicated in post traumatic brain injury, neurodegenerative disorders, genetic and metabolic conditions. A child should be considered for botulinum toxin injections when they have focal,

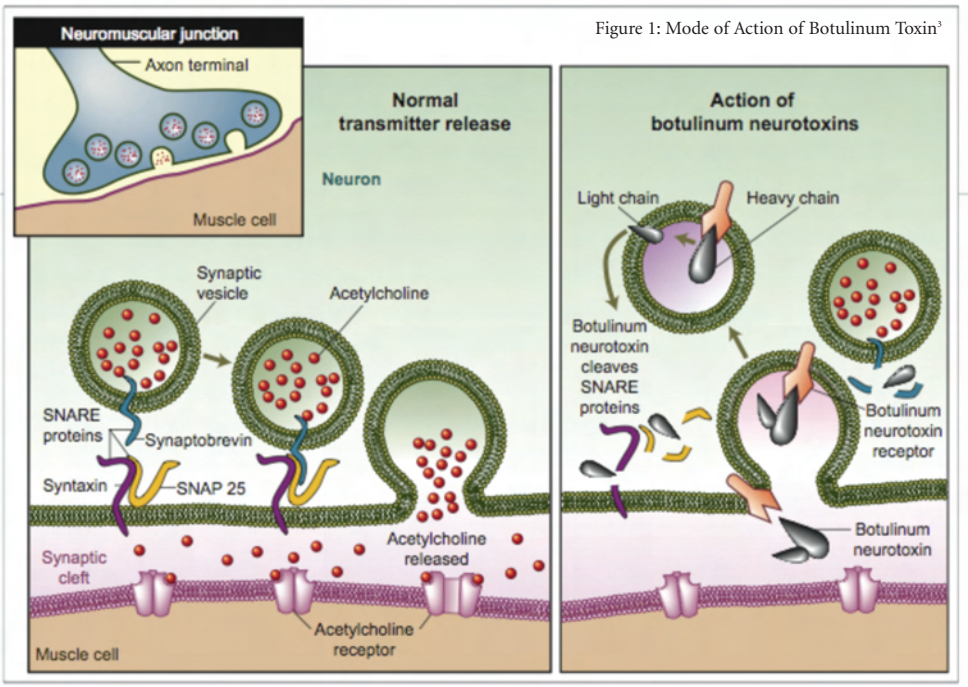


Figure 1: Mode of Action of Botulinum Toxin[3]

dynamic spasticity and/or dystonia. Botulinum toxin can be used as therapy for an ambulant child who has a poor, unstable walking gait. It can also be used in non-ambulant children to help improve seating and personal care. Botulinum toxin is also a useful treatment modality for children experiencing pain and spasms due to spasticity. Setting clear functional goals prior to injections helps to give an objective measure of whether a child has responded.

Botulinum toxin can be used in all ages but research suggests a better response in children less than eight years of age.[6] This is because younger children are less likely to have fixed contractures or have developed compensatory patterns of movement. Botulinum toxin is used in older children but has more success in those who have a dynamic component to their spasticity and when it is used in conjunction with other treatment modalities.

**Timing of use**

Growth of children makes managing spasticity a challenge. Ongoing growth spurts in childhood are a key difference when comparing using botulinum toxin in adults. Spasticity limits movement. This leads to contractures and deformities as the child grows. This is why targeting the correct children for botulinum toxin treatment early is crucial.

Botulinum toxin is taken up by the neuromuscular junction within 12 hours. The effects of botulinum toxin in children are seen at 3 to 6 days and they then peak at 6 weeks.[5] The neuromuscular connection is re-established between 12 and 16 weeks but the benefit may continue long after that. The interval for re-injection in children is approximately every 12 months.

**Pre-procedure assessment**

A careful assessment of where to inject children with spasticity is vital so existing function is not compromised. This involves a detailed assessment of a child's fixed muscle shortening versus dynamic muscle shortening. It is vital to consider the effects of relaxing individual muscles and to establish functional goals for each child.

***Assessment of spasticity***

There are many methods used to assess spasticity which help assess response to treatment with botulinum toxin. The Ashworth and Modified Ashworth scales grade resistance of a muscle to passive movement.[7] Formal gait analysis can identify changes in muscle tone in the lower limbs. Objective measures can be gained using video gait analysis. The Physician Rating Scale, which has good repeatability, assesses gait pattern and range of motion.[8] The Tardieu scale measures intensity and duration of muscle tone at different specified velocities.[9]

***Assessment of motor skills***

The Gross Motor Function Measure (GMFM) is an observational tool which evaluates change in function. It is validated in children from 5 months to 16 years and the ability to complete certain gross motor tasks is scored. In the upper limb, movement and function can be evaluated using the Quality of Upper Extremity Skills Test (QUEST). Paediatric Evaluation of Disability Inventory (PEDI) measures competence of children in the domains of self care, mobility and social function. The Physiological Cost Index is a reliable method of measuring gait efficiency. Quality of life measures are also fundamental when assessing children with cerebral palsy.

**Gross Motor Function Classification System (GMFCS)**

Level I: Walks without restrictions; limitations in more advanced gross motor skills.

Level II: Walks without devices; limitations walking outdoors and in the community.

Level III: Walks with assistive mobility devices; limitations walking outdoors and in the community.

Level IV: Self mobility with limitations; children are transported or use power mobility outdoors and in the community.

Level V: Self-mobility is severely limited even with the use of assistive technology.

**Procedure and injection technique**

Children usually attend as a day case and may be injected under local topical anaesthetic cream or oral sedation. The aim is to inject botulinum toxin into the target muscles near to the site of nerve penetration and arborisation as it is here that there is the highest concentration of neuromuscular junctions. Injection of botulinum toxin into the muscles of children can be done using electromyography guidance or ultrasound. This is important as correct identification of the target muscle is essential for a good outcome. Single or multiple muscles can be injected at each sitting and dosage is currently worked out based on body weight. Recommendations for maximum dosages of botulinum toxin in children are 30 units/kg Dysport and 12 units/kg Botox.[10]

**Key messages**

1. Growth in children makes managing spasticity challenging. Regular assessments are crucial
2. Botulinum toxin reduces spasticity, thus muscle shortening, which helps prevent deformity
3. A thorough pre-procedure assessment of spasticity using objective measures is important
4. Peak clinical effects of botulinum toxin are seen at 6 weeks and last an average of 16 weeks
5. Functional goal setting is essential

**Which muscles to target**

In spastic hemiplegia, injecting the gastrocnemius can improve dorsiflexion and targeting the elbow and wrist flexors helps to improve reach. Injecting botulinum toxin into the psoas muscle can help reduce hip flexion in children with spastic diplegia. In quadriplegia, the aim is to reduce secondary deformity, particularly in the hips and spine. The hip adductors and hamstrings are usually injected first.

**Adverse effects**

Botulinum toxin has an excellent safety profile.[11] Adverse events are rare but need to be relayed to parents and children prior to the procedure. They include mild generalised weakness, urinary incontinence, constipation or dysphagia in vulnerable children. Despite its use there remain concerns regarding the role of botulinum toxin in childhood spasticity. These relate to which muscles are best to target, optimum dose and the age at which maximum benefit is achieved. Most importantly, controversy surrounds whether there is a reliable evidence base for its effect.

