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# ACNR

Advances in Clinical Neuroscience & Rehabilitation

Conference and Society News • Journal Reviews • Diary of Events

**Andreas Hartmann**
Inflammation and Cell Death in Parkinson's Disease

**James Overell and Professor Hugh Willison**
Guillain-Barré Syndrome: Clinical Spectrum and Therapeutic Possibilities

**Chris Butler and Adam Zeman**
Syndromes of Transient Amnesia

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machines in susceptible patients. Injection site necrosis has been reported which may result in scar formation. Debridement or skin grafting required occasionally. If breaks in the skin occur advise patients to contact their physician before continuing with injections. With multiple lesions, stop therapy until healing occurs. With single lesions therapy may be continued. Advise patients to use an aseptic injection technique and rotate injection sites. Periodically review patients' self-injection procedures. Incidence of injection site reactions may be reduced by use of an autoinjector. *Drug interactions:* 28 days of corticosteroid or ACTH treatment has been well tolerated. Use of other immunomodulators is not recommended. A down regulation of hepatic cytochrome P450 has been reported with interferons e.g. anti-epileptics. Exercise caution when administering with drugs that have a narrow therapeutic index and are dependent on the hepatic cytochrome P450 system for clearance. Caution with any drugs affecting the haematopoetic system. **Side effects:** The following adverse events collected as spontaneous reports are classified as: very common ≥ 1/10, common ≥ 1/100 to < 1/10, uncommon 1/1,000 to < 1/100 , rare ≥ 1/10,000 to < 1/1,000 , very rare < 1/10,000. *Very common:* flu-like symptom complex; chills; fever; injection site reaction, inflammation, or pain. *Common:* injection site necrosis. *Uncommon:* anaemia, thrombocytopenia, leucopenia, increase in ALT, AST, hypertonia, depression, hypertension, nausea, vomiting, alopecia, urticaria, pruritus, rash, myalgia. *Rare:* thyroid dysfunction, convulsion, confusion, anxiety, cardiomyopathy, tachycardia, palpitation, bronchospasm, dyspnoea, pancreatitis, hepatitis, skin discoloration, suicide attempt, anaphylactic reactions, chest pain, increased blood bilirubin, γ-GT increased. For further information please refer to the SmPC. **Legal category:** POM **Basic NHS Price:** £596.63 for 15 x 3ml Betaferon vials with diluent. **PL numbers:** EU/1/95/003/003, EU/1/95/003/004 **PL holder:** Schering Akteingessellschaft, D-13353 Berlin, Germany. Date of preparation: 12 June 2006

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1. Murray T J. Diagnosis and treatment of Multiple Sclerosis. *Br Med J* 2006; **332**: 525–527.
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Date of Preparation: August 2006

George Orwell in *A Clergyman's Daughter*, has as one of his main characters, Dorothy develop a form of transient amnesia. This is probably psychogenic but how can one be sure. Chris Butler and Adam Zeman help us unpack this conundrum in their article on syndromes of Transient Amnesia. They explain the salient differences between transient global amnesia (TGA), transient epileptic amnesia (TEA) and other forms of this condition and do so from a position of great authority given their contribution to this subject especially TEA.

The role of inflammation in the pathogenesis of neurodegenerative disorders of the CNS is a controversial one and Andreas Hartmann takes us through the evidence for this in Parkinson's disease. He argues that recent imaging studies looking at activated microglial, post mortem studies in MPTP treated animals and patients as well as in idiopathic Parkinson's disease coupled to epidemiological studies, makes for a cogent argument in favour of a role for inflammation in the cell death seen in Parkinson's disease. This is a thoughtful article from someone who has worked closely in the field which I am sure will be stimulating to all those involved in neurodegenerative disorders of the CNS.

As the shortage of intravenous immunoglobulin strikes the UK we are reminded of its value in GBS and the fact that we still do not know the identity of the major epitope at the heart of the acute inflammatory demyelinating polyneuropathies of the Guillain-Barré type. This failure to identify a putative antigen restricts our possible therapeutic options for a condition that has a global incidence of about 1 in 100,000. It is a theme developed and discussed in the context of all forms of Guillain-Barré syndrome by James Overell and Hugh Willison – a lab that has provided significant insights into the pathogenic gangliosides and immune mechanisms underlying this form of peripheral nerve disorder. This is an enlightened and fascinating summary of an evolving field.

Andrew Larner embarks on a fascinating new series in this issue of the ACNR. He discusses entomopia a form of polyopsia in which a grid-like pattern of multiple copies of the same visual image is seen. This builds on an earlier article published in the ACNR by Dominic ffythche in 2004 on visual hallucinations and illusions.

The result of positive oligoclonal bands in the CSF is often taken as being diagnostic of MS without any real thought being given to what it actually means. Dr Maguire in an extremely helpful account tells us about the way that such bands are detected (or not) and the relevance of the differing patterns of such proteins seen in the CSF and blood. This clearly written account is a real gem and if you never understood isoelectric focusing you will after reading this article.

In the article on intrathecal baclofen by Sohail Ansari and Robert Redfern, we are taken through the necessary steps in the assessment, treatment and management of patients requiring this intervention for spasticity. It is clear that a multi-disciplinary approach both before and following the procedure is ideal, and that if done appropriately can have dramatically beneficial effects on patients with these types of problems.

The idea of restoring lower limb function in people with high spinal cord injuries has been a dream for many patients and the use of functional electrical stimulation to activate intact lower motor neurone/muscles is one way of attempting to do this. These devices have been around for some time but in her article Therese Johnston explains how they may be of benefit in children with spinal cord injury. Whilst the data in the article remains anecdotal it would seem to be an approach that has great potential in revolutionising the treatment of such patients….although may be superceded by other devices relying on motor cortical activity (See Journal Reviews).

Susanne Watkins and Geraint Rees bring to a close the wonderful Visual Neuroscience series, edited by Masud Husein. We are enormously grateful to Masud for his work in bringing together a memorable collection of articles, and this final review is a fitting conclusion dealing with visual attention – how we can focus on what we want to see. This ability to select visual items of interest involves a number of different processes which have been elucidated using functional imaging and lesion studies, and includes the famous study entitled 'Gorillas in our midst'. To understand this reference, you will need to read this review!!

On a final serious note, it was pointed out to us that one of the articles in our last issue of the ACNR had been extensively borrowed and plagarised from another authors work. Such behaviour is wholly unacceptable and we have written to the offending author outlining this, and have apologised to the author whose work was copied. We have also had the offending article removed from the ACNR website. On a more happy note, I am pleased to inform you that two new clinical cases are now posted on that website.

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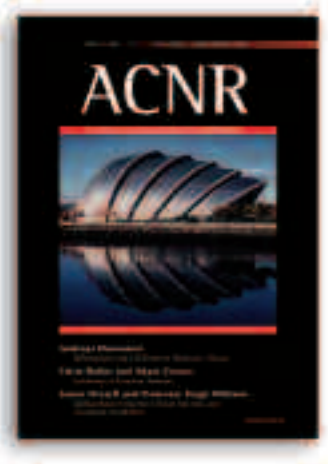


The cover picture shows the venue for the 10th Congress of the European Federation of Neurological Societies, September 2-5, 2006.
For further details visit: www.efns.org

# The first and only transdermal patch for early-stage Parkinson's disease

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- Proven efficacy in early Parkinson's disease[1,3]

Neupro®

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**Legal Category:** POM. **Product Licence Number:** EU/1/05/331/001-013. **Product Licence Holder:** SCHWARZ PHARMA Ltd, Shannon Industrial Estate, Shannon, Co. Clare, Ireland. **Date of Preparation:** March 2006 (3484). Neupro® is a registered trademark. Prescribers should consult the Summary of Product Characteristics for the full information on side-effects, warnings and precautions. Further information is available from SCHWARZ PHARMA Limited, Schwarz House, East Street, Chesham, Bucks HP5 1DG, United Kingdom. **Date of Literature Preparation:** March 2006.

**Information about adverse event reporting can be found at www.yellowcard.gov.uk**
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**References: 1.** Neupro Summary of Product Characteristics. **2.** Braun M *et al.* Poster presented at EFNS 2005. **3.** Watts RL *et al.* Poster presented at MDS 2004. Abstract P737.

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# Inflammation and Cell Death in Parkinson's Disease

Parkinson's disease (PD) is characterised by a slow and progressive degeneration of dopaminergic (DA) neurons in the substantia nigra (SN). This neuronal degeneration leads to the loss of DA terminals in the striatum but also in other basal ganglia and cortical brain regions.[1,2] Non-DA neurons located in various regions of the central nervous system also degenerate in PD.[3] The origin of this neuronal degeneration is unknown and may involve several molecular and cellular events, including oxidative stress, accumulation of altered proteins, excitotoxicity, proapoptotic mechanisms and mitochondrial dysfunction.[4]

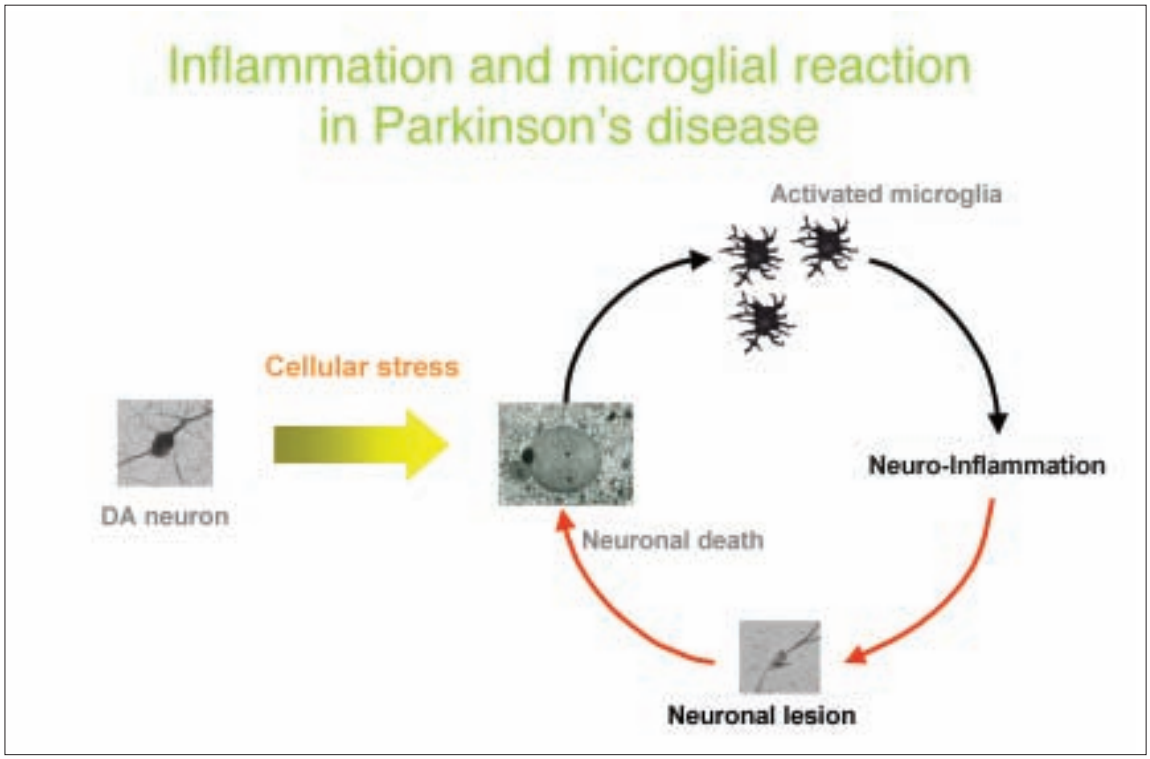
In addition, it has been suggested that a glial reaction and inflammatory processes may also participate in the cascade of events leading to neuronal degeneration. In 1988, McGeer and coworkers observed a strong astroglial and microglial reaction in the substantia nigra (SN) of PD patients.[5] Also, they reported a small number of CD8-positive T lymphocytes in the vicinity of degenerating neurons in the SN of a PD patients. In line with this, an increased density of glial cells expressing proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-1β was observed in the SN of PD patients, as well as an increased density of interferon-γ-positive cells compatible with the presence of lymphocytes.[6] However, until recently, it was unclear whether these inflammatory changes merely reflected a consequence of DA neuronal cell death or if this process was a self-sustaining, feed-forward loop contributing to ongoing cell demise in the SN (Figure).

Strong support for the latter hypothesis came from the study of young drug addicts who developed a parkinsonian syndrome after 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (MPTP) intoxication. In a paper on the postmortem neuropathological examination of three subjects with MPTP-induced parkinsonism, gliosis and clustering of microglial cells around DA neurons were detected despite survival times ranging from 3 to 16 years.[7] These findings not only indicated ongoing nerve cell loss after a time-limited insult, but also suggested that activated microglial cells may perpetuate neuronal degeneration. Reactive microglial cells have also been detected in the brain of MPTP-intoxicated monkeys.[8-10] Interestingly, as in humans, a microglial reaction was observed long after the last MPTP injection (up to one year), suggesting that MPTP had triggered an ongoing inflammatory process in which microglial cells may play an instrumental role.

In living PD patients, two recent studies have analysed the degeneration of the nigrostriatal DA system by PET imaging of pre-synaptic dopamine transporter using a specific ligand and 11C-PK11195 (1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3 isoquinoline carboxamide) imaging for activated microglial cell detection.[11,12] The findings were somewhat contradictory, either showing increased microglia in the midbrain[11] or in non-DA CNS regions[12] in PD patients compared to controls. Important methodological issues may account for these anatomical discrepancies; in any case, it is important to note that microglial activation in PD brains seemed to be present in early disease stages in both studies, thus potentially driving the disease via cytokine release. Also, the presence of microglial activation outside the midbrain supports the notion of PD as a multisystem disorder which may be linked to chronic inflammation in various CNS regions, as suggested by recent postmortem data.[13]

Epidemiological studies also suggest a role of inflammatory processes in susceptibility to PD, given that the use of non-steroidal anti-inflammatory drugs, in particular ibuprofen, seems to lower the risk of PD.[14,15] Whereas these data only provide very indirect evidence for neuroinflammation as a pathogenic factor in PD, they nevertheless add weight to the pressing debate whether glial activation and release of pro-inflammatory cytokines may represent a therapeutic target in PD.

Transgenic mice models have offered some clues in this regard. It has been shown that interferon-γ, inter-

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leukin-1β and TNF-α can induce the expression of the inducible form of nitric oxide synthase (iNOS) via the expression and activation of the low affinity receptor CD23.[6] Accordingly, iNOS knockout animals are more resistant to MPTP toxicitiy than their wild-type counterparts.[16,17] Moreover, mice deleted for cyclooxygenase-2, the rate-limiting enzyme in prostaglandin E2 synthesis, are relatively preserved against MPTP.[18,19]

Translated into pharmacological interventions in animal models of PD, peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, a member of the nuclear receptor super-family that has been shown to inhibit inflammatory processes, protect against MPTP toxicity in mice[20-22] and monkeys.[23] Other anti-inflammatory drugs such as minocycline have also been shown to protect DA neurons against MPTP intoxication by different groups, but other groups of investigators have reported a detrimental effect of this compound.[24] However, a preliminary clinical study investigating minocycline in PD patients has suggested a small but significant neuroprotective effect of of this compound over placebo during a one year course.[25] Inhibitors of COX-2 have also produced controversial results in PD animal models.[26] Yet, such variable results are very likely explained by the pharmacological profile and the specificity of the drugs used (salicylate, aspirin, meloxicam, indomethacin, paracetamol, diclofenac, ibuprofen, etc.).

To date, it remains unclear how glial cells are and remain activated in PD. One possibility involves cell necrosis and subsequent leakage of intracellular contents into the extracellular space, for instance of alpha-synuclein, a major constituent of Lewy bodies.[27] A humoral immune response triggering microglial activation has also been recently proposed.[28] Finally, suffering neurons may send distress signals related to increased oxidative stress to neighbouring microglial cells, thus generating a vicious circle resulting in apoptotic DA cell death.[29] These signals may be conveyed directly between neurons and microglia, or be relayed by astrocytes.[30]

In conclusion, the available data obtained both in animals and humans strongly suggest that (i) inflammation and glial reaction is a chronic process occcuring in the SN (and possibly other brain regions) of PD patients, (ii) that this process is not only a consequence of neuronal death but actively contributes to sustained DA cell demise and (iii) that targeting these deleterious processes may represent a worthwile therapeutic target in PD. At the present stage, it is however likely that inhibiting neuroinflammatory processes in PD will only achieve partial protection and that more upstream pathways must also be targeted.

Inflammatory changes in the substantia nigra of Parkinson's disease patients do not only reflect a consequence of dopaminergic neuronal death but are a self-sustaining process, ie. a feed-forward loop contributing to ongoing cell demise

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# Guillain-Barré Syndrome: Clinical Spectrum and Therapeutic Possibilities

Guillain-Barré syndrome (GBS) is the foremost cause of post-infectious neuromuscular paralysis worldwide, with a global incidence of ~1.5/$10^5$ spread across all age groups [Hughes and Cornblath 2005]. The lifetime likelihood of any one individual acquiring the disease is approximately 1 in 1000. Onset is rapid, and in ~20% of cases leads to total paralysis, occasionally requiring prolonged intensive care and mechanical ventilation. There remains a need to fully understand GBS pathogenesis as a prerequisite to developing effective contemporary immunotherapies. The therapeutic window for GBS is short and the current optimal treatment with whole plasma exchange (PE) or intravenous immunoglobulin (IVIg) therapy only halves disease severity. These approaches lack immunological specificity, and it is hoped that therapies directed against specific immunological targets will result in improved treatment efficacy.

