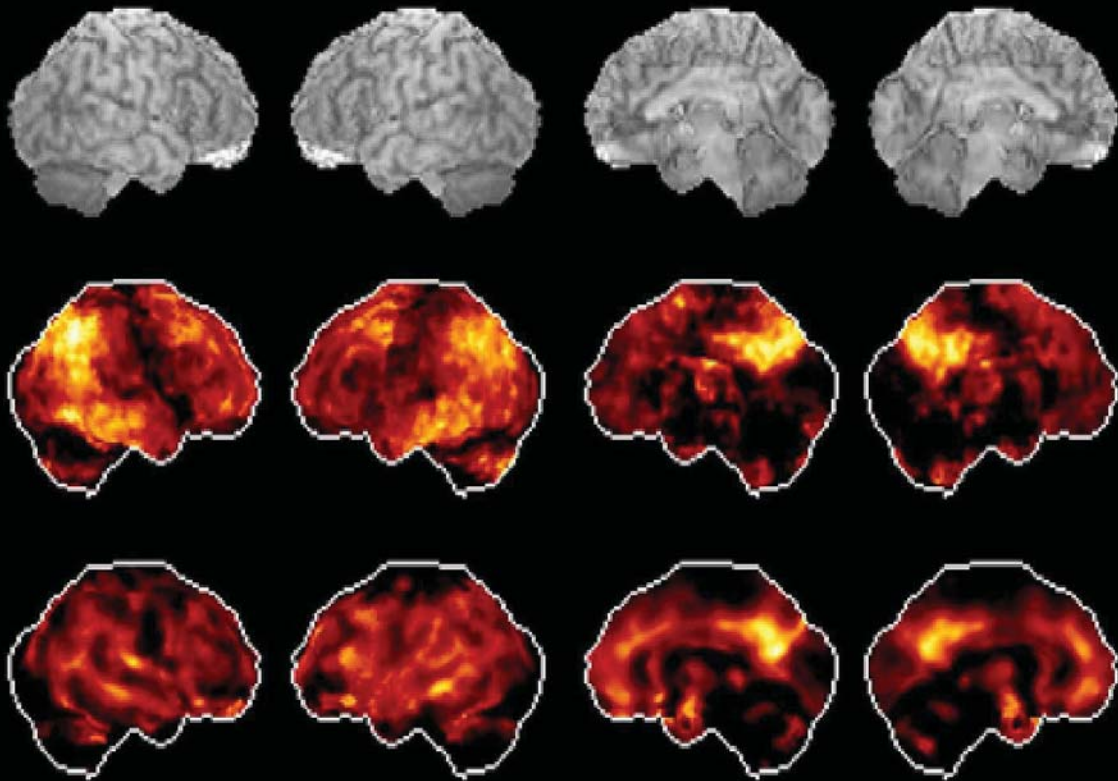


# ACNR

Advances in Clinical Neuroscience & Rehabilitation



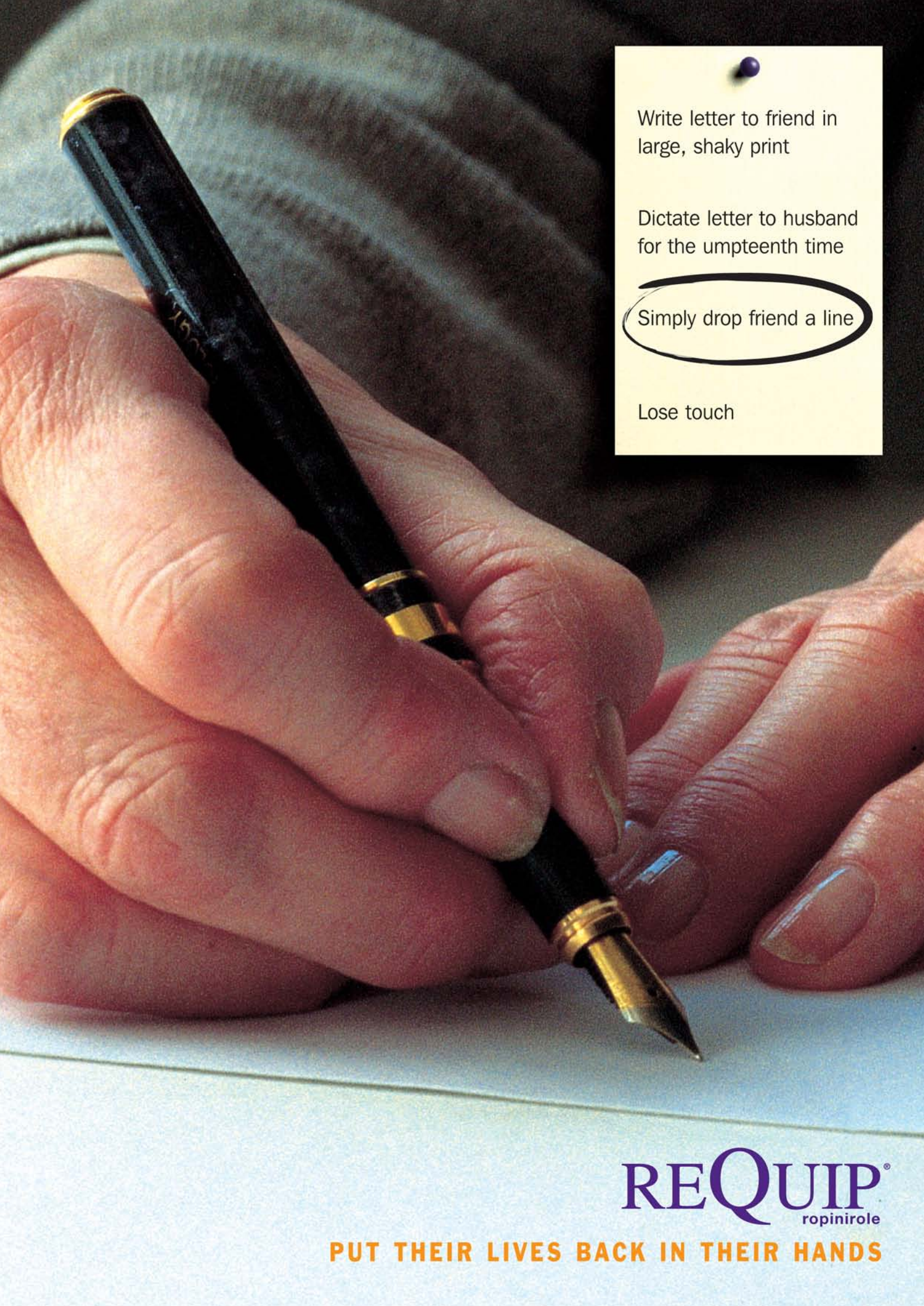
neuropathology article • conference news • drugs in neurology • events • journal reviews • industry news

**Review Articles** - Epidemiology and Management of ALS; Functional Imaging of Movement Disorders

**Management Topic** - The Management of Patients with Head Injury

**Cognitive Primer** - Agnosia

**Rehabilitation Article** - Sonographic Imaging for Guiding Botulinum Toxin Injections in Limb Muscles



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If using Follow On Pack, the dose for 5th week is 1.5 mg t.i.d., 6th week 2.0 mg t.i.d., 7th week 2.5 mg t.i.d., 8th week 3.0 mg t.i.d. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually by around 20%. When switching from another dopamine agonist follow manufacturer's guidance on discontinuation. Discontinue ropinirole by reducing doses over one week. **Renal or hepatic impairment:** No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. **Elderly:** Titrate dose in normal manner. **Children:** Parkinson's disease does not occur in children – do not give to children. **Contra-indications** Hypersensitivity to ropinirole, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Ropinirole has been associated with somnolence and episodes of sudden sleep onset. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction seen with other Parkinson's disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Adverse reactions** In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo, however, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see 'Precautions' and 'Effects on ability to drive and use machines'). **Effects on ability to drive and use machines** Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Overdosage** No incidences reported. Symptoms of overdose likely to be related to dopaminergic activity. **Marketing Authorisation Holder** SmithKline Beecham plc t/a GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. **Further information is available from:** Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; customercontactuk@gsk.com; Freephone 0800 221 441. **Date of preparation:** May 2004. ReQuip is a Registered Trademark of the GlaxoSmithKline Group of Companies. REQ/FPA/04/12702/1

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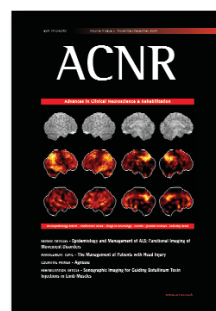
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The Oliver Zangwill Centre, UK - [www.acnr.co.uk/features.htm](http://www.acnr.co.uk/features.htm)

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Cover picture: Society of Nuclear Medicine's 'Image of the Year' 2004 was awarded to a group of investigators from Hamamatsu Photonics K.K., University of Washington, and University of Michigan. PET images of Alzheimer's disease were obtained using Siemens Medical Solutions PET equipment.



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Email: [CNS@rsm.ac.uk](mailto:CNS@rsm.ac.uk)

## Section of Clinical Neurosciences

2004/2005 Academic Session

Thursday 4 November 2004	- Immune mediated neuropathies
Thursday 2 December 2004	- The ITU Patient
Thursday 3 February 2005	- Gordon Holmes Prize (Please see note for further details >>>)
Thursday 3 March 2005	- The Visual System
Thursday 14 April 2005	- Neurodegeneration
Thursday 5 May 2005	- Aspects of the Neurological Examination
Thursday 2 June 2005	- The Past, Present and Future of Neurosciences & AGM

**Deadline for submission: Friday 26 November 2004**

(Trainees in neurology, neurosurgery, neurophysiology, neuropathology or neuroradiology are invited to submit summaries of research which they have carried out. Those considered to be the best will be asked to give a 15 minute presentation [including 5 minutes discussion] at a meeting of the Section to be held on Thursday 03 February 2005 at 6.00pm. The Gordon Holmes Prize, value £100 will be awarded for the best presentation)



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**Children;** Not recommended. **Contra-Indications:** **Pregnancy.** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Lactation:** Excretion into breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction

conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinus pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident.

Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £68.32. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £95.76. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** January 2002.

**References:** 1. Gauthier S, Feldman H, Hecker J, *et al.* *Curr Med Res Opin* 2002; **18** (6): 347-354. 2. Holmes C, Wilkinson D, Dean C, *et al.* *Neurology* 2004; **63**: 214-219. 3. Cummings JL, Donohue JA, Brooks RL. *Am J Geriatr Psychiatry* 2000; **8**: 134-140.



Welcome to another issue of ACNR. In this, our fifth issue of the year, we have the usual variety of articles, including some from our international colleagues. The two review articles in this issue include one from Professor Tysnes from Bergen in Norway, about the epidemiology and management of motor neurone disease. The second is by Paola Piccini and Ann Cheesman from the MRC Cyclotron Unit at the Hammersmith Hospital in London, and covers functional imaging in movement disorders.

The article by Professor Tysnes and colleagues is a very clear example of how the management of neurological conditions has evolved over the last few years. The typical approach to patients with motor neurone disease used to be rather limited, but now it is becoming increasingly clear that there are a number of things that can be done to help the patient, in the absence of any curative therapy. In this article, we not only hear about how motor neurone disease epidemiology has changed over recent years, but also how we should set about caring for such patients using a multidisciplinary approach. This beautifully crafted article is clearly written from a great deal of personal experience, and as result it is something that many units would aspire to in the management of this devastating disorder.

The second review article by Paola Piccini and Ann Cheesman is from the leading UK (possibly world) centre for functional imaging in movement disorders. The article takes us through various Parkinsonian states, as well as a range of other involuntary movement disorders, and highlights the contribution that functional imaging has made to our pathophysiological understanding of these disorders. In particular, it has not only identified defects in transmitter networks but also abnormalities in circuitry using activation studies, as well as the microglial response to disease. Indeed the development of new PET ligands has also meant that this field is likely to expand in the next few years, and with this we will gain even greater understanding on the normal organisation and functional capacity of the brain, as well as how it changes in disease and over time.

Peter Whitfield, in the third in his series on Neurosurgery, discusses the assessment and management of patients with head injury. This common condition has of late become an area of intense research with respect to its optimal management. Certainly in the past, managing patients with head injuries was somewhat eclectic, with mannitol and hyperventilation being the mainstay of therapy, and little in the way of active monitoring, all of which has changed with the birth of Neuro Critical Care Units. In this article Peter presents the rules and needs for the optimal assessment and treatment of patients with any type of head injury, highlighting possible interventions available at differing levels of severity. As usual this article is clear in its message, and again is steeped in experience.

The neuropathological review article in this issue is written by the retiring head of neuropathology at the Institute of Neurology in London,



Professor Francesco Scaravilli. He sets out to discuss the pathogenesis, clinical presentation and pathology of neurosarcoidosis and paraneoplastic neurological syndromes. The former condition is often difficult to diagnose, but it is important to distinguish it from MS or other CNS inflammatory disorders, so that appropriate long-term treatment can be instigated. In contrast, paraneoplastic neurological syndromes carry with them a poor prognosis, and long-term clinical response to immunotherapy or chemotherapy is often poor. We are very fortunate to have such an expert account, which as with all articles in these series is well illustrated with histological examples.

The cognitive primer concentrates on the fascinating topic of agnosia – the perceptual disorder of preserved sensation but a loss of stimulus meaning. This is explained in a clear, beautifully illustrated and educational account written from a position of great experience and authority by Eric Ghadiali. It tackles not only the phenomenology of these disorders and their neuroanatomical basis, but also how one can easily test for these deficits and differentiate them from other conditions such as semantic dementia.

The rehabilitation article has taken as its topic botox injections and the sonographic imaging of muscles. Steffen Berweck and Jörg Wissel from the University of Munich present a very cogent argument for the adoption of this technique, especially in the setting of cerebral palsy in children. The use of ultrasound as opposed to EMG to localise muscle targets is much better tolerated without any loss of anatomical fidelity, and thus improves the accurate delivery of botox to appropriate muscle groups. An illuminating read, especially as this technique might well gain prominence in adult neurological practice.

We also include a new item, which we are hoping to make a regular feature – namely Drugs in Neurology. In this first article David Burn and Naomi Warren have written about amantadine, a drug first developed as an anti-viral agent but which has a long association with Parkinson's disease (PD). Of late this drug has come back into fashion because of its reported benefit in the treatment of L-dopa induced dyskinesias of advanced PD. This article takes us through all the drug trials of amantadine in PD and concludes with comments on what this drug has been proven to do in PD and related conditions.

Finally, don't forget our web site where you can find a wonderful article by Berek and Mayr on the neurological prognosis after cardiopulmonary resuscitation – including clear tables highlighting predictors of outcome. So we hope you enjoy this issue with all the above and its usual selection of journal reviews and conference reports. Happy reading.

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

## BNA 18th National Meeting

Brighton, UK • 3rd to 6th April, 2005

An eclectic range of plenary lectures, symposia and more than 50 themed poster sessions representing the entire breadth of neuroscience research. There will also be an exhibition and an array of peripheral events and social gatherings for delegates to enjoy.

**DEADLINE FOR ABSTRACTS:**  
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**For further details:**

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Email: Brighton2005@bna.org.uk  
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**Plenary Lectures:**

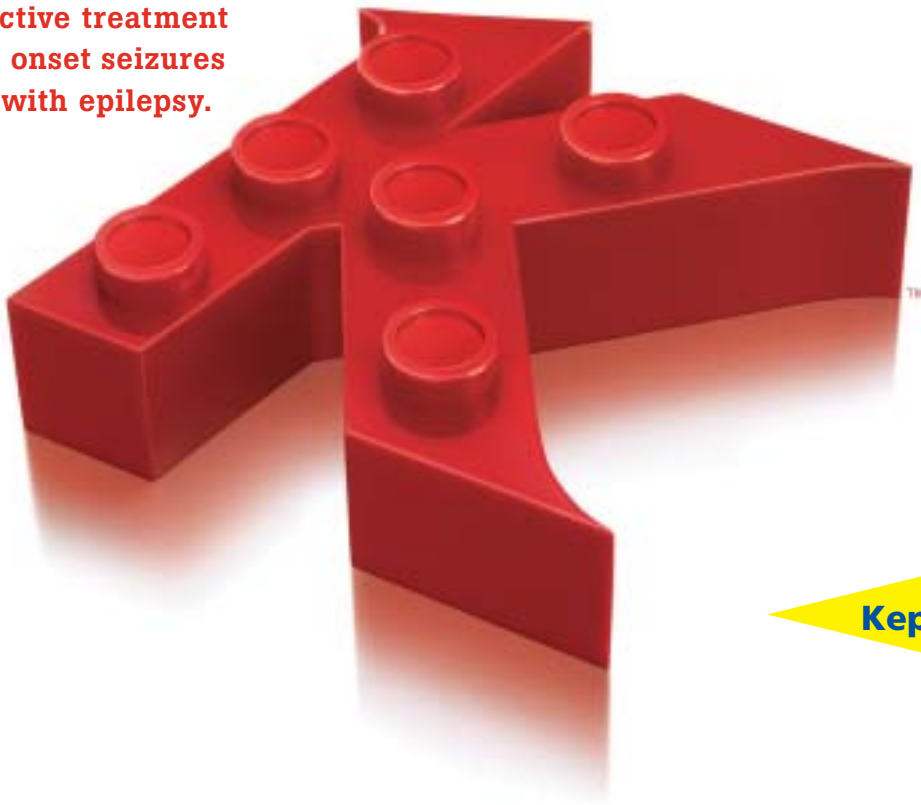
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- Pierre Magistretti (Lausanne)
- James McCulloch (Edinburgh)
- Hugh Perry (Southampton)
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**Symposia:**

- Plasticity of GABA-A receptor gene expression: molecular mechanisms
- Does synaptic plasticity provide the substrate for learning and memory?
- Strategies for repair after spinal cord injury
- Progress in stem cell biology
- The importance of human neuropathology for neuroscience research
- Nanotechnology and the brain
- Regulation of serotonergic neurotransmission and its relevance to mood
- Information coding in the auditory cortex

- Sensory integration for cognition and action
- Models of neurodegeneration
- Neuroinflammation: protagonists and antagonists
- Stem cell plasticity: can stem cells cross lineage boundaries?
- Curing Parkinson's Disease: progress on molecular and cellular biology of the disease and on therapies to neuroprotect and repair the brain
- Advances in Magnetic Resonance methodology
- Role of microglia in brain injury
- Promoting recovery after stroke
- Addictive behaviour
- The enteric nervous system: function, development and ageing of a complex peripheral neural network
- Animal modelling of psychiatric disease
- Gene silencing in the brain: functional genetics and therapeutics
- From spikes to sensation

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unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Undesirable effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (>10%): asthenia, somnolence. *Common* (between 1%–10%): GI disturbances, anorexia, accidental injury, headache, dizziness, tremor, ataxia, convulsion, amnesia, emotional lability, hostility, depression, insomnia, nervousness, vertigo, rash, diplopia. For information on post-marketing experience see SPC. **Legal category:** POM. **Marketing authorisation numbers:** 250 mg x 60 tabs: EU/1/00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1,000 mg x 60 tabs: EU/1/00/146/024. Solution x 300ml: EU/1/146/027. **NHS price:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1,000 mg x 60 tabs: £101.10. Solution x 300ml: £71.00. **Further information is available from:** UCB Pharma Ltd., 3 George Street, Watford, Herts WD18 0UH. Tel: 01923 211811. medicaluk@ucb-group.com **Date of preparation:** September 2004.

#### References:

1. Krakow K, Walker M, Otoul C, Sander JWAS. Long-term continuation of Levetiracetam in patients with refractory epilepsy. *Neurology*. 2001; 56: 1772-1774.
2. Patsalos PN. Pharmacokinetic profile of Levetiracetam: toward ideal characteristics. *Pharmacol Ther*. 2000; 85: 77-85.
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# Epidemiology and Management of ALS

ALS is an invariably fatal disease. It is the most frequent motor neurone disorder and the annual incidence in most countries ranges from 1 to 2 per 100,000 inhabitants. The disease is considered to be more frequent in men than women and usually it starts by pareses and atrophy of one or more extremities often in association with the presence of fasciculations representing involvement of the lower motor neurone. Very early in the course of the disease a generalised lower motor neurone abnormality may be detected by EMG and not clinically. The term Progressive bulbar palsy or "bulbar ALS" refers to pareses starting as speech or swallowing difficulties and occurs in 10-40% of all ALS cases. It is more frequent in women and in late onset cases. Generally the prognosis in bulbar cases has been considered worse than in spinal cases, but this may have changed with increasing use of non-invasive assisted ventilation.

## Increasing incidence of ALS?

During the last few years convincing evidence has been presented that the incidence of ALS has been increasing over the last decades.<sup>1,2</sup> Initially these data were interpreted as being due to the generally increasing age of the population as a whole, but this seems unlikely to be the whole explanation and indeed environmental factors may be contributing to this observed increase in ALS incidence. We have also reported that not only is there an increase in the annual incidence of ALS from 1.5 to 2.5 per 100,000 of the population, but there has been a change in gender affected by the disease during the period from 1960 to the mid nineties such that by the end of the observation period the risk was similar in men and women<sup>3</sup> (see Fig. 1). This could indicate that environmental factors contributed to the increased incidence and in this respect exposure to heavy metals and electric magnetic fields has been associated with the disease.<sup>4</sup> Moreover, studies of Gulf war veterans have indicated increased risk in veterans, especially in air-force and army personnel.<sup>5</sup> Overall it can be concluded that there is increasing incidence of ALS and whilst this is in part explained by the increasing age of the general population, it may also be related to environmental factors that affect the integrity of motor neurons.

## Care of the ALS patient

Although great progress has been made to better understand the pathophysiology of ALS, especially in genetic variants of the disease, the possibility of treatments that truly affect survival-time is still very limited. The glutamate antagonist Riluzole has been shown to prolong survival by an average of 3 months, and whilst great efforts have been made to study molecules affecting glutamate metabolism and trophic factors (inc. positive reports in transgenic mouse models of ALS), no other treatments than riluzole have been demonstrated to prolong survival in human ALS. In contrast to the paucity of disease modifying treatments in ALS, during the last decade there has been a substantial change in the management of the disease.