**Effectiveness of injections**

***Lower Limb***

There has been substantial research assessing botulinum toxin use for the lower limb in children with cerebral palsy.[12,13] Despite the limitations of studies, current evidence does suggest a role in reducing lower limb spasticity and improving gait.

Extensive studies show clinical improvement and functional outcome with the most commonly injected sites, gastrocnemius and soleus. Although fewer studies focus on injection of these muscles, significant improvements have been seen using botulinum toxin for tibialis posterior, peroneii, hamstrings, hip adductors and flexors. Research also suggests that injection of hip adductors reduces rate of hip dislocation.

***Upper Limb***

The first clinical trial using botulinum toxin for the hemiplegic upper limb was conducted in 1997 with 14 children participating.[8] A significant improvement in wrist/elbow tone and elbow extension was demonstrated in the botulinum group at two weeks and twelve weeks post injection. Subsequent studies focusing on injecting botulinum toxin to the upper limb have not been as promising.[1,14] They suggest some improvement in cosmesis following botulinum but little change in function. There is currently insufficient evidence to support or reject the effectiveness of botulinum toxin use in the upper limb.

***Drooling***

Children with spasticity often have poor oral motor control which can manifest as drooling. Saliva can irritate the face, damage clothing and be a source of stigma. By injecting the salivary glands, neuromuscular blockade prevents secretion of saliva. The evidence for this intervention in children is limited as botulinum toxin has only recently emerged as a treatment option for drooling. However, results from a study on 50 children in 2008 showed a significant improvement in drooling a month after intervention with botulinum toxin.[15]

**Conclusion**

The use of botulinum toxin is becoming a recognised treatment modality in cerebral palsy. It is surprising not to see a clearer evidence base for botulinum toxin given its physiological effects. This may be attributable to the diversity of children with cerebral palsy included in studies in respect to distribution and severity of tone disturbance. Problems measuring muscle tone and imprecision of assessment tools may also contribute. Future studies need to address these factors to produce more consistent, reliable evidence. ◆

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# Essential Neuropharmacology: The Prescriber's Guide

*Essential Neuropharmacology: The Prescriber's Guide* is a reference guide featuring the most commonly used drugs in neurological practice. The text is designed to be accessible and easily readable for neurologists at all stages of training, both for background reading as well as quick reference on the wards or in clinic. Each drug is presented systematically using consistent subheadings. *Therapeutics* presents basic pharmacology such as method of action, common indications and onset of action. *Adverse effects* describes common and life threatening adverse effects and how to address them correctly. *Dosing and use* describes usual dosage range, dose increments, tapering doses and symptoms of overdose. *Special populations* describes alterations that may be necessary in patients with chronic renal failure, hepatic failure, pregnant women and those breast feeding. *The art of neuropharmacology* provides a brief narrative overview of the main advantages and disadvantages as well as 'pearls' summarising the most important aspects of treatment.

By its remit, the book is ideal for use in the clinical environment and the authors have released an 'App' to facilitate this use – a well-judged addition, taking into account the frequent sightings of 'smartphones' in the current clinical environment!

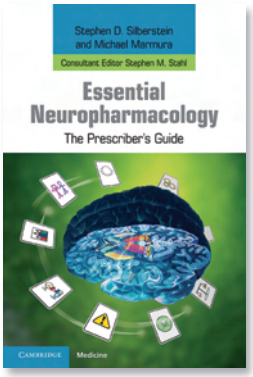
As a junior neurology trainee, you might imagine I would be in the optimal position to review this 'App'. However, it is at this stage that I must confess to my 'technophobe' status. Yet, like many, I recently ventured to purchase a 'smartphone' and I was very pleased to be asked to trial the *Essential Neuropharmacology* 'App'.

The 'App' is essentially an electronic version of the book. There is a contents page allowing rapid navigation to a particular drug. When selected, the drug reference is presented as it is in the paperback, allowing the user to browse the information. The interface is intuitive, even for the 'smartphone' novice.

The feature of the 'App' most useful in the clinical environment is the concise presentation of the drug reference. Simple sub-headings such as 'What to do about AEs' coupled with the bullet-point presentation allow the user rapidly to navigate the 'App' and find information to answer specific questions. For example, titration regimens for specific antiepileptic drugs are provided in detail. Frustratingly however, there are some notable omissions and these omissions tend to be the more novel agents in whose use questions are most likely to arise. An overview of alemtuzamab, for example, could be very useful but this drug does not feature.

Written as a concise summary, there is predictably little explanation, which is the text's primary limitation. However, for its purpose as a quick reference, particularly as an 'App', this is to be expected. Additional limitations include the small font without the ability to zoom in, compounded by the permanent menus encroaching further on the screen size. The text is difficult to read for any substantial period of time on the kind of pocket device for which it is designed.

The 'App' certainly proved successful as a reference guide in the clinical environment. Perhaps the biggest hurdle for its use is your colleagues' and patients' suspicion that you may be engaged in social networking rather than reviewing neuropharmacological options! ◆

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***Reviewed by:*** Graham Powell, Academic Clinical Fellow in Neurology, University of Liverpool.

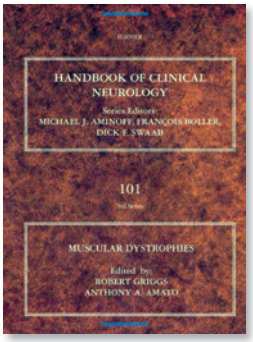
# Muscular Dystrophy Volume 101 (Handbook of Clinical Neurology)

This book on *Muscular Dystrophies* is an invaluable addition to the *Handbook of Clinical Neurology* series. With the great strides in our knowledge and understanding of the heterogeneous conditions often randomly grouped together under the heading of 'muscular dystrophies', this book helps bring some order by classifying into chapters the different forms of muscular dystrophies based on our current molecular and genetic understanding of these disorders.

Importantly, the phenotypical descriptions of the different muscular dystrophies are provided in some detail, allowing the book to be a useful source of reference. In addition, laboratory and radiological features are also described, where available, adding to the strength of this book as a source of reference. There is some detail of molecular mechanisms of the different conditions, where known, which can point the interested reader to the relevant literature for further reading if he or she so wishes.

The chapters of the book are authored by leading figures in the neuromuscular field, ensuring the material is as relevant and as up-to-date as a textbook possibly can be. The book contains clinical photographs of some of the more common conditions. One criticism is that some of the photographs appear relatively old and difficult to make out (for example those of the facial features of myotonic dystrophy in Chapter 15). Better quality photographs would have added immensely to the visual appeal and clarity of the book. Diagrams and figures clearly help illustrate descriptions in the text, while tables provide good summaries of important areas.

Overall, this book is probably aimed at neuromuscular specialists or dedicated students of the science of neuromuscular diseases. With such a fast moving field, the very latest developments will inevitably be missing. However, the book provides a strong foundation for the understanding of muscular dystrophies for those learning and for the learned; I highly recommend it. ◆

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# The Application of Optical Coherence Tomography (OCT) in Neurological Disease

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is a clinical neuroscientist currently working at the Institute of Neurology in Queen Square. She has taken some time out of her neurology training in Bristol to undertake a clinical trial on neuroprotection with phenytoin in optic neuritis. The trial is currently open to recruitment.

***Anand Trip***
is a Consultant Neurologist and Honorary Senior Lecturer at The National Hospital for Neurology & Neurosurgery and Northwick Park Hospital. He completed a PhD at the UCL Institute of Neurology which applied markers of axonal loss and myelination in the retina and optic nerve to patients with optic neuritis and multiple sclerosis.