## Patterns of disease

The clinical presentation of progressive, relatively symmetrical motor weakness developing rapidly to peak within four weeks of onset is well known to all neurologists. Sensory symptoms and signs are common, but generally mild. Cranial nerves are frequently affected, especially the facial nerve. Although areflexia is generally the rule, it may not be fully developed at presentation, and reflexes may occasionally be preserved, especially in variant forms of GBS. Autonomic features affecting cardiac, bowel and bladder function may be present. Acute inflammatory demyelinating polyneuropathy (AIDP), by far the commonest form of GBS, arises from segmental demyelination of the peripheral nerves. This is executed in part by macrophage-mediated stripping of the myelin sheath triggered by antibody and complement deposition on Schwann cell and myelin membranes [Hafer-Macko et al. 1996b]. The role of other inflammatory factors including T cells, nitric oxide and other soluble mediators is unknown in the human disease, but supported by some experimental evidence. The primary antigenic target(s) for immune attack in AIDP remains unknown, despite considerable research effort. In AIDP, demyelination may be extensive throughout the length of the nerve, but is especially prominent in proximal nerve roots and the distal intramuscular nerve segments where the blood nerve barrier (BNB) is weak. Axons are generally unaffected in AIDP, although may suffer so-called bystander injury, the mechanisms for which remain unclear.

In the GBS variant, acute motor (and sensory) axonal neuropathy (AMAN, AMSAN), the primary target is the motor and/or sensory nerve axolemmal membrane [Feasby et al. 1986]. Patients present with pure motor weakness and denervation atrophy often becomes evident as the illness evolves. In AMSAN, sensory symptoms and signs are also present. In AMAN, the inflammatory process occurs predominantly either in the nerve roots or distal nerve terminals [Hafer-Macko et al. 1996a;Ho et al. 1997]. Immune attack can lead to reversible axonal conduction block due to reversible axonal injury, or complete axonal transection. The relative extent of each of these processes is likely to dictate the clinical outcome, which will be especially poor if axonal transection occurs proximally at the level of nerve roots. Wallerian degeneration will occur distal to the site of axonal transaction, but otherwise myelin is unaffected. AMAN is highly associated with anti-ganglioside antibodies to GM1a, GM1b, GD1a, and GalNAc-GD1a [Ho et al. 1999;Ogawara et al. 2000]. Representative structures are shown in Figure 1. In addition, intriguing new evidence suggests ganglioside complexes composed of two interacting gangliosides might form important antigenic targets [Kaida et al. 2004;Kaida et al. 2006].

The regional variants of GBS only paralyse specific areas of the body, such as the eyes or face, or the afferent sensory and autonomic systems [Ropper 1994]. The most widely studied of these variants is the Miller Fisher syndrome (MFS), the pathogenesis of which was advanced

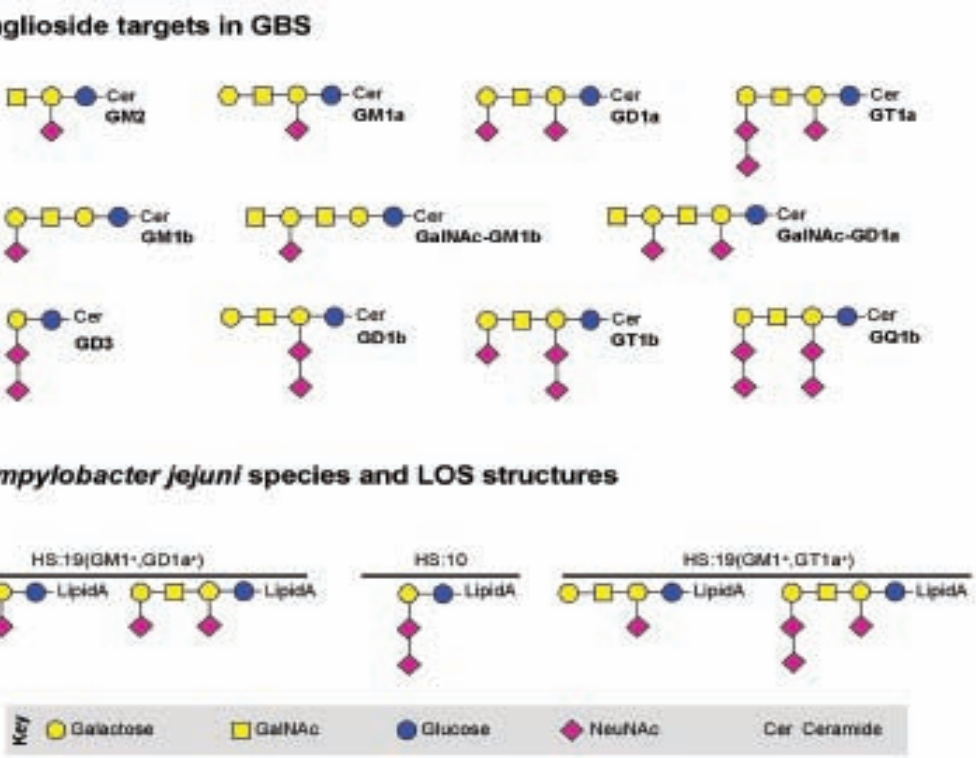


Figure 1: Representative examples of ganglioside and lipooligosaccharide structures targeted by anti-ganglioside antibodies in GBS.

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greatly by the discovery of the anti-GQ1b antibody marker [Chiba et al. 1992]. Anti-GQ1b antibody testing has allowed investigators to identify closely related 'forme frustes', including varying degrees of acute cranial motor neuropathy with or without ataxia, but associated with anti-GQ1b antibodies (the 'anti-GQ1b antibody syndromes'), and the pharyngeal-cervical-brachial variant closely associated with anti-GT1a IgG (which is structurally similar to anti-GQ1b, and often cross-reacts with it). The selective affliction of cranial and in particular extraocular nerves in the anti-GQ1b antibody syndromes is believed due to enrichment of the target antigen(s) in affected sites.

## Electrophysiological findings

Where there is clinical doubt, electrophysiological findings are often very helpful in classification of GBS subtypes. Strict criteria have been set for research purposes. Importantly, electrophysiological patterns may evolve during the course of the illness, and may even be normal early in the course of AIDP. Repeat examination is thus often helpful. The characteristic electrophysiology of AIDP is of delayed or absent F waves (indicating proximal conduction slowing or block), reduced motor conduction velocities with temporal dispersion and prolonged distal motor latencies. Compound muscle action potential (CMAP) amplitudes may be reduced. Small, but otherwise well formed CMAPs, in the absence or marked paucity of demyelinating features are characteristic of AMAN. When nerves are completely inexcitable, classification into AIDP or AMAN is not possible. Sensory nerve action potential amplitudes may be reduced or absent in AIDP, AMSAN and MFS, but are (by definition) normal in AMAN.

## Gangliosides and preceding infections

A wide range of infections are recognised as precipitating GBS. The discovery of ganglioside and glycolipid mimics on Campylobacter jejuni lipooligosaccharide (LOS) has led to a unifying view of molecular mimicry as the critical underlying concept in GBS [Yuki 2001]. Structures are shown in Figure 1. Both Haemophilus influenzae and Mycoplasma pneumoniae that often precede GBS also express glycolipid mimics. There are many structurally distinct gangliosides and other glycolipids in nerve that are synthesised in complex developmental, spatial and cell specific patterns [Kolter et al. 2002]. Some Campylobacter species express similar biosynthetic genes and thereby generate similar glycan structures to gangliosides [Godschalk et al. 2004]. Evidence from human and animal studies indicates a key role for this molecular mimicry in GBS pathogenesis [Bowes et al. 2002;Goodfellow et al. 2005;Goodyear et al. 1999], but in clinical practice specific infective triggers often fail to be identified, just as the antigenic targets that such putative triggers mimic remain elusive.

## The mechanisms of nerve injury induced by anti-ganglioside antibodies

Anti-ganglioside antibodies could potentially bind any ganglioside-containing membranes, provided that they can gain access and binding is not subject to steric inhibition locally in the membrane. Potentially important axonal and glial sites of injury are the ganglioside-dense axolemma at nodes of Ranvier and paranodal myelin in spinal roots and pre-synaptic nerve terminals - both sites are relatively unprotected by the blood nerve barrier and thus accessible to circulating antibodies. Considerable human and animal data support these as key sites of injury [Willison and Yuki 2002;Yuki 2005].

It is clear that complement activation with membrane attack complex (MAC) formation drives at least part of the neural membrane injury in animal models of GBS and in humans, as elucidated from autopsy and biopsy tissues.[Halstead et al. 2004;Lu et al. 2000]. It would thus appear likely that blocking MAC formation locally should prevent MAC-dependent tissue injury, even if anti-ganglioside antibody is deposited on the membrane. One therapy that has been used to investigate this is the complement inhibitor, APT070, comprising the C3/C5 convertase inhibiting region of CR1 [Halstead et al. 2005]. Antibody neutralisation or removal using therapeutic immunoabsorption columns studded with relevant glycan epitopes are another attractive possibility that might supplement traditional plasma exchange [Willison et al. 2004]. These approaches both represent possible future directed and specific therapeutic interventions in GBS.

## Prognosis and treatment

Gratifyingly, the majority of patients with all forms of GBS recover well, with 80% of affected patients walking independently by one year after onset. Recovery may continue for a considerable time (several years) in severely affected cases with extensive axonal degeneration, and a small proportion of cases are left permanently chair or bed-bound. Older age, rapid speed of onset, severe weakness at the peak of the illness and intercurrent illnesses (including complications of GBS) are all poor prognostic factors. Death is uncommon (5% or less). The mainstay of treatment is meticulous care to rapidly identify and avoid or treat the complications of bulbar and respiratory failure, autonomic dysfunction and motor debility. The role of both plasma exchange and intravenous immunoglobulin has been well documented, and either treatment, when administered within 2 weeks of diagnosis, approximately halves the number of patients requiring ventilation and doubles the speed of recovery. There is no evidence for any added benefit of combination therapy, and corticosteroids are ineffective.

## Conclusions

Whilst MFS and AMAN have been partially solved pathophysiologically, progress is most especially needed in the search for the putative AIDP antigen(s) and antibodies. It is ironic that AIDP, the common form of GBS that is easily recognised by most neurologists, is considerably less well understood from a pathogenic perspective than its rarer variants. The optimisation of acute therapy is paramount in GBS, because it is unlikely to ever be preventable. An important consequence of identifying antibodies as the main pathogenic mediators of GBS is that such knowledge should direct therapeutic approaches towards blockade of antibody-mediated effector pathways, such as complement inhibition or B cell suppression. Therapeutic progress in the GBS field is confounded by the fact that large trials are complex and time consuming to organise and execute. This reinforces the need to make rational choices for novel immunotherapy testing.

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Inhibitors of the cationic secretory transport system of the renal tubules such as cimetidine and amantadine may interact with pramipexole resulting in reduced clearance of either or both drugs. Consider reducing pramipexole dose when these drugs are administered concomitantly. The dosage of levodopa should be reduced, and other Parkinsonian medication kept constant, while increasing the dosage of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. Coadministration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** Effects of pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used in pregnancy unless the benefit outweighs the potential risk to the foetus. 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# Syndromes of Transient Amnesia

For most of us, transient lapses of memory are a familiar and at worst irritating feature of daily life. They are generally brief, item specific and alleviated by a pertinent cue. At the other extreme, the amnesic syndrome is characterised by a profound and usually permanent loss of the ability both to retrieve previously established memories (retrograde amnesia) and to form new ones (anterograde amnesia). A permanent amnesic syndrome is usually caused by extensive bilateral damage to the medial temporal lobes (as in limbic encephalitis or post-hypoxic damage) or to the diencephalon (as in Korsakoff's syndrome), brain regions which play a key role in declarative, 'conscious' memory for facts and events.[1] Some people, however, experience an episode of dense memory loss which is sudden in onset but self-limiting. These syndromes of transient amnesia are the focus of this article.

## Transient Global Amnesia (TGA)

The syndrome of TGA has an incidence of 3 to 10 per 100,000 and is characterised by the abrupt onset, usually in middle to old age, of a profound but transient deficit in the retention of new information together with a variable degree of amnesia for past events.[2] At least 50% of cases appear to be precipitated by a variety of acute stressors including exercise, immersion in cold water, sexual intercourse, pain, or a strongly emotional event. The anterograde amnesia is betrayed by repetitive questioning, usually related to attempts at self-orientation such as "What day is it?" or "What am I doing here?" The retrograde amnesia may cover a few hours prior to the attack onset or be much more extensive. There is no impairment of consciousness or of other cognitive functions such as attention, language or perception, and there are no focal neurological deficits. Spontaneous and apparently complete recovery typically occurs within 4 to 10 hours, although the individual is left with a permanent amnesic gap for the duration of the attack. Recurrence is rare, with most recent studies reporting a rate of between 3 and 10% per year. A single, uncomplicated episode requires minimal investigation and no specific treatment.

It is widely accepted that the pathological changes in TGA affect the medial temporal lobes, although precisely what those pathological changes are and why they occur is far from resolved. A number of studies have reported increased prevalence of migraine amongst TGA patients[3] and migrainous accompaniments, including headache, nausea and vomiting, are not uncommon during the amnesic period. This mechanism alone, however, would not explain the limited age range and rare recurrence of TGA. More recent studies using diffusion-weighted imaging have revealed punctate hippocampal lesions, supportive of a vascular aetiology, in a significant proportion of TGA cases.[4,5] Interestingly, given the frequency of Valsalva manoeuvre-like precipitants in TGA, it has also been found that patients have a higher prevalence of jugular vein incompetence than controls,[6,7] lending support to a hypothesis that increased pressure in the superior vena cava causes ischaemia in crucial memory-related brain structures.[8]

Episodes of transient amnesia occurring in the context of epilepsy or head injury and those accompanied by focal neurological symptoms or signs are usually excluded from the rubric of TGA (see Table 1). These are discussed below.

## Transient Epileptic Amnesia (TEA)

TEA is a relatively recently described condition in which transient amnesia is the principal manifestation of temporal lobe seizures.[9,10] The attacks are often mistaken for

**Table 1: Diagnostic criteria**

***Transient Global Amnesia (Hodges and Warlow 1993)***

1. *attacks must be witnessed and information available from a capable observer who was present for most of the attack*
2. *there must be a clear-cut anterograde amnesia during the attack*
3. *clouding of consciousness and loss of personal identity must be absent, and the cognitive deficit must be limited to amnesia (that is, no aphasia, apraxia, etc)*
4. *there should be no accompanying focal neurological symptoms during the attack and no significant neurological signs afterwards*
5. *epileptic features must be absent*
6. *attacks must resolve within 24 hours*
7. *patients with recent head injury or active epilepsy (that is, remaining on medication or one seizure in the past two years) are excluded*

***Transient Epileptic Amnesia (Zeman et al 1998)***

1. *a history of recurrent witnessed episodes of transient amnesia*
2. *cognitive functions other than memory judged to be intact during typical episodes by a reliable witness*
3. *evidence for a diagnosis of epilepsy based on one or more of the following:*
   a. *epileptiform abnormalities on electroencephalography*
   b. *the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations)*
   c. *a clear-cut response to anticonvulsant therapy.*

**Table 2: Characteristic features**

***TGA***

- *sudden onset often precipitated by exercise, immersion in water, emotional stress, etc*
- *dense anterograde amnesia with repetitive questioning*
- *lasts around 4 – 10 hours*
- *rarely recurs*
- *aetiology unknown*

***TEA***

- *recurrent, brief (usually < 1 hour) amnesic episodes*
- *often occur upon waking*
- *may be associated with olfactory hallucinations or automatisms*
- *responds to anticonvulsant medication*
- *persistent memory deficits*

***Psychogenic amnesia***

- *history of 'organic amnesia', psychiatric illness and/or substance abuse*
- *may be triggered by mild head injury or highly emotional event*
- *extensive retrograde amnesia often with loss of personal identity*
- *preserved new learning*
- *duration usually several days at least*

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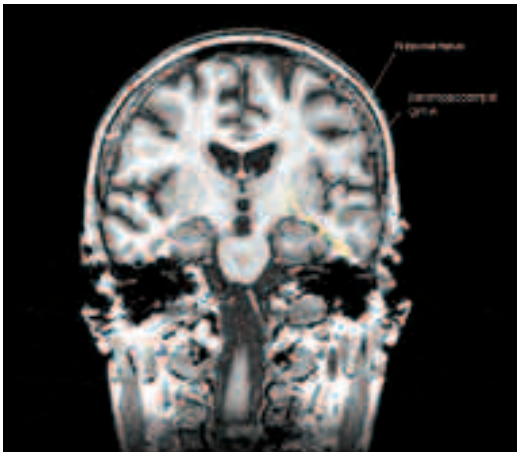

Figure 1: MRI scan showing the location of the hippocampus and parahippocampal gyrus in the medial temporal lobes. These areas are crucial for the processing of declarative memories.

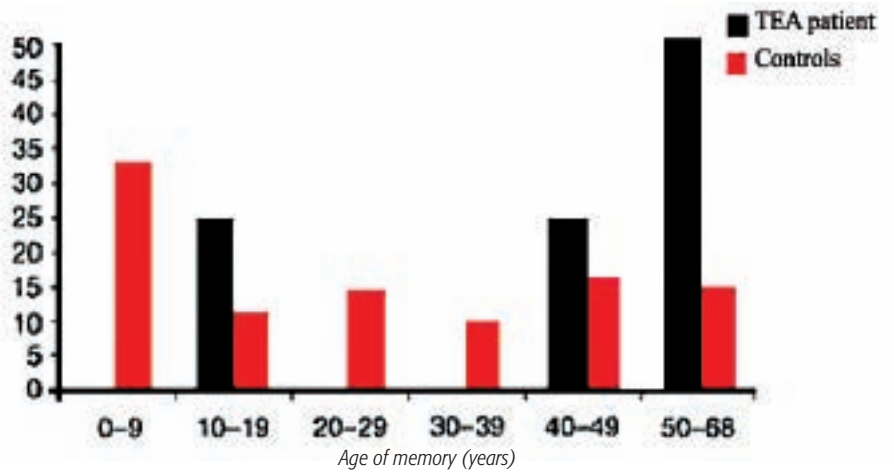


Figure 2: Autobiographical amnesia in TEA. When asked to produce personal memories relating to a particular word (eg 'boat'), a 68-year-old TEA patient failed to retrieve any episodes from his 20's or 30's. His performance on standard tests of anterograde memory was normal.