In the past, ALS patients were carefully diagnosed, but offered little support to manage their life as they developed increasing pareses. Most frequently the patients were hospitalised when the disease had progressed to a stage where the patient or family could not manage, possibly with the insertion of naso-gastric tubes in patients with bulbar palsy and swallowing difficulties. Today it is accepted that ALS patients are best treated in multidisciplinary ALS clinics with a team that includes a neurolo-

gist, specialised nurses, physical, occupational and speech therapists, social worker as well as pulmonologist and nutritionist. It has been demonstrated that such care is not only good for the well-being of the patient, but in fact increases survival at least as much as with the administration of riluzole.<sup>6</sup>

The ALS care at Haukeland University Hospital in Norway was organised in such a way so that it has had an ALS clinic from 1990, inspired from that which exists in the Department of Neurology at the University of Chicago (see Fig. 2). The diagnosis of ALS is not usually established in the out-patient clinic but during a stay at the Department of Neurology. This makes it easier to have all the necessary investigations performed before the diagnostic discussion is undertaken with the patient. Usually within a month the patient is seen in the multi-disciplinary ALS clinic, and a week before this consultation the patient receives a description of the clinic and the professions they may meet there. The patients will usually see most professions on their first consultation but later only when specific problems arise and need sorting out. Usually the first consultation in the clinic is used to ascertain the diagnosis and to inform the patients about the possible health outlook with this condition. The patients are given a card for the ALS nurse with all the possibilities of how to get in touch with the clinic as and when they need to do this. The ALS nurse is the primary contact point for the patient and will transfer requisites to actual professions, again as and when required. One of the most important aspects of management in the ALS clinic is to take the initiative for ensuring that the primary health care system engages and supports the patient in the community. As the disease is rare, most community based services have no experience on the management of ALS and so the resource group with the general practitioner, physical and occupational therapist and nurse need to be organised in the community. This group has regular meetings with the patient and his family and can at short notice, supply the patient with aids required for them to remain independent.

As the disease progresses the patients will need more sophisticated aids. This is organised through the ALS clinic, but the patients are frequently admitted for short periods to the ward in the Department. This could be for establishing PEG feeding or evaluation with regard to them developing respiratory failure. Usually establishment of PEG requires a 2-day stay in the ward and is established in collaboration with the gastroenterology section of the Department of Internal Medicine. After insertion of the PEG, the patient may stay another day in the Neurology ward to learn how to use the PEG and to

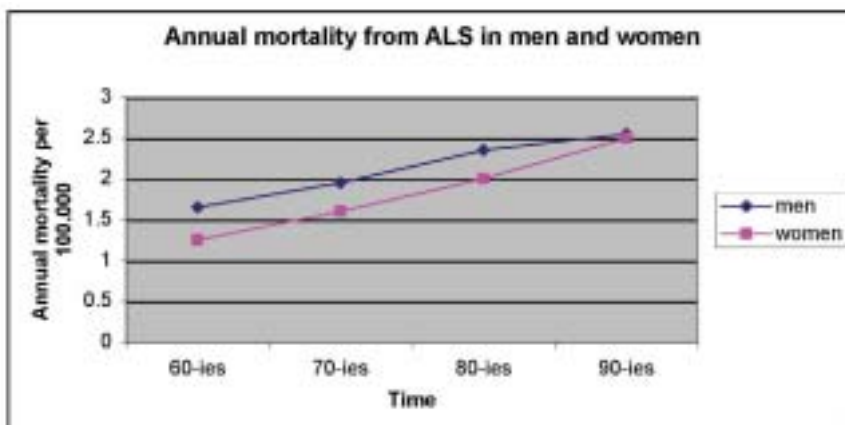


**Professor Tysnes** was born in Bergen in 1956. His medical education was at the University of Oslo. He became Specialist in Clinical Neurology in 1992 and Professor in Neurology at Haukeland University Hospital in Bergen in 1996. Together with Professor Aarli he has run the Department's ALS clinic since 1990.

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Figure 1





start to get used to the nutrition given through it. After 3 months the tube is changed to a Mic which is usually easier to handle as the tube can be troublesome for the patient (especially during night/sleep). Some patients have problems with drooling. These are treated either by one shot radiotherapy to the parotid and submandibular glands done in collaboration with the Department of Oncology. More recently we have also tried Botulinum toxin A injections to the parotid glands with some success. From a respiratory perspective, an increasing number of patients are offered non-invasive ventilation support when required. The evaluation of respiratory function is performed by pulmologists and during this evaluation the patients may have a short stay in the Department of Pulmology. Follow up of the BIPAP (Bilevel Positive Airway Pressure) is also done by the pulmologist associated with the ALS clinic. We thought that the more abundant use of BIPAP would lead to an increasing number of ALS patients deciding to have tracheostomy and permanent ventilation support, but this has not proven to be the case. Most patients decide not to continue life when the disease has progressed to a stage where they are totally dependent on family and care-givers for all their activities.

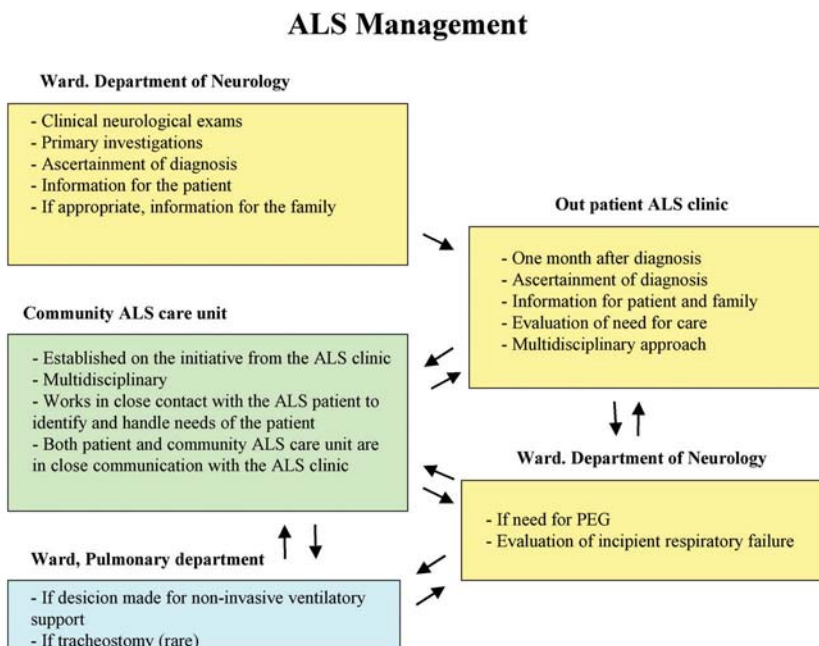
**Conclusion**

The incidence of ALS is increasing due in part to the increasing age of the general population together with an unknown factor that may be environmental. During the last decade there has been little development in the medical treatment of this disease but management has considerably changed from a passive attitude to a fatal disease to considerable work to help the ALS patient to live with his symptoms. Crucial for success in ALS management is a multidisciplinary approach tailored to the needs the patient as they develop and change during the course of the disease. Needs must be identified early and handled quickly. This requires close communication between an ALS clinic with the Neurological ward, the primary care unit and the Pulmonary Department.

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Figure 2



**Challenges in ALS Management**

**On time of diagnosis**

- To have a good relationship with the patient
- Realistic information but not without hope
- Not all information is needed at once
- Make sure that the patient has a place to make contact if needed

**Community ALS care unit**

- Organise multidisciplinary meetings in the home of the patient
- Fulfil needs within a short period of time (days)
- The psychological stress of the close relation to an invalidated ALS patient
- Take care of family members

**At follow ups in the ALS clinic**

- Information on current research in ALS
- Some patients want alternative treatments
- Deal with pareses and make aid items (walking aids, wheelchair, requirements to eat or for hygiene) available (occupational therapist).
- Deal with communication problems (speech therapist)
- Avoid delay in achievement of aid facilities
- Have options for the patient to make contact (telephone, E-mail).
- Short waiting time if consultation is needed
- Good organisation if PEG is needed
- Discussion of end-of-life issues. Use all experience to inform on expected life situation in case of permanent assisted ventilation.

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# Functional Imaging of Movement Disorders

The spectrum of movement disorders runs from simple tics to more complex multisystem degenerations such as progressive supranuclear palsy, and the vast majority remain clinical diagnoses with no diagnostic tests. In the past the importance of functional brain imaging has lain mainly in characterising the brain networks involved in the disorders and the changes effected by treatment. However in the future, the importance of such imaging paradigms may lie with progression studies as the most practicable objective method of evaluating the effects of potential neuroprotective agents and restorative interventions.

Functional imaging allows us to interrogate both resting brain function and task-related cerebral activation patterns *in vivo* in health and disease. For example,  $^{18}\text{F}$ -fluoro-2-deoxy-D-glucose positron emission tomography ( $^{18}\text{F}$ -FDG PET) provides a measure of resting regional glucose metabolism whereas  $^{15}\text{O}$ -labelled water ( $\text{H}_2^{15}\text{O}$ ) PET allows detection of changes in regional blood flow elicited by performing a task. Functional imaging also enables quantification of pre-synaptic properties, post-synaptic receptor availability, enzyme activity and neuroinflammatory changes. Indeed, the cellular sites which can be examined are limited only by the difficulties of developing practical radiotracers with sufficient specificity and kinetic characteristics to allow quantitative analysis. In this review we will consider the application of functional imaging, especially PET, to akinetic-rigid syndromes and involuntary movement disorders in turn. All involve alterations in the outputs from basal ganglia circuitry to cortex (Figure 1).

## Akinetic-rigid syndromes

### Parkinson's disease Diagnosis

The defining abnormality in Parkinson's disease (PD) is the progressive loss of dopaminergic neurons in the nigrostriatal pathway which can be imaged by PET most clearly at its termination in the striatum using markers for pre-synaptic properties.  $^{18}\text{F}$ -6-fluorodopa ( $^{18}\text{F}$ -dopa) PET reflects pre-synaptic dopa uptake, decarboxylation to dopamine and storage;  $^{18}\text{F}$ -dopa uptake rate constants have been shown to correlate with the number of functional dopaminergic neurons.<sup>1</sup>

$^{123}\text{I}$ -FP-CIT<sup>1</sup> single photon emission computed tomography (SPECT) visualises the pre-synaptic dopamine transporter with a sensitivity of detecting striatal dysfunction of 97% and a specificity of 100%.<sup>10</sup> It is now commercially available as DaTSCAN<sup>TM</sup> and may prove useful in cases of diagnostic difficulty.

### Aetiology

Other functional imaging studies have given insights into the aetiology and brain circuitry of PD and have provided a means of evaluating therapeutic interventions. The cause of PD is likely to be an integration of genetic susceptibility and various environmental factors, all varying in their relative contributions in the individual patient. An insight into the genetic contribution in sporadic PD has been given by  $^{18}\text{F}$ -dopa PET studies of twin pairs, one of whom was affected by PD at the beginning of the study.<sup>6</sup> At baseline the concordance for nigrostriatal dopaminergic dysfunction was significantly higher in monozygotic than in dizygotic pairs and it became even higher after 7 years of follow-up, with 4 of the 18 monozygotic and none of the 16 dizygotic co-twins developing clinical PD. These results suggest either a substantial direct role of inheritance in

sporadic PD or an associated increase in susceptibility to causative environmental agents.

### Pathophysiology and treatment effects

In recent years fluorodopa PET scanning has yielded relevant information about the pattern of dopaminergic depletion, involving predominantly the dorsal putamen in early disease,<sup>2</sup> rates of disease progression<sup>3</sup> and possible compensatory changes in early disease in other dopaminergic pathways: the nigrostriatal,<sup>4</sup> mesolimbic and mesocortical.<sup>5</sup>

$\text{C}^{15}\text{O}$  and  $\text{H}_2^{15}\text{O}$  PET both quantify regional cerebral blood flow (rCBF) and have been used to demonstrate that underfunctioning of the supplementary motor area (SMA) occurs in PD and is associated with akinesia and bradykinesia<sup>7</sup> and that activation of the dorsal prefrontal cortex in normal and PD subjects occurs only when making self-paced and not cued movements.<sup>7</sup>

The lateral parietal and premotor areas, regions targeted by cerebellar projections, show increased activation in PD patients performing sequential finger movements. It is mooted that, in PD, there is a partial switch in operation from dysfunctional basal ganglia circuits to other motor circuitry. The connections from globus pallidus interna via pedunculopontine nucleus to the cerebellum could mediate such a switch.

$^{11}\text{C}$ -raclopride PET enables estimation of dopamine release by measuring relative differences in  $\text{D}_2$  receptor occupancy before and after a dopamine releasing challenge. Using repetitive transcranial magnetic stimulation and  $^{11}\text{C}$ -raclopride PET, Strafella and colleagues have demonstrated that prefrontal cortical projections to the striatum can modulate dopamine release.<sup>9</sup>

The surgical interventions of medial pallidotomy and deep brain stimulation of the medial pallidum (globus pallidus interna: GPi) or subthalamic nucleus in PD are all intended to affect the overactivity of these nuclei in the



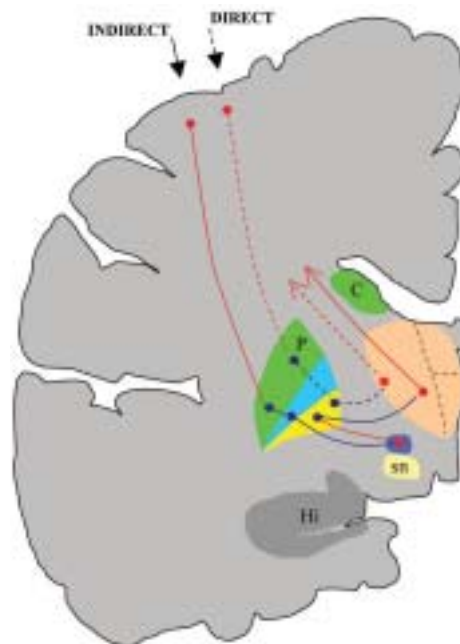
**Paola Piccini** is Senior Lecturer and Consultant Neurologist at Imperial College, Division of Neurosciences and Clinical Sciences Centre, Hammersmith Hospital, London. Her main research interests are functional imaging and movement disorders, specifically the use of imaging to provide insights into the pathogenesis, genetics and cell repair strategies in Parkinson's disease and Huntington's disease.



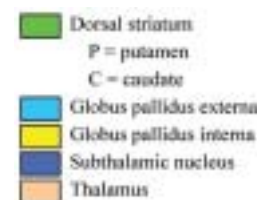
**Ann Cheesman** has undertaken research into the contributions of functional imaging to understand the heterogeneity of Parkinson's disease at Imperial College, Division of Neurosciences and Clinical Sciences Centre, Hammersmith Hospital, London. She has most recently been a LAT Registrar in Neurology at Homerton Hospital, London.

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**Figure 1:** Coronal section through the brain illustrating the indirect and direct pathways running from cortex via basal ganglia back to cortex: the cortico-striato-pallido-thalamo-cortical loops. The substantia nigra pars reticularis is also involved in parallel to the GPi (paths not shown). The balance of activity in the pathways is altered in many movement disorders, eg. reduced input from the direct and increased input from the indirect pathways to the GPi in Parkinson's disease. Red= excitatory (glutamate). Blue= inhibitory (GABA) Hi= hippocampus. sn= substantia nigra



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products which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias, monitor cardiac function carefully during initial dosage adjustments. Monitor all patients for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully. Caution when driving or operating machines. Doses of other antiparkinsonian treatments may need to be adjusted when Stalevo is substituted for a patient currently not treated with entacapone. Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dosage reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy. **Undesirable effects:** Levodopa / carbidopa – Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, depression, cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, dizziness, and somnolence. **Entacapone** – Most frequently relate to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and urine discolouration. Common: insomnia, hallucination, confusion and paroniria, Parkinsonism aggravated, dizziness, dystonia, hyperkinesias, diarrhoea, abdominal pain, dry mouth constipation, vomiting, fatigue, increased sweating and falls. See SPC for details of laboratory abnormalities, uncommon and rare events. **Legal category:** POM. **Presentations, basic NHS costs and**

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December 2003  
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disease. All have been shown to increase SMA resting rCBF or activation during arm or finger movements with reduced bradykinesia.<sup>11</sup> In addition restoration of activation of SMA and prefrontal cortex during a motor task has been shown in PD patients after bilateral striatal transplantation of human foetal mesencephalic cells.<sup>8</sup>

Indeed this transplantation of foetal nigral tissue into the putamen of PD subjects results in sustained motor improvement with restored dopamine storage and release, evaluated by <sup>18</sup>F-dopa PET and <sup>11</sup>C-raclopride respectively, in one case at ten years after transplantation.<sup>12</sup> The same group has presented data indicating that severe off-dyskinesias occasionally observed in PD after foetal dopaminergic cell transplantation are not directly related to increases in striatal dopamine storage after grafting as measured by <sup>18</sup>F-dopa PET.<sup>13</sup>

Glial cell line-derived neurotrophic factor (GDNF) has neurorestorative properties in animal models of PD and has now been used in man as part of phase I safety trials, delivered chronically by infusion to the putamen.<sup>14</sup> PET studies in the 5 subjects involved revealed a 28% increase in putaminal <sup>18</sup>F-dopa uptake 18 months after catheter implantation, supporting a restorative effect on dopaminergic function.

The REAL-PET study was an international double-blind study which evaluated the 2 year decline in putaminal <sup>18</sup>F-dopa uptake in 186 PD subjects taking either L-dopa or ropinirole, a D2/D3 agonist.<sup>15</sup> The finding of a significant difference in the fall from baseline of the ropinirole group compared to the L-dopa group supports either a protective role for ropinirole or a deleterious role for L-dopa on progression.

### Atypical Parkinsonism and differential diagnosis

Evaluation of pre-synaptic function with <sup>18</sup>F-dopa PET or <sup>123</sup>I-FP-CIT SPECT shows reductions in striatal uptake in the presence of nigrostriatal degeneration. They therefore display normal striatal uptake in drug-induced parkinsonism, dopa-responsive dystonia and essential tremor and reduced uptake in PD, multiple system atrophy (MSA), Lewy body dementia, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Further discrimination between the diagnoses of parkinsonism using other functional imaging studies is made difficult by imaging findings often overlapping between conditions. However, using <sup>18</sup>F-FDG PET in a case of chronic parkinsonism, only in PD is there lentiform (putamen + globus pallidus) and thalamic relative *hyper*metabolism contralateral to the clinically more affected limbs. In MSA, PSP and CBD there is usually lentiform and thalamic relative *hypometabolism*, the latter reflecting loss of afferent activity from the degenerating globus pallidus. A greater than 5% side-to-side asymmetry of parietal glucose uptake would support a diagnosis of CBD and cerebellar hypometabolism: PSP or MSA. To discriminate PSP from MSA with functional imaging is more difficult as both share more uniform loss of caudate and putamen <sup>18</sup>F-dopa uptake compared to PD, normal or reduced striatal raclopride binding and reduced lentiform N-acetylaspartate to creatine ratio (a marker of neuronal viability) on proton magnetic resonance spectroscopy (MRS) in the majority.<sup>16</sup> PSP would be more likely than MSA if frontal hypometabolism was evident.

### Involuntary movement disorders

#### Tics

Tourette's Syndrome (TS) is a neuropsychiatric disorder characterised by vocal and motor tics often associated with obsessive-compulsive symptoms. Functional imaging has implicated excessive dopaminergic innervation of the ventral striatum but not of the dorsal striatum and

excessive activation of sensorimotor cortices and SMA. Altered opioid binding and serotonergic transmission have also been implicated.<sup>17</sup>

#### Dystonia

Dystonia is characterised by slow, sustained muscle contractions causing abnormal posturing or twisting movements. It is known from microelectrode exploration before surgery in dystonia that sensory processing is altered with increased size and overlapping of receptive fields, so that, for example, reducing sensory inputs from the affected limb with local anaesthetic can ease writer's cramp. However, imaging studies have revealed underlying abnormalities in both sensory and motor networks affecting structures from the lentiform nucleus to the cortex with PET.<sup>18</sup> A unifying feature of both primary and secondary (for example, in the presence of a striatopallidal or thalamic lesion) dystonias appears to be inappropriate overactivity of basal ganglia projections to accessory motor areas.<sup>19</sup>

#### Huntington's disease

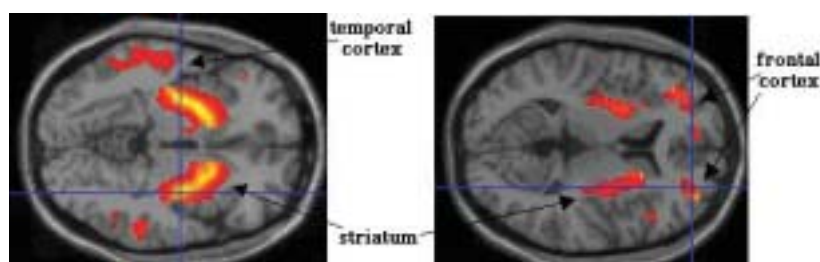
Huntington's disease (HD) is an autosomal dominantly inherited CAG trinucleotide repeat disorder in which the pathology initially targets the GABAergic medium spiny neurons of the striatum and subsequently progresses to involve multiple brain areas. As these neurons bear both D1 and D2 receptors, binding of both <sup>11</sup>C-SCH23390 (D1 receptor ligand) and <sup>11</sup>C-raclopride (D2) are progressively reduced in HD patients at a rate of about 5% per annum.<sup>20</sup> Reduced D1 binding has also been demonstrated in temporal and frontal cortex<sup>20</sup> of HD patients (Figure 2).