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Optical coherence tomography (OCT) was first described by Huang et al. in 1991[1] and was first used to image the retina in 1993.[2] OCT technology has evolved rapidly enabling the production of in vivo high resolution cross-sectional and three-dimentional images of the ocular microstructure in real time. These OCT images closely reflect histological sections of the macula and fovea, hence the term "optical biopsy."[3,4] The technique was initially used for the diagnosis and management of ophthalmological diseases but over the last decade has been increasingly recognized for its applications in neurology.

**Basic principles of OCT**

OCT is the optical analogue of B mode ultrasound, except that instead of using acoustic waves it uses light reflections to acquire images. A laser generated beam of near infrared light is scanned across the retina and the magnitude and echo time delay of backscattered light is measured. In contrast to standard ultrasound, direct detection of light echoes is not possible because of their high speed. A correlation technique is therefore required and OCT systems are based on the principle of low coherence tomography which was first described by Sir Isaac Newton. Acquisition of the OCT signal is based on splitting of the coherent light beam into two parts: a sample and a reference beam which are the same length but follow two different paths. When reflected light from each of the two paths reaches the detector at the same time they induce an interference signal. The image is acquired by measuring the amplitude of this interference signal (Figure 1).

There are currently two types of commercially available OCT techniques, called time domain and spectral domain OCT.

**Time domain OCT**

The earlier time domain OCT machines use a super-luminescent diode to direct low coherence light into the eye. The light beam is split into two parts by a beam splitter. One beam is directed into the eye and is reflected back from the different layers of the retina. The other reference beam is reflected by a reference mirror. A series of A scans are sequentially acquired one after another producing a final cross-sectional image, or B scan, with a resolution of approximately 8-10 μm.

**Spectral Domain OCT**

The first retinal images with spectral domain OCT were reported in 2002[5] and the technique became commercially available in 2006. Imaging is approximately 50 times faster than

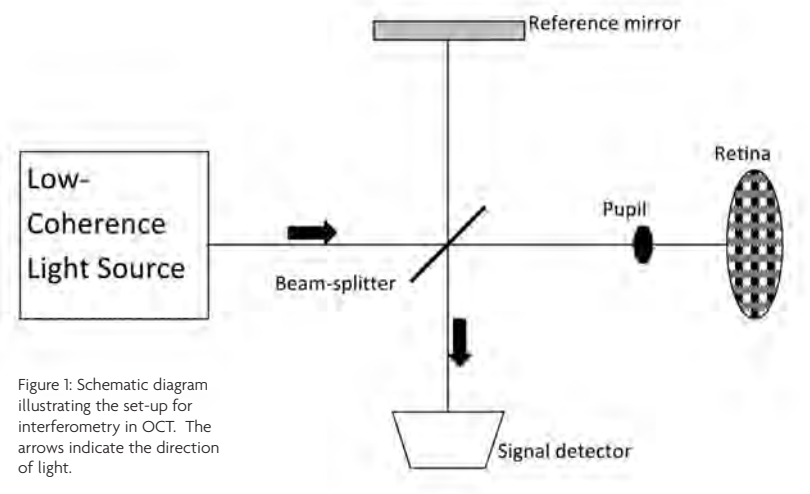
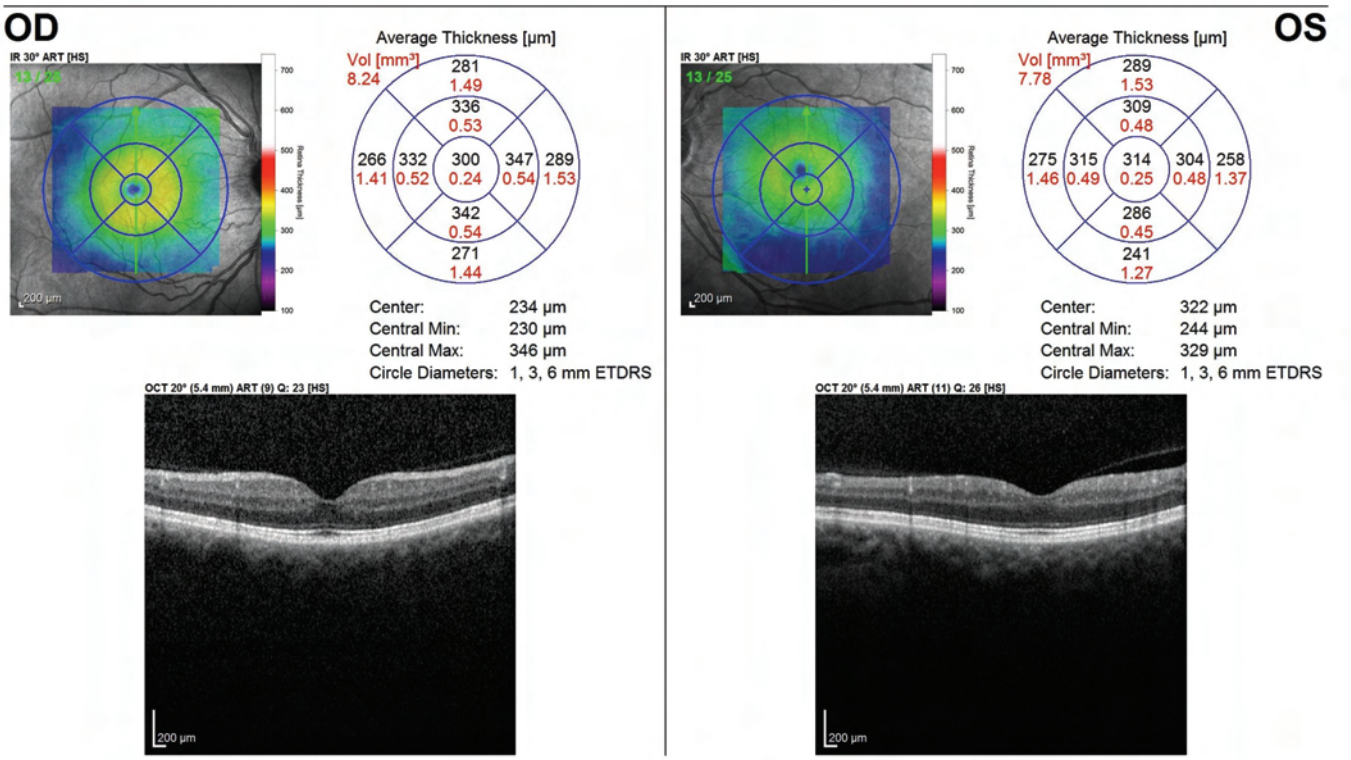



Figure 1: Schematic diagram illustrating the set-up for interferometry in OCT. The arrows indicate the direction of light.

Figure 2: A fast macular volume scan demonstrating reduced total macular volume 6 months post left optic neuritis.




time domain OCT with an acquisition speed of approximately 25,000 axial scans per second and an axial image resolution of approximately 5-7µm. There is also a significant reduction of artefact from ocular movements. Spectral domain also exceeds time domain OCT in its ability to form three dimensional maps of the retina and optic nerve. It is based on fast fourier transformation and it allows all echoes of light from the different retinal layers to be measured simultaneously and the interference signal is a function of their wavelength. This eliminates the need for a moving reference mirror.