TGA. They too occur in late-middle to old age and usually involve a mixed anterograde and retrograde amnesia, repetitive questioning and otherwise preserved cognitive functioning. However, there are a number of important distinguishing features. The attacks are recurrent and tend to be briefer than TGA, typically lasting less than one hour. They often occur upon waking and may be associated with other features suggestive of epilepsy such as olfactory hallucinations, oro-alimentary automatisms or a brief period of unresponsiveness. Anterograde amnesia may be incomplete such that, after the attack, the patient may report being "able to remember not being able to remember". The interictal EEG is positive in about one-third of cases, with sleep-deprived recordings having a significantly higher yield. The attacks are usually very responsive to anticonvulsant medication. However, patients frequently complain of persistent memory difficulties that may not be detected by standard neuropsychological testing. In particular, they describe 1) the accelerated forgetting, over days to weeks, of newly acquired memories, and 2) a patchy loss of memories for remote, salient autobiographical events such as holidays or weddings.[11] The extent to which these deficits improve with anticonvulsant treatment is not yet clear.

## Closed head injury

During recovery from violent cranial insult, the duration of post-traumatic amnesia, characterised by a severe learning deficit and a retrograde amnesia, is an important predictor of eventual outcome. The precise mechanism underlying this deficit is not understood. Occasionally, minor head injury, such as sustained during sporting activities, appears to trigger an episode of transient amnesia indistinguishable from TGA. The majority of reported cases have occurred in younger patients and several have been associated with a migraine-like headache reminiscent of Matthews' "footballer's migraine".[12,13]

## Transient Ischaemic Attacks

It is clear that the majority of TGA attacks are not associated with vascular risk factors and do not entail an increased risk of future cerebrovascular events.[14] However, some transient ischaemic attacks, particularly of the posterior circulation, can result in a transient memory disturbance that resembles TGA. In these cases, the physician should be alerted by accompanying neurological signs such as ataxia, dysarthria, nystagmus or hemianopia.[2]

## Psychogenic amnesia

Memory is a psychological function and distinguishing between psychological and physical causes of memory loss is a form of handwaving that reflects our current lack of understanding about the relationship between mind and brain. Nevertheless, certain cases of transient amnesia appear to be triggered by an apparently trivial event, related to periods of emotional stress, and have a neuropsychological profile that is difficult to reconcile with focal neurological dysfunction. These cases have variably been termed 'psychogenic', 'functional' or 'hysterical' amnesia. A distinction is made here from cases of 'malingering' in which the individual is believed to be intentionally deceiving medical personnel.

Psychogenic amnesia is typified by sudden onset of an inability to access memories from an extensive swathe of the past, often including loss of personal identity, a symptom otherwise only seen in the latest stages of degenerative brain disease.[15] In stark contrast, new learning is usually preserved. The memory loss may be associated with a period of wandering – the 'fugue state' – for which the individual is also later amnesic. Neuropsychological studies have not revealed any other consistent pattern of deficit that may help with diagnosis. A history of psychiatric disease or substance abuse is not uncommon and the patient may have experienced an episode of 'organic' transient amnesia in the past. Prognosis is variable with some individuals dramatically recovering their memories in response to a minor cue, and others remaining permanently disabled. However, the duration is usually considerably longer than in TGA or TEA.

Psychogenic memory loss can also be event-specific such as in the context of post-traumatic stress disorder and crime-related amnesia.


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# Intrathecal Baclofen Therapy for Spasticity

Spasticity is defined as a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks resulting from hyper-excitability of the stretch reflex, as one of the components of the upper motor neurone syndrome.[1] For some patients neurolysis or chemodenervation with botulinus toxin or phenol may be useful, particularly for focal spasticity. The intrathecal administration of baclofen (ITB) offers a safe and effective alternative to oral medications that may be ineffective in some patients with severe diffuse spasticity due to a variety of causes including multiple sclerosis, cerebral palsy, traumatic and hypoxic brain injury, and spinal cord injury. It is also effective in the management of spasticity resulting from cerebral palsy in children.[11] Several studies from North America have also shown considerable economic benefits resulting from reduced in-patient costs and related fees.[2,8,9]

## Intrathecal Baclofen (ITB)

ITB involves the continuous delivery of baclofen from an implanted pump, situated subcutaneously in the anterior abdominal wall, connected to a catheter whose distal end lies within the lower dorsal subarachnoid space (Figure 1). ITB therapy is a good alternative when physical methods and oral medication (including muscle relaxants and oral anti-spasticity drugs) fail to produce satisfactory control of spasticity or are poorly tolerated.[4] Baclofen is an agonist to a bicuculline-insensitive variety of GABA receptors, known as GABA-B. A possible explanation for its effect on spinal cord functioning is triggering of a cascade of events that includes neuronal hyperpolarisation, with prevention of calcium influx and thus facilitation of potassium conductance and inhibition of release of excitatory neurotransmitters. This eventually leads to pre-synaptic inhibition with reduction of both mono- and poly-synaptic reflexes and motor activity. As a consequence abnormal muscle tone and stretch reflex hyperexcitability are reduced, bringing about reduced spasticity.

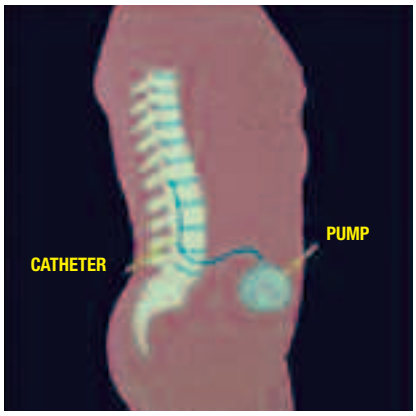

Figure 1: Diagram of implanted programmable pump.

Since baclofen is hydrophilic it crosses the blood-brain barrier poorly, leading to low CSF concentrations when administered orally. Intrathecal delivery circumvents this property and intrathecal doses are typically 100 – 1000 times smaller than oral doses to achieve the same effect. The negative effects on arousal and cognition can thus be avoided. The effects of ITB are reversible and the treatment does not involve destruction of neural tissue.

## Inclusion criteria for ITB therapy

After a multidisciplinary assessment, treatment goals are agreed. Motivation and commitment of patients, families and caregivers should be taken into consideration. Clinical, functional and psychosocial factors may also have a bearing on the suitability of a patient for ITB therapy.[5] It may also be helpful to discuss alternative treatment options in advance, in the event that ITB therapy proves to be ineffective or poorly tolerated.

## Contraindications to ITB therapy

Relative contraindications include unmasking of poor trunk control due to latent weakness of muscle groups following resolution of spasticity. Patients on anticoagulant medication should have this stopped temporarily during the intrathecal baclofen trial and for the subsequent implantation of the pump.

ITB therapy is absolutely contraindicated in patients with active infection, allergy to baclofen, and in pregnancy (since baclofen may be teratogenic).[5]

***Chart 1: Contraindications to ITB therapy***

***Relative contraindications***
- *Poor trunk control with reduced spasticity*
- *Pre-existing bladder problems*
- *Anticoagulation therapy*

***Absolute contraindications***
- *Active infection*
- *Allergy to oral baclofen*
- *Pregnancy*

## Benefits of ITB therapy

Objective improvements are seen in the form of reduced muscle tone, spasms and pain with increased mobility, and improvement in speech, sleep quality, bladder control and self-image. Improvements may also be seen in activities of daily living (ADLs), self-care, dressing, sitting tolerance, movement, transfers, orthotic wear and in overall comfort.[10]

## Approach to ITB therapy

a. Patient selection
b. Screening
c. Pump implantation
d. Dose adjustment
e. Pump maintenance

### a. Patient selection

The preferred approach involves a multidisciplinary assessment. Potential candidates for treatment will have severe spasticity which has been inadequately controlled by, or who have experienced significant side-effects with, standard drug treatments.

***Chart 2: Indications for ITB therapy***

- *Severe multiple joint spasticity, particularly in the lower limbs*
- *ADLs and mobility limited by spasticity*
- *Spasticity that interferes with nursing care and hygiene*
- *Spasticity refractory to other treatment modalities*
- *Severe side-effects with other treatment modalities*
- *Complications of spasticity (contractures, pressure sores)*
- *Painful spasms*
- *Clonus interfering with transfer and mobilisation*
- *Medical stability (infection-free, no unresolved medical issues)*

### b. Screening trial – intrathecal testing

A variety of trial regimes may be utilised, the purpose being to ascertain if spasticity can be controlled with intrathecal baclofen, After establishing CSF access with a lumbar spinal drain we give an initial intrathecal test dose of 5 micrograms (mcg) of baclofen to exclude any allergic response. Thereafter incremental doses of

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baclofen are given twice daily with a dosage interval of at least eight hours, and increasing the dose by 25mcg each time. The response to each dose and any adverse effects are noted. With severe dystonia it can be helpful to undertake a trial of continuous infusion of baclofen.

The onset of action of a single dose of baclofen is about two hours, with a peak effect occurring usually in four to six hours. A positive response is on average a one point drop in the Ashworth scores in the affected limbs, but other factors to be noted include reduced pain or spasms, improvement in range of motion, positioning, and mobility.

Latent weakness may be uncovered after the baclofen and this may limit its usefulness in some patients. It is limited to about six to eight hours after a bolus administration. Excessive length of weakness may be seen in patients with multiple sclerosis.

**c. Surgical implantation**

Prior to implantation of the ITB pump the patient should be medically stable, infection-free, but may continue on oral spasmolytic medication (which can be gradually withdrawn in the early postoperative period).

The site of pump placement is evaluated and marked on the skin, taking into consideration factors such as the patient's belt line, the wheelchair armrest position, and any orthosis. It may also be necessary to consider the position of any stoma site since many of these patients may have a colostomy, urinary diversion or feeding gastrostomy. Ideally the positioning of the pump site should be agreed with the patient, family and carer. Informed consent should include a discussion about expectations of treatment with ITB, and the proposed arrangements for aftercare and the need for periodic refilling of the pump; and the need for the pump to be replaced after an interval of approximately five to seven years, the average battery life.

The pump is implanted under general anaesthesia. Incisions are made in the lower midline lumbar region and in the right hypochondrium, at the site selected preoperatively. A fine bore lumbar catheter is passed via a Tuohy needle such that its tip lies in the lower thoracic region and CSF flow is established. In passing the lumbar catheter care should be taken to pass it slightly off the midline to minimise the risk of late damage to the catheter by the 'scissoring' action of the adjacent lumbar spinous processes. From the abdominal incision a second catheter is tunnelled subcutaneously, attached to the lumbar catheter, and anchored

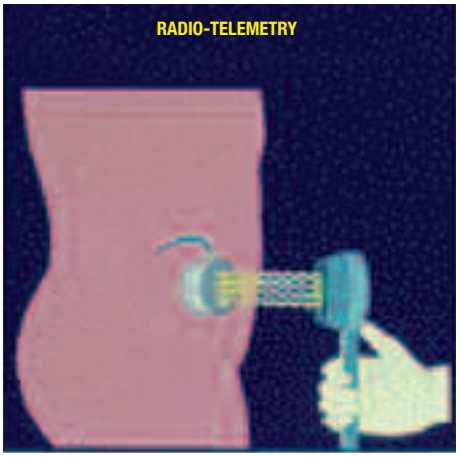


Figure 2: Diagram of telemetry wand.


Figure 3: The Synchromed II infusion system.

to the subcutaneous tissues. A subcutaneous abdominal pocket is now fashioned, just large enough to contain the pump, and passing distally far enough that the pump does not lie beneath the incision, thereby minimising the risk of wound dehiscence. The pump is now filled with baclofen and the proximal end of the catheter attached prior to placement of the pump within the pocket to which it is anchored with retaining sutures. The procedure usually takes about one hour. The pump can be programmed so that the catheter is flushed and a therapeutic rate of baclofen delivery is commenced at the end of the procedure.

Since the effectiveness of baclofen given intrathecally seems to be greater with continuous administration rather than with a single bolus dose, a simple guide to total daily administration is to set the pump to deliver 1.5 times the minimal effective bolus dose established during the ITB trial. The eventual rate of delivery will need to be established somewhat empirically over the next few days by titrating the dose to the observed response.

Postoperatively a pressure dressing may be applied to the abdominal wound and the patient should lie flat to minimise the risk of spinal headache due to CSF leakage and also to prevent development of fluid accumulation within the abdominal pocket.

**d. Dose adjustment**

If a manual pump has been placed (Cordis 'Secor' or Pudenz-Schulte system) patients can decide for themselves when to pump, although a daily routine is preferred. Once the pump has been activated it cannot be reactivated again until after a delay in order to prevent accidental or deliberate overdosage.

Constant-rate infusion systems have a pressurised gas-filled chamber deep to the reservoir; the gas is further compressed when the pump is refilled and, by virtue of the high resistance of the outlet tubing from the reservoir, the flow rate (and thus the delivery of drug to the CSF) remains constant until the pump is refilled. With such pumps (Therex 300 or Infusaid 400) dosage can only be adjusted by emptying the pump and refilling it with a different concentration of baclofen.

With programmable pumps (Medtronic SynchroMed range) the rate can be adjusted using an external programmer that interrogates and re-programmes the chip in the pump (Figure 2). The pump can be set to deliver at rates by day and by night – or even more frequent alterations. The SynchroMed Infusion System (Figure 3) consists of a small titanium disk about 7.5cm in diameter and 2.5cm thick which contains a refillable reservoir and a computer chip that regulates the battery-operated pump; and, in common with other systems, a fixable silicone catheter that serves as a pathway from the pump to the intrathecal space. Dosage should not be adjusted more frequently than every 24 hours in order to allow for stabilisation of the intrathecal baclofen concentration and incremental increases, if indicated, of 10-20% should be made for patients with spasticity of spinal cord origin, and of 5-10% for children and for adults with spasticity of intracerebral origin. Typical maintenance doses in our series of patients receiving ITB for spasticity from a wide range of causes is of the order of 100-200 mcg per 24 hours.

**e. Pump maintenance**

Periodic refilling of the reservoir with baclofen will need to be performed approximately every 6-12 weeks depending upon the rate of daily infusion. Dose titration can be further fine-tuned during this stage, the aim being to control (but not to abolish) spasticity to the point that the limbs can be managed easily and the

Since its introduction in the 1980s long-term administration of ITB has proved to be a safe, well-tolerated and cost-effective treatment for severe spasticity in adults and children

patient is enabled to perform functional tasks. Careful re-assessment should be undertaken at regular intervals.

To refill the reservoir the pump is emptied and a new supply of baclofen (for intrathecal administration) is injected using a special refill kit supplied by the manufacturers. This involves the use of a non-coring 22-gauge, Huber-type needle to reach the reservoir through its silicone septum. The pump is then reprogrammed. The programmable pumps emit a low reservoir alarm sound if a preset level is reached (usually 2ml of their 18ml capacity).

The procedure is performed with sterile precautions in a clean environment. We have found it beneficial to have each patient allocated to a dedicated nurse trained in spasticity assessment and in pump maintenance. This not only gives a useful point of contact for the patient and their carer, but also reduces the infection risk that might arise with pump refilling being performed by less experienced staff undertaking the procedure on an occasional ad hoc basis.

## Further rehabilitation after ITB pump placement

Since the problems caused by spasticity are numerous and multi-faceted a team approach for continuing management is required. Further treatment may involve stretching, strengthening, conditioning and motor retraining. Serial casting or tendon release procedures can also be undertaken to achieve maximum elongation after spasticity has been successfully treated.

***Chart 3: Rehabilitation guidelines after ITB pump placement***

- *Re-assess the patient as new*
- *Elongate shortened tissues through stretching and serial casting or tendon release procedures*
- *Initiate strengthening programme, knowing spastic muscles are weak*
- *Attempt to re-establish motor control and coordination*
- *Re-evaluate orthoses, adaptive equipment and seating systems*
- *Modify the home programme and family training*
- *Employ other antispastic medicines to optimise the functional outcome eg Botulinum toxin injections to treat residual focal spasticity*

## Adverse effects of baclofen

ITB has CNS depressant properties causing sedation, somnolence, dizziness, drowsiness, ataxia and possible cardiac and respiratory depression.

Rapid reduction of baclofen administration may result in ITB withdrawal syndrome, a rare and life-threatening condition consisting of pruritus, rash, anxiety, disorientation, fever and cardiovascular instability.[7]

## Complications of ITB therapy

Complications of ITB treatment are common and in most cases mild and reversible but some, particularly those related to the catheter, can be troublesome to diagnose even though ultimately fairly simple to rectify. It is important to explain to patients in advance of implantation that such complications may arise since once established ITB is generally well tolerated and can bring about considerable improvement in quality of life. Examples of the range of complications are given in Chart 5.

One of the commoner complications is catheter leakage, due to kinking or fracturing, and this usually presents as an apparent loss of efficacy of ITB with increasing spasticity or unpredictable variation in effectiveness of the drug.

Occasionally the spinal catheter tip can cause irritation of a lumbar nerve root with resulting unilateral sciatica. Re-opening of the lumbar incision under general anaesthetic and withdrawal of the catheter by 1-2cm usually results in complete resolution of this problem.

ITB has CNS depressant properties and sudden withdrawal may result in a rare but potentially life-threatening condition (see above). Baclofen overdosage can be dealt with by adjusting the rate of administration but with major overdosage the patient may become weak, apnoeic or unconscious. (Such a condition may arise if, for example, the patient is inadvertently placed in an MRI scanner, for which reason extreme caution should be taken before subjecting patients with implanted infusion devices to such investigation. Temporary explantation of the pump may even need to be considered if a strong indication for MRI scanning exists). Treatment of the condition requires intensive care unit admission where endotracheal intubation and assisted ventilation may be required. The pump should be stopped (or removed) and respiratory depression should be reversed with physostigmine 1-2mg intravenously.