Characteristically in HD there is glucose hypometabolism on <sup>18</sup>F-FDG PET of the caudate and putamen and this appears to precede atrophy of these structures, in addition, there are relative mediotemporal and occipital metabolic reductions and increases respectively.<sup>21</sup> This covariance pattern allows discrimination between controls and pre-symptomatic gene carriers and between the latter and early-stage HD patients.

Activation studies whilst moving a joystick revealed underactivation of striatum and frontal projection areas<sup>22</sup> including the SMA which could explain the background bradykinesia invariably present in choreic HD patients.

Grafting of human foetal striatal cells into the striatum of HD patients is currently under evaluation and PET measures of D1 and D2 binding would be expected to provide a more specific measure of survival and growth of graft tissue. However, in one published study using FDG PET, it was demonstrated that there were local striatal increases in transplanted patients and restoration of distant (cortical) metabolism away from the site of surgery where local glucose metabolism may be difficult to interpret.<sup>23</sup>

Clinical studies evaluating potential neuroprotective agents in HD have required large numbers of patients, for example 347 patients with established HD over 30 months



**Figure 2:** PET with <sup>11</sup>C-raclopride (D2 receptor tracer) in a group of patients with Huntington's disease. Transaxial projections of statistical parametric maps (SPM). The yellow-red areas superimposed on a standard MRI template represent regions of the brain where a significant decrease in D2 receptor binding was found in the HD patients in comparison to normal volunteers.<sup>20</sup>

to assess coenzyme Q10.<sup>24</sup> Coenzyme Q10 300mg b.d. showed a trend in the slowing of functional decline. PET measures of striatal D1 or D2 dopamine binding could be used in the future to interrogate the rate of progression associated with different dosages of coenzyme Q10 and other neuroprotective agents. Indeed functional imaging

could aid in the practical assessment of emerging disease modifying treatments for this condition, and this could include the asymptomatic HD mutation carriers as whilst they have been shown to be actively progressing on PET (=50% of subjects),<sup>25</sup> they have no clinical signs with which to monitor progression.

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## The International League Against Epilepsy (UK Chapter) Annual Scientific Meeting

15th-17th June 2005

*The Waterfront Hall, Belfast*

(starting at 13:30 on Wednesday 15<sup>th</sup> June 2005)

#### Sessions include:

- ◆ Teratogenesis and anti-epileptic drugs
- ◆ Hippocampus and memory
- ◆ Paediatric epilepsy surgery
- ◆ Hormones in epilepsy
- ◆ Educational/discussion session with interactive presentations focusing on diagnostic issues
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## UNITED IN CARE THE 1ST NATIONAL CONFERENCE

1st December 2004  
Royal College of Physicians, London

This conference aims to identify ways to improve interdisciplinary collaboration among the health professionals providing health care for older people. The morning topics will include:

- Understanding syncope and falls
- Parkinson's disease
- Treatment update on the dementias
- Stroke

The afternoon will provide an opportunity for a discussion led by a panel to examine the team approach to feeding issues in hospital, led by a well-known 'personality' in the field and representatives from the multi-disciplinary teams.

Full participation of the audience will be encouraged to make this as interactive as possible.

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# The Management of Patients with Head Injury

Relatively few patients with head injury require the operative skills of a neurosurgeon. However, concerns that some patients with head injury die unnecessarily and other patients suffer long-term sequelae due to inappropriate management were raised in a report from the Royal College of Surgeons of England in 1999.<sup>1</sup> This highlighted inadequacies in the provision of head injury services for these patients, many of whom are initially, and sometimes exclusively seen by relatively junior doctors. The National Institute of Clinical Excellence has published admission, CT scan and specialist referral guidelines.<sup>2</sup> Neurosurgeons should take a leading role by ensuring access to specialist care is appropriate and timely in order to be effective, and by closely collaborating with other health care workers to ensure an optimal pathway of care is organised.

## Epidemiology

Head injuries occur in all age groups, with a peak incidence in males between the ages of 16 and 25 years and a second peak in the elderly who have a high incidence of chronic subdural haematomas. The majority of head injuries in the UK are closed rather than open and are caused by road traffic accidents, falls and assaults.<sup>3</sup>

## Haematoma evacuation

The Glasgow Coma Scale is a validated measure of level of consciousness that has been universally adopted.<sup>4</sup> It is of paramount importance in communicating information about patient status. The age, neurological status, mechanism of injury and pupillary reactions all input to the decision making process when evaluating the need for haematoma evacuation. The major questions addressed by the surgeon are:

- 1) Is the conscious level depressed?
- 2) Are there other signs of raised ICP (eg oculomotor palsy)?
- 3) Does the scan show a haematoma or contusion with mass effect (midline shift/ ventricle effacement/ dilatation of contralateral ventricle/ loss of basal cisterns/ sulcal effacement)?
- 4) Is expansion of the mass anticipated (eg contusions)?
- 5) Where is the mass (temporal lobe lesions are considered dangerous due to the association with uncal herniation compressing the midbrain)?

These questions must be rapidly addressed and any surgery performed with an appropriate sense of urgency. The majority of procedures require a large craniotomy flap. This provides adequate access to traumatised brain, potential sources of haemorrhage and can prove useful in reducing ICP if the bone flap is left out. The classical scalp incision for many lesions extends in a question mark shape to the pre-auricular region. Modification such that the posterior limb of the flap passes posterior to the ear increases the ease of exposing the temporal and parietal regions. Extradural haematomas are usually readily evacuated and bleeding controlled by placement of multiple "hitch" stitches around the periphery of the bone flap and a central hitch stitch from the dura through 2 drill holes in the bone flap. Acute subdural haematomas after low impact injury in the elderly are often associated with a readily coagulated small cortical artery. After a high velocity injury, an acute subdural haematoma is frequently associated with contusions and reflects a severe brain injury. In extreme cases a "burst" lobe may be evident. Such severe haemorrhagic contusions may necessitate resection of brain in the form of a lobectomy. Brain resection requires rapid but careful surgery pre-

serving the middle and anterior cerebral arteries. Haemostasis can be difficult to achieve during trauma surgery. Good illumination, excellent access and patience are required. If the underlying brain is swollen at the time of closure it is prudent to leave the dura open, not replace the bone flap and close the scalp in anatomical layers. A subdural multilumen capillary drain (Yates) tunnelled to a colostomy bag applied to the scalp provides a very effective means of wound drainage. An ICP monitor is inserted in all cases with the exception of uncomplicated extradural haematoma evacuation where rapid recovery is anticipated.

Chronic subdural haematomas usually present with headache, confusion, focal neurological signs or reduced level of consciousness several weeks after minor head trauma. Frequently there is no history of trauma. The haematoma is drained through 2 burr-holes that also permit intraoperative irrigation of the subdural space to remove any clot debris.

## Critical care management of head injury

After the initial assessment and resuscitation of patients with craniocerebral trauma – including the management of life-threatening injuries – a period of intensive supportive care with multimodality monitoring is instituted to prevent secondary insults to the brain. Many centres now use protocol driven therapy during this phase of care (Figure 1).

## Monitoring

Intracranial pressure monitoring is used in all head injured patients with any abnormality on CT scanning who do not obey commands. The monitor is usually placed in the right frontal region via a twist drill hole. Since an external ventricular drain is placed in over 50% of severely injured patients the exact positioning of the ICP monitor needs to be able to accommodate a nearby ventriculostomy incision.

## Intracranial pressure and cerebral perfusion pressure management

Continuous monitoring of arterial blood pressure and calculation of mean cerebral perfusion pressure (CPP) is performed ( $CPP = \text{mean arterial BP} - \text{mean ICP}$ ).<sup>5</sup> Management of the ICP is undertaken in accordance with the algorithm in Figure 1. An ICP of <25 mmHg and a mean CPP of >70 mmHg are targeted. Simple manoeuvres frequently used to reduce intracranial pressure include ensuring venous drainage is not obstructed by endotracheal tube tapes, elevation of the head by 20–30°, avoidance of hypoxia and prolonged expiratory cycles and maintaining normothermia. If the ICP is raised CT scans will exclude significant haematomas or contusions. Ventriculomegaly at this early stage is unusual but placement of an EVD will usually reduce ICP if the ventricles are not fully effaced. If the ventricular catheter has not resulted in CSF at a depth of 7cm the trajectory is incorrect. Check that the entry point is not too far anterior (should be just anterior to the coronal suture), ensure that in the AP plane the tip is directed to the tragus and direct the catheter from the entry site toward the midline at the target depth, in the coronal plane. The catheter is tunnelled posteriorly to keep it clear of any subsequent bifrontal craniectomy flap.

## PaCO<sub>2</sub> manipulation and jugular venous oximetry (SjvO<sub>2</sub>)

The next phase of care involves further monitoring of the patient with jugular venous oximetry and the use of inotropic support.<sup>6</sup> Reduction of the arterial PaCO<sub>2</sub> can



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shake and move funny.  
It made him very sad  
too.



He doesn't so much now.  
I think he's happier.

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Address the distress of Parkinson's disease

#### Prescribing Information UK

#### Mirapexin® (pramipexole) Presentation:

Mirapexin 0.08mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing 0.125mg, 0.25mg and 0.9mg respectively of pramipexole salt (hydrochloride monohydrate). **Indications:** The treatment of the signs and symptoms of idiopathic Parkinson's disease, alone without levodopa or in combination with levodopa. **Dosage and Administration:** Adults and Elderly Patients: Administration: One tablet orally with water in equally divided doses three times per day. Initial treatment: 2 x 0.08mg base (0.125mg salt) per day for first 5-7 days. Then 3 x 0.08mg base (0.125mg salt) per day to 57 days, and then 3 x 0.18mg base (0.25mg salt) per day to 57 days. Increase the daily dose by 0.54mg base (0.75mg salt) at weekly intervals to a maximum dose of 3.6mg base per day (4.5mg salt per day). If necessary, increase the maintenance dose to a dose higher than 1.08mg base per day (1.5mg salt per day). Maintenance treatment should be in the range of 1.08mg base (0.75mg salt) to a maximum of 3.6mg base (4.5mg salt) per day. Adjust dose based on clinical response and tolerability; reduce doses used in frail and maintenance doses if necessary. Treatment discontinuation: All of the symptoms of a given type (tremor) can lead to the development of a severe malignant syndrome. Reduce dose by 0.54mg base (0.75mg salt) per day to 0.54mg base per day (0.75mg salt) per day. Thereafter reduce dose to 0.25mg base (0.375mg salt) per day. Serial treatment: See IFC for revised dosage schedules. Repeat treatment: Dose adjustment is typical; tablet is provided not necessary. **Contraindications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings and Precautions:** Reduce dose in renal impairment; other patients that

tolerate poorly (renal impairment). Sometimes and uncommonly, sudden sleep onset have been reported; patients who have experienced these must refrain from driving or operating machinery. A reduction of dosage or administration if needed may be considered, if drowsiness occurs in combination with an episode during initial treatment of pramipexole in advanced Parkinson's disease, the time of levodopa should be reduced. Patients with psychiatric disorders should only be treated with extreme caution if the potential benefits outweigh the risks. **Contraindications:** Smoking: a recommended diet regime with or without alcohol is not recommended. In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. **Drug Interactions:** There is no pharmacological interaction with levodopa and dopamine agonists of the tubular-dopamine receptor system of the central nervous system, such as amantadine and anticholinergics may interact with pramipexole resulting in reduced clearance of other at high doses. Consider reducing pramipexole dose when these drugs are administered concomitantly. The dosage of levodopa should be adjusted and other Parkinsonian medication kept constant, while monitoring the degree of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. **Concomitant use 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 or while the benefits outweigh the potential risk to the fetus. Pramipexole should not be used during breastfeeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, vertigo, dizziness and peripheral oedema occurred more often than with placebo. More frequent adverse reactions in combination with

levodopa were dizziness. Constipation, nausea and dizziness tended to disappear with continued therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin is titrated too fast. Mirapexin has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. **Overdose:** There is no clinical experience with massive overdosage. Expected adverse events include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive measures may be required, along with gastric lavage, intravenous fluids and electrocardiogram monitoring. **Basic NHS Code:** 0.08mg x 30 tablets EU1/01, 0.18mg x 30 tablets EU1/02, 0.7mg x 30 tablets EU1/03, 0.18mg x 30 tablets EU1/04, 0.18mg x 30 tablets EU1/05, 0.18mg x 30 tablets EU1/06, 0.18mg x 30 tablets EU1/07, 0.18mg x 30 tablets EU1/08, 0.18mg x 30 tablets EU1/09, 0.18mg x 30 tablets EU1/10, 0.18mg x 30 tablets EU1/11, 0.18mg x 30 tablets EU1/12, 0.18mg x 30 tablets EU1/13, 0.18mg x 30 tablets EU1/14, 0.18mg x 30 tablets EU1/15, 0.18mg x 30 tablets EU1/16, 0.18mg x 30 tablets EU1/17, 0.18mg x 30 tablets EU1/18, 0.18mg x 30 tablets EU1/19, 0.18mg x 30 tablets EU1/20, 0.18mg x 30 tablets EU1/21, 0.18mg x 30 tablets EU1/22, 0.18mg x 30 tablets EU1/23, 0.18mg x 30 tablets EU1/24, 0.18mg x 30 tablets EU1/25, 0.18mg x 30 tablets EU1/26, 0.18mg x 30 tablets EU1/27, 0.18mg x 30 tablets EU1/28, 0.18mg x 30 tablets EU1/29, 0.18mg x 30 tablets EU1/30, 0.18mg x 30 tablets EU1/31, 0.18mg x 30 tablets EU1/32, 0.18mg x 30 tablets EU1/33, 0.18mg x 30 tablets EU1/34, 0.18mg x 30 tablets EU1/35, 0.18mg x 30 tablets EU1/36, 0.18mg x 30 tablets EU1/37, 0.18mg x 30 tablets EU1/38, 0.18mg x 30 tablets EU1/39, 0.18mg x 30 tablets EU1/40, 0.18mg x 30 tablets EU1/41, 0.18mg x 30 tablets EU1/42, 0.18mg x 30 tablets EU1/43, 0.18mg x 30 tablets EU1/44, 0.18mg x 30 tablets EU1/45, 0.18mg x 30 tablets EU1/46, 0.18mg x 30 tablets EU1/47, 0.18mg x 30 tablets EU1/48, 0.18mg x 30 tablets EU1/49, 0.18mg x 30 tablets EU1/50, 0.18mg x 30 tablets EU1/51, 0.18mg x 30 tablets EU1/52, 0.18mg x 30 tablets EU1/53, 0.18mg x 30 tablets EU1/54, 0.18mg x 30 tablets EU1/55, 0.18mg x 30 tablets EU1/56, 0.18mg x 30 tablets EU1/57, 0.18mg x 30 tablets EU1/58, 0.18mg x 30 tablets EU1/59, 0.18mg x 30 tablets EU1/60, 0.18mg x 30 tablets EU1/61, 0.18mg x 30 tablets EU1/62, 0.18mg x 30 tablets EU1/63, 0.18mg x 30 tablets EU1/64, 0.18mg x 30 tablets EU1/65, 0.18mg x 30 tablets EU1/66, 0.18mg x 30 tablets EU1/67, 0.18mg x 30 tablets EU1/68, 0.18mg x 30 tablets EU1/69, 0.18mg x 30 tablets EU1/70, 0.18mg x 30 tablets EU1/71, 0.18mg x 30 tablets EU1/72, 0.18mg x 30 tablets EU1/73, 0.18mg x 30 tablets EU1/74, 0.18mg x 30 tablets EU1/75, 0.18mg x 30 tablets EU1/76, 0.18mg x 30 tablets EU1/77, 0.18mg x 30 tablets EU1/78, 0.18mg x 30 tablets EU1/79, 0.18mg x 30 tablets EU1/80, 0.18mg x 30 tablets EU1/81, 0.18mg x 30 tablets EU1/82, 0.18mg x 30 tablets EU1/83, 0.18mg x 30 tablets EU1/84, 0.18mg x 30 tablets EU1/85, 0.18mg x 30 tablets EU1/86, 0.18mg x 30 tablets EU1/87, 0.18mg x 30 tablets EU1/88, 0.18mg x 30 tablets EU1/89, 0.18mg x 30 tablets EU1/90, 0.18mg x 30 tablets EU1/91, 0.18mg x 30 tablets EU1/92, 0.18mg x 30 tablets EU1/93, 0.18mg x 30 tablets EU1/94, 0.18mg x 30 tablets EU1/95, 0.18mg x 30 tablets EU1/96, 0.18mg x 30 tablets EU1/97, 0.18mg x 30 tablets EU1/98, 0.18mg x 30 tablets EU1/99, 0.18mg x 30 tablets EU1/100. Further information is available from Boehringer Ingelheim, Ltd., Bielefeld Avenue, Basingstoke, Hampshire RG24 9YS. **Date of preparation:** 1 September 2004.

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reduce the intracranial blood volume due to capacitance vessel constriction reducing intracranial pressure. However, preliminary cerebral blood flow PET data indicate that such an approach can cause arterial vasoconstriction and relative cerebral ischaemia. Jugular venous oximetry is therefore used as a tool to titrate hyperventilation to the global cerebral metabolic response. If  $\text{SjvO}_2$  reduced below 60% a state of relative ischaemia exists and this is likely to be exacerbated by further reduction of  $\text{PaCO}_2$ .

## Inotropic support

Augmentation of mean arterial pressure may help delivery of oxygen and glucose to the brain averting the progression of cytotoxic oedema and reducing ICP. However intracranial pressure may increase with pressure support due to the loss of cerebral autoregulation, resulting in a passive cerebral circulation in which increases in arterial pressure causes further elevation of ICP due to pressure waves and vasogenic oedema. In clinical practice the response is variable, therefore therapeutic manoeuvres require careful monitoring. Augmentation of the CVP to 8 or 10 cm ensures adequate circulatory volume is present before enhancing stroke volume with inotropes. Norepinephrine appears to be more predictable and efficient at augmenting CPP when compared with dopamine.<sup>7</sup>

## Osmotherapy

The reduction in ICP following mannitol administration has been well documented.<sup>8</sup> The mode of action has traditionally been ascribed to the osmotic diuretic effect by which water follows the osmotic gradient from the injured brain to vascular compartment across the blood-brain-barrier. Other postulated mechanisms of action include a free radical scavenging effect, volumetric augmentation and improved capillary flow due to the rheological properties of mannitol. Other osmotic agents such as hypertonic (7.5%) saline are also undergoing clinical trials to establish whether they have a validated therapeutic role in the management of raised ICP.

## Hypothermia

Hyperthermia increases the metabolic rate of brain tissue and is associated with a poorer outcome from head injury. However, a recent large multicentre randomised trial of hypothermia in the management of a heterogenous head injured population has not established a case for the widespread use of this therapy.<sup>9</sup> The selective use of hypothermia may be appropriate in some subgroups of patients, for example those with raised ICP.

## Refractory elevation of ICP

Refractory elevation of ICP can produce a stalemate situation during the intensive care management of head injured patients. Secondary insults such as hypoxia and hypovolaemia can lead to an acutely raised ICP and reduction in CPP that is life threatening. A therapeutic decompressive craniectomy increasing the volumetric capacity of the cranial cavity can significantly reduce the ICP and may be beneficial in this group of patients.<sup>10</sup> The RESCUE trial is evaluating this procedure.

Barbiturates reduce cerebral metabolic demand and it has been postulated reduce cytotoxic oedema. However, their use is controversial with a poorly defined evidence base.<sup>11</sup> Thiopentone is cardiotoxic and induces a prolonged comatose state that precludes clinical assessment of conscious level and makes treatment withdrawal a protracted issue. To avoid inappropriate use, an infusion is only considered if ICP elevation is refractory and a reduction in ICP is observed after administering a test dose.

## Outcome after head injury

### Neuropsychological deficits

Survival with moderate or severe disability is common after all grades of head injury. Even after mild injury 47% of patients have disabling persistent neuropsychological deficits.<sup>12</sup> Frontal lobe dysfunction occurs most commonly resulting in loss of motivation and drive, increased fatigability, concentration and attention deficits, defective problem solving and impaired cognitive endurance. Coupled with a lack of insight and loss of social judgement severe social handicap can result. Temporal lobe damage causes memory deficits, word finding difficulties, irritability, mood lability, depression, anxiety and a loss of self-esteem. SSRIs may be useful in managing these complications. Unfortunately only a minority of these patients receive help from a specialist in rehabilitation, a clinical neuropsychologist or social services. Improved provision of rehabilitation facilities is needed to minimise the cognitive and social sequelae of injury. Assessment of rehabilitation needs is required at an early stage by all patients with intermediate and severe head injuries and transfer to a well-resourced rehabilitation centre with physiotherapy, speech and language therapy, occupational therapy and neuropsychology is appropriate when patients are medically and surgically stable. Although some severely disabled or vegetative patients will ultimately require transfer to a nursing care facility such a decision should not be made precipitously.