## OCT in ophthalmology

A detailed review of OCT in ophthalmology is beyond the scope of this article but some examples are mentioned here. OCT has the potential to permit early diagnosis of glaucoma, even in the absence of clinical signs or visual symptoms. The early detection of structural damage to the retinal nerve fibre layer (RNFL) helps to identify those patients who require preventative therapy.[6] The response to treatment of exudative age-related macular degeneration with photodynamic therapy and the newer intra-vitreal anti-vascular endothelial growth factor antibodies can be quantified by comparing serial OCT macular thickness measurements. Similarly, OCT measurement of macular thickness can be useful in diabetic macular oedema by demonstrating diffuse retinal thickening, cystoid macular oedema, serous retinal detachment and vitreomacular interface abnormalities.[7] OCT was also used to detect the development of macular oedema in the recent trials of fingolimod in multiple sclerosis (MS).[8]

## OCT in optic neuritis and multiple sclerosis

Over the past seven years there has been an increasing number of publications on the use of OCT of the retina as a biomarker for neurodegeneration in MS. Although for a long time MS was considered a primarily demyelinating disease there is compelling evidence that axonal loss occurs early on during the course of the disease and is related to irreversible disability.[9,10]

The retina has often been described as the window into the central nervous system (CNS) and the afferent visual system represents an exciting prospect for MS researchers specifically with regards to the processes of neurodegeneration and repair. This is because the retina is unique in the CNS in that it contains unmyelinated axons, which comprise the retinal nerve fibre layer (RNFL), the most proximal part of the afferent visual system and therefore changes primarily represent axonal loss. OCT measurement of RNFL thickness in MS is reliable and reproducible.[11]

When an acute lesion affects the optic nerve during an episode of optic neuritis there is transaction of axons followed by retrograde axonal degeneration culminating in loss of retinal ganglion cells and axons in the RNFL, which manifest as loss of macular volume (Figure 2) and thinning of the RNFL (Figure 3).

Optic neuritis is a common manifestation of MS and is the first symptom in up to 20% of patients and will occur in as many as 70% of patients at some point during the course of the disease.[12] Also, there are structural, electrophysiological and clinical outcomes that can be easily measured after an episode of optic neuritis, which have been shown to correlate with OCT RNFL measurements.[13,14] It is hoped that the neurodegenerative process occurring in the retina can be extrapolated to the processes occurring in the rest of the brain and spinal cord in patients with multiple sclerosis. This would allow the retina to be used as a biomarker for monitoring neurodegeneration in MS and also for measuring the therapeutic efficacy of neuroprotective drugs.

In 2005, Trip et al. investigated 25 patients after a single episode of optic neuritis (with an intentional bias towards poor visual recovery) in a retrospective cross-sectional study. The mean RNFL thickness and total macular volume of affected eyes was reduced by 33% and 11% respectively compared with controls. RNFL thinning predicted worse LogMAR visual acuity, visual field, colour vision and visual evoked potential (VEP) amplitudes, consistent with axonal degeneration.[13] The group also looked at the cross-sectional area of the optic nerve as measured by magnetic resonance imaging (MRI) and found that the optic nerve area of the affected eye was significantly reduced when compared with fellow eyes and controls and that the RNFL and macular volume of the affected eye

correlated significantly with optic nerve area.[14]

In a 12 month longitudinal study, Costello et al. demonstrated that 74% of patients had RNFL thinning after acute optic neuritis and the majority of this occurred within the first three to six months, the temporal sector being the earliest involved. They also suggested a threshold for RNFL thickness of 75 µm below which visual function, as measured by automated perimetry, declined linearly.[1]

Fisher et al. demonstrated that low contrast letter acuity scores were significantly correlated with average RNFL thickness and every one line decrease in low contrast letter acuity was associated with an average 4mm thinning of the RNFL.[16]

Subsequently, several studies have shown that average RNFL thickness can differentiate between MS subtypes with lower values in progressive forms of MS when compared with patients with clinically isolated syndromes suggestive of MS,[17,18,19] and overall disability, as measured by the expanded disability status scale (EDSS), correlates with the RNFL thickness.[20]

In 2010, Henderson et al. performed a prospective study on 23 patients with acute unilateral optic neuritis. Patients underwent OCT, visual assessments and visual evoked potentials (VEPs) at 3,6,12 and 18 months. They found that 90% of the retinal nerve fibre degeneration occurred within a mean 2.38 months from onset of the disease and that poorer visual function was associated with greater decline in RNFL thickness during the first three months. They also performed sample size calculations which have paved the way for future neuroprotection trials using OCT as a primary outcome measure.[21]

With the emergence of high resolution SD-OCT it is now possible to segment the different retinal layers. Of particular interest is the retinal ganglion cell layer (GCL) as a potential marker for neuronal loss. The Balcer group has developed a segmentation algorithm and in a study of 122 MS patients and 31 controls found that the GCL and inner plexiform layer (IPL) (Figure 4) were significantly decreased in MS eyes versus controls and in MS optic neuritis eyes versus non-optic neuritis eyes. GCL atrophy is comparable to grey matter atrophy in MRI and may emerge as a structural marker of disease progression in the future.[22]

## OCT in neuromyelitis optica

OCT has also been considered as a biomarker for axonal loss in neuromyelitis optica (NMO). Mean RNFL thickness is significantly reduced in optic neuritis eyes in NMO patients compared with controls and RNFL atrophy after optic neuritis is more severe in NMO than in MS.[23,24,25]

Ratchford et al. estimated that one episode of optic neuritis in NMO causes 24 µm more RNFL atrophy than in relapsing remitting MS.[25] In NMO, mean RNFL thickness correlated with EDSS and visual disability.[23]

## OCT in Alzheimer's disease & Parkinson's disease

OCT may have applications in other neurodegenerative conditions. Several groups have demonstrated RNFL thinning in Alzheimer's disease patients when compared with age-matched controls.[26,27] These changes occur early during the course of the disease and correlate with the severity of cognitive impairment.[28] Thinning of the RNFL has also been reported in Parkinson's disease. Inzelberg et al. demonstrated a significant reduction in inferotemporal peripapillary RNFL thickness when compared with age-matched controls.[29] Currently the functional and clinical implications of these structural abnormalities are unknown.