***Chart 4: Side effects and overdose symptoms of baclofen[6]***

***Common side effects***

- *Drowsiness, tiredness*
- *Increased weakness*
- *Dizziness, lightheadedness*
- *Mild confusion*
- *Constipation*
- *Bladder disturbance*
- *Sleep disturbance*
- *Ataxia*

***Symptoms of overdose***

- *Drowsiness*
- *Lightheadedness*
- *Sudden onset of blurred vision of diplopia*
- *Vomiting*
- *Seizures*
- *Fever*
- *Coma*

***Chart 5: Complications of ITB therapy***

***Patient-related***
- *Hypersensitivity to baclofen*

***Operator-related***
- *Programming error*
- *Drug concentration error*

***Complications of test doses***
- *Nausea or vomiting*
- *Sedation*

***Procedure-related***
- *CSF leak and spinal headache; CSF collection*
- *Pump socket seroma*
- *Infection*
- *General anaesthesia risks*

***Pump-related***
- *Flipping of pump*
- *Failed pump*
- *Power failure*

***Catheter-related***
- *Kinking*
- *Fracture*
- *Occlusion*
- *Dislodgement*
- *Catheter tip fibroma*

## Summary

Since its introduction in the 1980s long-term administration of ITB has proved to be a safe, well-tolerated and cost-effective treatment for severe spasticity in adults and children. It is of benefit in patients with spasticity due to cerebral or spinal causes and the beneficial effects tend to be maintained in the longer term. The reduction in spasticity leads to functional improvement and pain relief and, in patients with severe disability, ease of nursing care. Furthermore the reduction in severe diffuse spasticity in stroke patients is not accompanied by adverse effects on arousal or on cognition.[3] However there is a risk, particularly in ambulatory patients, of unmasking underlying muscle weakness. Although complications are relatively common these tend to be amenable to relatively simple measures.

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# The Detection of CSF Oligoclonal IgG by Isoelectric Focusing

When the clinical presentation is not diagnostic, paraclinical information is needed to diagnose multiple sclerosis.[1] The principal paraclinical investigations used are magnetic resonance imaging and cerebrospinal fluid (CSF) analysis for oligoclonal IgG. Here I describe the principles underlying the detection of oligoclonal IgG in CSF, together with examples of patterns which may be obtained and their clinical significance.

To detect oligoclonal IgG, it is first necessary to separate the individual bands from one other. Although polyacrylamide electrophoresis was used originally[2] to separate IgG bands, isoelectric focusing is now the standard method.[3] Once separated, a sensitive method is needed to detect the bands, as they are present at low concentration in CSF. Separated bands can be detected by silver staining, but detection by Western blotting is more sensitive and specific. Rigorous attention to analytical technique is required to produce reliable results[4], and standardised criteria are available for the performance and interpretation of CSF analysis.[3]

## Isoelectric focusing

If a serum protein in solution is placed in an electric field it will be attracted to and migrate towards the anode (positive pole), the greater the charge on the protein, the faster it will migrate. The overall charge on a protein is determined by its amino acid composition (eg negatively charged glutamate or positively charged asparagine) and the number and structure of any negatively charged carbohydrate side chains attached to it. In practice most serum proteins are negatively charged.

In vitro it is possible to alter the charge on a protein by altering the pH of the solution in which the protein is dissolved. At low pH (high hydrogen ion concentration) carboxy groups are more likely to be protonated and therefore lose their negative charge and amino groups are more likely to gain a proton and become positively charged. If the pH of the solution were gradually lowered, there would come a point when the overall charge on the protein was zero (Figure 1). The pH at this point is called the pI or isoelectric point of the protein. If a protein was placed in a solution which had a pH equal to the pI of the protein, the protein would be uncharged and therefore would not move in an electric field. This is the basis of isoelectric focusing.

In this technique a stable pH gradient is created in a gel by the application of an electric potential to a gel containing a mixture of low molecular weight 'ampholytes'. These ampholytes contain positive and negative charges and migrate at speeds determined by their charge and therefore (as the ampholytes with the lowest pI will be the most negatively charged) they line up along the gel in the order of their pIs. The ampholytes are chosen to have pIs which span the pIs of the proteins of interest. When a protein is added to this gel it will migrate at a rate determined by its charge. At the high pH end of the gel, most proteins are negatively charged and they will therefore migrate towards the anode. The anodic side of the gel is also the side of low pH so that when the proteins migrate they enter a region of the gel of lower pH and become less negatively charged. When they reach the part of the gel which has a pH equal to their pI they stop migrating. A protein therefore migrates to the region of the gel as which it is uncharged, ie to its pI.. Even if the protein starts to diffuse away from this part of the gel it will encounter a pH at which it is charged and will migrate back. Therefore very tight bands of protein are formed.

Isoelectric focusing has a high resolving power and separates proteins which may only have a very small charge difference. For instance, the carbohydrate side chains attached to a particular protein are not always the same. There may be differences in their number and structure. These differences lead to so called micro-heterogeneity. These differences may not be picked up by simple electrophoretic techniques but can be picked up by isoelectric focusing. Thus a protein which runs as a single band on normal electrophoresis may run as several bands on isoelectric focusing.

IgG on simple electrophoresis runs as a polyclonal band. This is the result of there being many different individual molecules each at low concentration and each with a unique amino acids composition. The many overlapping bands are not resolved from one another. However, when a small number of B cell clones predominantly react in an inflammatory response, a number of individual IgG molecules derived from these clones will be present at relatively high concentrations. These IgG molecules may not be sufficiently different to be resolved by normal electrophoresis, but isoelectric focusing can resolve these bands. Indeed this was one of the earliest applications of the technique.[5]

## Western blotting

Immunoglobulin in CSF is present at low concentrations and a sensitive method is required to detect it. This technique involves the transfer of all the proteins in a gel to a nitrocellulose membrane. The individual protein of interest (IgG) is detected using a specific antibody to which an enzyme (peroxidase) is attached. The location of the protein is visualised by incubation with a substrate of peroxidase which generates a coloured insoluble product.

## CSF oligoclonal IgG patterns

Freedman et al[3] identifies five classical patterns. However, there is now evidence that the classical positive pattern can be subdivided on the basis of the number of oligoclonal bands.[6,7] The various patterns which may be observed are shown in Figure 2. Most samples show some faint background banding seen in both the CSF and serum. In practice this faint banding does not lead to any difficulties in interpretation. Different ampholyte preparations from different manufacturers behave differently in this regard.

**Negative pattern** (Figure 2a) - No oligoclonal bands are detected. This is the normal pattern.

**Negative pattern** (Figure 2b) - Similar oligoclonal bands in both serum and CSF. This pattern is found in systemic inflammatory conditions. Since CSF is essentially an ultrafitrate of plasma, any oligoclonal IgG present in plasma will find its way into CSF. As mentioned above this oligoclonal IgG may not be apparent on ordinary serum protein electrophoresis.

**Negative pattern** (Figure 2c) - Similar oligoclonal bands in both serum and CSF. This pattern indicates the presence of a serum monoclonal band such as is found in association

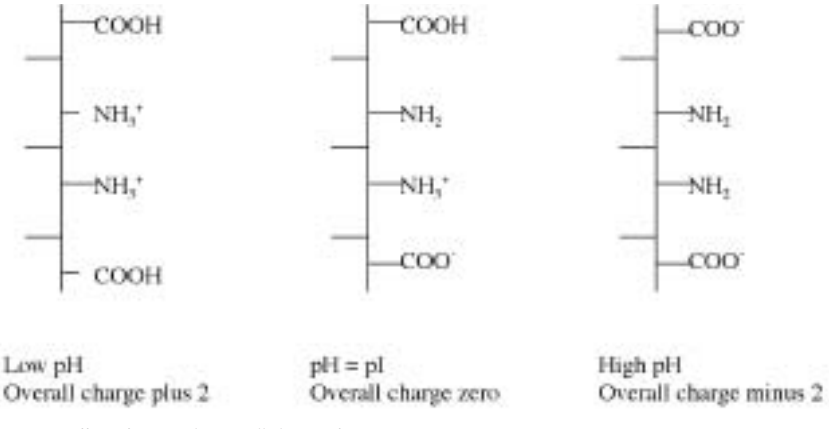


Figure 1: Effect of pH on the overall charge of a protein.

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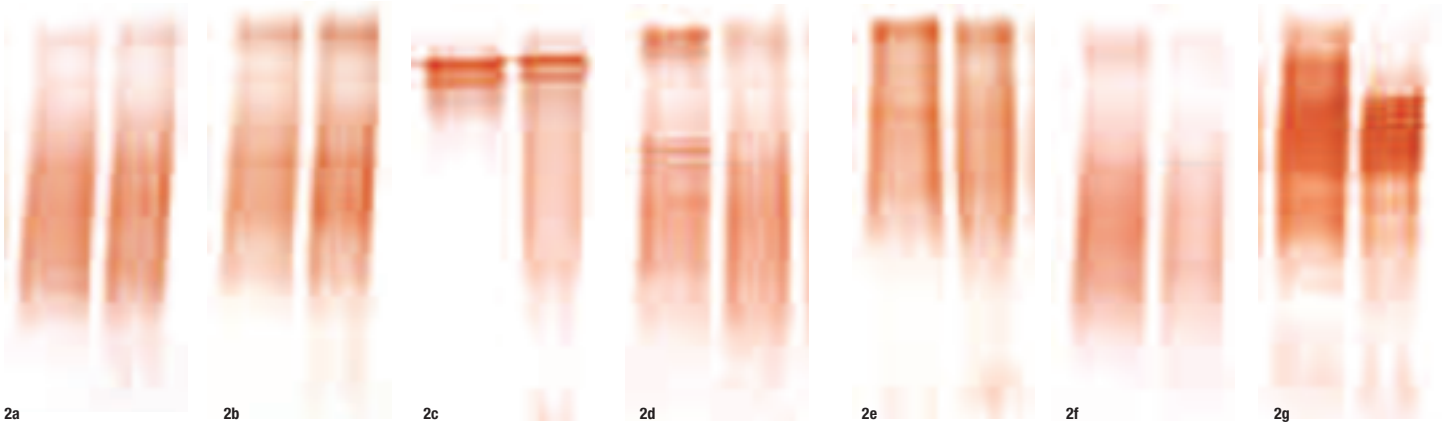


Figure 2: Examples of patterns of csf oligoclonal banding. In each pair the left hand lane is csf and the right hand lane is serum diluted 1 in 300.

with myeloma. The greater resolving power of isoelectric focusing resolves the single band found in serum protein electrophoresis into several bands which differ as a result of different degrees of glycosylation.

**Positive pattern** (Figure 2d) - There are multiple IgG bands. This pattern, in which there are more than ten bands unique to the CSF is highly specific for MS. Only 7 of 593 patients with neurological disease other than MS had this pattern[6] giving a specificity of 99%. However only 46% of patients with MS have this pattern.

**Positive pattern** (Figure 2e) - There are fewer than ten but more than three unique bands. This pattern has a sensitivity of 85% and and specificity of 92% in MS.[6]

**Positive pattern** (Figure 2f) - A single unique band in CSF. About a third or patients with this pattern go on to develop typical oligoclonal bands. About a quarter revert to normal on follow up. The rest are associated with a variety of non-demyelinating conditions which may include cerebral lymphoma.[7]

**Positive pattern** (Figure 2g) - Oligoclonal bands in both serum and CSF with some unique csf bands. This again supports the diagnosis of MS. This figure illustrates a sample from a patient with MS in whom there was a monoclonal band in the serum as well as unique bands in CSF.

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**Date of preparation:** April 2006.

**Adverse events should be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone). Information about adverse event reporting can be found at www.yellowcard.gov.uk**

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# Visual Attention

A typical visual scene contains far too much information for the human brain to process simultaneously. In order to use visual information to effectively guide behaviour (eg Figure 1), some kind of selective mechanism is required. Attention is the name given to the process of selecting out the 'important' aspects of a visual scene for further processing, while relegating the rest to limited analysis. Parietal and prefrontal cortex appear to be critical in mediating the control of this selective process. Visual attention plays a remarkably important role in our perception of the world. Despite the subjective impression that we are aware of the entire visual field, it is surprising how little we actually see when we do not pay attention.

Figure 1: A crocodile hiding in the grass. In complicated and cluttered visual scenes it can be vital for survival that 'important' visual information is processed efficiently.

## Attentional Selection

Selection appears to occur at all stages of visual processing. The geometry and physical construction of the eye acts as a type of passive selector, preserving some types of information about the visual scene and not others. For example, outside the central fovea the sampling density of retinal cones and ganglion cells declines rapidly, placing limits on visual acuity. At early stages of processing in the visual cortex, individual neurons have 'receptive fields' that sample information from small parts of the visual field. This represents a selection of information represented at a higher resolution at earlier stages of processing such as the retina. However, even with such passive selection the visual system is still faced with far too much information. The crucial part of visual attention is active selection.

## Spatial attention

Humans can choose to actively attend to a particular location in space. This act of voluntary spatial attention enhances the processing of stimuli at that location. Studies of spatial attention typically require subjects to focus attention on a small part of the visual scene and report information at the focus of attention. For example, in a cueing paradigm, subjects are required to respond as quickly as possible to the onset of a light or other simple visual stimulus. This target stimulus is preceded by a 'cue' whose function is to draw attention to the occurrence of a target in space. Cues come in various forms, eg a symbol, like an arrow, indicating where attention should be deployed[1] (Figure 2a). In this case, spatial attention is deployed voluntarily to the cued location and this facilitates detection of and response to stimuli presented at the cued location.[2,3] However, cueing can also be involuntary and driven by 'bottom up' factors such as the brightening of the location where the cued object will subsequently appear[4] (Figure 2b), A common analogy is to describe attention as a spotlight that enhances the efficiency of the detection of events within its beam.

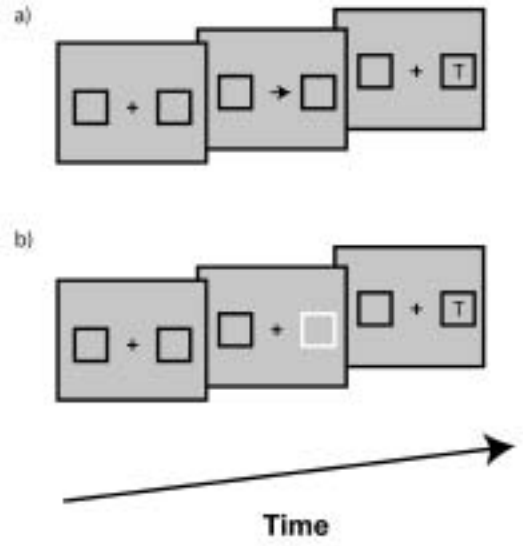


Figure 2: Cueing paradigms. a) Subjects fixate on the central cross at the beginning of a trial. An arrow appears indicating the direction in which attention should be deployed. Subjects are required to covertly attend (without moving their eyes or head) to the cued location in the peripheral visual field and press a button in response to target onset as quickly as possible. b) Subjects fixate on a central cross at the beginning of a trial. The outline of one peripheral box brightens briefly. Attention is involuntarily drawn to the location of the box.

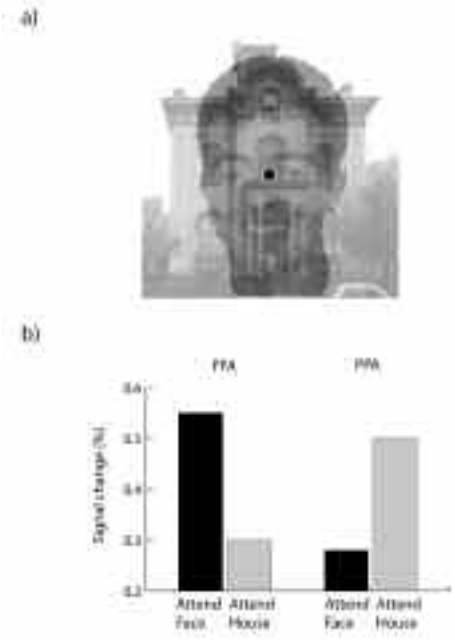


Figure 3: Object-based attention. a) Subjects fixate on the central circle and are asked to attend to either the face or the house. b) Cortical activity measured using fMRI in the fusiform face area (FFA) and the parahippocampal place area (PPA). The FFA and PPA are functionally defined cortical areas in the ventral visual stream that respond selectively to faces rather than objects (FFA), or objects rather than faces (PPA). When subjects attend to a face, activity is higher in the FFA compared to when they attend to a house and when subjects attend to a house activity is higher in PPA than when they attend to a face. Subjects are able to differentially attend to faces or houses even when they overlap in space. Adapted by permission from Macmillan Publishers Ltd: Nature, O'Craven KM et al, copyright 1999.

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- increased T2 active lesions[2]
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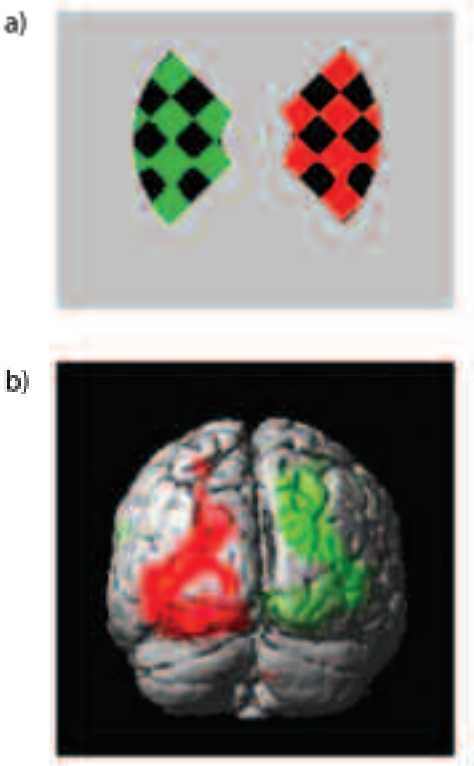


Figure 4: fMRI data showing the effect of visual attention on striate and extrastriate visual cortex. a) Subjects are asked to fixate on a central cross and covertly attend to either the green or red checkerboard. b) Cortical activation is shown projected onto a 3D representation of the posterior cortical surface, showing the occipital cortex. The pattern of activation is shown in green for attending to the green checkerboard and red for the red checkerboard (courtesy of Elliot Freeman).