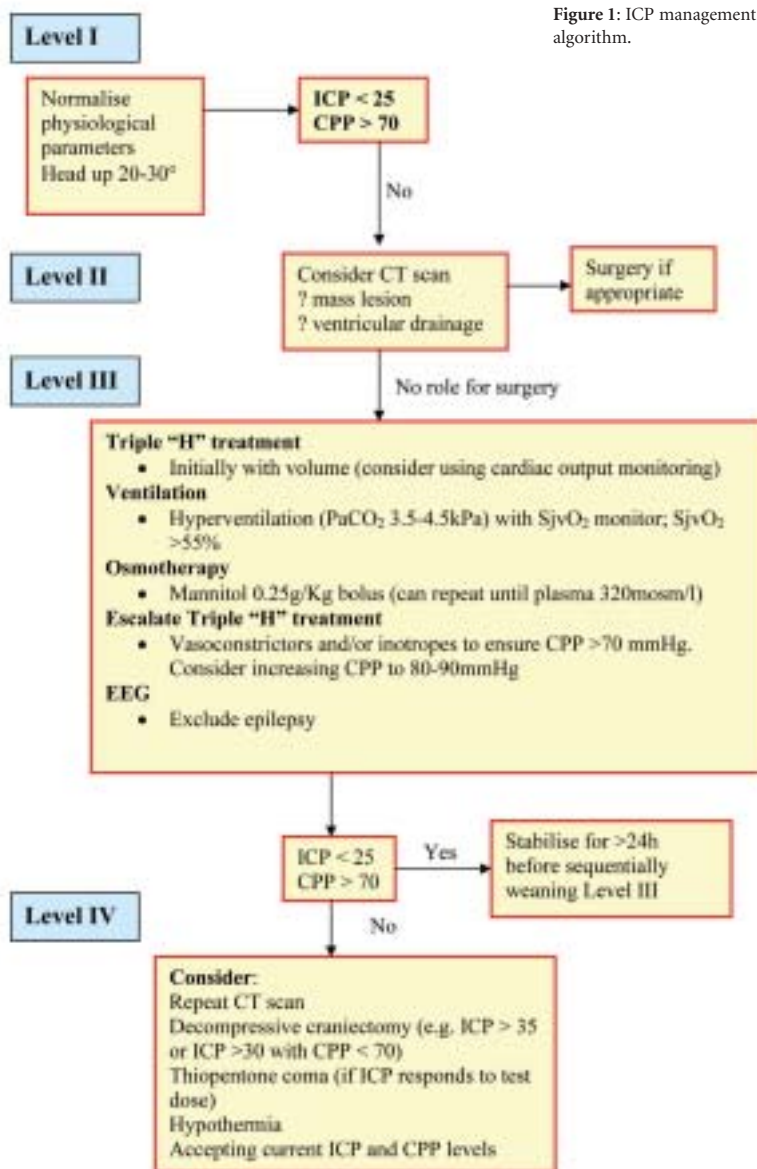


Figure 1: ICP management algorithm.



### Post-traumatic epilepsy

Ventilated head injured patients can sustain occult seizure activity that is a potential cause of raised intracranial pressure. EEG monitoring to exclude fits as a contributory factor is therefore appropriate in patients with refractory raised ICP.

Overall, up to 5% of patients sustain early post-traumatic epilepsy – defined as seizures within 1 week of injury. Usually such patients are administered intravenous phenytoin at, or soon after, the time of the fit. The majority of these patients do not develop long-term epilepsy and prolonged use of anticonvulsants is not beneficial.<sup>13</sup>

The incidence of long-term post-traumatic epilepsy is influenced by the type and severity of the brain injury. Depressed fractures with dural tears and intraparenchymal injuries are both associated with long-term epilepsy in over 25% of cases. 50% of these patients will have their first fit within 1 year of the injury with over 80% having fits within 4 years of the injury. However, a significant minority will sustain a first seizure more than decade after the trauma.<sup>14</sup> Established anticonvulsants such as sodium valproate or carbamazepine are appropriate first-line drugs in these patients.

### Care pathways

Standardisation of the care system for head injured patients requires a multi-faceted approach with an increase in resources. Renovation and expansion of accident and emergency departments with provision of observation beds has been recognised as a nationwide requirement and is underway. An improvement in the infrastructure of radiological departments, with fully staffed CT scanners and image transfer facilities, is required. More neurosurgical intensive care beds and

rehabilitation facilities are required in almost all regions. The health and social service departments must work in partnership to serve the needs of patients and their families. Continuing medical education programmes for doctors in all specialities that are involved in head injury care need to include sessions allocated to head injury management, to ensure improvements in management are incorporated into clinical practice.

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## Alzheimer's Disease: the reality behind the confusion

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## Traumatic Brain Injury - the Road to Recovery

Monday 6 December 2004

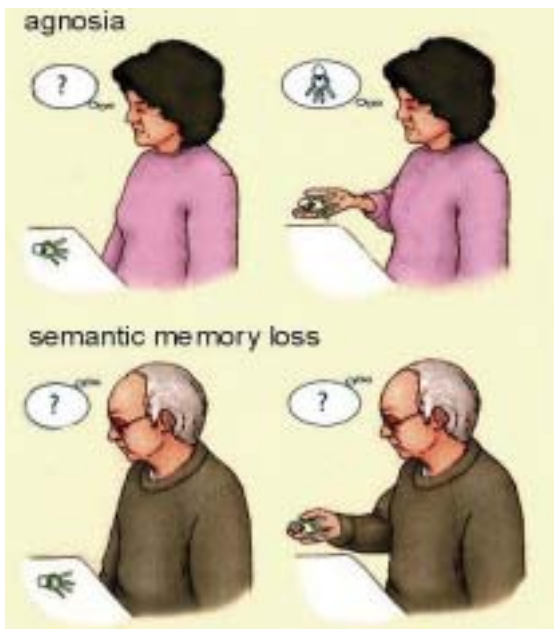
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This conference is timed around the publication of the National Service Framework (NSF) for Long Term Neurological Conditions. The programme is designed for a multi-disciplinary audience of doctors, nurses, professions allied to medicine and also for managers and commissioners of health and social services. It follows the patient journey from the acute injury to living with the long-term effects of brain injury and addresses some of the issues for implementation of the NSF to support people with brain injury and their families along to road to recovery.

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# Agnosia

**A**gnosia is a perceptual disorder in which sensation is preserved but the ability to recognise a stimulus or know its meaning is lost. Agnosia means “without knowledge”. Patients with agnosia cannot understand or recognise what they see, hear or feel. Agnosia results from lesions that disconnect and isolate visual, auditory and somatosensory input from higher level processing. Perceptual skills have a hierarchical and parallel organisation. The nature and severity of perceptual impairment depends upon modality affected and the level at which sensory processing has been interrupted. It is rare in its pure form. Less than one percent of all neurological patients have agnosia.<sup>1</sup> When assessing agnosia, it is important to establish that sensation is preserved; the patient is alert, intelligence is intact (or near intact) with no language or memory disorder. Examination involves assessing what the patient sees, hears or feels when presented with objects, pictures or sounds using a combination of clinical procedures and neuropsychological tests.



**Figure 1:** It is essential to rule out memory problems when diagnosing agnosia.

## Classification

Lissauer (1890) made a distinction between a deficit in the ability to perceive stimuli consciously and a deficit reflecting an inability to ascribe meaning to what is perceived, a disorder he referred to as *Seelenblindheit*, or “soul blindness”.<sup>2</sup> In current literature, a distinction is made between apperceptive agnosia and associative agnosia. Apperceptive agnosia describes a failure in object recognition primarily due to problems in early stage perceptual processing. Associative agnosia refers to a disorder when early stage perceptual processing is intact; the patient can develop a percept of an object but is unable to access memory or knowledge of the object. The object is perceived as an object but it has no meaning. Research has led to more refined taxonomies. Most cases of associative agnosia probably have deficits in early stage processing and perceptual and memory representations in object recognition are not clearly distinct.<sup>3,4</sup> Boundaries of apperceptive agnosia and associative agnosia are not as clear as once thought, although the classification remains useful. Agnosia is classified according to modality:-

- Visual
- Auditory
- Tactile

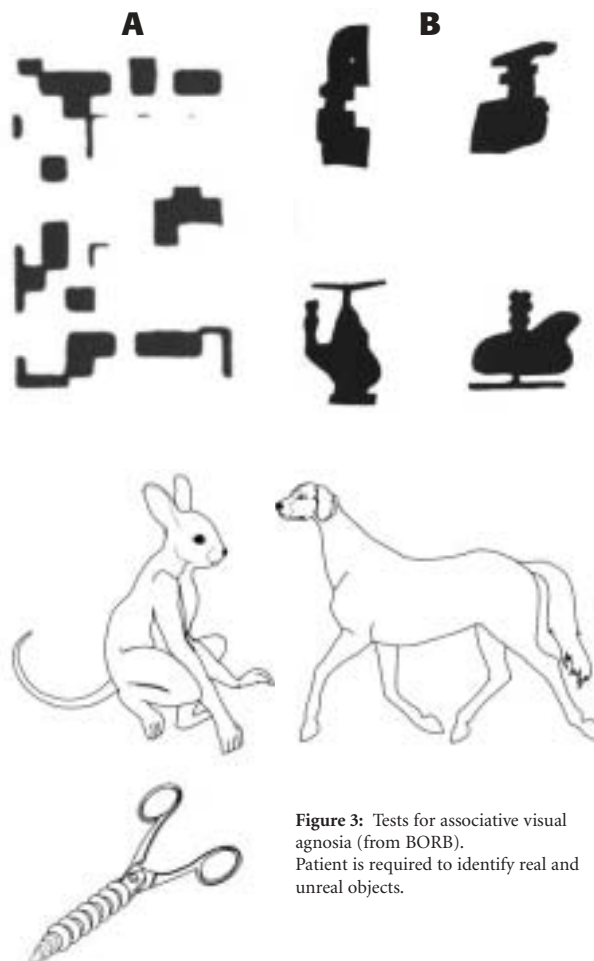
## Visual Agnosia

Visual agnosia is a deficit in object recognition confined to the visual modality, despite intact elementary visual processes and which is not due to problems in language, memory or intellectual decline. It is the most common and best understood form of agnosia. There are two broad categories; apperceptive visual agnosia and associative visual agnosia.

## Apperceptive Visual Agnosia

Apperceptive visual agnosia is characterised by an intact visual ability on a basic sensory level, but a defect in early stage visual processing prevents a correct percept of the stimulus being formed. The patient is unable to access the structure or spatial properties of a visual stimuli and the object is not seen as a whole or in a meaningful way. Stroke, anoxia and carbon monoxide poisoning are common causes and it is often associated with diffuse, posterior lesions. Patients fail tests such as visual matching, discriminating shapes, comparing similar figures and copying drawings. Useful tests are incomplete letters, object decision and silhouettes sub-tests from the Visual Orientation and Space Perception Battery (VOSP), the Gollin Figures and usual/unusual views test from Birmingham Object Recognition Battery (BORB).<sup>5,6</sup>

**Figure 2:** Tests for apperceptive visual agnosia (from VOSP); (a) incomplete letters (b) object decision; patient is shown four silhouette drawings and has to identify which one of the four is a real object.



**Figure 3:** Tests for associative visual agnosia (from BORB). Patient is required to identify real and unreal objects.



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### Associative Visual Agnosia

In associative visual agnosia, primary sensory and early visual processing systems are preserved. The patient can perceive objects presented visually but cannot interpret, understand or assign meaning to the object, face or word. Associative visual agnosia is usually the result of bilateral damage to the inferior temporo-occipital junction and subjacent white matter. The cause is most often infarction of the posterior cerebral artery bilaterally. Other causes include tumour, haemorrhage and demyelination. It is more common than apperceptive visual agnosia. Common sub-types are:-

- **Visual object agnosia**

Patients are able to copy objects and pictures, often with great accuracy, but do not recognise the objects or understand what they have drawn. This can be assessed by presenting the patient with pictures of objects and asking them to name, describe functions and sort according to use or category to which they belong. Analysis of errors will enable the examiner to exclude anomia and semantic memory problems, both of which can cause naming and recognition problems. For example, a patient with visual object agnosia will be unable to name or recognise a picture of a kangaroo. The same patient will have no difficulty naming and describing the characteristics of a kangaroo if requested via the auditory modality. Patients with anomia will be unable to name the picture and may respond, "it's found in Australia, it jumps...can't think of its name," demonstrating intact recognition. Patients with semantic dementia have central loss of knowledge and will be unable to name the picture or demonstrate any knowledge of the object regardless of modality. The Graded Naming Test provides a source of pictures of objects from different categories.<sup>7</sup> Useful tests are the real/unreal object test from the Birmingham Object Recognition Battery and The Pyramid and Palm Trees test, a matching test that requires the patient to select one of two pictures connected with the target picture.<sup>8</sup> Verbal content is minimal making it suitable for patients with aphasia.

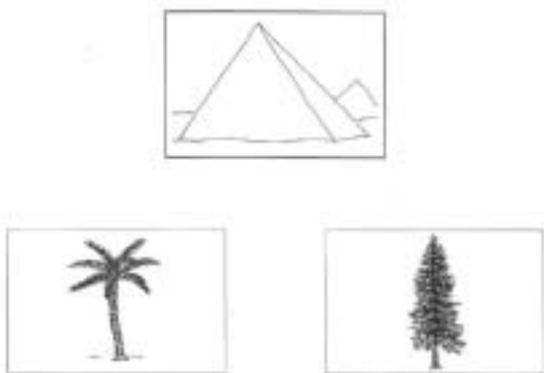


Figure 4: Pyramids and Palm Trees Test. Assesses ability to access meaning from words and pictures.

- **Simultanagnosia**

Simultanagnosia is characterised by an inability to perceive more than one aspect of a visual stimulus and to integrate visual detail into a coherent whole. For example, if a patient with simultanagnosia is asked to name a picture of spectacles, they may respond "there is a circle, another circle, it is joined by a cross piece – it must be a bicycle!" If the same task was given to a patient with severe apperceptive visual agnosia, the patient would be unable to perceive the constituents of the picture such as the circle. Balint's syndrome is a rare disorder consisting of the triad of simultanagnosia, gaze apraxia, and optic ataxia. It is caused by bilateral occipitoparietal lesions. The patient

may appear blind, bumping into walls and furniture, making haphazard and uncoordinated movements in attempting to reach for objects. If asked to focus on a small visual area, the patient may describe this accurately and in great detail.

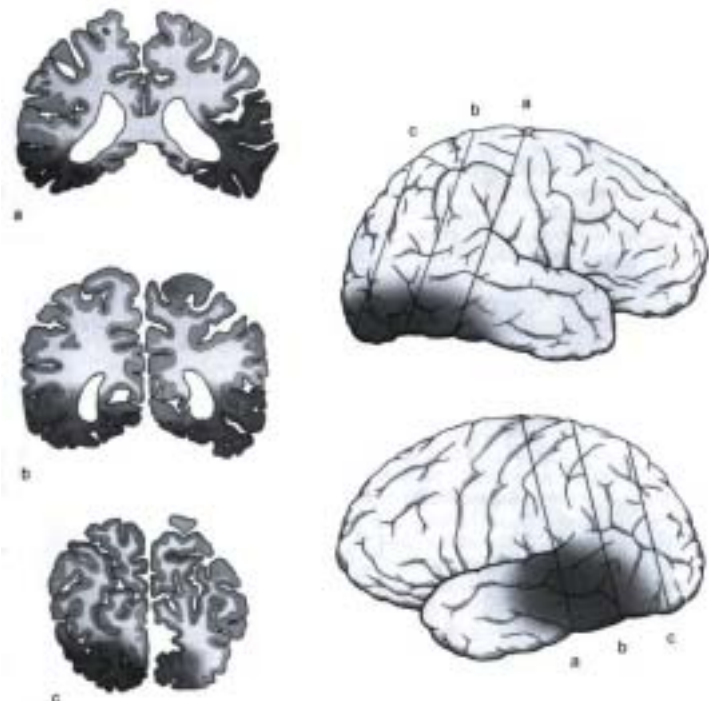
- **Category specific agnosia**

Impaired recognition of objects within a certain category.<sup>9</sup> Studies have reported selective recognition deficits in categories including animate vs. non-animate, living vs. non-living, metals, fruit, vegetables and musical instruments. Artefacts caused by poor matching of picture sets on variables such as familiarity, task difficulty and complexity complicate interpretation.<sup>10</sup>

- **Prosopagnosia**

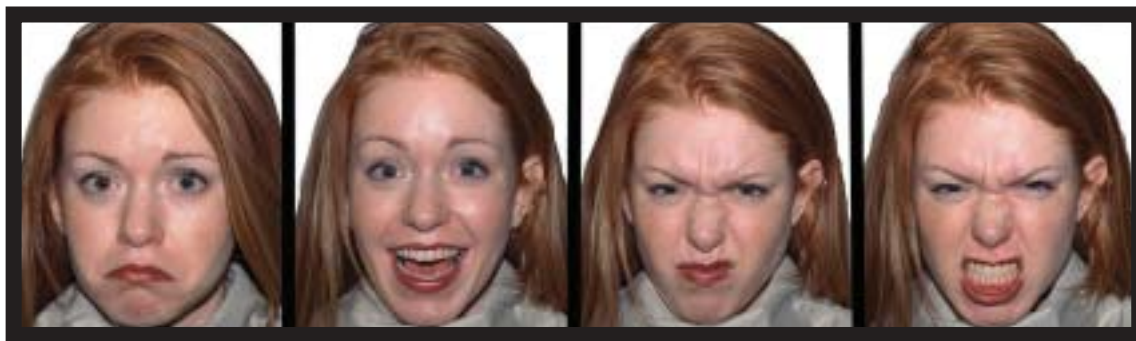
Prosopagnosia is a disorder of face recognition. Patients can identify facial parts, recognise a face as a face but with no recognition of the person. In severe cases, patients cannot recognise their own face. Affected people can use cues such as hairstyle, glasses and clothing and will recognise the person as soon as they speak. It can be acquired or developmental. Lesions causing prosopagnosia usually occupy the bilateral inferomesial visual association cortices and subjacent white matter. Prosopagnosia may occur in isolation suggesting that there are specific areas of the brain that process visual information pertaining to face recognition. Disorders in face recognition can be assessed with the Benton Facial Recognition test and informally using photographs of well-known politicians and celebrities, ensuring that the photographs are culturally and age appropriate.<sup>11,12</sup> The ability to recognise emotional expression may be dissociated from the ability to identify faces. Deficits in recognition of facial emotional expression have been reported following amygdalotomy.<sup>13</sup>

Figure 5: Region of brain lesions (shaded area) in a patient with prosopagnosia.



- **Pure alexia**

Also known as alexia without agraphia or pure word blindness. Pure alexia is a perceptual disorder causing impairment in reading words and letters. The patient can copy words and letters and in the act of copying the words or tracing out the letters will recognise the word or letter. The patient can write to dictation but is unable to read back what has been written.



**Figure 6:** Patients with damage to the amygdala have difficulties in recognising emotion from facial expression.



**Figure 7:** A sheep farmer with prosopagnosia failed a facial recognition test in which he had to identify a familiar face (Norman Tebbit) from unfamiliar faces. In contrast, he was able to recognise familiar and unfamiliar sheep.<sup>16</sup>

● **Colour agnosia**

Loss of colour knowledge. Patients find it difficult to colour black and white drawings of objects. For example, they may colour an apple blue.

**Auditory agnosia**

Inability to appreciate meaning of sound despite normal perception of pure tones. Non-verbal and verbal forms may exist independently or may co-exist. Audiological assessment is required.

● **Non-verbal auditory agnosia**

Impaired understanding and recognition of non-linguistic sounds such as bells, whistles or animal noises. It is associated with right temporal or parietal lobe lesions or bilateral lesions of the auditory association cortex.

● **Pure word deafness**

Inability to comprehend spoken language despite normal hearing and no aphasia. Patients can copy and write spon-

taneously, follow written commands but cannot write to dictation and are impaired on word repetition tasks. It is caused by lesions that disconnect Wernicke's area from auditory input.

● **Amusia**

Impairment in musical expression or perception. It is highly dependent upon culture, environment and individual experience and may be unnoticed. There is a loss in the ability to sing, hum or whistle and no recognition or emotional response to music. Anatomical correlates are multiple. Patients with aphasia can often sing and this supports a role of the right hemisphere in musical expression. Assuming the examiner has the necessary musical skill, it can be assessed informally by humming or whistling familiar melodies such as "Happy Birthday" or by using formal tests.<sup>14</sup>

**Tactile agnosia**

Selective impairment of object recognition by touch despite relatively preserved primary and discriminative somesthetic perception. It is a unilateral disorder usually resulting from lesions of the contralateral inferior parietal cortex. The ability to recognise basic features such as size, weight and texture may be dissociated from the ability to name or recognise the object.<sup>15</sup>

**Treatment and recovery**

In the early stages of recovery, lack of awareness of the deficit, anosognosia, may lead to therapeutic resistance. Partial recovery is more likely in traumatic and vascular lesions and less likely in anoxic brain damage due to widespread diffuse lesions and additional cognitive impairment impeding acquisition of compensatory strategies. Controlled treatment studies are rare. Many case reports show improvement following intensive rehabilitation. Principles of treatment are restitution, repetitive training of impaired function, and compensation, with utilisation of spared function to compensate for the deficit.

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# Inflammatory Disease of the CNS III: Sarcoidosis and Non-neoplastic Diseases Associated with Neoplasia

In contrast to the previous articles on the neuropathology of organism-related disorders, this article deals with inflammatory diseases that are not, as far as it is known, due to infections, but are most likely mediated by aberrant immune host reactions. Neurosarcoidosis should be regarded as a granulomatous, probably hyperimmune, inflammatory disorder, whereas paraneoplastic syndromes are associated with the presence of a variety of tumour-related antibodies and give rise to a wide range of clinical presentations.

## Neurosarcoidosis

Sarcoidosis is an inflammatory granulomatous disorder affecting virtually all organs, particularly the lungs. The nervous system, both central and peripheral, is involved in 5-15% of patients.<sup>1</sup> Ante-mortem diagnosis is possible only in 50% of cases.

It occurs world-wide, in all races, both sexes and at all ages (usually between 20 and 40 years) and is considered the second commonest respiratory disease in young adults after asthma. Its prevalence has been estimated at 50/100000 and it is most common among Black North Americans and in northern Europe.<sup>2</sup>

Although the aetiology of sarcoidosis remains unknown, there are data supporting the role of environmental factors in genetically susceptible individuals, who would respond with an unusually strong Th1-immune reaction.<sup>2</sup> The lymphocytes taking part in the reaction are phenotypically CD4 helper and produce cytokines. Possible environmental factors include infections (in particular *Mycobacterium tuberculosis*) as well as exposure to various chemicals (pesticides and insecticides), pine pollen, silica, talc, metal dusts and artificial fibres. The existence of a few clusters of disease within families further supports a genetically-related mechanism.