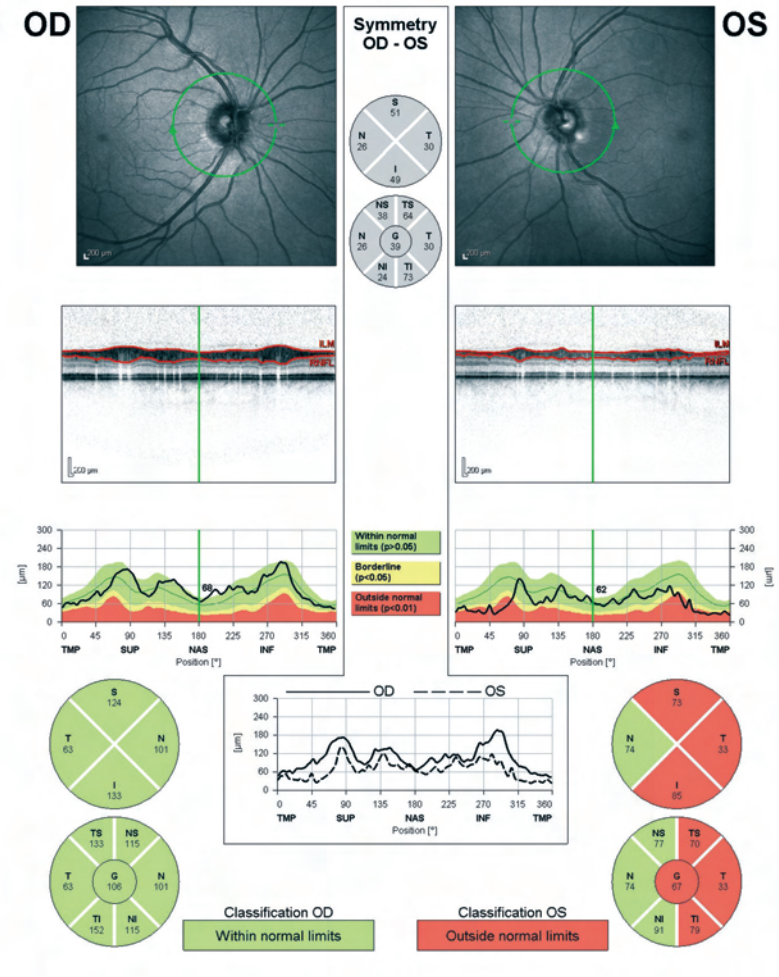
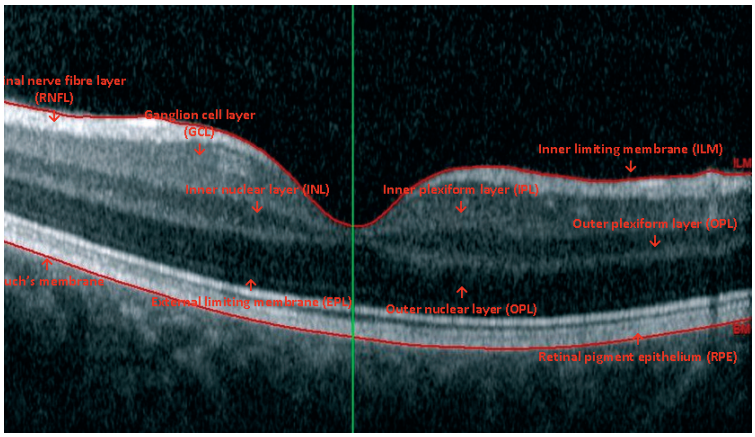



Figure 3: Thinning of the temporal sector of the RNFL 12 months post left optic neuritis.

## Conclusion

OCT is a relatively new technique that has greatly advanced our understanding, diagnosis and management of ocular diseases. The introduction of spectral domain instruments has improved acquisition speeds and allows high resolution, three-dimensional images to be produced. It is able to provide quantitative measurements of retinal structures with a high degree of reproducibility. More recently there has been much interest in its use in evaluating CNS diseases that affect the afferent visual system, using the eye as a window into the CNS in order to visualise the processes of neurodegeneration and neuroprotection and providing us with outcome measures to assess the efficacy of neuroprotective treatments. ◆

Figure 4: A macular B scan centred on the fovea demonstrating the different retinal layers.



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# ebrain and a distance learning diploma in clinical neurology

## – a revolution in medical education

***Dr Pooja Dassan***
graduated from Guy's and St Thomas' Medical School, London, in 2001. She is currently working as a neurology registrar in London. Her specialist interests are in stroke medicine and medical education.

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Online education has revolutionised our learning experience and ebrain, a new e-learning programme in clinical neurology, is no exception. ebrain was launched at the end of last year and is available free of charge for all UK neurologists via their Joint Neuroscience Council (JNC) membership and similarly for European neurologists via their European Federation of Neurological Societies (EFNS) and European Neurological Society (ENS) memberships.

ebrain was originally intended to be part of a Department of Health initiative, e-learning for healthcare, which recently collapsed due to cut backs executed as result of the financial crisis. E-learning for healthcare was set up by the Labour government to deliver professional healthcare training to hospital trainees and consultants across all specialities via a quality-assured online programme. The JNC had been contacted to develop the neuroscience section and Mr Simon Thomson (Consultant Neurosurgeon at Leeds Teaching Hospital NHS Trust) and Professor Simon Shorvon (Professor of Clinical Neurology at University College London) were selected as the clinical leads to oversee its development. However, following the financial crisis, with the project just getting underway, funding was summarily withdrawn. The clinical leads and the JNC, however, did not abandon the project and approached the EFNS, ENS and UCL for financial support to continue with its development. This was granted and Dr Hannah Cock (from the ENS) and Dr Thomas Berger (from the EFNS) joined as clinical leads. It is because of the vision of the JNC and its clinical leads that the clinical neurosciences programme was not abandoned and developed into this online educational resource. ebrain can be accessed via the web at (http://ebrainjnc.com), with access freely available to members of the JNC organisations (almost all British clinicians in the various neuroscience disciplines), the EFNS societies, and members of the ENS.

The core curriculum has been written by neurologists both from the UK, including many from Queen Square, and also from Europe. The curriculum includes about 550 e-lectures covering a comprehensive range of topics within clinical neurology, including, neurosurgery, neurophysiology and neuropathology. There are clear objectives at the start of each lecture (see Figure 1 for an example) followed by a summary of the main learning points at the end. The sessions explain the current understanding and scientific basis underpinning common neurological diseases but in addition give an insight into recent research advances and developments within each field. There are also self-assessment questions at the end of each lecture and coupled with this, answers and explanations are provided for each question. Certificates are provided for

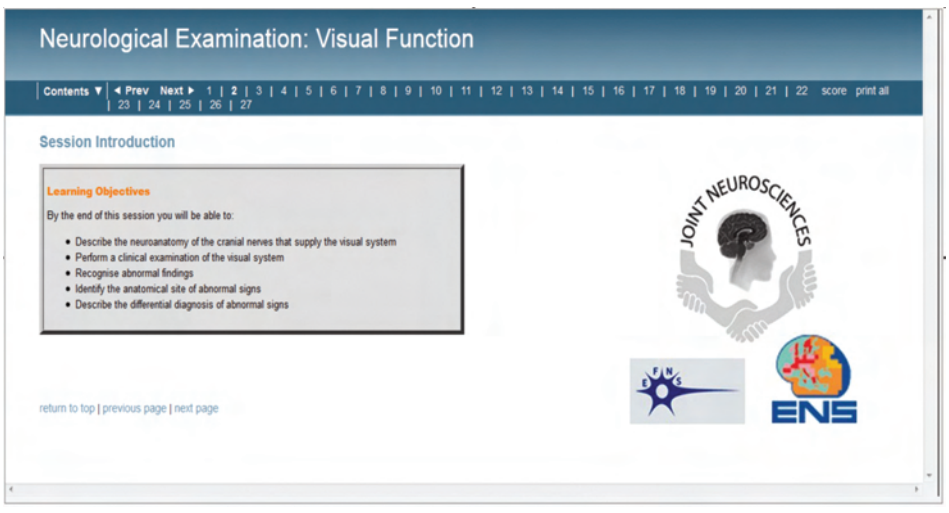


Figure 1: An example of the clear learning objectives provided at the start of each lecture.