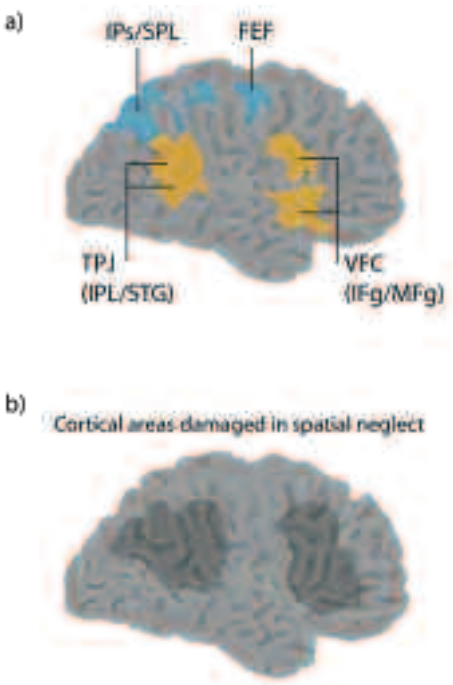


Figure 5 a) Dorsal and ventral fronto-parietal networks involved in attentional control. Areas in blue indicate the dorsal fronto-parietal network. Frontal eye field (FEF) and the intraparietal sulcus/superior parietal lobule (IPs/SPL) are involved in top down attentional control. Areas in orange indicate the stimulus-driven ventral fronto-parietal network. Temporo-parietal junction (TPJ = inferior parietal lobule/superior temporal gyrus [IPL/STG]) and the ventral frontal cortex (VFC = IFg/MFg inferior frontal gyrus/middle frontal gyrus [IFg/MFg]) are involved in stimulus driven attentional control. b) Cortical areas often damaged in the neglect syndrome. These areas are strikingly similar to the areas known to mediate bottom up control of attention. Adapted by permission from Macmillan Publishers Ltd: Nat. Rev. Neurosci, Corbetta M and Shulman GL, copyright 2002.

## Non-spatial attention

Humans can also attend to individual target objects and ignore distractor objects even when they are overlapping in space[5] (Figure 3). For example, Neisser and Becklen[6] presented two different movie sequences that entirely overlapped with each other in space. Subjects were asked to attend to one of the two overlapping movies. Throughout viewing, subjects were able to follow actions in the attended movie. Odd events in the unattended movie were rarely noticed. Because both scenes overlapped each other, this demonstrates that selective attention cannot be purely space-based. Rather, attentional selection was based on objects and events. Visual attention can also be directed to an individual feature of the visual scene such as color, shape or direction of motion. The extent to which spatial, object-based and featural attention of this kind share common neural mechanisms remains an open question under active investigation.

In addition to varying across space, the visual scene also changes rapidly with time. People need to be able to extract behaviorally relevant information from this rapid flux at particular times. Attention can be deployed at different moments in time to facilitate information processing. For example, if a stream of visual items is rapidly presented at central fixation (rapid serial visual presentation, RSVP), subjects are generally very good at temporal selection and able to accurately detect a single target even when visual items are presented at up to 25 items per second.[7] However, although subjects can report single targets very accurately, if a second target (T2) is presented within half a second of the first target (T1) then there is significant impairment of a subject's ability to detect T2. This inability to report T2 for a time after T1 is known as the attentional blink,[8] a measure which reveals limitations in the rate that visual stimuli can be selected. The visual system seems to take a finite amount of time to process T1 and during this time T2 cannot be processed.

## Potential neural mechanisms underlying visual attention

Directing attention to a spatial location in the visual scene has many behavioural advantages: improving the accuracy and speed of responses to target stimuli at that location;[9] increasing perceptual sensitivity, reducing interference from distractors[2,10] and improving acuity.[11] The neural basis of these behavioural effects is still an issue of active investigation. Visual attention is thought to affect neural processing in several ways: amplification of neural responses to an attended visual stimulus;[12,13] filtering of unwanted information by suppressing nearby distractors;[10,14] increasing baseline activity of an attended location in the absence of visual stimulation; and increasing the stimulus salience by enhancing the neuron's sensitivity to stimulus contrast.[12] It is clear from the above that visual attention is not one unified process and indeed the neuronal processes involved in selecting appropriate visual information may be different in different parts of the visual system. Functional MRI of human subjects shows that selective visual attention can affect cortical responses to a visual stimulus not only as early as the lateral geniculate nucleus[15] but also further down the processing stream in striate or extrastriate visual cortex[16] (Figure 4). Selective attention therefore operates at multiple levels in visual processing.

## How is visual attention controlled?

The control of visual attention reflects both cognitive ('top down') factors such as knowledge and current goals and stimulus-driven ('bottom up') factors that reflect the salience of sensory information. Typically, these two factors dynamically interact to control where and to what we pay attention.[17] There is increasing evidence that two partially segregated neural networks underpin top-down control on the one hand, and bottom-up salience-driven selection on the other. The first system involves the dorsal parietal cortex and frontal cortex and is involved in the top down cognitive control of attention. The second system involves the right temporo-parietal junction and ventral frontal cortex and may be involved with the detection of salient objects even when irrelevant to a current task.

## Top down control of attention

Humans are better at detecting an object in a visual scene if they have prior knowledge about its features, such as location, colour, motion or the time at which it will appear.[18-20] This advance information about the object can be used to bias neurons analysing the incoming visual information in order to facilitate detecting the appropriate object in the visual scene. In studies of top down visual attention, advance information is typically provided in the form of a cue that instructs observers about a relevant aspect of the forthcoming visual scene (Figure 2a). Many studies in both monkey and human have now demonstrated that the dorsal parietal cortex, along the intraparietal sulcus (IPS) extending into the superior parietal lobule (SPL), and the dorsal frontal cortex at the intersection of the precentral and the superior frontal sulci (frontal eye fields) are activated by tasks involving top down spatial attention (Figure 5). There is growing evidence that the fronto-parietal network that is recruited for spatial attention is also involved in 'feature based' attention. It may be that space is just another type of feature.

## Bottom-up control of attention

Bottom-up mechanisms operate on raw sensory signals, rapidly and involuntarily shifting attention to salient visual features. For exam-

ple, a sudden movement in the grass may warn of an approaching predator (Figure 1). The attention grabbing effect of a salient stimulus can be demonstrated by flashing a light at a specific location in the visual field and measuring how long it takes for a subject to respond to a subsequent target in that location compared to another location in the visual field (Figure 2b). Even when this cue provides no information about the location of the forthcoming target, the cue facilitates detection and discrimination at the cued location. The facilitation produced by these 'bottom up' sensory cues is more rapid than that produced by top down cognitive cues. In addition sensory cues cause a prolonged inhibition of processing at the cued location after the early facilitation (known as 'inhibition of return'). These differences in the effects of cognitive and sensory cues have led to the idea of a functional distinction between top down and bottom up orientating systems. Functional imaging studies of bottom up attention have demonstrated a ventral network consisting of the right temporo-parietal junction (TPJ) and the ventral frontal cortex (Figure 5). These areas are thought to direct attention to salient stimuli outside the current locus of processing. Early studies proposed that salient stimuli attract attention automatically regardless of the current task. However, recent studies have demonstrated that the situation is not that simple. The salience of an object is highly dependent on its behavioural relevance. For example, if we search for a friend wearing a green coat then we are more likely to notice other people with green clothing. The bottom up (sensory) salience of green objects depends on the ongoing cognitive task of finding a green object.

## Attention and perception

Attention seems to play a critical role in visual perception. When people do not pay attention, they show surprisingly little awareness for events occurring outside the focus of their attention. This provides a dramatic illustration of the importance of attention in perception. For example, in one study observers were asked to engage in a continuous task, counting the number and type of passes among players wearing white shirts playing basketball while ignoring players wearing dark shirts.[21] After about thirty seconds, a person wearing a gorilla suit walks through the action in plain view. Surprisingly, the majority of observers do not report seeing this unexpected event, even though it is clearly visible to observers not engaged in the task. Such inattentional blindness suggests that attention is crucial for conscious perception.

Attention also appears to play an important role in detecting change. While we think that we can simultaneously detect multiple changes occurring throughout the visual field, when tested experimentally this intuitive belief is incorrect.[22] Observers are greatly impaired in their ability to notice changes in any but the currently attended object, unless the change grossly alters the overall meaning of a scene. Thus, while a great amount of detailed information is available in natural scenes, the amount of information that is consciously retained from one view to the next, or from one moment to the next, appears to be extremely low.

## Disorders of visual attention: the syndrome of neglect

Visual neglect is a common neurological condition following right hemisphere stroke. The hallmark of the disorder is a failure to report, orient towards, or respond to stimuli in contralesional space, that cannot be attributed to primary motor or sensory dysfunction.[23] Although neglect is a complex disorder of spatial attention, motor programming, spatial representation and arousal, a 'core' problem is an inability to direct attention to one side (usually the left) of visual space. In severe cases patients suffering from neglect will completely ignore the visual world contralateral to the side of the lesion. Visual extinction is one component of the neglect syndrome, and only becomes apparent when the patient is confronted with bilateral competing stimuli with 'extinction' of the contralesional stimulus from awareness. Both behavioral and neuroimaging studies demonstrate that despite reduced awareness for contralesional visual stimuli there may be substantial residual processing in the neglected hemifield.[24] However, despite this residual processing, patients are still unable to orient attention to the neglected hemifield. Lesions of the right hemisphere are far more likely to lead to neglect than left hemisphere damage. Cortical damage involving the right inferior parietal lobe or nearby temporo-parietal junction has classically been implicated in causing neglect. It has become apparent, however, that the syndrome may also follow focal lesions of the inferior frontal lobe; although lesions confined to the frontal lobe may lead to a more transient neglect. More commonly, however, large middle cerebral artery strokes span both the critical parietal and frontal regions, resulting in a severe and persistent neglect syndrome that has a profound impact on the daily behavior of patients. The cortical areas commonly damaged in neglect are strikingly similar to the areas known to mediate bottom up control of attention (See Figure 5b).

## Conclusion

Visual attention plays a critical role in selecting important information out of the vast array of visual information impinging on peripheral sensory receptors. The loss of this ability to direct attention can be profoundly disabling despite an intact primary sensory system. Clearer descriptions of the brain mechanisms underlying visual attention are beginning to emerge, but much remains to be discovered.


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STA2348

# Implanted Functional Electrical Stimulation for Upright Mobility in Pediatric Spinal Cord Injury

## Introduction

The ability to walk short distances and perform activities in standing are often goals of people with spinal cord injuries, and physiological and psychological benefits have been shown.[1,2,3] Long leg braces (LLB) are typically prescribed for those who desire upright mobility and have the physical ability to use LLB. Users frequently abandon the use of LLB (30-71%) due to issues including poor fit into a wheelchair, bulkiness beneath clothing, skin irritation, and difficulty in donning.[2,4] A potential alternative to LLB is implanted functional electrical stimulation (FES). In addition to addressing the more common reasons for abandonment of LLB, FES may provide benefits of enhanced functional upright abilities by allowing a quicker transition from sitting to standing with greater independence. It is important to note however that the goal of FES is not to eliminate the need for a wheelchair.

## FES Systems for Upright Mobility

Our laboratory has conducted research on two implanted systems for upright mobility, one with eight channels (NeuroControl Corporation, Valley View, OH) available for muscle stimulation[5] and one with 22 channels (Cochlear Ltd, Lane Cove, NSW, Australia).[6] The 8-channel system was implanted in nine children and adolescents and the 22-channel system was implanted in three adolescents/young adults. Both systems provided stimulation for upright mobility (Figure 1); however the 22-channel system also provided stimulation for bladder and bowel function. Two of the three subjects using this system received electrodes for bladder and bowel management.

For individuals with SCI to be eligible for an implanted FES system, the lower motor neurons to the targeted muscles must be intact in order to obtain a stimulated response. Therefore individuals with low thoracic or lumbar injuries may not qualify for these systems.[7]

## Surgical Implantation

Each system included an internal control unit, implanted beneath the skin over the abdomen or lower rib cage (Figure 2). Electrodes were placed near the motor point of the muscle or adjacent to the nerve branch to the muscle. For the 8-channel system, electrodes were placed using a percutaneous approach, in which electrodes were placed using a series of cannulas, thus requiring only a small incision. For the 22-channel system, larger incisions were made to access the nerve branches to the targeted muscles. For both systems, leads were then passed beneath the skin to connect to the internal control unit.

Five subjects with the 8-channel system were growing children at the time of the surgical implantation. To accommodate for growth of the pelvis and proximal femur, extra lead wire was placed for each electrode in an S-shape along the path to the stimulator.[8]

## External Control Unit

To operate each system, a radio frequency antenna was placed on the skin over the implanted control unit to allow an external controller to communicate with the internal components. The external controller for the 8-channel system was approximately the size of a standard cell phone, while the controller for the 22-channel system was a pocket computer. Users placed the external controller on a belt, pants pocket, or on the assistive device. Both systems were simple to activate, allowing the user to activate the system through a push button or by tapping on the computer screen.

Therese E Johnston, PT, PhD, MBA, is a physical therapist and Research Specialist at Shriners Hospitals for Children in Philadelphia. She has worked in the research department there for the past nine years, studying interventions using functional electrical stimulation for children and adolescents with spinal cord injury or cerebral palsy. Her areas of interest include improving function and overall health and fitness in these two populations. Dr. Johnston's recent doctoral dissertation examined the biomechanics of cycling in children with cerebral palsy.

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Figure 1: A subject stands with his FES system to use a vending machine. The external control unit is placed on his belt.

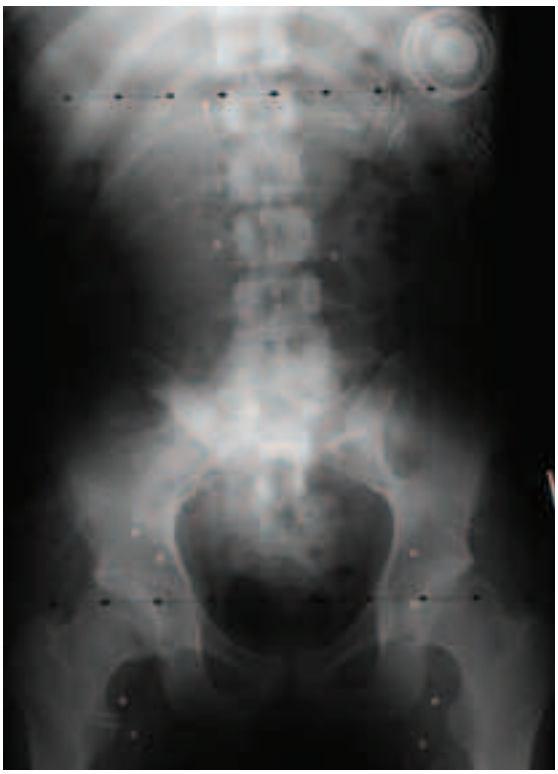

Figure 2: X-ray of the implanted 22-channel FES system. The internal control unit is located near the left lower ribcage. Circular electrodes were placed adjacent to the nerve branches and passed beneath the skin to connect to the internal control unit.

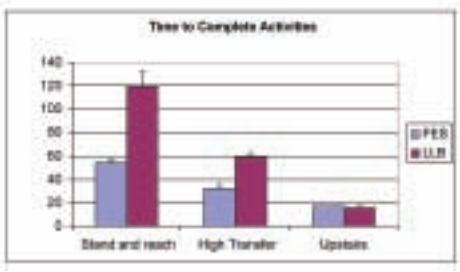


Figure 3: Results for an eight year old boy with T1 paraplegia using a walker as an assistive device. Two activities (standing to reach an object and transferring to a higher surface) involved transitions from sitting to standing, and he was able to complete these activities faster with FES than with LLB. He required a comparable amount of time to ascend stairs with FES and LLB. These results are typical of other children in the study. Time to complete activities is measured in seconds.

## FES for Upright Mobility

The first use of implanted FES for upright mobility in our laboratory involved stimulation to eight lower extremity muscles, including the quadriceps muscles via the femoral nerve for knee extension, the gluteus medius for hip abduction, the gluteus maximus for hip extension, and the posterior head of the adductor magnus for hip extension and adduction. All muscles were activated continuously to allow standing or walking. In this study, the use of FES for upright mobility was compared to the use of traditional LLB during eight short duration activities for nine children and adolescents with paraplegia. Subjects completed the activities with FES at least as fast as they did with LLB and were faster during activities involving transitions between sitting and standing (Figure 3). With LLB, users must first lock the knees into extension prior to standing. With FES, the knees can begin in flexion and stimulation ramps up during standing, potentially reducing the effort of the upper extremities. In addition to being faster with some activities with FES, the younger children also gained greater independence for several activities, requiring minimal physical assistance with LLB and only supervision with FES.

The 8-channel system allowed users to walk by swinging both legs together while using an assistive device to support the body weight during the swing. A reciprocal pattern with FES is another option and the subsequent 22-channel system provided this ability. With this system, 18 electrodes were designated for lower extremity stimulation, providing use of muscles to flex and extend the hip, knee, and ankle. This provided the ability to create stance and swing with users activating a step through push buttons on the assistive device. With this device, additional testing was performed to examine activities of longer duration than with the 8-channel system, including a six minute walk and maximum standing time. Two of the three subjects could perform the six minute walk, walking 39.3 ± 5.7m (subject 1) and 215.1 ± 9.3m (subject 2) during that time. Maximum standing time for the three subjects ranged from two minutes, two seconds to 40 minutes, 33 seconds.

## Conclusions

These implanted FES systems provided subjects with an alternative means for upright mobility. Functionally, subjects were faster and more independent with FES than they were with LLB during upright mobility activities. Overall, the results of this study suggest that implanted FES systems are a realistic alternative for children and adolescents with paraplegia.

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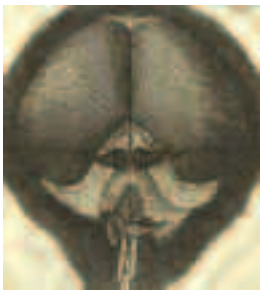
# Entomopia

## Case Report

A 39-year-old lady was seen in the neurology clinic with an eight-month history of episodes in which her vision became blurred, as if she were looking through a prism. She described the experience as "this is how a fly sees", meaning that she saw multiple copies of any object she looked at. Episodes lasted up to 25 minutes, during which she felt unwell and lay down, preferably in the dark, with a sharp pain in the left temporal region, although there was no nausea. Neurological examination was normal. A diagnosis of migraine with aura was made, the aura characterised by entomopia.