## Clinical syndromes

Neurosarcoidosis can present with various clinical forms, depending on its localisation and speed of progression.<sup>1</sup> As a general rule, the course is slow, with relapses and remissions. On the other hand, less frequently, the disorder can progress to death within a few weeks. Clinically, neurosarcoidosis can present with involvement of the cranial, or peripheral, nerves, meningitis, diffuse brain or spinal lesions responsible for seizures, psychiatric symptoms or various forms of paralysis.<sup>3</sup>

1. The form with involvement of single or multiple cranial nerves carries the best prognosis and the facial nerve is the most commonly affected.<sup>1</sup> Involvement of the optic nerve can be uni- or bilateral and chronic progressive, responding poorly to steroids, or acute and with a good response. Papilloedema is a relatively common complication, particularly in young women. Heerfordt's syndrome, suggestive of sarcoidosis and involving the cranial nerves, most commonly the facial, is characterised by uveitis, swelling of the parotid gland and fever. On the other hand, peripheral neuropathy is definitely rare and can affect large or, more commonly, small, including autonomic, fibres.
2. Meningitis may appear in acute or chronic forms. When localised to the basal regions, it accounts for

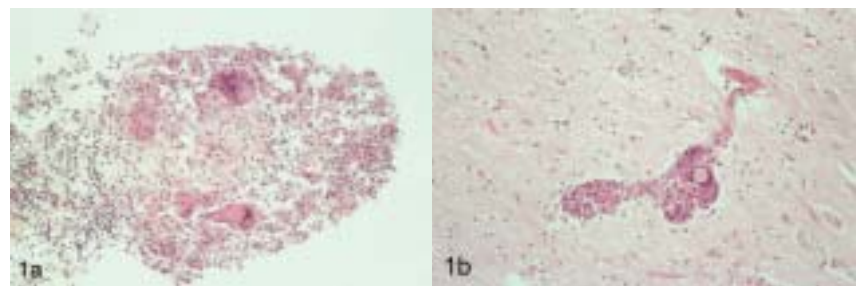
involvement of the cranial vessels. Acute forms respond favourably to steroid treatment; the chronic variant may recur. Hydrocephalus can result from obstruction of the foramina by the inflammatory process.

3. Brain involvement results from the presence of smaller or, more rarely, larger granulomas in the extra-subdural localisation or within the brain tissue itself;<sup>4</sup> resulting symptoms are similar to those of any other space-occupying lesion with the same localisation. The most common brain localisation is in the hypothalamus and pituitary gland, resulting in endocrine disturbances. Granulomas can extend to the vessels, resulting in granulomatous angiitis and cerebral infarcts from vascular obstruction.
4. Spinal sarcoidosis may present as arachnoiditis, extra- or intra-medullary lesions, the latter being an extremely rare complication. Unfortunately granulomas in this location cannot be distinguished clinically and radiologically from neoplasms. Patients can present with a transverse myelopathy or radicular or cauda equina syndromes.
5. Neurosarcoidosis may be responsible for the appearance of seizures or psychiatric conditions.

## Neuropathology

Microscopic diagnosis requires the presence of the sarcoid granuloma. In its active stage, it shows a core of epithelioid and multinucleated giant cells (Fig. 1a), surrounded by B and T lymphocytes, mononuclear cells and fibroblasts. A chronic granuloma is characterised by fewer T cells. A feature distinguishing this from tuberculous granuloma is an area of central necrosis, typically present in the latter. Admittedly a small necrotic centre can be seen also, albeit uncommonly, in sarcoidosis. However, in this case it does not present the caseous appearance seen in tuberculosis.

Granulomas, localised predominantly in the leptomeninges, may extend to the intraparenchymal perivascular spaces and to the brain tissue (Fig 1b). They may be confluent and form tumour-like masses surrounded by an astrocytic reaction. Involvement of the ventricles is known. Granulomatous vasculitis with the possibility of vascular complications has already been mentioned above.



**Figure 1: Sarcoidosis**

(a) Sarcoid granuloma of the leptomeninges. Note its central core of epithelioid cells, the peripheral halo of small inflammatory cells, the multinucleated giant cell and the absence of any necrosis (H&E). (b) Granulomas of variable size may be seen within the brain parenchyma; small ones may be circumscribed to the perivascular spaces (H&E).

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**Laboratory diagnosis, neuroradiology and treatment**

The diagnosis of sarcoidosis can be established according to the criteria laid down by Baughman et al:<sup>5</sup> 1) presence of a granulomatous lesion not showing tuberculous, mycotic or neoplastic features or any other causes in a patient with clinical signs supporting this disease; 2) in the absence of biopsy, a diagnosis of bilateral hilar adenopathy on chest X-ray, erythema nodosum, uveitis and maculo-papular skin lesions support this diagnosis.

Neuroradiology and CSF abnormalities do not provide the best diagnostic support for neurosarcoidosis as their findings are non-specific. The latter shows pleocytosis, high protein content and, in some instances, mildly decreased glucose levels. Kveim and diagnostic support may be provided by Mantoux tests and hypercalcaemia.

Treatment consists of steroids or, if steroid sparing agents are required or steroids are contraindicated, then cytotoxic drugs may be needed.<sup>3</sup>

**Paraneoplastic neurological syndromes**

The term paraneoplastic neurological syndromes (PNS) encompasses a number of uncommon disorders associated with systemic malignancies. The definition of PNS requires that malignancies should not invade, compress or metastasise to the nervous system to produce their neurological effects. The identification of these disorders dates to the first half of the past century.<sup>6</sup> A breakthrough<sup>7</sup> consisted in the identification in the serum and CSF of patients with PNS of auto-antibodies reacting both with the tumours and the central nervous system.

The incidence of these syndromes, first estimated at around 25 to 66%, was subsequently established between 0.31 and 1%.<sup>8</sup>

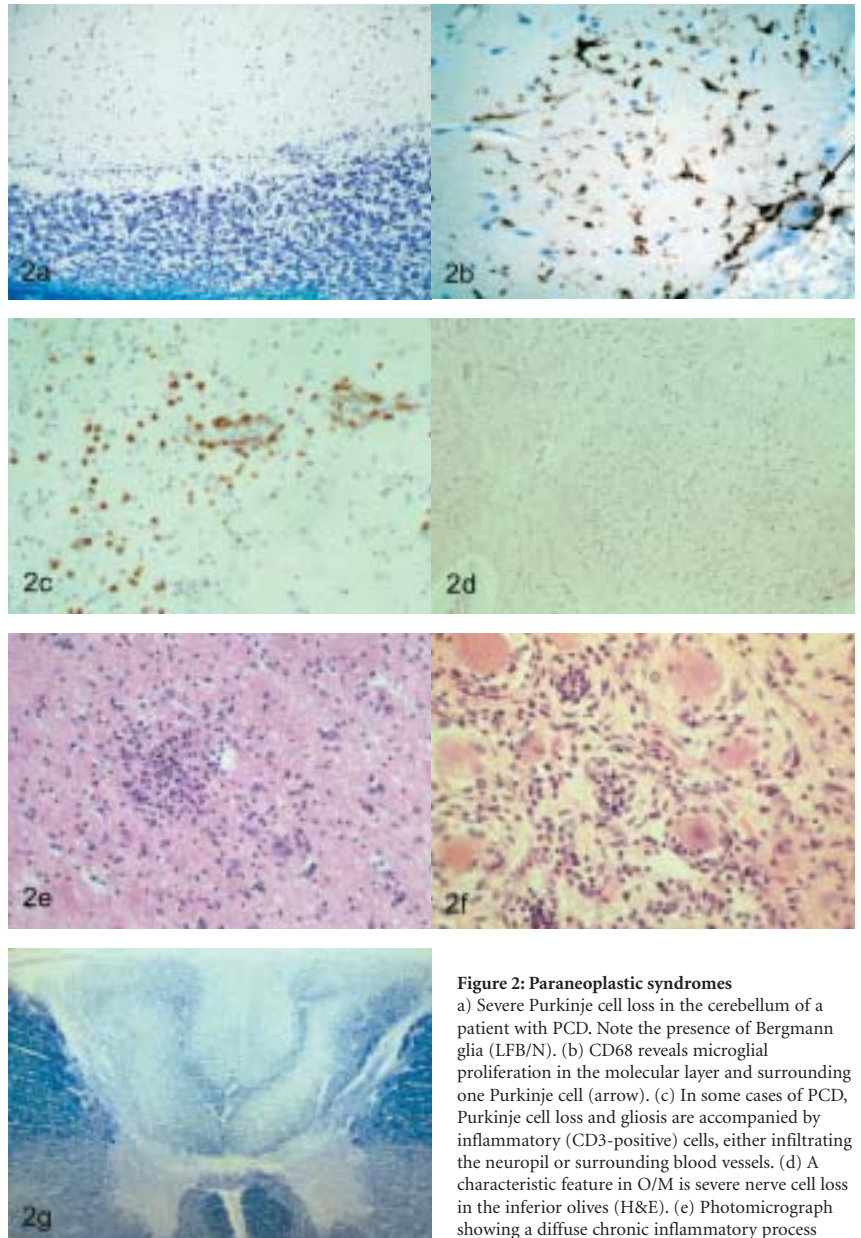
When considering paraneoplastic disorders, the following points should be taken into consideration:

1. correlation between the type of neoplasm and the neurological syndrome is not absolute;
2. in some syndromes both gross and histological abnormalities may be absent;
3. they may become clinically manifest before, or at the same time as the discovery of the neoplasm;
4. their outcome is almost invariably fatal.

For the purpose of this review, these syndromes are classified according to their pathological appearance. They can involve 1) the CNS; 2) the peripheral nervous system; 3) both these systems; 4) the neuromuscular junction (see table).

**Table 1 Classification of Paraneoplastic neurological syndromes**

1) Involving the CNS	<ul style="list-style-type: none"> <li>• Paraneoplastic cerebellar degeneration</li> <li>• Opsoclonus-myoclonus</li> <li>• Retinopathy</li> </ul>
2) Involving the peripheral nervous system	<ul style="list-style-type: none"> <li>• Sensory-motor neuropathy</li> <li>• Autonomic neuropathy</li> </ul>
3) Involving both systems	<ul style="list-style-type: none"> <li>• paraneoplastic encephalomyelitis/</li> <li>• sensory neuropathy</li> </ul>
4) Involving the neuromuscular junction	<ul style="list-style-type: none"> <li>• Lambert-Eaton myasthenic syndrome (LEMS)</li> </ul>



**Figure 2: Paraneoplastic syndromes**

a) Severe Purkinje cell loss in the cerebellum of a patient with PCD. Note the presence of Bergmann glia (LFB/N). (b) CD68 reveals microglial proliferation in the molecular layer and surrounding one Purkinje cell (arrow). (c) In some cases of PCD, Purkinje cell loss and gliosis are accompanied by inflammatory (CD3-positive) cells, either infiltrating the neuropil or surrounding blood vessels. (d) A characteristic feature in O/M is severe nerve cell loss in the inferior olives (H&E). (e) Photomicrograph showing a diffuse chronic inflammatory process involving the grey matter (H&E).

(f) Similar changes are seen in affected dorsal root ganglia. Note one nodule of Nageotte replacing a disappeared neurone (H&E). (g) Degeneration of dorsal root fibres following dorsal root ganglion cell loss in paraneoplastic ganglionitis results in pallor of the dorsal columns of the spinal cord (LFB/N).

**Clinico-pathological subtypes of paraneoplastic disorders****Paraneoplastic cerebellar degeneration (PCD)**

The neurological disorder usually precedes the discovery of the neoplasm, is characterised by incoordination of gait, dysarthria and often nystagmus. Though associated with any type of malignancy, gynaecological tumours are the commonest, followed by lung tumours (especially small cell) and lymphomas of the Hodgkin type.

“Neurosarcoidosis occurs world-wide, in all races, both sexes and at all ages (usually between 20 and 40 years). Sarcoidosis is considered to be the second commonest respiratory disease in young adults after asthma.”

Macroscopically, the cerebellum may appear globally atrophic. The salient histological finding is a severe Purkinje cells loss (Fig. 2a) with preservation of baskets. There may be axonal swelling, microglial proliferation (Fig. 2b), hyperplasia of the Bergmann glia and decreased numbers of granule cells. Degeneration may be associated with lymphocytic infiltration of the leptomeninges and perivascular spaces (Fig. 2c).

*Paraneoplastic opsoclonus-myoclonus (O/M)*

It occurs in association with neuroblastoma in children and with a number of tumours in adults. Patients present with ataxia and myoclonus of the head, palate, trunk, limbs, head and diaphragm. Although it occurs only in 2% of the children with neuroblastoma, 50% of those with this disorder have neuroblastoma.

Neuropathological changes go from being completely absent in some patients, to complete loss of olivary neurones in others (Fig. 2d) and the presence of small inflammatory cells in the periaqueductal grey matter.

*Paraneoplastic retinopathy*

It is a rare disorder characterised by a triad of symptoms: severe photosensitivity, scotomatous visual loss and attenuation in calibre of the retinal arterioles. The commonest neoplasm (90%) is small cell cancer of the lung, followed by melanoma, breast and prostate carcinoma and uterine sarcoma.

Changes of the eye include diffuse degeneration of photoreceptor cells with relative sparing of cones, almost complete cell loss of the outer molecular layer and presence of melanin-laden macrophages in the outer retinal layer. The other retinal layers and the optic nerve are preserved.

*Peripheral neuropathy*

Denny-Brown (1948)<sup>9</sup> established the relationship between peripheral neuropathy and carcinoma; although the incidence of this syndrome is difficult to establish.<sup>8</sup> The majority of patients with this syndrome have lung cancers; however GI tract, breast, uterus and prostate may also be implicated.

Clinically, peripheral neuropathies are subdivided into sensory, sensory-motor and autonomic, mixed forms being more common than pure ones.

Neuropathological changes include axonal degeneration, segmental demyelination, sometimes with onion bulb formation. A perivascular lymphocytic component

may extend to the dorsal root ganglia (DRG). Discrete degeneration of the DRG and posterior columns and anterior horn cells has been reported.

*Paraneoplastic encephalomyelitis/sensory neuropathy (EM/SN)*

The disorder appears in association with any form of carcinoma; however a bronchial carcinoma of the small cell type was detected in 77% of the patients.<sup>10</sup>

The pathological process underlying this syndrome is of a polioencephalomyelitis (Fig. 2e) in the central and a ganglioradiculoneuritis (Fig. 2f) in the peripheral nervous system with neuronal cell loss and microglial hyperplasia and reactive gliosis. As symptoms vary, according to the distribution of the lesions, the following clinicopathological forms have been defined:

1. Limbic encephalitis presents with hallucinations, abnormal behaviour, fits and loss of recent memory. Pathological changes are seen in the hippocampus, cingulate gyrus, pyriform cortex, frontal orbital region of the temporal lobe, insula and amygdala.
2. Brain stem encephalitis can pose considerable diagnostic problems with other disorders involving the brain stem, in particular vascular and motor neurone disease, MS, infectious and inflammatory disorders and intrinsic tumours.
3. Myelitis presents as poliomyelitis involving both anterior and posterior horns and involving variable number of spinal segments. The existence of a pure form of motor neurone disease (MND) is debated;<sup>10</sup> however, the discovery of specific autoantibodies associated with MND suggests that further studies may shed light on this issue.
4. Ganglio-radicle neuritis and autonomic neuropathy may present in isolation or associated with lesions of the CNS. Involvement of the ganglia may be selective and symmetrical, or diffuse and result in degeneration of the dorsal columns of the spinal cord (Fig. 2g). Disappearance of DRG is accompanied by an increase of nodules of Nageotte; the remaining neurones may show cytoplasmic vacuolation, chromatolysis and nuclear shrinkage. Inflammation appears as diffuse

Antibody	Clinical syndrome	Ca. most frequent	IHC	Western blotting	Antigen
Anti-Hu/ ANNA-1	EM/SN	Small, non-small lung Ca.	Staining of all neuronal nuclei; less perikarya	35-40 kDa	Neuron specific RNA binding proteins
Anti-Yo/ PCA-1	Acute/subacute cerebellar syndrome	Ovarian, breast, uterus	Purk cell cytoplasm, coarse	34 and 62kDa in Purkinje cells	DNA binding, gene transcription regulators
Anti-Tr	Slowly progressing cerebellar syndrome	Hodgkin's disease	Purkinje cell cytoplasm, coarse	No protein detected yet	Not known
Anti-Ri/ ANNA-2	O/M	Breast, small cell lung	All CNS nuclei	55 and 80 kDa protein NOVA	RNA-binding protein
Anti-amphiphysin	Stiff Person syndrome	Breast	Synapses of CNS neurones	128 kDa neuronal pr.	Amphiphysin in synaptic vesicles
Anti-VGCC	LEMS	Small cell lung Ca.	Presynaptic	VGCC	ACh release
Anti-Ta	Limbic encephalitis	Testicular Ca.	Nuclei, perikarya	40 kDa	Unknown

EM/SN - Paraneoplastic encephalomyelitis/sensory neuropathy • O/M - Paraneoplastic opsoclonus-myoclonus • LEMS - Lambert-Eaton myasthenic syndrome



# Mestinon in Myasthenia Gravis:



Are your patients getting the most out of Mestinon?

- Mestinon is known as the 1st-line symptomatic treatment for Myasthenia Gravis<sup>1-4</sup>

However:

- Optimum efficacy can only be achieved if your patient takes Mestinon **FREQUENTLY** throughout the day<sup>2,5</sup>

Half-life = 3-4 hours

Dosing = 5-6 times a day

**FREQUENCY MATTERS**

## Prescribing Information

**Presentation:** Each tablet contains 62.5mg pyridostigmine bromide (equivalent to 60.0mg of the base). **Indications:** Myasthenia Gravis, paralytic ileus and post-operative urinary retention. **Dosage and Administration: Myasthenia Gravis** – Adults – Doses of 30 to 120mg are given at intervals throughout the day. The total daily dose is usually in the range of 5-20 tablets. **Children** – Children under 6 years old should receive an initial dose of half a tablet (30mg) of Mestinon; children 6-12 years old should receive one tablet (60mg). Dosage should be increased gradually, in increments of 15-30mg daily, until maximum improvement is obtained. Total daily requirements are usually in the range of 30-360mg. The requirement for Mestinon is usually markedly decreased after thymectomy or when additional therapy is given. When relatively large doses of Mestinon are taken by myasthenic patients, it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects. It should be noted that the slower gastrointestinal motility caused by these drugs may affect the absorption of Mestinon. In all patients the possibility of "cholinergic crisis", due to overdose of Mestinon, and its differentiation from "myasthenic crisis" due to increased severity of the disease, must be borne in mind. **Other indications: Adults** – The usual dose is 1 to 4 tablets (60-240mg). **Children** – 15-60mg. The frequency of these doses may be varied according to the needs of the patient. **Elderly** – No specific dosage recommendations. **Contra-indications, Warnings etc: Contra-indications** – Gastro-intestinal or urinary obstruction, known hypersensitivity to the drug and to bromides. Extreme caution is required when administering Mestinon to patients with bronchial asthma. **Warnings** – care should also be taken in patients with bradycardia, recent coronary occlusion, hypotension, vagotonia, peptic ulcer, epilepsy or Parkinsonism. Lower doses may be required in patients with renal disease. **Use in pregnancy:** The safety of Mestinon during pregnancy or lactation has not been established. Experience with Mestinon in pregnant patients with Myasthenia Gravis has revealed no untoward effects. Negligible amounts of Mestinon are excreted in breast milk but due regard should be paid to possible effects on the breast-feeding infant. **Side effects:** These may include nausea and vomiting, increased salivation, diarrhoea and abdominal cramps. **Drug interactions** – None known. **Pharmaceutical Precautions:** **Storage** – Recommend maximum storage temperature 25°C. Protect from light and moisture. **Legal Category:** POM. **Package Quantities:** Amber glass bottles with aluminium screw caps and desiccant, containing 200 tablets. **Basic NHS Price:** £50.15. **Product Licence Number:** PL 15142/0006. **Product Licence Holder:** Valeant Pharmaceuticals Limited, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire RG24 8WD Telephone: +44 (0)1256 707744 e-mail: sales@valeant.com Internet: www.valeant.com **Date of Preparation:** August 2004.

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lymphocytic infiltration or cuffing of the vessels and may extend to the roots.

#### Paraneoplastic syndromes and auto-antibodies

Although the role of antibodies in the pathogenesis of the various syndromes is still unclear (anti-Hu antibody was also detected in patients with Sjögren syndrome), their detection is a useful tool both in the diagnosis of the disorders and for giving clues in the search for the neoplasm. Table 2<sup>e</sup> provides a list of antigens and antibodies so far identified. Three antibodies (anti-Hu, -Yo and P/Q voltage-gated calcium channels – VCGG) have been observed in a large series of patients and their predictive clinical value is now well established.

#### Lambert-Eaton myasthenic syndrome (LEMS)

Patients with this disorder complain of weakness and fatigue, particularly in the proximal limbs, whereas ocular symptoms are less obvious than in myasthenia gravis and autonomic symptoms are present.<sup>11</sup>

Neuropathology is limited to the neuromuscular junction which shows reduced numbers and disorganisation of motor nerve terminal active-zone particles, probably representing calcium channels involved in the release of ACh.

#### Pathogenetic mechanism in paraneoplastic disorders

The role of antibodies in paraneoplastic disorders has been demonstrated conclusively only in Lambert-Eaton myasthenic syndrome.<sup>12</sup> These patients develop antibodies against the P/Q-type voltage gated calcium channels (VGCC) located at the pre-synaptic level of the neuromuscular junction. They block the entry of calcium necessary for the release of quanta of acetylcholine resulting in neuro-muscular weakness.

On the other hand, in some paraneoplastic disorders there is circumstantial evidence supporting a pathogenetic role for T-lymphocytes: 1) presence of intense inflammatory infiltrates of mononuclear cells including CD4 and CD8; 2) the presence of cytotoxic and memory helper T-cells; 3) the presence, within tumours of patients with paraneoplastic disorders, of MHC class I and II antigens.