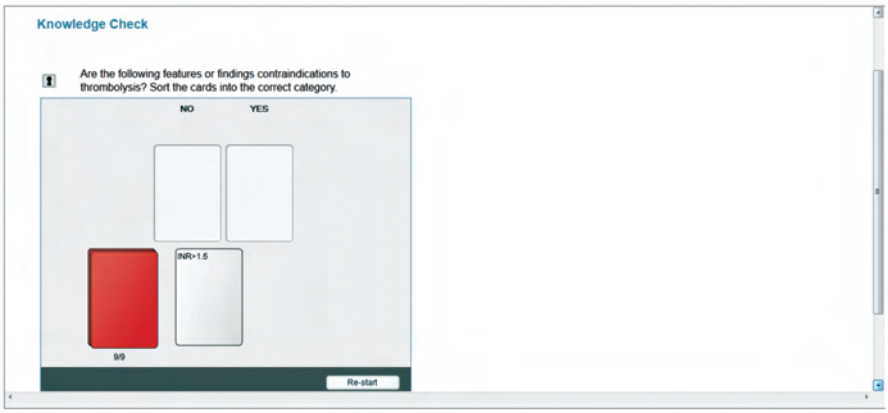


Figure 2: An example of an interactive feature ("drag and drop"); candidates have to sort the cards into the correct category according to whether the feature is or isn't a contraindication for acute stroke thrombolysis therapy.

users on completion of each session and these can be a valuable addition to anyone's portfolio. In addition, there is an inbuilt system which makes it mandatory for all users to provide feedback for all the sessions they have used, allowing the programme to be continuously revised and edited accordingly.

A salient feature of this online programme is the use of high-tech animations and features (see Figure 2 for an example), including interactive graphs and tables, which enhance the learning experience. There are also several videos embedded in the course content, and these are used to illustrate important physical signs such as an abnormal gait, a specific tremor or a speech disorder, to name but a few, which otherwise can be very difficult to teach.

The core curriculum, along with other online resources, is also available as a UCL degree – the Distance Learning Diploma in Clinical Neurology. The diploma is an ideal solution for doctors from around the world who don't have the time or opportunity to attend traditional classes. The main advantage of a distance learning course over traditional face-to-face teaching is that candidates can work at their own pace, in their free-time and without fixed timetables or the need for regular attendance. As it is entirely online, the course can be completed as quickly or as slowly as the candidate wishes, and can be accessed from home or the office. The target audience for the diploma includes neurology trainees and consultants, and other doctors with a keen interest in neurology. All candidates receive regular online support and also tutorials (via skype) with their personal tutor based at Queen Square, as well as emails and a discussion forum. The regular tutorials permit a personalised one-to-one interaction which is an important aspect of the course. There are also regular assessments throughout the course in the form of multiple choice questions, short answer questions and short essays. It is anticipated that most candidates will take approximately 12-18 months to complete the course. Further details about this diploma can be found by visiting this website: http://www.ucl.ac.uk/ion/education/courses/distancelearningdiplomaneurology. The JNC would be happy to consider approaches from other universities to include aspects of this online programme in other degree courses.

In conclusion, technology is continuously advancing and its effects on education to date have been profound. Online programmes such as ebrain are a prime example of this. ◆

*To list your event in this diary, email brief details to Anna Phelps at anna@acnr.co.uk by 6th June, 2012*

## 2012

### May

**7th World Congress Of NeuroRehabilitation**
16-19 May, 2012; Melbourne, Australia
www.dcconferences.com.au/wcnr2012

**Biomarker discovery: Driving technologies**
17 May, 2012; London, UK
T. 07507 799380
E. enquiries@euroscicon.com
www.regonline.co.uk/Biomarker2012

**Annual meeting in MS: from disease management to patient management**
18-19 May, 2012; Valencia, Spain
T. +39 06 420 4131
E. info@seronosymposia.org

**Essentials of medical genetics for clinical practice today**
21 May, 2012; London, UK
www.rsm.ac.uk/academ/mgc03.php

**ESC 2012 – European Stroke Conference**
22-25 May, 2012; Lisbon, Portugal
E. esc@congrex.com

**18th European Congress of Physical and Rehabilitation Medicine**
28 May – 1 June, 2012, Thessaloniki, Greece
T. +30 210 3274570
E. info@esprm2012.eu

**ABN Annual Meeting**
29-31 May, 2012; Brighton, UK
T. 020 7405 4060
E. abnexhibition@affinityevents.co.uk

### June

**10th European Conference of Neuropathology**
6-9 June, 2012; Edinburgh, Scotland
T. 0141 434 1500
E. ecnp2012@meetingmakers.co.uk

**ENS 2012 – 22nd Meeting of the European Neurological Society**
9-12 June, 2012; Prague, Czech Republic
E. info@ensinfo.org
www.congrex.ch/ens2012/

**Memory Conference 2012**
14 June, 2012; Hildenborough, UK
T. 01732 833924
E. pa@raphaelmedicalcentre.co.uk

**Blooms Day Basic Movement Disorder Course**
16 June, 2012; Dublin, Ireland
T. +1 414 276 2145
E. info@movementdisorders.org
www.movementdisorders.org

**16th International Congress on Parkinson's Disease and Other Movement Disorders**
17-21 June, 2012; Dublin, Ireland
T. +1 414 276 2145
E. info@movementdisorders.org
www.movementdisorders.org

**Epilepsy in Children: 9th National Neuroscience Conference 2012**
20 June, 2012; London, UK
T. 020 7501 6762
E. conferences@markallengroup.com

**British NeuroOncology Association 2012**
27-29 June, 2012; Manchester, UK
T. 07974 436202
E. communications@bnos.org.uk

### July

**Childhood Epilepsy Masterclass**
5 July, 2012; Lingfield, UK
T. 01342 832243 ext 296
E. epilepsytraining@youngepilepsy.co.uk

**Autism Today Summer Meeting**
5-6 July, 2012; London, UK
T. 020 7501 6762
E. conferences@markallengroup.com

**Joint meeting of the Anatomical Society and Sociedad Anatómica Española: Motor Neurones and Diseases of Motor Neurones . e-learning: Interactive electronic teaching in anatomical sciences education**
10-12 July 2012, Edinburgh, UK
E. as.meetings@ed.ac.uk,
www.anatsoc.org.uk/Meetings

### August

**10th World Congress on Sleep Apnea**
27 August – 01 September, 2012; Rome, Italy
E. mario.fabiani@uniroma1.it

### September

**ISCOS - International Spinal Cord Society**
3-5 September, 2012; London, UK
T. 020 7383 8030
E. iscos@kenes.com

**Laboratory Skills**
3-14 September, 2012; Warwick, UK
T. 024 7652 3540
E. Charlotte.Moonan@warwick.ac.uk
www.warwick.ac.uk/go/labskills

**The 8th International Conference on Frontotemporal Dementias**
5-7 September, 2012, Manchester, UK
T. 0207 383 8030
E. ftd@kenes.com

**10th Meeting of the European Association of NeuroOncology**
6-9 September, 2012: Marseille, France
E. eano2012@medacad.org
www.eano.eu

**16th Congress of the European Federation of Neurological Societies**
8-11 September, 2012; Stockholm, Sweden
T. +41 22 908 04 88
E. headoffice@efns.org
www.efns.org/efns2012

**Multiple Sclerosis: MS Trust Study Day on Postural Management**
25th September 2012; Leeds U.K.
(Advanced Level)
E: eduction@mstrust.org.uk
www.mstrust.org.uk/professionals/

### October

**Royal College of Physicians of Edinburgh: Neurology Symposium**
Thursday 4 October, 2012; Edinburgh, UK
Contact Christine Berwick,
E. c.berwick@rcpe.ac.uk
http://events.rcpe.ac.uk/events/179/neurology

**Complex Epilepsy Conference for Professionals**
12 October, 2012; Birmingham, UK
T. 01392 832243
E. epilepsytraining@youngepilepsy.org.uk



# PREVIEW: Pain Therapeutics

***Conference details:*** 21 & 22 May 2012; Copthorne Tara Hotel, London, UK.

**Examine practical issues within the industry and network with leading experts at SMi's Pain Therapeutics conference**

SMi Group proudly presents the 12th annual Pain Therapeutics conference, which will once again bring together key industry leaders and delegates to discuss the latest advances in drug development practice.