## Discussion

Entomopia, meaning literally 'insect eye', is the name which has been given to a form of polyopia in which a grid-like pattern of multiple copies of the same visual image is seen.[1]

Insects have compound eyes built up of simple elements called ommatidia ('small eyes'), first illustrated by Robert Hooke in his *Micrographia* of 1665 (see Figure). Each ommatidium has an outer lens which refracts light onto a photoreceptor element at its inner end, the retinula. Information from all the ommatidia is integrated in the insect brain to assemble a 'mosaic' image, the resolution of which is determined by the divergence angle between ommatidia. The term 'compound' eye is recognised to be potentially misleading, since its function is like that of other eyes, and is not compound in the sense of representing an aggregate of eyes. Advantages of this type of compound eye include a wide visual field and ability to detect movement, but objects are in focus only at a certain distance from the eye.

Polyopia, defined as multiple copies of a visual percept, sometimes with visual field defect, is also reported in migraine, albeit rarely.[2] Polyopia has often been associated with palinopsia, the perseveration or the recurrent appearance of a visual image after the stimulus has disappeared (sometimes known as pseudodiplopia because patients may complain of seeing two of things).[3] Visual alloaesthesia, the illusory transposition of an object seen in one visual field to the contralateral visual field, may be related. These visual phenomena may be associated with occipital or occipito-parietal lesions, both structural and functional, bilateral or confined to the nondominant hemisphere, but they have also been described with anterior pathway (retina, optic nerve) pathology and in the absence of cerebral disease.[4,5]

What cerebral mechanism(s) might account for the phenomena of entomopia, polyopia, palinopsia and visual alloaesthesia? Complex grid and lattice like hallucinations fall into that group associated with visual pathway, as opposed to brainstem/cholinergic hallucination syndromes.[6] A defect of visual integration and fixation, consequent upon occipital lobe disease or spreading depression, has been postulated,[7] or incomplete visual processing due to poor visuospatial localisation in a hemianopic field,[8] but ultimately the mechanism(s) remains unknown. Fortunately, reassurance may be the only treatment required, as in this case.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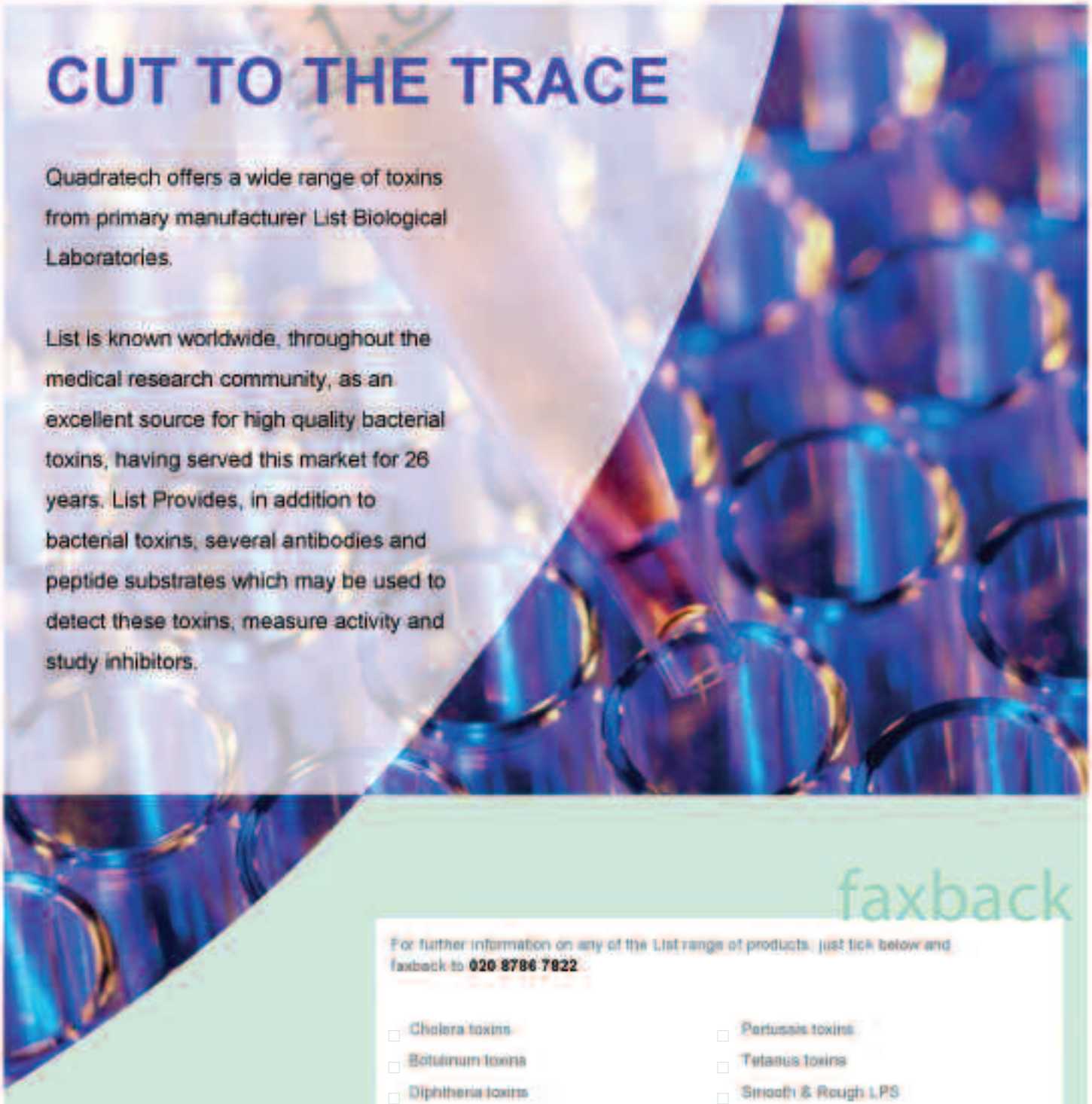

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## EDITOR'S CHOICE

### Imagine that…

The notion of using cerebral activity to control external electronic devices and movement has always been regarded as belonging in the realm of fantasy. The idea is that people with high spinal cord lesions, but intact supraspinal structures, could use electrical signalling from these intact pathways to bypass the obstruction and activate muscles and devices which in turn may be able to control actions. This interesting area has currently been highlighted in two papers in Nature and an excellent 'News and Views' article by Stephen Scott in the same issue. One of these studies involves a single patient and the second is a primate study, the details of which are somewhat harder to extract. In the first study by Hochberg et al, a single patient (MN) with a complete C3-4 spinal cord lesion was studied. He received this traumatic lesion (from a knife) in 2001 and had an array of electrodes implanted into the Ms1 motor arm area in June 2004, with data collected over a nine month period. The patient was then trained to think about doing an action which then was translated into moving a cursor on a computer screen, a process that was only made possible by previous work looking at motor cortical neuronal firing in non-human primates. As the authors conclude "These results indicate that, even years after spinal cord injury and in the absence of kinaesthetic feedback and limb movement, M1 neurons can still be actively engaged and encode task-related information during the intention to move the limb ordinarily controlled by that M1 region". Whilst of limited clinical and practical value, this is nevertheless a clear demonstration that using neuronal activity to think about movements in the absence of a motor pathway still enables the brain to control actions through electronic interfaces. The second study by Santhanam et al is more technical and seeks to improve the information throughput that such systems will require in order to be more efficient and effective using the primate dorsal premotor cortex as the site of signal collection. Whilst there remain major problems in the widespread adoption of these approaches, these studies are very exciting new developments and build on the established use of cochlea implants as well as functional electrical nerve stimulation for locomotion and standing in paraplegic patients (see the review by Johnston et al in this issue of the ACNR). Indeed as our ability to use electronic technology improves in parallel with our better understanding of motor cortical control of movement, we can expect to see advances such as this which could ultimately radically change the prognosis and outlook of patients with spinal cord lesions. - ***RAB***

**Scott S H.**
***Neuroscience: converting thoughts into action.***
**NATURE**
**2006;442:141-2.**

**Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, BrannerA, Chen D, Penn RD, Donoghue JP.**
***Neuronal ensemble control of prosthetic devices by a human with tetraplegia.***
**NATURE**
**2006 Jul 13;442(7099):164-71.**

**Santhanam G, Ryu SI, Yu BM, Afshar A, Shenoy KV.**
***A high-performance brain-computer interface.***
**NATURE**
**2006 Jul 13;442(7099):195-8.**

## CARPAL TUNNEL SYNDROME: Endoscope or get a better job

Carpal tunnel release is one of the most frequently performed surgical procedures: 350,000 annually in the US. And recently endoscopic methods have been introduced with the claimed benefit over traditional open surgery of less pain and more rapid return to work. This Swedish group puts that claim to the test in a single-centre study of 128 patients. The number of patients reporting pain at three months was 33 (52%) in the endoscopic group and 53 (82%) in the open group, giving a number needed to treat of 3.4 (95% C.I 2.3 to 7.7). Taking into account the operating time (nine minutes for the endoscopic method and 15 minutes for the open technique), and using some dodgy maths, this means endoscopy is 5.6 more times effective at reducing pain per operating session….. Before the accountants get too excited, there was no difference in the number of patients reporting improvement in symptoms (about 70% each group), or in the time off work. In fact, the main message for work was that you went back sooner if you had a white collar job (median 21 versus 36 for 'blue collar'). There must be a moral in that …quite what I am not sure…-***AJC***

**Atroshi I, Larsson GU, Ornstein E, Hofer M, Johnsson R, Ranstam J.**
***Outcomes of endoscopic surgery compared with open surgery for carpal tunnel syndrome among employed patients: randomised controlled trial.***
**BRITISH MEDICAL JOURNAL**
**2006;332:1473.**

## EPILEPSY: A reassuring lack of progress

Unverricht-Lundborg disease is classed as one of the progressive myoclonus epilepsies (PME), characterised by epilepsy, ataxia and myoclonus with less cognitive decline than is seen in some PME. Twenty patients from Southern France and Northern Italy were identified with this condition and followed for a mean of 25.7 years. Mean age of onset was 12 years (range 6 to 17). They were last assessed in 2002. Fourteen walked independently and seven of these were in full time employment. Three walked with support, two were wheelchair-bound and one was bed-ridden. Eighteen patients had normal intellectual function, two had mild impairment. One patient had never had a major seizure and three had only ever had one seizure each. After ten years, median seizure frequency was less than one per year. Treatments were generally valproate, clonazepam, levetiracetam or piracetam. The main disabling symptom for most patients was myoclonus, which was classed as moderate to severe for most patients, on a criterion based on interference with ambulation. This study highlights exactly how good the prognosis is of this condition compared to other causes of PME. - ***MRAM***

**Magaudda A, Ferlazzo E, Nguyen V-H, Genton P.**
***Unverricht-Lundborg disease, a condition with self-limited progression: long-term follow-up of 20 patients.***
**EPILEPSIA**
**2006;47:860-66.**

## HEADACHE: Glutamate and trigeminal activation

Much headache research has focused on electrophysiological and other studies of the neuronal pathways activated in cranial nociception, in attempts to understand the pathology of migraine and other head pains. This article focused on the neurotransmitters involved in activation of pathways relevant to nociceptive processing in headache. The paper summarised data from microdialysis experiments in the rat trigeminal nucleus caudalis (TNC) during dural stimulation. Microdialysis allowed the direct measurement of changes in extracellular concentrations of neurotransmitters in vivo. Extracellular amino acids in the deep lamina of the trigeminal nucleus caudalis were quantified during stimulation of the dura with an inflammatory 'soup' compared to saline. After inflammatory application there was a transient decrease in glutamate levels at 30 minutes, followed by a three-fold increase at three hours. The latter correlated with changes in sensory thresholds on the face of the rat from electrophysiological recordings of secondary sensory neurons in the TNC. There were no changes in levels of another excitatory amino acid, aspartate, or the inhibitory amino-acids gamma-aminobutyric acid or glutamine. This work suggests that glutamate plays a role in central sensitisation of neurons in the trigeminal nucleus caudalis, and suggests an important role of glutamate in allodynia and hyperalgia seen in headache. The authors postulate that increased extracellular glutamate may induce sensitisation of neurons with receptive fields outside the initial area of activation, and that this mechanism may be relevant to the increase in size of sensitive areas of the face that occurs during a migraine. It provides an experimental example of the neurochemical changes that may underlie an acute migraine episode. - ***HAL***

**Oshinsky ML, Luo J.**
***Neurochemistry of trigeminal activation in an animal model of migraine.***
**HEADACHE**
**2006;46(s1):S39-S44.**

## REPAIR: A cocktail for spinal cord injury

This John Hopkins group has been working for a while on transplanting motor neurones, derived from embryonic stem cells, to repair spinal cord damage, specifically in their case due to the 'neuradapted Sindbis virus'which selectively depletes motor neurons of adult rats. Their usual experience is that only 2% of the transplanted neurons get into the ventral roots and none connect with muscles, and – unsurprisingly – there was no functional recovery. This paper reports the effects of three strategies to promote the efficacy of the transplants… to good effect. In one group of animals, before transplantation, the ES cells were dipped in dibutyryl cyclic adenosine monophosphate, which is believed to promote motor neuron survival and axonal growth.

Another group of animals were given rolipram subcutaneously; this inhibits phosphodiesterase type 4 and neutralises the inhibitory effects of myelin on axonal outgrowth. Finally, and cleverly, they transplanted other cells into the sciatic nerves of another groups of rats that were induced to secrete glial cell-line derived neurotrophic factor to attract growing axons out of the cord from the transplanted neurons. There were a few controls, and a few lucky rats got all the goodies. The outcome measures were comprehensive. By deriving their embryonic stem cells from animals knocked-in for green fluorescent protein under a motor neuron promoter, they were able to follow the fate of transplanted cells with ease. Only in the rats receiving all three treatments did GFP positive cells find muscle targets. They looked as though they had made anatomical connections, first noticeable at three months after transplantation, and had induced clustering of ACh receptors. Electrophysiological measurement of motor unit number (not straightforward in a rat, I would imagine) showed an improvement in the combination group only, first observed at four months. And this was the only group that showed any functional recovery, albeit incomplete. In a rather nice side-experiment, some animals had received motor neuron transplants into both sides of the spinal cord, but a GDNF-secreting transplant into only one sciatic nerve: there was only motor recovery on the GDNF side…..Which goes to show three things. Firstly, that embryonic stem cells may yet live up to their promise as repair agents, despite initial disappointments. Secondly, as in so many other situations, that efficacy comes with complex combination treatments. And finally, that this very promising treatment would not have emerged without understanding the basic science of neuronal development. - ***AJC***

**Deshpande DM, Kim YS, Martinez T, Carmen J, Dike S, Shats I, Rubin LL, Drummond J, Krishnan C, Hoke A, Maragakis N, Shefner J, Rothstein JD, Kerr DA.**

***Recovery from paralysis in adult rats using embryonic stem cells.***

**ANNALS OF NEUROLOGY**

**2006 Jul;60(1):32-44.**

## STROKE: Releasing the potential for recovery

Recovery from stroke is hampered by the activity of the so-called 'unaffected' side. Just as the preferred and prevalent use of the unaffected hand can rob the impaired hand of its chance to practice and regain function, so too can the contralesional hemisphere of the brain dampen down activity in the lesioned hemisphere. But there is a way to foil the good hemisphere's controlling influence to give the poor damaged hemisphere more chance to marshal its remaining connections and improve the function of the impaired hand. A group in Boston have shown that inhibitory repetitive transcranial magnetic stimulation applied over the contralesional cortex results in better and long lasting performance of hand function, and in shorter simple and choice reaction times, in those with clumsy hands after stroke. The rTMS was delivered for 20 minutes a day over a course of five days, at a rate which has previously been shown to cause inhibition. Ten patients received this treatment and five others were randomly allocated to receive sham treatment. The performance of the rTMS patients' affected hands improved substantially more than the performance of their unaffected hands or the hands of the sham treated control patients. What is more, these differences were still evident at a follow up assessment two weeks later. Some people may be worried about the safety of rTMS as a treatment for stroke; after all these are people with damaged brains who are at greater risk of seizures than normal subjects. Cognitive function and EEG analysis showed no signs of deterioration with time or treatment group. These are very promising results from this phase II study. We'll wait now for the results of a larger RCT, but maybe in the future we'll be pepping up recovery in rTMS clinics. – ***AJT***

**Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJL, Wagner T, Fecteau S, Rigonatti SP, Riberto M, Freedman SD, Pascual-Leone A.**

***A sham controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients.***

**STROKE**

**2006;37:2115-22.**

## EPILEPSY: Convulsive status in London's children – epidemiological data

Reliable epidemiological data is always helpful in guiding management and giving prognoses; so this study is to be welcomed. Over two years, from 2002-2004, all children aged 29 days to 15 years, living within a specific region of London, who were admitted with convulsive status epilepticus, were notified to the study. The catchment population was 605,230 and 226 children suffered status, for 176 of whom it was a first episode and 50 had suffered status previously. For 16% of patients the condition recurred in the first year. Using an alternative ascertainment method, it was felt that case ascertainment in this study was 86%. This gave a crude incidence of first status of 17-23/$10^5$ children per year. The highest incidence was in children under one year at 51/$10^5$ compared with 29/$10^5$ in those aged 1-4, 9/$10^5$ in those aged 5-9 and 2/$10^5$ in those aged 10-15. One third was febrile status and 17% were due either to acute metabolic derangement or CNS infection. Of those who also had a fever, 11% had bacterial meningitis. Children with a pre-existing neurological abnormality were 2.9 times as likely to have a recurrence in their first year. Seven children died. - ***MRAM***