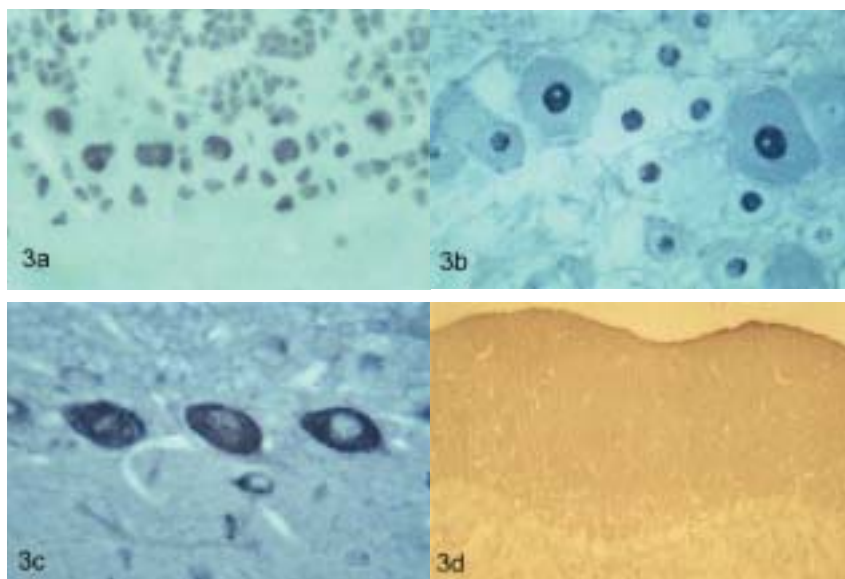
However, it is also possible that these disorders may result from non-immune mediated mechanisms. These include: 1) synthesis of hormone-like substances; 2) competition for substrate between the tumour and the nervous system; 3) secretion of cytokines by the tumour or by the inflammatory infiltrates.<sup>13</sup>

#### Treatment of paraneoplastic disorders

When the issue of the treatment of these disorders is considered<sup>6</sup> the following facts have to be taken into consideration:

1. In most of these patients in whom antibodies can be detected, the tumour is usually small and its progress follows a rather indolent course;<sup>14</sup>
2. Spontaneous regression has been described with small cell lung carcinoma in patients with antibodies<sup>15</sup> and neurological improvement without treatment has been reported.<sup>16</sup>

In paraneoplastic encephalomyelitis with cerebellar degeneration, disappointing results were obtained using various immunosuppressive strategies, such as steroids, plasmapheresis and intravenous immunoglobulins. On the other hand improvement of neurological symptoms



**Figure 3: Paraneoplastic syndromes**

a) & b) Nuclear staining by anti-Hu antibodies of cerebellar and dorsal root ganglion cells. c) Nuclei of Purkinje cells stained by anti-Yo antibody, which also stains nuclei of dorsal root ganglion cells. Only the former are stained by anti-Ri antibodies. d) Anti-amphiphysin antibody stains diffusely the cytoplasm of the cerebellar cortex.

has been obtained in LEMS or in O/M from the treatment of the underlying tumour or by the reduction of the antibody titre with plasmapheresis or intravenous immunoglobulins.

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## Acute Stroke Treatment, Second Edition

This is one of those books in which the chapters are written by multiple contributors - predominantly from the USA and Europe. It covers the "Present Stage" of acute stroke treatment and has "A Look at the Future". The problem with any volume such as this is that it is bound to have a limited lifespan but for the next few years at least it will serve as a pretty creditable attempt to cover the basic issues in stroke care and also some of the more esoteric ones. In some ways it is concerned with acute assessment as well as treatment.

There is an excellent chapter on the often neglected and overlooked behavioural issues affecting the acute stroke patient. Although not specifically addressing their treatment this section at least highlights their existence and discusses lesion location. The Allen Score (!) makes a comeback in the section on clinical scales - here the authors refreshingly admit that no scoring system has ever proved more accurate than sound clinical judgement, although of course they are a necessary tool for clinical trials.

Imaging concentrates on CT with MRI techniques - some of which are now part of accepted clinical practice eg DWI - relegated to only a couple of pages. The sections on the general early management and possibilities for intensive stroke care are comprehensive if a little dogmatic. On thrombolysis

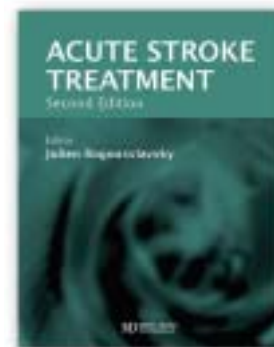
the evidence for intravenous and intraarterial delivery is well presented, although perhaps not in a questioning or critical way. For instance the licensing for rt-Pa being on the basis of one trial, the neutrality of other rt-Pa studies (and the possible reasons why), the pitfalls of post-hoc subgroup analyses, the continuing uncertainties are all rather glossed over.

Some aspects of haemorrhagic stroke and subarachnoid haemorrhage are covered. However the ISAT trial is missing as is STICH. This section of the book is therefore out of date already.

The "Look at the Future" includes what is already current by summarising existing guidelines but does also speculate on the future of neuroprotection (perhaps in conjunction with thrombolysis), gene therapy and cell therapy.

There are bound to be weaknesses in this type of book but as a neurologist with a vascular interest I would wish to have a personal copy. Neurologists with other areas of specialist interest would also learn plenty from it but perhaps they could access it from the department library rather than their personal bookshelf.

*Peter Martin, Addenbrooke's Hospital,  
Cambridge.*



Edited by: J Bogousslavsky  
ISBN: 1-84184-078-5  
Publisher: Martin Dunitz  
Price: £75

## Plasticity in the Human Nervous System: Investigations with Transcranial Magnetic Stimulation

Readers of ACNR will be very familiar with the growing interest in plasticity of the nervous system and the implications for normal development, learning and repair after injury. Transcranial Magnetic Stimulation (TMS) has become established as one of the more important techniques for studying plasticity directly in humans alongside MEG and functional imaging. Unlike these latter modalities, however, TMS has the potential to modify plasticity actively and thus be used (eventually) therapeutically. Typically an electrical current pulse is passed through a figure-of-eight coil held over the cortex in an awake subject. This induces a magnetic field which is relatively unaffected by scalp and skull structures, which in turn induces current flow in underlying neurones, resulting in depolarisation and generation of action potentials.

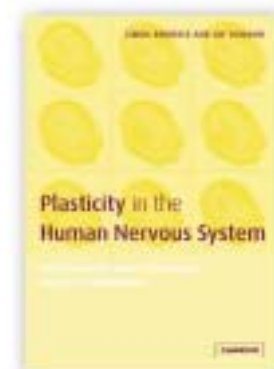
As a relatively painless and non-invasive technique, TMS offers several related approaches to the study of plasticity. Firstly it can be used to map (and demonstrate changes secondary to other interventions in) regions of the cortex that can elicit particular, usually motor, responses upon stimulation (albeit at fairly low spatial resolution). Secondly, it can provide standardised stimuli whose external effects can be modified by practice. Thirdly, when delivered as a chain of repetitive stimuli (repeated TMS or rTMS) the effect is to functionally

"lesion" underlying cortex in a reversible manner.

This book serves as a thorough and well-set out review of the use of TMS and rTMS in the investigation of brain plasticity. It is clearly written and readily comprehensible, and the editors have succeeded in consolidating the chapters into a coherent whole. It begins with a general discussion of plasticity and a critical review of the extent to which long-term potentiation (LTP) and long-term depression (LTD) can be assumed to underlie it. There follows a very clear discussion of TMS/rTMS techniques. The processes of plasticity underlying physiological development in infancy and childhood, normal practice-dependent learning and recovery from cortical injury in the older child and adult as demonstrated by TMS are then compared. Most of the brain-injury data relates to unihemispheric stroke. TMS has been used to demonstrate modification of motor maps and specifically the ability of current rehabilitative techniques to promote motor reorganisation. This type of approach could potentially provide invaluable proxy endpoints in comparative trials of rehabilitative therapies. Furthermore rTMS has potential as a therapeutic modality.

I would recommend this book as an authoritative yet highly accessible introduction to this topic.

*RJ Forsyth, Royal Victoria Infirmary, Newcastle.*



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# Sonographic Imaging for Guiding Botulinum Toxin Injections in Limb Muscles

## Preliminary note

This short review on the use of sonography to guide botulinum toxin injections is written from the perspective of a neuropaediatrician. Children are very sensitive to pain, rarely cooperative and don't like any procedures that require them holding still for a length of time. Sonography was always therefore very popular in paediatrics, and consequently, it seemed the obvious choice to utilise this technique for muscle identification and injection control. It is important to understand the paediatric background because an experienced neurologist who specialises on adult patients is used to applying electromyography (EMG) and muscle stimulation with usually excellent results, and thus would not feel any need for introducing a new technique. Nevertheless, even for adult patients, sonographic imaging offers a completely different approach (eg. visual vs. acoustic control) and it has the potential to evolve into a procedure that may equal the current gold-standard.

This article focuses on the treatment of spastic movement disorders, although many principles are also applicable to other indications such as focal or cervical dystonia.

## Introduction

Botulinum toxins (Btx) are used to treat spastic muscles in children with cerebral palsy, and in adults, eg. following stroke. A prerequisite for successful therapy is the anatomically correct administration of the substance into the muscle belly.

Orientation on anatomical landmarks and muscle palpation alone provide inadequate guidance for reliable needle placement. Thus, 63% of injections were incorrectly placed when trained neurologists attempted to target arm muscles without electromyographic assistance.<sup>1</sup> Chin and colleagues experienced similarly high failure rates in children with cerebral palsy. Needle placement by palpation alone failed the targeted muscles in between 22% (gastrocnemius muscle) and 88% (tibialis posterior muscle, flexor carpi radialis muscle) of cases.<sup>2</sup> Therefore, correct needle placement, especially in small and deep-seated muscles, is a challenging task even for the experienced user and requires assisted control techniques.

Electromyography and electrical muscle stimulation can

provide effective and valuable assistance.<sup>3</sup> However, these methods are of limited use in children because the procedure is painful, time consuming, and requires the patient's cooperation. As an alternative, imaging techniques were introduced, especially to guide injections into deep seated muscles. Among the various possibilities, the ultrasound guided injection technique is by far the most convenient one. It has been introduced primarily for use in children.<sup>4</sup> This review will cover the technical requirements, benefits and problems of this technique with specific reference to guided injections in Btx treatment.

## The Technique of Sonographic Guidance

### Technical requirements

Ultrasonography is well established as a reliable and reproducible imaging method in muscle anatomy.<sup>5</sup> The necessary equipment comprises a standard ultrasound system with 7.5 MHz linear transducer. This provides sufficient resolution for superficial muscles but is also able to depict deep-seated muscles. A 'small parts' setting or any other preprogrammed setting of the system is sufficient.

### Imaging of muscles

The transverse viewing mode is arranged such that the medial part of the limb is seen on the left, the lateral part on the right side of the monitor screen. The musculature appears poorly echogenic, while the perimysia and fascicular tissue between the muscle bellies is echogenic.

Three principles of muscle identification proved useful.

### 1. Recognising the characteristic pattern of individual muscles

The transverse sonogram corresponds to transverse anatomic sections. Each individual muscle has a characteristic contour line. An example is shown in Figure 1. These muscle specific patterns allow prompt (within a few seconds) identification of individual muscles.

### 2. Imaging of neighboring structures

Visualisation of neighbouring bones and vessels helps



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**Prof. Jörg Wissel, MD** is Head of the Neurological Rehabilitation Clinic Beelitz-Heilstätten, Germany. Since 1995 he has been board Certified Neurologist. He is member of the faculty of the Department of Neurology, University of Innsbruck, Austria. Jörg Wissel has a special interest in movement disorders in children and adults. His broad experience in botulinum toxin treatment of dystonia, spasticity and cerebral palsy is certified by numerous publications in peer-reviewed journals.

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Figure 1 a, b: Sonogram of flexor carpi radialis muscle (fcr) and neighbouring muscles in a five years old girl (a) and a 29 year old man (b) with same adjustment of the ultrasound system to allow comparison of muscle dimension. Fcr shows up as a characteristic bulge to the right, which caps the pronator teres muscle. This characteristic appearance is reproducible in every patient so that the identification of fcr in daily routine results from its pattern recognition. Abbrev.: r=radius, u=ulna, pt=pronator teres, fcr=flexor carpi radialis, fds=flexor digitorum superficialis, fdp=flexor digitorum profundus, br=brachioradialis muscle. Ultrasound system: Philips® Sonoline 5500 with 11-3L linear transducer.

#### DYSPORT® PRESCRIBING INFORMATION

**Presentation:** Vials of 500 units of *Clostridium botulinum* type A toxin-haemagglutinin complex. **Indications:** The treatment of focal spasticity, including: arm symptoms associated with focal spasticity in conjunction with physiotherapy in adults; and dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, 2 years of age or older. Spasmodic torticollis, blepharospasm and hemifacial spasm in adults. **Administration:** Dysport should only be injected by specialists who have had administration training. Blepharospasm and hemifacial spasm, reconstitute 500 units in 2.5ml normal saline. Spasmodic torticollis and focal spasticity, reconstitute in 1ml. **The units of Dysport are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.** **Posology:** The dose should be lowered for patients with low muscle mass or in whom the suggested dose may result in excessive weakness. See SPC for recommendations. **Arm spasticity:** The recommended dose is 1,000 units in total, distributed among the most active arm muscles; biceps brachii (300-400 units); flexor digitorum profundus (150 units); flexor digitorum superficialis (150-250 units); flexor carpi ulnaris (150 units); flexor carpi radialis (150 units). Sites of injection should be guided by standard EMG locations, although actual sites will be determined by palpation. All muscles should be injected at one site, except for the biceps which should be injected at two sites. **Paediatric cerebral palsy:** Starting dose is 20 units/kg body weight given intramuscularly as a divided dose between calf muscles. Subsequently the dose may be titrated between 10 and 30 units/kg body weight, depending on response. If only one calf is affected, the dose should be halved. The maximum dose administered must not exceed 1,000 units/patient. Injections may be repeated approximately every 16 weeks or as required to maintain response, but not more frequently than every 12 weeks. **Spasmodic torticollis:** The

initial recommended dose is 500 units given intramuscularly as a divided dose to the two or three most active neck muscles, which will likely include splenius capitis and sternomastoid. The split amongst muscles will vary according to the type of torticollis diagnosed. Doses within the range 250-1,000 units are recommended. Injections should be repeated approximately every 12 weeks or as required to prevent recurrence of symptoms. **Blepharospasm and hemifacial spasm:** The initial recommended dose is 120 units per affected eye; injections are given subcutaneously, medially and laterally into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of each eye. Injections should be repeated approximately every 12 weeks or as required to prevent recurrence of symptoms. Subsequently the dose may be reduced to 80 units per eye and then to 60 units by omitting the medial lower lid injection. **Contraindications:** Dysport is contraindicated in individuals with known hypersensitivity to any component of Dysport. **Warnings and precautions:** Dysport should be administered with caution to patients with existing swallowing or breathing difficulties or with subclinical or clinical evidence of marked defective neuromuscular transmission. Careful consideration should be given to the use of Dysport in patients with a history of allergic reaction to a product containing botulinum toxin type A or in patients with prolonged bleeding times, infection or inflammation at the proposed injection site. Dysport contains a small amount of human albumin. The risk of transmission of viral infection cannot be excluded with absolute certainty following the use of human blood products. Antibody formation to botulinum toxin has been noted rarely in patients receiving Dysport. **Interactions:** Drugs affecting neuromuscular transmission, eg. aminoglycoside antibiotics, should be used with caution. **Pregnancy and lactation:** Safety in this patient group has not been demonstrated. Dysport should not be used unless clearly necessary. **Side effects:**

Side effects may occur due to deep or misplaced injections of Dysport temporarily paralysing other nearby muscle groups. In general, adverse events reported in clinical trials included: *common:* generalised weakness, fatigue, flu-like syndrome, pain/bruising at injection site; *uncommon:* itching; *rare:* neuralgic amyotrophy, skin rashes. **Arm spasticity:** *common:* dysphagia, arm muscle weakness, accidental injury/falls. **Paediatric cerebral palsy:** *common:* diarrhoea, vomiting, leg muscle weakness, urinary incontinence, abnormal gait, accidental injury due to falling. **Spasmodic torticollis:** *very common:* dysphagia; *common:* dysphonia, neck muscle weakness; *uncommon:* headache, diplopia, blurred vision, dry mouth; *rare:* respiratory disorders. **Blepharospasm and hemifacial spasm:** *very common:* respiratory disorders; *common:* facial muscle weakness, diplopia, dry eyes, tearing, eyelid oedema; *uncommon:* facial nerve paresis; *rare:* entropion, ophthalmoplegia. **Overdose:** Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. There is no specific antidote; antitoxin should not be expected to be beneficial and general supportive care is advised. **Pharmaceutical precautions:** Unopened vials must be maintained at temperatures between 2°C and 8°C. Reconstituted Dysport may be stored in a refrigerator (2-8°C) for up to 8 hours prior to use. Dysport should not be frozen. **NHS Cost:** £329.48 per pack of two 500 unit vials. **POM:** PL 6958/0005. **MA Holder:** Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE. **Date of preparation of PI:** October 2004. 2701. Dysport® is a registered trademark. **Date of preparation:** October 2004. 2708.



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to accurately determine the injection site in muscles whose perimysia are too thin for proper imaging. An example is shown in Figure 2.

- 3. **Passive movements, visible as concurrent oscillations**  
Especially in the upper limb, movement of target muscles through passive movement of the corresponding part of the body may help to resolve any difficulties with correct anatomic allocation. Already passive movements of very small amplitudes are visible as concurrent oscillations of the intramuscular echo. In this way, even individual fascicles of the superficial and profound finger flexors can be clearly identified.

**Sonography guided injection**

The needle is inserted closely aligned to the middle of the broad side of the transducer (Figure 3). As the needle penetrates the skin, its path through the tissue to the target site for injection is continually monitored on the screen. Slight movements of the needle along its longitudinal axis can help to obtain a satisfactory image. Upon injection, the solution spreads out in the muscle, usually as an echogenic cloud, sometimes with echo-obliteration (Figure 4). The injected solution is still visible for approximately 3 minutes after injection of the full dose is completed.

**Significance of Sonographic Imaging to Guide Btx Injections**

The current experience after thousands of injections suggests that sonography allows an anatomically precise injection of Btx. Table 1 summarises the characteristics compared to EMG and muscle stimulation.

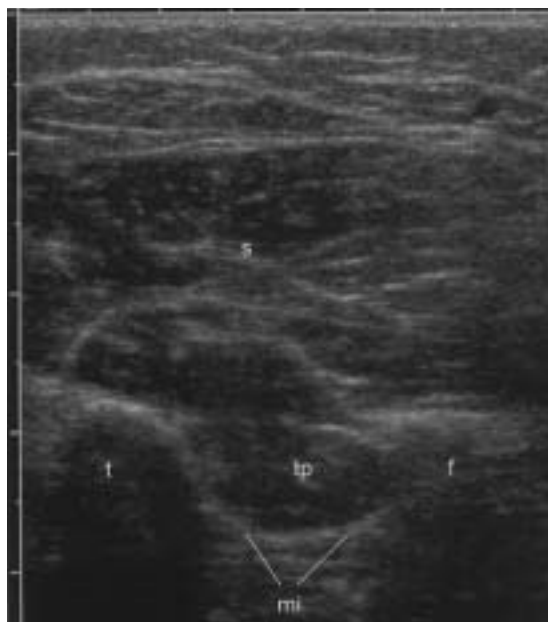


Figure 2: Sonogram of tibialis posterior muscle, situated in the valley formed by tibia and membrana interossea. Abbrev.: t=tibia, f=fibula, s=soleus muscle, tp=tibialis posterior muscle, mi=membrana interossea.

Most importantly, sonography guided injection is visually controlled. By seeing the whole process, the operator gains a better understanding of the individual anatomy. This enables a more differential target selection and helps to further improve the injection technique. One example is shown in Figure 5.

Although so far no comparative studies have been

**Table 1**  
**Characteristics of different approaches to guide Btx injections.**  
+: advantageous, o: acceptable, -: unfavourable.

	Passive EMG	Active muscle stimulation	Sonography
Accuracy of needle placement	o	+	+
Time required for muscle identification	-	o	+
Availability of technical equipment	o	o	+
Pain and distress caused by procedure	-	-	+
Dependency on expert knowledge	-	-	o
Necessary number of stabs	-	-	+
Control of injection depth	o	+	+
Differentiation of neighbouring (co-contracting) muscles	-	o	+
Differentiation of muscle tissue from surrounding structures (eg vessels, nerve, bone)	-	-	+
Independency on patient cooperation	-	+	+
Possibility to ascertain correct placement after finishing the injection	-	-	+
Possibility to document the injection	-	-	+
Disturbance through analgesedation*	-	+	+
Identification of proximity to motor-endplates	+	+	-
Identification of muscular hyperactivity	+	o	-
Identification of muscle dimension	o	o	+
Identification of muscle fibrosis	o	o	+
Potential for further development	-	-	+

\*Analgesedation = combined analgesia + sedation with rectal pethidine + midazolam



Figure 3 left: Positioning of the transducer and the injection needle to inject the iliopsoas muscle, distal injection site (please refer also to Figure 5).

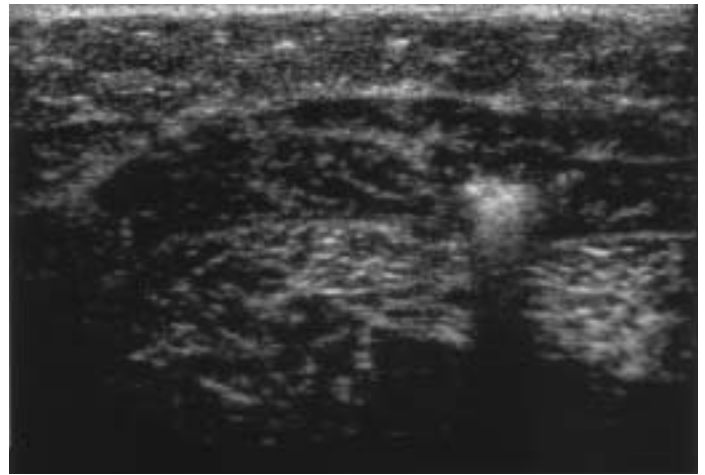


Figure 4 right: Intramuscular cloud-like echogenic appearance immediately after injection of botulinum toxin solution in gastrocnemius muscle, lateral head.