Pain is the most common reason patients seek medical care and has significant sensory and emotional components. Despite the advances in pain management, few significant advancements have been made, making it harder to get analgesics to market in recent years. With budgetary cuts being made, it is now even more important for companies to improve their R&D methods so that drugs being put forward for clinical trials have the best chance of success.

**Keynote Speakers**

SMi Group is pleased to introduce Chas Bountra, Chief Scientist, Structural Genomics Consortium, University of Oxford, who will give a presentation on the greater emphasis on experimental models needed for the success of analgesic development, giving delegates insight on how understanding of experimental pain models needs to improve.

The conference will also present key presentations from speakers including Philip Kym, Associate Director II, Pain Discovery Research, Abbott Laboratories. His presentation on the discovery of differentiated TRPV1 antagonists that separate efficacy from hyperthermic effects will look at identifying a new generation of modality-specific TRPV1 antagonists.

Kevin Lee, CSO, Orphan & Genetic Diseases, Pfizer will give a presentation entitled Epigenetics in inflammation and beyond, giving an overview of the role of epigenetics in inflammation and how this knowledge can be used to improve treatments.

Visit www.pain-therapeutics.co.uk for the full speaker line-up, which includes presentations from: Bristol-Myers Squibb; Merck; Convergence Pharmaceuticals; Grünenthal and University Of New England.

**Interactive workshops**

Delegates can choose between two workshops, both held on 23rd May, 8.30am - 12.30pm. EU Paediatric Requirements in Developing Drugs for Pain Treatment, led by Dr Klaus Rose, Managing Director, Klausrose Consulting, Switzerland will discuss in depth the specific paediatric challenges in drug development for pain treatment and lead through the stages of the EU Paediatric Investigation Plan (PIP). Utilising Industry + Academic Alliances in the Development of Pain Treatments, led by Fiona Boissonade, Head of Neuroscience Research Group, School of Clinical Dentistry, University of Sheffield aims to address the benefits to be gained by making use of cooperation between pharmaceutical companies and academic institutions. ◆

Visit www.pain-therapeutics.co.uk for more details or contact Andrew Gibbons on
Tel: +44 (0) 207 827 6156,
Email: agibbons@smi-online.co.uk

# The Society for Research in Rehabilitation – Winter Meeting

***Conference details:*** 24th January, 2012; Ely, Cambridgeshire, UK. ***Reviewed by:*** Dr Anna Maw, consultant paediatric neurologist, Cambridge.
***Host:*** Dr Andrew Bateman, Oliver Zangwill Centre.
***Keynote speakers:*** Eivor Oborn (London, Cambridge), Terry Dickerson (Cambridge), Fergus Gracey (Cambridge), Tom Manly (Cambridge).

This winter's SRR conference was held on a damp foggy January day in the beautiful setting of the Maltings in Ely, Cambridgeshire, bringing together leading academics and practitioners in rehabilitation and research implementation from across the UK and beyond.

The SRR is the leading multidisciplinary rehabilitation research society in the UK promoting education and research into all aspects of rehabilitation. The conference itself is a masterclass in how to think about and evaluate the wide range of interventions and outcomes in rehabilitation, and the research methodologies which are available to do this. Going beyond this, the conference focussed not just on research and research findings, but devoted the first symposium to the challenges and barriers of implementing research into service provision; "Good science in a bad system will not improve care". It is a testament to the dynamism and progressive thinking of the SRR that this subject was given such a high profile.

**First symposium – Bridging the type 2 gap, service implementation research**

Eivor Oborn (Royal Holloway School of Management, London and Judge Business School, Cambridge) asked the question "How do we transfer research findings into practice?" and began with an exploration of the nature of information, data and knowledge and how these are transferred between individuals and groups. Explicit knowledge which can be written and shared is relatively easy to transfer between groups. Tacit knowledge which, as health practitioners, we all recognise as an essential part of our practice and learning, is intuitive, instinctive and embedded in our thought and behaviour patterns. This knowledge may make sense within a particular group, but effective exchange of knowledge across communities or practice is key if we are to bring our research findings into practical service delivery.

This theme was further developed by Dr Terry Dickerson, Assistant Director of Health Care Design at the Engineering Design Centre in Cambridge (EDC), looking at the complexities and challenges of bringing principles of system design into the health care setting. Using design knowledge and expertise from the manufacturing world, the group at the EDC are working to encourage clinicians and managers to move away from the traditional reactive model of service development (plan-do-study-act). His group have used process simulation techniques to turn tacit knowledge about an organisation into explicit knowledge which can be communicated between different groups, allowing risks in a system to be monitored before rather than after implementation.

**Symposium 2 – A novel intervention of rehabilitation of executive function.**

Tom Manly and Fergus Gracey (MRC Cognition and Brain Science Unit, Cambridge) spoke jointly about the background and results of the Assisted Intention Monitoring (AIM) trial for rehabilitation of executive function in adults with acquired brain injury. Rehabilitation of goal-directed behaviour within executive function is notoriously difficult because the very skills which are needed to access the rehabilitation process (error detection and awareness, the ability to solve new problems and respond flexibly) are often damaged after brain injury. Building on the success of the neuropage service at the Oliver Zangwill Centre, and on a line of research into content-free cueing pioneered by Dr Manly at the MRC-CBU, this study looked at the effect of content-free external cueing in helping participants complete tasks of day-to-day living (i.e. assisting them to monitor their intentions).

Participants were taught set times to ring the researchers' answerphone each day. During the intervention phase of the trial, participants received daily content-free text message alerts to their mobile phones. During the control phase, no prompts were delivered. The ability of the participants to remember to contact the answerphone was assessed during both control and intervention conditions as a way of objectively measuring outcome. The AIM intervention showed a strong effect on this measure. However, there was no significant effect for participants' own daily intentions. It could be that these are more difficult to measure, or that people were more motivated to do things for the researchers than for themselves. The study has also had a direct impact on local clinical practice. Materials developed for the study have been used by one of the research team in her work as an OT to improve identification and rehabilitation of executive problems in stroke patients.

Free paper sessions were interspersed throughout the day demonstrating the breadth of subject matter and methodology within rehabilitation research. The clinical emphasis of the papers (5/9) was on stroke rehabilitation, but the real value of these sessions to a wider audience was in the exposure to a range of qualitative research methodologies – semi-structured interviewing, thematic analysis, focus groups – as a way of appraising the interventions and services we provide.

Particular highlights included:

- Two papers looking at the effect of psychological interventions. One, from the University of Swansea, looked at the cost-effectiveness of group cognitive behavioural therapy in people with low mood in MS. The study demonstrated reduced distress, depression and anxiety in the intervention group over an 8 month period along with reduced service uptake and cost-saving of £493 per person. The second, from the Oliver Zangwill Centre, demonstrated the effectiveness of neuropsychological rehabilitation in reducing patient and carer reports of dysexecutive behaviours and carer stress.