**Chin RFM, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC for the NLSTEPSS Collaborative Group.**

***Incidence, cause and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study.***

**LANCET**

**2006;368:222-9.**

## DEMENTIA: Killing two birds with one stone

Frontotemporal dementia (FTD) is second only to Alzheimer's disease amongst the causes of dementia in mid-life. The FTD concept emerged in the last quarter of the twentieth century, applying to a heterogeneous group of conditions originally described by Arnold Pick some one hundred years earlier. All cases have in common clinical presentation with progressive impairment in behaviour and/or language function and severe focal atrophy of the frontal and/or temporal lobes. Within the spectrum of FTD is a range of clinical syndromes and a plethora of pathological, molecular and genetic abnormalities, which have become ever more complex with the passage of time. One FTD curiosity in particular concerns its genetic linkage to the chromosome 17q21 locus. The link to chromosome 17 was made as far back as the 1980s and the first mutations in the tau gene at 17q21 were reported in 1998, with many more tau mutations following. This resonated not only with the frequent occurrence of abnormal deposits of tau in the brains of FTD patients but also with tau deposition being a pathological hallmark of Alzheimer's disease (i.e. neurofibrillary tangles). The curiosity, however, rests in an increasing number of FTD families linked to chromosome 17q21 despite normal tau sequencing. The finding of Baker, Cruts and their respective colleagues, of null mutations in the progranulin gene at 17q 21 in familial FTD (12 different mutations in 20 families) is, therefore, not only highly significant but is unique among recent advances in FTD for making the field less rather than more perplexing. There is, of course, neurology 'trivia' value in the coincidence (unique?) of a single syndrome linked to one locus through two separate genes (2Mb apart). But the implications for our understanding of neurodegenerative disease, given that progranulin is a growth factor involved in inflammation, tissue repair and tumorigenesis are far from trivial. - ***RD***

**Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boeve B, Feldman H, Hutton M.**

***Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17.***

**Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, Rademakers R, Vandenberghe R, Dermaut B, Martin JJ, van Duijn C, Peeters K, Sciot R, Santens P, De Pooter T, Mattheijssens M, Van den Broeck M, Cuijt I, Vennekens K, De Deyn PP, Kumar-Singh S, Van Broeckhoven C.**

***Null mutations in progranulin cause ubiquitinpositive frontotemporal dementia linked to chromosome 17q21.***

**NATURE**

**E-pub July 2006.**

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

## Physical Medicine and Rehabilitation Principles and Practice - 4th edition


**Published by:** Lippincott Williams & Wilkins 2004
**Author:** Joel A De Lisa et al
**ISBN:** 0-7817-4130-0
**Price:** £113 / $199

You may find a few specialities with blurred boundaries or disagreements about the way they are practised in different places. But for a speciality that cannot even agree on its name, that must be an indication of a serious identity crisis. What we know here in the UK and Australia as Rehabilitation Medicine is called Physical and Rehabilitation Medicine in continental Europe and Physical Medicine and Rehabilitation in North America. The different names reflect different ways of practice, commissioning and philosophy. This problem didn't just affect clinicians being unable to practice freely in different countries or finding it difficult to collaborate in training and academic activities, but it also made it difficult to agree on the standard textbooks, as they can feel like they are dealing with a different speciality depending on where they were published.

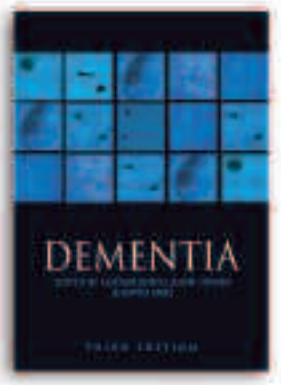
During my training I tried to find that definite Rehab textbook. De Lisa seems the perfect answer, but with 1926 pages and 88 chapters, I always felt intimidated by it. At last I have managed to overcome my fears and started to get to know it better. I was not disappointed. The book comes in two big volumes. The first deals with physical medicine. I looked at that first, as some chapters sounded very exotic, like Aquatic Rehabilitation and Art Medicine. Despite the fact that all the chapters are written by different authors, they all adopt the same format, starting with an interesting historical perspective and then going through the principles of the current clinical practice and the recent advances. The chapters dealing with issues such as interactions with medicolegal system seemed surprisingly relevant, as the principles are the same everywhere around the world. The bulk of the first volume deals with the standard physical disorders such as low back pain and sports medicine and the information was more than enough for a rehab generalist.

I felt more familiar with the second volume, which deals with rehabilitation medicine. The chapters dealing with rheumatological disorders were basic even for me. The chapters dealing with neurological rehabilitation were interesting enough but were full of epidemiological data and description of services in the US, which I found interesting to read but not very useful. I felt there was a lack of depth in dealing with disorders like traumatic brain or spinal injuries, which are the bread and butter of rehabilitation practice in the UK.

Overall, I feel much more secure now having De Lisa on my bookshelf. I strongly commend it for trainees and specialists, as it is clearly the most comprehensive textbook available. However, once a British text with such depth and detailed presentation of all the components of rehabilitation medicine arrives it will probably take its place on the top of my shelf and De Lisa might be relegated to the section next to my old ACNRs.

*Tarek A-Z K Gaber, Leigh Infirmary, Greater Manchester, UK.*

## Dementia - 3rd edition




A Burns, J O'Brien, D Ames (eds.)
**Published by:** Hodder Arnold 2005
**ISBN:** 0-340-81203-6
**Price:** £145.00

The first two editions of this multi-author text (1994, 2000) have established its place on the bookshelves of old age psychiatrists and neurologists with an interest in cognitive disorders. In this third edition, the layout is similar, but there is a new section devoted to mild cognitive impairment (MCI), reflecting the increasing interest in this area, although it is also argued (by Ritchie and Artero) that MCI may be no more than prodromal AD. The 'Vascular dementia' section becomes 'Cerebrovascular disease and cognitive impairment' reflecting the changes in emphasis which have developed in recent years. Newcomers include a chapter on 'Quality of life in dementia', 'Trial design', 'The cerebellum and cognitive impairment' and 'One caregiver's view'; losses include 'Inflammatory mechanisms in the pathogenesis of Alzheimer's disease' and 'Cognitive dysfunction in multiple sclerosis'. The section on 'Services to people with dementia: a worldwide view' has now expanded to a gazetteer of 19 subsections. Information is up to date to the end of 2004 in most chapters. Production values are generally high, there are inevitable typos ('basic ganglia', p 569, being perhaps the most glaring).

Standout contributions for me included the back-to-back chapters on pharmacological and psychosocial approaches to behavioural and psychological symptoms in dementia (BPSD). I sympathised with Jane Byrne's argument (p 652) against the UK prohibition of use of atypical antipsychotics for BPSD based on epidemiological evidence of increased stroke risk, and her plea for individual patient risk:benefit assessment. Andrew Graham and John Hodges' chapter on Pick's disease is a model of clarity in the light of the historical record. Elsewhere, coverage of APP, PS1 and PS2 mutations in AD might be deemed somewhat perfunctory.

At £145 this book is not cheap, but when I recall paying £125 and £155 for the first two editions respectively, it may be considered excellent value for money. Most old age psychiatrists and neurologists with an interest will want access to it.

*AJ Larner, Cognitive Function Clinic, WCNN, Liverpool, UK.*

# XIth International Congress on Neuromuscular Diseases

Istanbul, Turkey, 2-7 July, 2006.

Among four teaching courses, 25 plenary lectures, 14 focused symposiums and 10 workshops, over 150 oral presentations, more than 300 posters, plus two drug company sponsored satellite symposia, spread over six days and four floors of the grand Lutfi Kirdar Convention and Exhibition Centre in Istanbul, I can only present selected highlights, which may be biased towards personal interest, and, at least in part, my inability to be in more than one place at one time.

## Muscle

The early morning plenary lectures ranged from basic sciences/biology to clinical and research in myopathies/muscular dystrophies. A special session was devoted to Dr Duchenne de Boulogne's 200th centenary and was given by the eminent French neuropathologist, Michel Fardeau. The work of Duchenne was really impressive by its scope, as well as by the number of technical innovations that made it possible: electrical stimulation of the muscles, muscle biopsy samples studied microscopically and finally, photography for the analysis of the physiology of facial expression. His achievements are still more impressive when one considers that they were those of a simple medical practitioner, whose life had very difficult moments.

Novel ways to treat muscular dystrophy (especially Duchenne type) may include axon skipping, stop codon read-through, upregulation of utrophin, myostatin inhibition, myogenic cell transplantation. However, significant technical challenges remain regarding their use in humans and these approaches will take several more years before being widely available in a clinical setting.

## Neuromuscular junction

Investigation of congenital myasthenic syndromes (CMS) has disclosed a diverse array of molecular targets. Andrew Engel linked the clinical, eletrophysiologic, and morphologic studies of endplates for detecting CMS-related mutations in each subunit of presynaptic, synaptic, postsynaptic receptor defects, including MuSK as a new target for mutations which decrease the density of AChR on the junctional folds. John Newsom-Davis delivered a succinct overview of MG and pointed out there are still many unresolved issues such as whether thymectomy is beneficial in the non-thymomatous MG patient. This debate may be resolved by an ongoing large multicentre international single blind randomised clinical trial (RCT) of thymectomy. RCTs of mycophenolate mofetil in generalised MG and prednisone treatment in ocular MG are also ongoing.

Bertrand Fontaine delivered an excellent review of exercise tests coupled to electromyography to increase the sensitivity of the diagnostic procedure for channelopathies, enabling prediction for groups of mutations that can be subsequently directed by molecular diagnosis.

## Peripheral nerve

P James Dyck Jr from the Mayo clinic gave an account of the utility of targeted proximal fascicular nerve biopsies from abnormal sites demonstrated by MRI (3 Tesla). Their experience showed proximal biopsy, despite being invasive, may be justifiable because of low morbidity and significant therapeutic implications.

Although some progress has been made in the evidence base for treatment of uncommon peripheral nerve disorders, most notably the inflammatory neuropathies, no trials with neuroprotective and neuroregenerative agents have been concluded yet. Experimental trials have shown, however, that erythropoietin prevents distal axonal degeneration in a mouse model of taxol-induced neuropathy (John Hopkins group).

## Amyotrophic lateral sclerosis(ALS) / Spinal muscular atrophy (SMA)

Since its description by Charcot, the mechanism of selective death of motor neurons in ALS has remained elusive. DW Cleveland from San Diego reported the use of antisense oligonucleotides to interfere with expression of the abnormal SOD1 gene in models of familial ALS. The authors are now preparing to test this treatment in primates and the first (phase 1) clinical trial may be ready to start in 2007.

Whereas SMA is an inherited neuromuscular disorder which affects all components of motor unit, the gene SMN, which codes for SMN protein, is either missing or reduced. Kathyrn Swoboda (Utah) presented data from two completed open label studies of several compounds which enhance SMN expression in patient cell lines or prolong survival in an SMA animal model.

## Conclusion

Some of the advances presented at this congress had immediate clinical relevance. The best management of the neuropathic consequences of glucose intolerance or metabolic syndrome is by treating the underlying cause. Also, prednisolone usage in neuralgic amyotrophy and enzyme replacement therapy in Fabry's neuropathy were presented. In the future, conditions such as ALS or DMD may have mechanism-specific disease-modifying treatments, as they share the final common pathway of endoplasmic reticulum stress induced proteins.

*Dr J H Tho, SpR in Clinical Neurophysiology, St Bartholomew's Hospital, London, UK.*

# CONFERENCE PREVIEW: Epilepsy Specialist Nurse Association (ESNA)

Birmingham, UK, 22-24 November, 2006.

The 2006 ESNA annual conference offers a two and a half day programme which provides support, information and advice to health care professionals caring for people with epilepsy. It will include workshops by epilepsy nurse specialist in paediatrics Pipa Hall, who will demonstrate a project that increased epilepsy awareness in the education system through theatre/acting. Phil Tittensor, epilepsy nurse specialist in adults, will present the research he has undertaken in complimentary therapies in epilepsy. Dr Simon Nightingale, a consultant neurologist, will discuss his experience in taking a neurological history. Dr Hugh Richards, a neuropsychiatrist, will discuss mental health issues and epilepsy. Alice Hanscombe will lead on how to develop skills on telephone work.

Platform presentations include Beth Irwin, epilepsy nurse and midwife, who will update us on the UK pregnancy register. Jayne Fotheringham, chief technician, will discuss the use and interpretation of EEG in epilepsy. Dr Leslie Mac, paediatric neurologist, will talk on the subject of MRI.

You will have the choice of listening to specialists in paediatrics, adults and learning disabilities on the topic of 'It's not always epilepsy'. An afternoon on 'How to get the best from you and your patient' will be led by Dr John Paul Leach, consultant neurologist. As well as sharing his clinical experience of working with people with epilepsy there will be workshops in the three specialist areas. Finally there will be the ESNA Annual General Meeting and presentation of the Malcolm Taylor Award for the best poster presentation and the Achievements in the Care of Epilepsy Awards.

For further information contact:
melesina.goodwin@ngh.nhs.uk

To list your event in this diary, email brief details to Patricia McDonnell at events@acnr.co.uk by September 22nd, 2006

## 2006

### September

**10th European Federation of Neurological Societies Congress**
2-6 September, 2006; Glasgow, UK
F. +43 1 88 92 581 E. headoffice@efns.org
W. www.kenes.com/efns2006/

**1st Joint Meeting of European National Societies of Immunology Under the auspices of EFIS 16th European Congress of Immunology**
6-9 September, 2006 - Paris, France
ECI Paris 2006
T. +33 1 44 64 15 15
F. +33 1 44 64 15 16
E. eci2006@colloquium.fr
W. www.eci-paris2006.com

**8th Eilat Conference On New Antiepileptic Drugs**
10-14 September, 2006, Sitges, Spain
E. eilatviii@targetconf.com
W. www.eilat-aeds.com
T. +972 3 5175150
F. +972 3 5175155

**6th International Congress of Neuropsychiatry**
10-14 September, 2006; Sydney, Australia
T. +61 2 9241 1478
E. info@inacongress2006.com

**XXVIIIth International Congress of Clinical Neurophysiology**
10-14 September, 2006; Edinburgh, UK
E. info@iccn2006.com
T. +44 (0)141 331 0123
W. www.iccn2006.com

**MS Trust General Study Days**
12 September, 2006; Hereford/Worcester, UK
T. +44 (0)1462 476704
W. www.mstrust.org.uk/education.jsp

**18th Congress of the European Sleep Research Society**
12-16 September, 2006; Innsbruck, Austria
W. www.esrs2006.at/

**XXXI Congress of the European Society of Neuroradiology**
13-16 September, 2006; Geneva, Switzerland
W. www.esnr.org/02.asp

**'Pain in Europe V', Triennial meeting of EFIC (European federation of IASP chapters)**
13-16 September, 2006; Istanbul, Turkey
Ms. S.Wheeler,
E. efic@internet.gr,
F. 30-210-992-6382
W. www.efic.org

**ECNS 2006**
13-17 September, 2006; Boston, MA, USA
W. www.ecnsweb.com/cn_2006.htm

**Talk: Cannabis and the brain**
14 September, 2006; London, UK
T. 0207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

**Sally Letson Symposium - Neuro-Ophthalmology Update**
14-16 September, 2006; Ottawa, Canada
T. +613 232 4414
F. +613 232 0120
W. www.eyeinstitute.net
E. info@confersense.ca

**EANO VII : European Association for NeuroOncology Congress**
14-17 September, 2006; Vienna, Austria
W. www.eano.de

**Understanding and dealing with behavioural problems following brain injury**
15-16 September, 2006; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

**3rd Congress of the Euro Huntington Disease Network (followed by the meeting of the European Huntington Association)**
15-17 September, 2006; Blankenberge, Belgium
W. www.huntington-disease.org

**19th ECNP Congress**
16-20 September, 2006; Paris, France
W. www.ecnp.nl/Congresses/frames/Congrframe.html

**Multiple Sclerosis Care in the Community (distance learning)**
18 September, 2006; Leeds, uk
T. +44 (0)113 2835918
E. CCNSenquiries@leedsmet.ac.uk/
W. www.leedsmet.ac.uk/health/cns/courses/mscep/index.htm

**16th Migraine Trust International Symposium**
18-20 September 2006; London, UK
Hampton Medical Conferences Ltd
T. +44 (0) 20 8979 8300
E. mtis@hamptonmedical.com
W. www.migrainetrust.org

**The International League Against Epilepsy (UK Chapter) Annual Scientific Meeting**
20-22 September, 2006; Newcastle, UK
Denise Hickman
T. +44 (0)1323 740612
F. +44 (0)1691 670302
E. denise@conference2k.com
W. www.conference2k.com

**Eurospine2006**
20-23 September, 2006; Istanbul, Turkey
W. www.eurospine2006.org

**6th Annual Brain Injury Legal Seminar-London**
21 September, 2006; London, UK
Lynn Bellgard
T. +44 (0)208 780 4500 Ext 5161
F. +44 (0)208 780 4530
E. lbellgard@rhn.org.uk

NEW
**Workshop: Art of the Brain**
21 September, 2006; London, UK
T. +44 (0)207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

**STARS Annual Conference at the UK Heart Rhythm Congress 2006**
21 September, 2006; Birmingham, UK
W. www.ukheartrhythm.org.uk

**18th Annual Scientific Meeting**
24-26 September, 2006; Cambridge, UK
E. enquiries@sleeping.org.uk

NEW
**MSc Epilepsy Practice (e-learning)**
27 September, 2006; Leeds, uk
T. +44 (0)113 2835918
E. CCNSenquiries@leedsmet.ac.uk/
W. www.leedsmet.ac.uk/health/cns/courses/mscep/index.htm

NEW
**MSc Multiple Sclerosis Practice (e-learning)**
27 September, 2006; Leeds, uk
T. +44 (0)113 2835918
E. CCNSenquiries@leedsmet.ac.uk/
W. www.leedsmet.ac.uk/health/cns/courses/mscep/index.htm

**Talk: Genes and criminal behaviour**
27 September, 2006; London, UK
T. +44 (0)207 019 4914
E. enquiries@edab.net
W. www.danacentre.org.uk

**BSRM/University of Nottingham 9th Annual Advanced Rehabilitation Course**
27-29 September, 2006; Derby, UK
Kirsty Sprange
T. +44 (0)1332 785680
E. kirsty.sprange@nottingham.ac.uk