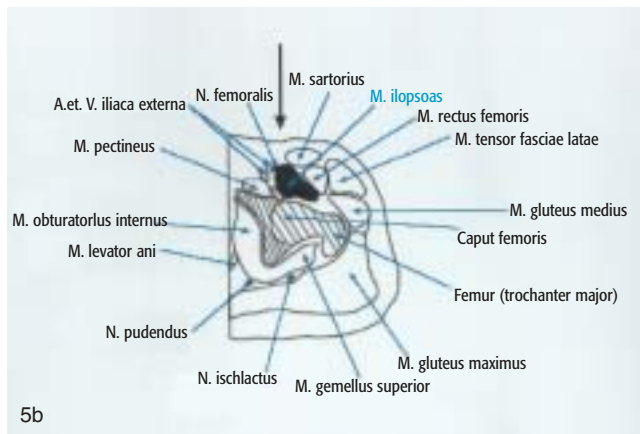
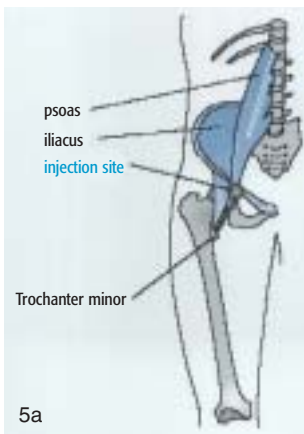


Figure 5 a, b, c: (a) Illustration of distal injection site for the iliopsoas muscle, (b) cross-sectional view (at the level of the inguinal ligament, arrow indicating the position of the transducer), and (c) corresponding sonogram. Due to the distal position of the injection site, there is no need to inject through the muscular abdominal wall and peritoneum. General anesthesia, used to ensure a completely relaxed abdominal wall, is therefore unnecessary. In contrast to the conventional proximal approach, distal sonography-guided injection only requires analgesedation, as recommended for any muscle injection in a paediatric setting.<sup>8,9</sup> Abbrev.: ip=iliopsoas muscle, f=femoral head, s=sartorius muscle, r=rectus muscle, v=vena iliaca.

done, we expect that sonography can identify muscles with similar accuracy as that obtained with muscle stimulation.

Sonography cannot measure muscular hyperactivity when the clinical situation is uncertain. Furthermore, it is not possible to detect motor endplate regions, which may have some implications in the treatment of large muscles.<sup>6</sup> On the other hand, the sonogram provides information about muscle size and fibrosis, factors that can be important in decision making.

To summarise, in children sonography has overcome some restrictions of the EMG/muscle stimulation technique and is regarded as a further step in increasing the accuracy and quality of Btx injections.<sup>7</sup> Especially in patients who do not cooperate, it may be very helpful in the identification of small muscles, such as single fascicles of finger flexors in spasticity and in focal dystonia.

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## CORRECTIVE STATEMENT

At the request of the MHRA GlaxoSmithKline (GSK) have been asked to provide a corrective statement regarding the promotion of Lamictal.

During the first quarter of 2004 GSK issued advertising materials for Lamictal containing a reference to cognitive function. Subsequently, at the request of the MHRA, GSK voluntarily withdrew these materials.

The advertisements were considered to be misleading since they indicated that the product did not impair cognitive function, however, listed in section 4.8 of the Summary of Product Characteristics (SPC) were adverse events that may impair cognitive function, such as dizziness, drowsiness, confusion and hallucinations.

By disregarding these adverse events, the advertisements did not present an objective view of the product and exaggerated its properties.

We regret that messages contained in these advertisements were not perceived as intended and apologise for any confusion that may have been caused by them.

Should you have any further questions about these matters or about Lamictal please contact the GSK Customer Contact Centre, freephone 0800 221441, fax 020 89904328 or email [customercontactuk@gsk.com](mailto:customercontactuk@gsk.com).

### Lamictal (lamotrigine) **Brief Prescribing Information.**

**Presentation:** Pale yellow tablets containing 25mg, 50mg, 100mg and 200mg lamotrigine, and white dispersible/chewable tablets containing 2mg, 5mg, 25mg and 100mg lamotrigine.

**Uses: Monotherapy:** Not recommended in children under 12 years. Adults and children over 12 years for partial epilepsy with or without secondarily generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. **Add-on therapy:** Adults and children over 2 years for partial epilepsy with or without secondary generalised tonic-clonic seizures and in primary generalised tonic-clonic seizures. Seizures associated with Lennox-Gastaut syndrome.

**Dosage and Administration:** Initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash.

**Monotherapy:** Initial dose is 25mg daily for two weeks, followed by 50mg daily for two weeks. Dose should be increased by a maximum of 50-100mg every 1-2 weeks until optimal response. Usual maintenance dose is 100-200mg/day in one dose, or two divided doses. **Add-on therapy: Adults and Children over 12 years:** To sodium valproate with or without ANY other antiepileptic drug (AED), initial dose 25mg every alternate day for two weeks, followed by 25mg/day for two weeks. Dose should be increased by 25-50mg every 1-2 weeks until optimal response. Usual maintenance dose 100 to 200mg/day in one dose, or two divided doses. To enzyme inducing AEDs with or without other AEDs (but NOT valproate), initial dose is 50mg daily for two weeks, followed by 100mg/day in two divided doses for two weeks. Dose should be increased by 100mg every 1-2 weeks until optimal response. Usual maintenance dose is 200 to 400mg/day given in two divided doses. **Children aged 2-12 years:** To be dosed on a mg/kg basis until the adult recommended titration dose is reached. Add-on to sodium valproate with or without ANY other AED, initial dose is 0.15mg/kg bodyweight/day given once a day for two weeks, followed by 0.3mg/kg/day given once a day for two weeks. Dose should then be increased by a maximum of 0.3mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 1 to 5mg/kg/day given in one dose, or two divided doses. Add-on to enzyme-inducing AEDs with or without other AEDs (but NOT valproate) is 0.6mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2mg/kg/day for two

weeks given in two divided doses. Dose should then be increased by a maximum of 1.2mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 5-15mg/kg/day given in two divided doses. Weight of child should be monitored and dose adjusted as appropriate. If calculated dose is 1-2mg/day then 2mg may be taken on alternate days for the first two weeks. **Dose Escalation:** Starter packs covering the first four weeks treatment are available for adults and children over 12 years. When the pharmacokinetic interaction of any AED with Lamictal is unknown the dose escalation for Lamictal and concurrent sodium valproate should be used. **Elderly patients:** No dose adjustment required. **Contra-indications:** Hypersensitivity to lamotrigine.

**Precautions:** Adverse skin reactions, mostly mild and self-limiting, may occur generally during the first 8 weeks of treatment. Rarely, serious, potentially life threatening rashes including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Patients should be promptly evaluated and Lamictal withdrawn unless the rash is clearly not drug related. High initial dose, exceeding the recommended dose escalation rate, and concomitant use of sodium valproate have been associated with an increased risk of rash. Patients who acutely develop symptoms suggestive of hypersensitivity such as rash, fever, lymphadenopathy, facial oedema, blood and liver abnormalities, flu-like symptoms, drowsiness or worsening seizure control, should be evaluated immediately and Lamictal discontinued if an alternative aetiology cannot be established. **Hepatic impairment:** Dose reductions recommended. **Withdrawal:** Avoid abrupt withdrawal, except for safety reasons. **Pregnancy: Lamictal was not carcinogenic, mutagenic, teratogenic or shown to impair fertility in animal studies. There are insufficient data available on the use of Lamictal in human pregnancy to evaluate its safety. Lamictal should not be used during pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risk to the developing foetus.** **Driving:** As with all AEDs, the individual response should be considered.

**Interactions:** Antiepileptic drugs which alter certain metabolising enzymes in the liver affect the pharmacokinetics of Lamictal (see Dosage and Administration). This is also important during AED withdrawal.

**Side and Adverse Effects:** With monotherapy: headache, tiredness,

rash, nausea, dizziness, drowsiness, and insomnia. Other adverse experiences have included diplopia, blurred vision, conjunctivitis, GI disturbances, irritability/aggression, agitation, confusion, hallucinations and haematological abnormalities. Also movement disorders such as tics, unsteadiness, ataxia, nystagmus and tremor. Severe skin reactions including SJS and TEN have occurred rarely, with or without signs of hypersensitivity syndrome. Elevations of liver function tests and rare reports of hepatic dysfunction. Very rarely, increase in seizure frequency has been reported.

**Legal category:** POM.

**Basic NHS costs:** £16.45 for Monotherapy Starter Pack of 42 x 25mg tablets (PL0003/0272); £27.98 for Non-Valproate Starter Pack of 42 x 50mg tablets (PL0003/0273); £8.23 for Valproate Starter Pack of 21 x 25mg tablets (PL0003/0272). £64.37 for pack of 56 x 100mg tablets (PL0003/0274); £109.42 for pack of 56 x 200mg tablets (PL0003/0297). £21.95 for pack of 56 x 25mg tablets (PL0003/0272). £37.31 for pack of 56 x 50mg tablets (PL0003/0273). £8.75 for pack of 28 x 5mg dispersible tablets (PL0003/0346). £21.95 for pack of 56 x 25mg dispersible tablets (PL0003/0347). £64.37 for pack of 56 x 100mg dispersible tablets (PL0003/0348). £9.37 for pack of 30 x 2mg dispersible tablets (PL0003/0375).

**Product Licence Holder:** The Wellcome Foundation Ltd, Middlesex UB6 0NN. Lamictal is a registered trademark of the GlaxoSmithKline Group of Companies.

**Further information is available on request from** GlaxoSmithKline Limited, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

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**Date of Preparation:** September 2004

LAM/FPA/04/14763/1

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## 2004

### November

#### Systematic Reviews

3 November, 2004; Oxford, UK.  
Tel. 01865 286942, Fax. 01865 286934,  
E. [cpdhealth@conted.ox.ac.uk](mailto:cpdhealth@conted.ox.ac.uk)

**BNS Autumn Meeting: Symposium to commemorate 100 years since the first descriptions of fronto-temporal dementia**

3-4 November, 2004; London, UK  
Tel. 0115 970 9119,  
E. [georgina.jackson@nottingham.ac.uk](mailto:georgina.jackson@nottingham.ac.uk)

#### Health Status Measurement

4 November, 2004; Oxford, UK  
Tel. 01865 286942, Fax. 01865 286934,  
E. [cpdhealth@conted.ox.ac.uk](mailto:cpdhealth@conted.ox.ac.uk)

**British Orthopaedic Foot Surgery Society: Diabetic Foot & Rheumatoid Foot & Ankle**

4-6 November, 2004; Cheshire, UK  
Tel. 01257 256248, Fax. 01257 256292,  
E. [uplimb@wrightington.org.uk](mailto:uplimb@wrightington.org.uk)

#### Systematic Reviews

5 November, 2004; Oxford, UK  
Tel. 01865 286942, Fax. 01865 286934,  
E. [cpdhealth@conted.ox.ac.uk](mailto:cpdhealth@conted.ox.ac.uk)

**2nd International Symposium on Concussion in Sport**

5-6 November, 2004; Prague, Czech Republic  
Simone Micheletti, Fax. +41 15 622 259, [Emicheletti@ihf.com](mailto:Emicheletti@ihf.com)

#### Ketogenic diets for epilepsy

8 November, 2004; London, UK  
E. [courses@ich.ucl.ac.uk](mailto:courses@ich.ucl.ac.uk)

**Birmingham Neuro-Ophthalmology Course**

10 November, 2004; Birmingham, UK  
Contact Hilary Baggott,  
Tel. 0121 507 6785,  
E. [hilary.baggott@swbh.nhs.uk](mailto:hilary.baggott@swbh.nhs.uk)

**Eastern Rehab Group Meeting: Behavioural Problems in Cognitive Impairment: clinical and legal issues**

12 November, 2004; Norwich, UK  
Dr Benedicte Mancel,  
Tel. 01603 711649,  
E. [benedictem2003@yahoo.com](mailto:benedictem2003@yahoo.com)

**Neurological Assessment Short Course for Nurses**

15 November, 2004; London, UK  
Tel. 020 7836 5454,  
E. [sue.woodward@kcl.ac.uk](mailto:sue.woodward@kcl.ac.uk)

#### Children & Sleep

15 November, 2004; London, UK  
Jacqueline Warner on  
Tel. 020 7290 3941,  
E. [sleep.disorders@rsm.ac.uk](mailto:sleep.disorders@rsm.ac.uk)

**Short Courses: Neurological Assessment**

15 November, 2004; London, UK  
Tel. 020 7836 5454,  
E. [sue.woodward@kcl.ac.uk](mailto:sue.woodward@kcl.ac.uk)

**Sino-British Joint Conference on Neurology**

15-17 November, 2004; Beijing, China  
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E. [info@theabn.org](mailto:info@theabn.org)

**8th Mediterranean Epilepsy Meeting**

18-20 November, 2004; Marrakesh, Morocco  
Fax. +212 37 77 05 68,  
E. [evenementiel@menara.ma](mailto:evenementiel@menara.ma)

**RCN Rehabilitation & Intermediate Care Nursing Forum: Where are we with Intermediate Care?**

19 November, 2004; London, UK  
Contact Sonia Lynch,  
Tel. 020 7647 3859,  
E. [rehabilitation@rcn.org.uk](mailto:rehabilitation@rcn.org.uk)

**National Symposium on Epilepsy & Vagus Nerve Stimulation Therapy**

20th November, 2004, Sheffield, UK  
Tel. 0800 521629, E. [fablepr@aol.com](mailto:fablepr@aol.com)

**Pain Management Short Course**

20 November, 2004 - 30 June, 2005 - various dates/locations  
E. [meier@health-homerton.ac.uk](mailto:meier@health-homerton.ac.uk)

**Norwegian Neurological Association Annual Scientific Meeting**

22-26 November, 2004; Oslo, Norway  
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**West of England Seminars in Neurology**

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Tel: 01225 825447.

**Altered Haemodynamics - A new concept in manual therapy**

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E. [ACNRvents@aol.com](mailto:ACNRvents@aol.com)

### December

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1 December, 2004; London, UK  
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E. [info@mepltd.co.uk](mailto:info@mepltd.co.uk)

**Epilepsy and Intellectual Disability**

2 December, 2004; London, UK  
Sara Nettleship, Tel. 020 7290 3934,  
Fax. 020 7290 2989  
E. [learning.disability@rsm.ac.uk](mailto:learning.disability@rsm.ac.uk)

**International Symposium on ALS/MND**

2-4 December, 2004; Philadelphia, US  
Tel. 01604 250505, Fax. 01604 638 289  
or E. [pam.aston@mndassociation.org](mailto:pam.aston@mndassociation.org)

**The American Epilepsy Society 58th annual meeting**

3-8 December, 2004, New Orleans, USA. [www.aesnet.org](http://www.aesnet.org)

**Presenting a Conference Paper**

6 December, 2004; Nottingham, UK  
Tel. 0115 970 9765,  
E. [joanne.elliott@nottingham.ac.uk](mailto:joanne.elliott@nottingham.ac.uk)

**Diagnostic Treatment of Attention Deficit & Hyperactivity Disorders**

7 - 8 December, 2004; Riyadh, Saudi Arabia  
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**Spasticity Evidence based Measurement and Treatment**

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**BNA Christmas Symposium**

15 December, 2004; London, UK  
[www.bna.org.uk](http://www.bna.org.uk),  
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**Writing for Publication**

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## 2005

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**SRR Winter Meeting**

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Fax. 01353 652164  
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### February

**Short Courses : Neuro-Medical / Surgical Nursing**

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E. [wood@health-homerton.ac.uk](mailto:wood@health-homerton.ac.uk)

**Advanced practice in epilepsy**

February 2005, NSE, Chalfont St Peter, UK  
Training department, National Society for Epilepsy, Tel. 01494 601 371.

**33rd Annual Meeting of the International Neuropsychological Society**

2-5 February, 2005; St Louis, US  
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**International Stroke Conference**

2-4 February, 2005; New Orleans, US  
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**British Neuropsychiatry Association Annual Meeting**

9-11 February, 2004; London, UK  
Gwen Cutmore,  
Tel/Fax. 01621 843334,  
E. [gwen.cutmore@lineone.net](mailto:gwen.cutmore@lineone.net)

**Workshop on Botulinum Toxins in Neurological Practice**

11 February, 2005; Innsbruck, Austria  
E. [khenley@movementdisorders.org](mailto:khenley@movementdisorders.org)

**Short Courses: Neurological Assessment for Nurses**

14 February, 2005; London, UK  
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**Dementias 2005**

24-25 February, 2005; London, UK  
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E. [conference@markallengroup.com](mailto:conference@markallengroup.com)

### March

**Acute Medical Emergencies**

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E. [ame@confcomm.co.uk](mailto:ame@confcomm.co.uk)

**The Visual System - RSM Clinical Neurosciences Section**

3 March, 2005; London, UK  
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**Standardised Assessment in Occupational Therapy with special emphasis on Dementia, Part 2**

3 March, 2005; London, UK  
Tel. 020 7834 3181

**9th International Congress of Parkinson's Disease and Movement Disorders**

5-8 March, 2005; New Orleans, US  
E. [congress@movementdisorders.org](mailto:congress@movementdisorders.org)

**GCNN 2, 2nd Global College of Neuroprotection and Neuroregeneration Annual Conference**

7-10 March, 2005; Innsbruck, Austria  
E. [info@gcnpnr.org](mailto:info@gcnpnr.org)

**The British Pain Society Annual Meeting**

8-11 March, 2005; Edinburgh, UK  
Tel. 020 7631 8870,  
E. [meetings@britishpainsociety.org](mailto:meetings@britishpainsociety.org)

**7th International Conference on Progress in Alzheimer's and Parkinson's Disease**

9 - 14 March, 2005; Sorrento, Italy  
Fax. 08451 275 687,  
E. [adpd@kenes.com](mailto:adpd@kenes.com)

**1st Joint International Meeting on Degos Disease**

18-19 March, 2005; Berlin, Germany  
E. [judith@degosdisease.com](mailto:judith@degosdisease.com)

**ABN Spring Meeting**

30 March - 1 April; Belfast, UK  
Tel. 020 7405 4060,  
E. [info@theabn.org](mailto:info@theabn.org)

### April

**18th National Meeting of the BNA**

3-6 April, 2005; Brighton, UK  
[www.bna.org.uk](http://www.bna.org.uk)

**Clinical Neurophysiology BSCN Course**

3-9 April, 2005; Oxford, UK  
E. [robin.kennett@rh.nhs.uk](mailto:robin.kennett@rh.nhs.uk)

**American Academy of Neurology (AAN) Annual Meeting**

9-16 April, 2005; Florida, US  
<http://am.aan.com/>

**3rd World Congress Of The ISPRM**

10-14 April, 2005; San Paulo, Brazil  
E. [ispmr2005@isprm.org](mailto:ispmr2005@isprm.org)

**Certificate Course in Neurological Rehabilitation**

11-29 April, 2005, Newcastle, UK  
Tel/Fax. 0191 2195695,  
E. [traceymole@actionfordisability.co.uk](mailto:traceymole@actionfordisability.co.uk)

**Neurodegeneration - RSM Clinical Neurosciences Section**

14 April, 2005; London, UK  
Tel. 20 7290 2984/2982,  
E. [cns@rsm.ac.uk](mailto:cns@rsm.ac.uk)

**BGS Spring Meeting**

14-15 April, 2005; Birmingham, UK  
British Geriatric Society,  
Tel. 0207 6081369

**Second International Neuroanthocytosis Symposium**

"Expanding the Spectrum of Choreatic Syndromes"  
17-20 April, 2005; Montreal, Canada  
Tel. 0207 937 2938;  
E. [gingerirvine@usa.net](mailto:gingerirvine@usa.net)

### May

**Short Courses : Neuro-Medical / Surgical Nursing**

May, 2005; Cambridge, UK  
E. [wood@health-homerton.ac.uk](mailto:wood@health-homerton.ac.uk)

**6th World Congress on Brain Injury**

1 - 4 May, 2005; Melbourne, Australia  
E. [braininjury@icms.com.au](mailto:braininjury@icms.com.au)

**Aspects of the Neurological Examination - RSM Clinical Neurosciences Section**

17-20 April, 2005; London, UK  
Tel. 20 7290 2984/2982,  
E. [cns@rsm.ac.uk](mailto:cns@rsm.ac.uk)

**4th BASP Thrombolysis Training Day**

6 May, 2005; Nottingham, UK  
Pamela Nicholson, sec to Professor Lees, E. [pcn1w@clinmed.gla.ac.uk](mailto:pcn1w@clinmed.gla.ac.uk),  
Tel. 0141 211 2176.

**Neurochirurgie 2005**

7-11 May, 2005; Strasbourg, France  
Fax. +49 3 028 449 911,  
E. [nch2005@porstmann-kongresse.de](mailto:nch2005@porstmann-kongresse.de)

**12th European Congress of Clinical Neurophysiology**

9-11 May, 2005; Stockholm, Sweden  
E. [secretary@ec-icfn.org](mailto:secretary@ec-icfn.org)  
[weerd@ipe.nl](mailto:weerd@ipe.nl)

**Alzheimer's Disease: Update on Research, Treatment, & Care**

19-20 May, 2005; San Diego, US  
E. [joellier@ucsd.edu](mailto:joellier@ucsd.edu)

**Annual Meeting of the German Section of the International League Against Epilepsy**

20-22 May, 2005; Freiburg, Germany  
[www.ctw-congress.de/liga](http://www.ctw-congress.de/liga)

**14th European Stroke Conference**

25-28 May, 2005; Bologna, Italy  
E. [m.g@eurostroke.org](mailto:m.g@eurostroke.org) or [daffertshofer@eurostroke.org](mailto:daffertshofer@eurostroke.org)

**International Society of Posture and Gait Research 2005 - ISPGR XVIIth Conference**

29 May - 2 June, 2005; Marseilles, France  
E. [assaant@dpm.cnrs-mrs.fr](mailto:assaant@dpm.cnrs-mrs.fr) or [ispgr2005@atout-org.com](mailto:ispgr2005@atout-org.com)



## The British Neuropsychiatry Association Annual Meeting

### 9/10/11 February 2005 - The Institute of Child Health, Guilford Street, London

• Dementia • Catatonia • Child psychiatric disorders in adult life • Neuropsychiatry in literature

The BNPA is pleased to announce that the 2005 meeting will be over 3 days with day one being held in collaboration with Institute of Social Psychiatry.