- Stroke and Social Identity – a study from Sheffield looking specifically at social identity changes in people affected by stroke, and the role of stroke clubs in maintaining and rebuilding a positive social identity.

- Who are intermediate care patients and what are their needs? This study from Sheffield of 11 different care teams across England over a 12 month period demonstrated the huge variability in service provision, team composition and workload. By quantifying the data in a rigorous and reproducible way, it helped to convert tacit knowledge (that services often reflect the historical interests within a locality rather than patient need) into explicit knowledge with which to inform service provision in the future.

This conference is an excellent opportunity to spend time immersed in a multidisciplinary group, expert in and wholly committed to producing high quality, rigorous health research. The emphasis of the whole program, including the excellent array of poster presentations, is on applicability and improving outcomes. For those who are uninitiated in the complex methodology of qualitative research, it is an unrivalled place to start. Highly recommended. ◆

## *Fujifilm's new NHYes website*

Fujifilm are proud to be launching their new website, dedicated to their range of DR solutions that are now approved and available via the NHS Supply Chain Framework. Fujifilm's NHYes website can be found at http://www.fujimed.co.uk/yes, and explains how their innovative new DR technology can improve image quality and increase throughput, as well as help to streamline procurement and reduce costs. With a collaborative approach, Fujifilm delivers exceptional solutions and support, which is now all available via the NHS Supply Chain.

The informative website also features the range of equipment available from Fujifilm, via the NHS Supply Chain:

- The newly developed direct conversion Flat Panel Detector, FDR AcSelerate.
- The FDR Amulet, providing enhanced breast imaging capability, increased usability and patient comfort.
- The fast, flexible and lightweight FPD System, FDR D-EVO.
- The high performance and highly mobile portable CR X-ray unit, FCR Go.

A brief synopsis of each product, as well as full product and technical details are available, as well as informative product demonstration video clips. There is also a contact page that enables visitors to leave feedback comments and subscribe to the Fujifilm newsletter.

***For further information Tel. 01234 326780.***


## ABN Annual Meeting Brighton 2012

29 May 2012 - 31 May 2012
The Brighton Centre, Brighton, UK

Tel: 020 7405 4060
Email: info@theabn.org • www.abn.org.uk
The ABN, Ormond House, 27 Boswell Street, London WC1N 3JZ

## The Third Oxford Neurology Course

### 27-29 June 2012

UNIVERSITY OF OXFORD

**After its successful launch in 2010, we would now like to invite you to attend the third "Oxford Neurology Course," which will run from 27th June – 29th June 2012. The course is aimed at neurology trainees and consultants. We have again been able to attract a number of highly acclaimed speakers, who will cover a wide range of neurological topics. In our programme, we are aiming to continue our popular combination of down to earth practical issues as well as science related themes and their clinical application. We are looking forward to a few days of interesting talks and lively discussion in the surroundings of an Oxford summer – including living and dining in College, and the option of a walk through the medical history of Oxford. We hope you will be able to join us.**

**We have applied for 15 CPD credits by the Royal College of Physicians (London).**

**For further information, please contact Marion Greenleaves• E-mail: marion.greenleaves@nda.ox.ac.uk**
**Telephone: 01865 231513 • Fax: 01865 231534 • Website: www.ndcn.ox.ac.uk/courses/onc**


# Annual Meeting May 28th – 31st, 2012

## Programme at a glance

| | Monday 28th | Tuesday 29th | Wednesday 30th | Thursday 31st |
|---|---|---|---|---|
| 0730 | | Registration opens | Registration opens<br>Fun Run<br>Hall 2: Breakfast with the experts | |
| 0800 | | | | Hall 2: Breakfast symposium sponsored by Biogen |
| 0830 | | | Hall 1: Teaching/Science session: Neuroscience | |
| 0900 | | Hall 1: Welcome & opening address, followed by Teaching/ Science session: Epilepsy | | Hall 1: Case presentation competition |
| 1000 | | | Coffee, Exhibition & Posters | |
| 1015 | | | | Hall 1: Plenary lecture |
| 1030 | | | Parallel sessions:<br>Hall 1: Epilepsy<br>Hall 2: Cerebrovascular | |
| 1045 | | Coffee, Exhibition & Posters | | |
| 1100 | | | | Coffee, Exhibition & Posters |
| 1115 | | Parallel sessions:<br>Hall 1: Neuromuscular<br>Hall 2: Commissioning | | |
| 1130 | | | | Hall 1: Teaching/Science session: HIV in neurology |
| 1200 | Registration opens | | Lunch, Exhibition & Posters<br>Hall 2: Lunch symposium sponsored by UCB | |
| 1230 | | Lunch, Exhibition & Posters<br>Hall 2: Lunch symposium sponsored by Biogen<br>Small meeting room: ABNT meeting | | |
| 1300 | West Bar: Medical student Roadshow<br>Hall 2: SPR teaching | | | Lunch<br>Small meeting room: ABNT forum<br>Hall 2: Vitamin B Debate |
| 1315 | | | Hall 1: Research Forum | |
| 1330 | | | Hall 1: Poster session with the authors | |
| 1400 | | Hall 1: 18th Gordon Holmes lecture | | Hall 1: Teaching/Science session: Antibody mediated neurology |
| 1430 | | | Hall 1: ABN Medallist lecture | |
| 1445 | | Hall 1: Teaching/Science session: Head Injury | | |
| 1530 | | | Coffee, Exhibition & Posters | Hall 1: Clinicopathological conference |
| 1600 | | | Hall 1: Movement Disorders video session | |
| 1615 | | Coffee, Exhibition & Posters | | |
| 1630 | | | | Hall 1: Presentation of prizes & close of meeting |
| 1645 | | Parallel sessions:<br>Hall 1: Neurodegeneration<br>Hall 2: MS | | |
| 1730 | | | Hall 1: AGM | |
| 1800 | Drinks reception & light refreshments | Hall 1: Neurological Quiz & Welcome reception | | |
| 1830 | | | 1830 for 2000: Gala dinner at Brighton Dome | |
| 2000 | | ABNT Dinner | | |


# Copaxone. Helping RRMS patients maintain a working life

As effective as high-dose IFN-beta at reducing relapses, with less flu-like symptoms[1,2]

**COPAXONE®**
(glatiramer acetate)
Standing up to RRMS every day

**COPAXONE® (glatiramer acetate)**
**PRE-FILLED SYRINGE PRESCRIBING INFORMATION**
**Presentation** – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. Children (12 - 18 years) No specific studies. Limited published data suggest the safety profile of 20mg administered sub-cutaneously once daily is similar to that seen in adults. Children (<12 years) Not recommended. Elderly No specific data. Impaired renal function No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). Pregnancy. **Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. Other undesirable effects more than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** – Store Copaxone in refrigerator (2ºC to 8ºC). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15ºC to 25ºC) once for up to one month. Do not freeze. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £513.95. **Product Licence Number** – 10921/0023 **Further Information** – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. **Date of Preparation** – February 2012.

C0212-806 February 2012

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

**References**
1. Mikol DD et al. Lancet Neurology 2008; 7:903-914.
2. O'Connor P et al. Lancet Neurology 2009; 8:889-897.

Teva Pharmaceuticals Ltd