NEW
**BISWG South Wales and the West Country Regional Meeting**
28 September, 2006; Cardiff, UK
Kate Coles
T. 02920 224871
E. kate.coles@hughjames.com

### October

**Neuro-Ophthalmology HST Study Day**
1 October, 2006; London, UK
Kate Ricketts
T. 0207 935 0702
F. 0207 935 9838
E. skills.centre@rcophth.ac.uk
W. www.rcophth.ac.uk

NEW
**RSM Neuropathic Pain**
3 October, 2006; London, UK
W. www.rsm.ac.uk/academ/a10-neuro.htm or contact Primrose Ante-Bennett
T. +44 (0)20 7290 2965
F. +44 (0)20 7290 2977
E. primrose.ante-bennett@rsm.ac.uk

**Towards an understanding of Parkinson's disease**
4 October, 2006; Devon, UK
T. 01392 405171

**ABN Autumn Scientific Meeting**
4-6 October, 2006; London, UK
E. info@theabn.org
W. www.abn.org.uk

**Visual Perceptual Dysfunction following brain injury, Part 1**
6-7 October, 2006; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

**Congress of Neurological Surgeons Annual Meeting**
7-12 October, 2006; Chicago, USA.
Congress of Neurological Surgeons
T. +847 240 2500
F. +847 240 0804
E. info@1CNS.org
W. www.neurosurgeon.org

**Third International Forum on Disability Management**
8-10 October, 2006; Brisbane, Australia
3rd IFDM Secretariat, C/o CONROD
T. +617 3365 5560
F. +617 3346 4603
E. IFDM2006@somc.uq.edu.au

**11th Annual Meeting of the ACTRIMS**
8 October, 2006; Chicago, USA
W. www.actrims.org

**131st Annual Meeting of the American Neurological Association**
8-11 October, 2006; Chicago, USA
W. www.aneuroa.org
E. lorijanderson@msn.com

**International Congress of Immunogenomics and Immunomics**
8-12 October, 2006; Budapest, Hungary
W. www.bcii2006.org/

**Brain Inspired Cognitive Systems - BICS 2006**
10-14 October, 2006; Island of Lesvos, Greece
W. http://www.icsc-naiso.org/conferences/bics2006/bics06-cfp.html

**AANEM Annual Scientific Meetings**
11- 14 October, 2006; Washington DC, USA
AANEM
T: +(507) 288-0100
F: +(507) 288-1225
E: aanem@aanem.org

**Primary Care Neurology 2006**
12 October, 2006; Sheffield, UK
W. www.p-cns.org.uk

NEW
**International Meeting of Epilepsy Experts - The National Centre for Young People with Epilepsy (NCYPE) and the Institute of Child Health (ICH)**
12-14 October 2006, London and Surrey, UK.
Nina Kelly
T. 0207 1734072
E. NCYPE.meeting@medicusgroup.com

## CONFERENCE PREVIEW: ABN 2006 Autumn Meeting

London, UK, 4-6 October, 2006.

The ABN 2006 autumn meeting will be held at the Royal College of Physicians, London from 4-6 October.

Clinical symposia include Professor Peter Goadsby on Chronic Migraine, Professor N Quinn and Dr KR Chaudhury on Movement Disorders (including a video teaching session), and Professors Nigel Leigh and Chris Shaw on Neurodegeneration.

As usual, papers from the Association's members cover a wide range of clinical and basic science topics, including the role of surgery in epilepsy, reports on the clinical use of Campath 1 and Natalizumab in multiple sclerosis, the clinical diagnosis of dysferritonopathy and the frequency of conversion symptoms in clinical practice.

We have introduced expert-led poster presentations on Thursday lunchtime to allow broader discussion of the scientific and clinical work presented in these sessions. We have a case presentation competition (CPC), and after a great success in Brighton the CPC returns for neurologists in training! In a joint session with the Primary Care Neurology Society the role, of primary care neurology will be debated.

The way neurologists train is changing and Professor Mark Wiles will give an account of MiniCEX and DOPS, with feedback from trainees, following the trial of a knowledge-based neurology exam.

Highlights of the meeting also include presentation of the ABN medal to Professor Richard Hughes and a guest lecturer from Professor Simon Wesseley on the neuropsychiatry of the Gulf War syndrome.

Dinner on the Thursday evening is in Middle Temple Hall.

I look forward to welcoming you to what promises to be a packed and exciting meeting.

*Stephen J Wroe, ABN Meetings Secretary.*

ROYAL SOCIETY OF MEDICINE SYMPOSIA:

*Bench to Bedside:*

**Neuroprotection, regeneration and restoration of function in the nervous system**

**Date:** Tuesday 12 December 2006

**Venue:** The Royal Society of Medicine, 1 Wimpole Street, London

**Educational Aims and Objectives:**

Recent progress in stem cell research and its probable clinical applications will be reviewed, together with potential alternative approaches to management of neurodegenerative processes. The objectives are to provide up-to-date information from leading authorities and to develop a greater understanding of the interactions between natural recovery processes and novel therapeutic interventions now being developed.

**Topics include:**

- **Cell therapies for Parkinson's disease**
- **Clinical trials in neuroprotection**
- **Synaptic plasticity and stroke**
- **Cell transplantation and spinal cord injury**
- **Understanding and manipulating CNS damage: the first 72 hours**

For further information or to book, please contact
**Ms Tina Lanzara.** Tel: 0207 290 3844
E-mail: tina.lanzara@rsm.ac.uk
Alternatively, visit out website at **www.rsm.ac.uk/diary**

The ROYAL SOCIETY of MEDICINE

# The British Neuropsychiatry Association Annual Meeting

BNPA

**22/23 February 2007**
**The Institute of Child Health, Guilford Street, London**

- Neuropsychiatry and Neuroscience
- Epilepsy
- Parkinson's Disease

The BNPA is pleased to announce their 20th Anniversary 2 day Annual General Meeting on 22/23 February 2007.

A detailed programme and registration form can be found on our website www.bnpa.org.uk

For details of exhibition/sponsorship opportunities, contact Jackie Ashmenall on
Email: jashmenall@yahoo.com

UCL

***INSTITUTE OF NEUROLOGY***
*in association with*
**THE NATIONAL HOSPITAL FOR NEUROLOGY AND NEUROSURGERY**
Queen Square, London WC1

GlaxoSmithKline Advanced Lectures on Clinical and Experimental Neurology

*Autumn Term 2006*

## 'Social Cognition'

This series will be given on WEDNESDAY EVENINGS during the Autumn term 2006. **The first lecture will commence at 5.15pm**; there will be a break for coffee at 5.50pm and the **second lecture will commence at 6.05pm**.

The venue will be the Wolfson Lecture Theatre, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1.

***Please note that these lectures are open only to those practicing and researching in the relevant specialism or associated disciplines.Those interested are invited to attend, free of charge, on production of a staff/student identity card.***

## Wednesdays
## 25 October - 13 December 2006

The lecture programme is available on our website at **www.ion.ucl.ac.uk** or from:
Education Unit, Institute of Neurology
23 Queen Square, London WC1N 3BG
Tel: 020-7829-8740, Fax: 020-7278-5069
Email:J.Reynolds@ion.ucl.ac.uk

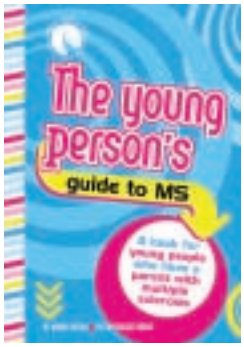
*The Institute of Neurology promotes teaching and research of the highest quality in neurology and the neurosciences*

**UNIVERSITY COLLEGE LONDON**

## The young person's guide to MS

The MS Trust has worked with MS specialist nurse Kerry Mutch to produce a booklet for young people who have a parent with MS. It is primarily aimed at 10-15 year olds. The guide aims to answer some of the questions young people may have about MS, as well as enabling them to explore their feelings about how MS affects them.

The young person's guide to MS has been produced with the help of lots of young people who know what it is like to have a parent with MS. They share their experiences, worries and emotions about living with MS in their family to ensure that other young people recognise they are not alone when facing the challenges posed by MS in the family.




*To order a copy please send your name and postal address to: info@mstrust.org.uk or Tel: +44 (0)1462 476700.*

## New Advanced Imaging Demonstration Suite

Researchers are now able to experience the latest advanced imaging equipment at Nikon UK's headquarters at Kingston upon Thames. The demonstration suite houses state-of-the-art Confocal, TIRF and digital imaging systems for live cell imaging applications, supported by a knowledgeable team of dedicated biological imaging specialists.

Robert Forster, the General Manager of Nikon UK Instruments, and Professor Trevor Powell from the Department of Physiology, University of Oxford declared the Imaging Suite officially open at a well-attended ceremony.

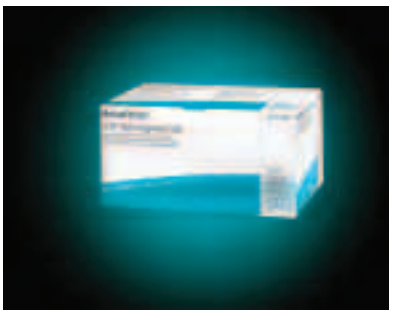
The fully equipped suite enables scientists to experiment with a variety of imaging systems away from the distractions of a busy laboratory. Nikon's team of experts are on hand to advise on and demonstrate the capabilities of the equipment.

General Manager, Robert Forster and Professor Trevor Powell from the Department of Physiology University of Oxford.

*For further information contact the Kingston Imaging Centre: Tel: +44 (0)20 8247 17 17, Email: discover@nikon-instruments.com Web: www.nikon-instruments.com*

## Landmark BENEFIT trial results of Betaferon®

Schering UK announced today that results from the BENEFIT (Betaferon® in Newly Emerging Multiple Sclerosis for Initial Treatment) clinical trial were published in an expedited manner in this week's online issue of Neurology. The results show that Betaferon 250mcg reduces the risk of developing clinically definite multiple sclerosis (MS) in patients having a first clinical event suggestive of MS by 50% compared with placebo.[1] Furthermore, patients in the Betaferon group were two times better protected[2] against developing MS, as defined by the McDonald diagnostic criteria.[3]



Left untreated in the placebo group, about half of the people who experienced a first clinical attack developed MS as defined by the McDonald criteria within the next six months. Eventually, 85% of people in the placebo arm who experienced a first clinical event went on to be diagnosed with MS within two years according to the same criteria, underscoring the importance of early treatment.

Based on the findings of the BENEFIT study, Schering was granted marketing authorisation in the UK and Europe for the extension of its indication to include the treatment of patients with a first clinical event suggestive of MS.

*For further information Email: customer.care@schering.co.uk Tel: +44 (0)845 609 6767.*

References
1. 50% risk reduction based on adjustment for a standard set of baseline covariates.
2. At the end of the study period of two years.
3. McDonald et al. *Recommended Diagnostic Criteria for MS*. Ann Neurol 2001;50:121-7.

## NSE information service

An innovative information service, which provides information for people with epilepsy in hospital and healthcare settings, has been given a 100% approval rating by neurologists from across the country. All of the neurologists and epilepsy specialists who responded to a recent survey stated that the National Society for Epilepsy's (NSE) Epilepsy Information Network (EIN) complemented the services they already offer.

The EIN is a network of epilepsy information services throughout the UK, manned by trained volunteers. This unique service offers information leaflets and support to people with epilepsy, their families, carers and others in the community.

NSE has a comprehensive range of information available about epilepsy. Log onto www.epilepsynse.org.uk or contact our helpline on 01494 601 400, Monday to Friday, 10-4, for details.

*For more information contact Elaine Falkner on Tel: +44 (0)1494 601 391 or Email: elaine.falkner@epilepsynse.org.uk*

## Neural Stem Cell Phenotyping by FACS

A constant challenge in neural stem cell (NSCs) cultures is to determine the percentage of cells of a given phenotype. Phenotypic characterisation of the entire cell population is of utmost importance when evaluating efficacy of culture conditions to differentiate cells.

It is our hope that by offering IntraCyte™ Intracellular FACS Kits, FACS analysis will be more accessible to, and used more often by, neuroscientists.

The Stem Cell Kit is a powerful analytic tool to analyse the neural and glial cells within your culture. While the use of intracellular detection by flow cytometry has been introduced and characterised recently by Naveil et al (http://www.orionsolutions.com/downloads/FACS) this kit takes things to a new level….

Just fix the cells, wash and block, add primaries, wash, add secondary, wash, proceed to FACS analysis. Its that simple!

The IntraCyte kit technology and the precision and accuracy of flow cytometry, enables you to get statistically significant, multi-parameter data at the single-cell level on thousands of cells per sample in seconds! Users can now double and triple label with GFAP Markers that are also available through Stratech.

*For further information please contact Stratech by Email: info@stratech.co.uk or visit www.stratech.co.uk*

## New additions to Nikon's Digital Camera Systems

**Three New Additions to Nikon's Fully Interchangeable Digital Camera Systems**

Nikon has announced the addition of its DS-Fi1 digital camera head and DS-L2 and DS-U2 control units to its Digital Sight Series.

The DS-Fi1 camera head improves resolution, expands dynamic range, reduces noise and features an increased frame rate. The 5.0 million-pixel resolution produces high-quality brightfield, darkfield, phase contrast, DIC and fluorescence images, and the new IR filter improves red colour reproduction.

The two new control units give the user a choice of a simple-to-use stand-alone system, or a hub controller for connection to a PC.

The stand-alone DS-L2 controller can capture, observe and record live images without being connected to a PC. The built-in 8.4-inch monitor can be split to display a still alongside a live image, and the unit can be connected to any printer supporting the PictBridge standard.

The DS-U2 controller can perform every step from advanced image capture to image analysis through connection to a PC with

NIS-Elements software, and the USB 2.0 port enables faster transfer of image files.

*For further information contact*
*Nikon Instruments Europe,*
*Tel: +31 2044 96222,*
*Email: info@nikon-instruments.com*
*Web: www.nikon-instruments.com*

## White water rafting

Headway - the brain injury association - has a range of exciting fundraising opportunities for you and your colleagues to take part in, including exciting international treks and bike rides in exotic locations such as Peru, Vietnam and Cuba; skydiving with the Red Devils; parachuting; whitewater rafting; outward bound and survival weekends.

*For further information please contact Rachel Broughton at Headway on +44 (0)115 924 0800.*

To have your news item included contact Patricia McDonnell on email Patriciamcdonnell@btinternet.com or tel/fax: +44 (0)288 289 7023.

**LICENSED AS A SPECIALIST OPTION IN MIGRAINE PROPHYLAXIS**

# Help keep migraines and patients apart

Topamax 100 mg/day reduced migraine frequency by:

- ≥ 50% in 46% of patients[1]
- ≥ 75% in over 25% of patients[1]

TOPAMAX® (topiramate)

**Every migraine-free day is a good day**

**TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation:** Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. **Uses: Epilepsy:** Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. **Migraine prophylaxis:** when 3 or more attacks/month; attacks significantly interfere with daily routine. Six monthly review. Use in acute treatment not studied. Initiation: specialist care. Treatment: specialist supervision/shared care. **Dosage and Administration:** Oral. Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. **Epilepsy:** Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3-6 mg/kg/day (two divided doses). Initiate at 0.5-1 mg/kg nightly with weekly or fortnightly increments of 0.5-1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5-9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1-3 mg/kg. **Migraine:** Over 16 years: Usually 100 mg/day (in two divided doses). Initiate at 25 mg nightly with weekly increments of 25 mg. Longer intervals can be used between dose adjustments. Children under 16 years: Not studied. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. **Contra-indications:** Hypersensitivity to any component. **Precautions and Warnings:** Withdraw gradually. Renal impairment delays achievement of steady-state. Caution with hepatic impairment. May cause sedation; so caution if driving or operating machinery. Depression/mood alterations have been reported. Monitor for signs of depression; refer for treatment, if appropriate. Suicidal thoughts: Patients/ caregivers to seek immediate medical advice. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and require discontinuation of Topamax and treatment. Increased risk of renal stones. Adequate hydration is very important. Bicarbonate level may be decreased so monitor patients with conditions/drugs that predispose to metabolic acidosis and reduce dose/discontinue Topamax if acidosis persists. Galactose intolerant, Lapp lactase deficiency, glucose-galactose malabsorption: do not take. **Migraine:** Reduce dose gradually over at least 2 weeks before discontinuation to minimise rebound headaches. Significant weight loss may occur during long-term treatment. Regularly weigh and monitor for continuing weight loss. Food supplement may be required. **Interactions:** Possible with phenytoin, carbamazepine, digoxin, hydrochlorothiazide, pioglitazone, oral contraceptives, haloperidol and metformin. Caution with alcohol/CNS depressants. **Pregnancy:** If benefits outweigh risks. Discuss possible effects/risks with patient. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). **Lactation:** Avoid. **Side Effects:** Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diarrhoea, diplopia, dry mouth, dyspepsia, headache, hypoaesthesia, fatigue, mood problems, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis reported rarely. Suicidal ideation or attempts reported uncommonly. Bullous skin and mucosal reactions reported very rarely. **Pharmaceutical Precautions:** Tablets and Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed. **Legal Category:** POM **Package Quantities and Prices:** Bottles of 60 tablets. 25 mg (PL0242/0301) = £19.08, 50 mg (PL0242/0302) = £32.12; 100 mg (PL0242/0303) = £55.31; 200 mg (PL0242/0304) = £102.80. Containers of 60 capsules. 15 mg (PL0242/0348) = £15.70, 25 mg (PL0242/0349) = £23.55, 50 mg (PL0242/0350) = £35.57 **Product licence holder:** JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ UK. **Date of text revision:** 8th June 2006. **APIVER080606 Date of preparation:** June 2006.

**Reference:** 1. Bussone G, Diener H-C, Pfeil J *et al.* Topiramate 100mg/day in migraine prevention: a pooled analysis of double blind randomized controlled trials. Int J Clin Pract 2005; 59(8): 961-968.

**Information about adverse event reporting can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Janssen-Cilag Ltd.**

JANSSEN-CILAG Ltd

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