This meeting is especially directed at clinicians (in old age psychiatry, geriatric medicine, neurology), allied health and other professions seeking a broader understanding of and an update on Dementia, its treatment and impact. Day two will focus on the Neuropsychiatry of the Dementias and the afternoon session on Catatonia. Day three will be for members papers and Child psychiatric disorders in adult life, Neuropsychiatry and Literature with a special guest speaker.

For a copy of the meeting programme and booking form, or for details of exhibition/sponsorship opportunities, contact Jackie Ashmenall on Phone/Fax 020 8840 9266 • Email: [admin@bnpa.org.uk](mailto:admin@bnpa.org.uk) or [jashmenall@yahoo.com](mailto:jashmenall@yahoo.com) • Web: [www.bnpa.org.uk](http://www.bnpa.org.uk)

# European Federation of Neurological Societies

4-7th September, 2004; Paris, France.

The excellent September weather in Paris which coincided with the 8th Annual meeting of the European Federation of Neurological Societies may, along with the charms of the city, have attracted some delegates away from the conference halls of the Palais des Congrès. Your correspondent, however, remained diligently at his post in order to compile this report (with just one brief exception, to be mentioned later).

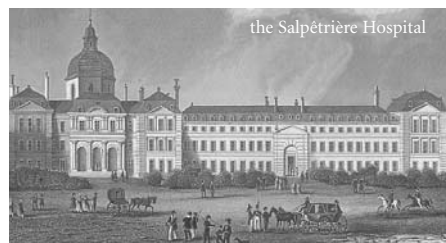
A broad bill of fare was on offer: Main Topics (relatively didactic presentations from experts in the field), short communications (presenting new, or relatively new, information), focused workshops, posters (over 1000 presentations), special sessions, and satellite symposia sponsored by drug companies. As with almost all international conferences, the scheduling of multiple concurrent sessions means that any report is bound to be somewhat arbitrary, its selections dependent upon the author's particular interests and, possibly, prejudices. With this caveat in mind, I found the following presentations of particular interest:

**Mendelow (Newcastle):** The International Surgical Trial in Intracerebral Haemorrhage (ISTICH) randomised over 1000 patients in over 100 centres in 27 countries to either "early surgical intervention" or "initial conservative treatment" within 72 hours of ictus. Outcome at six months was determined with the Glasgow Outcome Scale. Favourable outcome occurred in 26.1% of the early surgery group and 23.8% of the conservative group, a difference which was not significant. Hence, the optimum management of intracerebral haemorrhage remains uncertain, and likely to be judged on an individual basis.

**Ducros (Paris):** Thunderclap headache (TCH) may be a reversible or benign angiopathy. Early angiography in patients with recurrent TCH may show "string of beads" appearances which resolve within 2 months. Prior use of vasoconstrictors prescribed for rhinitis, SSRIs, and recreational use of cannabis, may be relevant to TCH pathogenesis, and awareness of the angiographical changes may influence advice to patients about their subsequent use.

**Mehrabian (Sofia):** A family with autosomal dominant early-onset Alzheimer's disease (AD) was reported, in which progressive dementia was complicated by spastic paraparesis and extrapyramidal signs. A novel mutation in the presenilin-1 gene (L381V) was detected, but no pathological data were available.

**Brandel (Paris):** A review of the clinical and investigational findings in sporadic and iatrogenic Creutzfeldt-Jakob disease (CJD). Clinical criteria for the diagnosis of CJD are good, but nonetheless diagnosis is often late. An early marker of disease is still required. Iatrogenic disease may be due to cerebral inoculation (dura mater grafts much commoner than cornea transplants or stereotactic neurosurgery, especially in Japan) or peripheral inoculation (cadaveric growth hormone use much commoner than



gonadotrophin use, cases of the latter only in Australia). Cerebral inoculation produces a clinical picture similar to sporadic CJD, peripheral inoculation produces a syndrome more akin to kuru with dementia occurring late.

**Gauthier (Montreal):** A discussion of the use of cholinesterase inhibitors (ChEI) in Alzheimer's disease (AD), particularly possible disease-modifying effects. In the AWARE study, patients initially not thought to benefit from ChEI were randomised to either placebo or continued ChEI. Around two-thirds of the latter group showed benefit at 24 weeks. Hence initial deterioration does not necessarily imply lack of response to ChEI, nor does it preclude benefit in domains other than memory (eg behaviour). An observational study suggests time to nursing home placement is longer in those AD patients receiving ChEI. Use of ChEI in mild cognitive impairment to delay conversion to AD remains questionable: a 6 month study detected improvement but a longer trial (3 years) showed reduced conversion in the first 18 months but with curves converging by the end of the trial; any effect seems not to be sustained.

**Marchini (Naples):** Brain imaging of patients with unilateral asterixis following stroke suggested that damage to the contralateral corticospinal tract plus either the medial lemniscus or basal ganglia was the most common finding.

**McGregor (London):** An internet based survey of migraineurs showed that most had used OTC medication. Need for a second dose of medication was lower in those receiving triptans as compared with other treatments.

**Cerbo (Rome):** Headache accounts for about 1% of admissions to an emergency unit, yet the percentage with secondary headache (eg meningitis, subarachnoid haemorrhage) is low, perhaps 20%. Hence, some hospitals are developing headache centres within the emergency department to manage acute primary headache disorders. In this 3 month study, 190/237 (= 80%) of patients seen had migraine, of whom only 14% had seen a headache specialist prior to presentation and only 10% had used a triptan before presentation, suggesting that migraine is underdiagnosed and undertreated.

**Mills (Liverpool):** Hypothalamic involvement in multiple sclerosis is frequently noted in post-mortem tissue, yet brain imaging studies of MS with hypothalamic change are restricted to case reports. A retrospective study of 67 "MS protocol" MR scans found single hypothalamic plaques in 3 patients (4.5%).

Particular highlights of the EFNS meeting for

me are the sessions devoted to "Neurology and Art" and "History of Neurology". These were, appropriately for a meeting held in Paris, dominated by the life and work of Jean Martin Charcot (1825-1893). Both sessions featured talks by Professor Christopher Goetz from Chicago who has written on Charcot.<sup>1</sup> In the former session, he alluded to Charcot's drawings in patient case notes which often capture key clinical features. Subsequent speakers discussed Charcot's artistic interests and his possible influence on authors such as Daudet (his patient), Zola, Schnitzler, Tolstoy, Turgenev (another patient), Strindberg, Munthe and Bjornstjerne Bjornson. The History of Neurology session included talks on the development of neuropsychology in Paris by Professor Boller, focusing particularly on the work of Hecquen and F Lhermitte, and the history of the Salpêtrière Hospital with its role call of neurological greats (Pinel, Vulpian, Raymond, Dejerine, Marie, Guillain). Professor Goetz gave the Clifford Rose Lecture, lucidly describing Charcot's "methode anatomo-clinique", adapting for the purposes of neurology the methodology of Laennec.

The subsequent History of Neurology Tour (my one desertion from the conference venue) visited both the Musée d'Histoire de la Médecine in the rue de l'École de Médecine and the Salpêtrière Hospital. At the former, there was a chance to see the original 1887 painting of Charcot's Lecture by Brouillet, featuring many attentive students who later attained renown (Babinski, Marie, Gilles de la Tourette, Fere, Brissaud). Exhibits in the museum adjacent record other contributors to the history of neurology (Pourfour du Petit, Itard, Meige, Lermoyez, and Brissaud: the latter apparently undertook, in 1896, the first skull X-ray to identify an intracranial projectile, requiring an exposure time of one and a half hours!). Professors Bonduelle<sup>1</sup> and Boller conducted the tour of the Salpêtrière, with a visit to the Charcot library (the famous painting of Pinel removing the chains of the patients is in the foyer) as well as a walk around the hospital site. Many ancient buildings remain cheek-by-jowl with more modern facilities, and I was interested to note the Cellule Nationale de Référence des Maladies de Creutzfeldt-Jakob was housed in one of the former. Charcot's statue no longer stands adjacent to the gate of the hospital, having been removed (like so many Parisian statues) during the Second World War. Vulpian, however, still stands (in stone) in the rue de l'École de Médecine.

Published posthumously in 1964, Ernest Hemingway's book memorably described Paris as a "Moveable Feast". Likewise the EFNS, which next meets in Athens in 2005.

AJ Larner, Walton Centre for Neurology and Neurosurgery, Liverpool.

1. Goetz CG, Bonduelle M, Gelfand T Charcot: *Constructing Neurology*. Oxford: OUP, 1996.

# 9th International Conference on Alzheimer's Disease and Related Disorders

17-22 July, 2004; Philadelphia, USA

**D**ramatic developments in imaging techniques and therapeutic interventions were reported at the recent 9th International Conference on Alzheimer's Disease and Related Disorders.

In the first study to show a positive treatment effect on progression from cognitive impairment (MCI) to AD, the acetyl cholinesterase inhibitor donepezil slowed progression by about six months compared to placebo. The study randomised 769 people with mild cognitive impairment to vitamin E (up to 2000IU/day), donepezil (5mg per day for six weeks, increasing to 10mg) or placebo. They were followed up for three years and evaluated every six months. Reporting the results, Ronald Petersen, Mayo Clinic, Rochester, Minnesota, USA, said, "Progression to AD was slower with donepezil during the first 18 months of the study, but was then similar to placebo." Vitamin E had no effect.

Progression from MCI to AD was significantly slower with donepezil at 6 months ( $p < 0.001$ ), 1 year ( $p < 0.009$ ) and 18 months ( $p < 0.035$ ). The average delay in disease progression was about six months in people who progressed to AD. This risk reduction was lost at three years, when progression to AD was similar in all three treatment groups. "It appears there is protection against progression to AD for the first 18 months of treatment," Dr Petersen noted, adding, "Perhaps we can intervene at an earlier stage of disease than previously thought – pre-AD."

An open label extension study of patients with MCI treated with flexible dosing of galantamine up to 24mg/day showed similar results, with a reduction in conversion to dementia during the first few months of treatment but no significant difference at two years. However, Michael Gold, Johnson & Johnson Pharmaceutical Research and Development, Titusville, USA, said there was reduction of about 20% in new conversions in favour of galantamine. He added that there was also a significant reduction in whole brain atrophy in favour of galantamine (0.619 for placebo vs 0.413 for galantamine).

The benefits of continuing donepezil treatment in patients showing unclear benefit after 12 weeks was demonstrated in results from the AWARE (Aricept Washout and Rechallenge) study showing behavioural benefits compared to those discontinuing therapy. The study randomised 193/619 patients who showed unclear benefit with 12 weeks' donepezil (10mg/day) to continue with the drug or switch to placebo. Results showed significant improvement in behaviour after a further 12 weeks' treatment with donepezil ( $p < 0.05$ ) – with particular improvement in depression and dysphoria.

Reporting the results, Peter Johannsen, Righospitalet, Copenhagen, Denmark, said, "Behavioural symptoms should be considered when evaluating the treatment response in patients with mild to moderate AD."

Patients with AD living in residential care treated with donepezil on a long-term basis showed greater functional and cognitive benefits than those who stopped treatment, according to a retrospective analysis. The study – one of the first to study long-term treatment with donepezil – included 420 patients with AD who had been treated with donepezil for at least 60 days, with half (210) continuing donepezil therapy and half stopping treatment. Results showed that continued donepezil treatment resulted in significant improvements in behaviour frequency ( $p < 0.05$ ), behaviour alterability ( $p < 0.05$ ) and quality of life ( $p < 0.05$ ), compared to baseline assessment. Patients discontinuing treatment showed significant declines in cognitive status ( $p < 0.001$ ) and functional mobility ( $p < 0.0001$ ).

A cost-effectiveness analysis showed that discontinuing donepezil was associated with an increase in average daily care costs, with a saving of \$6.90 per patient per day for patients remaining on treatment. David Smith, Texas A&M University, Texas, USA, reported, "Behaviour and quality of life improved; care costs of those who continued treatment were lower than for those who stopped."

Alzhemed (NC758) – an anti-A-beta amyloid agent – proved safe and well tolerated in a study of 58 patients with mild to moderate AD. Paul Aisen, Georgetown University Medical Center, Washington, USA, reported that the drug was detected in the cerebrospinal fluid (CSF), suggesting that it crossed into the brain. Results showed that levels of beta-amyloid protein circulating in the CSF fell after three months' treatment with the highest dose of NC758. "This indicated less amyloid accumulation in the brain," he proposed. He reported that there were no serious side effects associated with the drug.

A multicentre, randomised trial of A-beta immunotherapy AN1792 in 300 patients was stopped early after meningoencephalitis occurred in 6% of immunised subjects (18/300). Although stopped early, after most patients had been given only two of six planned injections, 19.7% (59) developed an antibody response. No differences were found in cognitive measures including MMSE but Sid Gilman, University of Michigan, Ann Arbor, USA, reported that there was a difference in a composite score of several memory tests favouring antibody responders.

Results also showed that CSF-tau was reduced in antibody responders. Whole brain volume was decreased and ventricular volume increased. Autopsy samples suggested evidence of plaque clearance in all cases. Dr Gilman considered these were promising – although very early – therapeutic results.

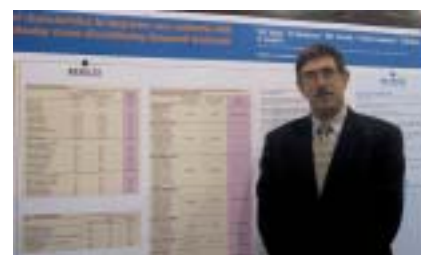
## Imaging Studies Reveal AD Progression

Several studies were reported with the amyloid imaging PET tracer, Pittsburgh Compound-B (PIB), a novel amyloid-specific tracer. High specific activity PIB PET scanning data from a preliminary study of five people with MCI showed that the subjects fell into two distinct groups – one showed similar levels of amyloid deposition to normal, age-matched controls, while the second group showed evidence of amyloid deposition that was indistinguishable from patients with AD. PIB distribution closely resembled the known post-mortem distribution of amyloid in AD.

William Klunk, University of Pittsburgh, Pittsburgh, USA, said, "PIB-PET imaging may provide a quantitative assessment of amyloid deposition in living brain." He added, "Amyloid imaging with PET may be useful for predicting which people with MCI will progress to Alzheimer's in the near future. It might also help to determine the effectiveness of anti-amyloid therapies."

Dr Klunk noted that six centres throughout the world were now using Pittsburgh Compound-B in more than 100 different studies. He suggested that it could potentially be used in diagnosis (before symptoms), investigating pathophysiology and developing anti-amyloid therapies – with effects on PIB being used as a surrogate endpoint of efficacy. A very preliminary study from one patient treated with the anti-amyloid agent AN-1792 showed a remarkable decrease in PIB, he reported.

Another PET technique, using [F-18]FDDNP, which



binds to amyloid plaques and tangles of abnormal tau protein, showed that global [F-18]FDDNP binding was significantly higher for 13 patients with AD compared to that in 10 controls (1.17+0.03 vs 1.04+0.03;  $p < 0.0001$ ). Global binding in 5 patients with MCI was also higher than in controls (1.10+0.05;  $p = 0.005$ ). Different brain regions showed the expected pattern of AD pathology distribution.

Gary Small, University of California, Los Angeles commented, "These findings demonstrate the ability of [F-18]FDDNP binding to differentiate various degrees of cognitive decline in older populations." He added, "We believe this is the first time tau accumulation has been visualised in living patients. This technique may help us better differentiate between AD and other forms of dementia."

### Prevention Studies

The importance of lifestyle factors in AD was illustrated in several studies showing that body weight, blood pressure, cholesterol level, lung function, leisure activity and dietary intake of vegetables were all linked to the risk of developing the disease.

A 10-year study from the Karolinska Institute, Stockholm, showed that individuals who were obese in middle age were

twice as likely to develop dementia later as those of normal body weight. For those who also had raised cholesterol and blood pressure, the risk of dementia was six times higher.

Another study suggested that leisure pursuits involving mental, social or physical activity all seemed to offer some protection against dementia. The greatest benefit came from complex pursuits combining two or three types of activity.

Findings from the long-running Nurses' Health Study demonstrated that high intake of leafy, green (such as spinach), or cruciferous (eg broccoli), vegetables was associated with less decline on cognitive tests than lower intake. "The difference amounted to being about one to two years younger in terms of cognitive ageing," reported Jae Hee Kang, Harvard Medical School, Boston.

"Although Alzheimer's is a complex disease with complex causes, studies at the conference bolstered evidence that we may be able to influence at least some factors in the mix," concluded William Thies, Vice-President of Medical and Scientific Affairs with the Alzheimer's Association.

Susan Mayor PhD,  
Freelance Medical Journalist, London.

## Epilepsy Specialist Nurse (ESNA) Conference

13-14th September 2004;  
Sheffield, UK.

This is the third year the ESNA conference has been held in Sheffield. Organisers Chris Morley and Debbie Coker aimed to make the 2-day conference the best yet, adapting it based on members' comments about previous years. Speakers at the conference all work in the field of Epilepsy and presented current work or services in development. A group of excellent speakers covered a wide range of subjects, and this was well received by members (nurses working with adults, young people or children with Epilepsy, or nurses with an interest in Epilepsy). ESNA also held its Annual General Meeting. Below is a brief summary of the conference presentations.

Professor Trimble from the National Hospital for Neurology & Neurosurgery explained about innovative approaches to target seizure activity, including Transcranial Magnetic Stimulation, Vagal Nerve Stimulation, and Biofeedback.

Heather Sullivan, Epilepsy Nurse Specialist in Learning Disability, presented Dr Steven Brown's and the Epilepsy Nurses' findings of a telemedicine appointment for people with a learning disability in Cornwall. This initiative has been funded by Action on Neurology. It has helped to reduce waiting times to see the Consultant, reduced costs for travel expenditure and recorded some patients' seizures.

Dr Selway, Consultant Neurosurgeon at Kings College Hospital, London, discussed the different effects of brain stimulation to treat seizure symptoms. For example, subthalamic stimulation can help patients with partial seizures and caudate stimulation may affect mesial temporal lobe epilepsy and status epilepticus.

Julia Ackril, Senior Dietician for the Neurology Team at Birmingham Children's Hospital, spoke about the Ketogenic diet and the theory of how it can suppress seizures. She also highlighted common problems associated with the diet and presented a successful case study. Discussion followed on the diet's long term effects, risk of relapse, use with PEG feeds and the age at which patients could commence the diet.

Dr Turnpenny, Clinical Geneticist, Exeter, delivered a presentation on the risk for women with epilepsy taking anti epileptic drugs in pregnancy. Two teams from Exeter and Aberdeen have been helping to identify and follow up children with problems associated with anti convulsant

syndrome (ACS). He concluded that Nurses may be in a unique position to identify families affected by ACS.

Dr Marcus Reuber, Consultant Neurologist at the Royal Hallamshire Hospital, Sheffield, described seizure classification from 1052 BC to the present day. He explained the reasons the ILAE classification 1981/89 is changing. The new ILAE classification is recommended by the forthcoming NICE guidelines.

Mel Goodwin (ESNA chairman) and Jeff Bolton, Senior Product Manager, Pfizer Ltd announced a Nursing Award Practice for Achievements in the Care of Epilepsy. The details will be published in ACNR this year and the awards will be presented in 2005. There will be 3 categories with a total of 5 awards and prize money of £500 per winner. Epilepsy Action has been sponsored by Pfizer to send questionnaires to Epilepsy Nurse Specialists to identify their role. Watch out for your questionnaire arriving by post.

Jill Atkins, Lecturer at Buckingham University, discussed the results of her study on Epilepsy in later life. Her results conclude that it was most likely that the GP diagnosed that the patient had epilepsy - all the elderly people had hidden their diagnosis from their family, and the subject of their epilepsy was the main focus of the study. Also, the patients who had Epilepsy Nurses felt that they provided a lot of support. The patients wish they were seen in their own home. Jill aims to publish her study this year.

From my experience of talking to members, this was a very good conference. For those members who couldn't make it, I hope this brief update gives you some insight into the proceedings - and we hope to see you next year.

Finally the Malcolm Taylor award was won by Heather Gregory. Heather received her prize from Mrs Taylor, who spoke about her late husband's dedication to improving services for people with epilepsy.

Sally Collins,  
Epilepsy Nurse Specialist, Rotherham General Hospital.



Mrs Anne Taylor, left (wife of Dr Malcolm P Taylor), presenting the Malcolm Taylor Award to Heather Gregory.



See [www.acnr.co.uk/conferences.htm](http://www.acnr.co.uk/conferences.htm) for an additional report on the BSRM/Dutch Rehabilitation meeting.

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### AIMS OF THE CONFERENCE

TO PRESENT A REVIEW AND UPDATE ON THE CURRENT DEVELOPMENTS IN THE DEMENTIAS;

- IN THE FIELDS OF RESEARCH
- INVESTIGATIONS
- CLINICAL CARE
- SERVICE AND POLICY ISSUES

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# The Use of Amantadine in Parkinson's Disease and other Akinetic-Rigid Disorders

## Introduction

Amantadine was originally introduced as an antiviral agent to treat influenza A and was coincidentally found to ameliorate symptoms in a patient with Parkinson's Disease (PD) in 1969.<sup>1</sup> Since that time many clinical trials have investigated the efficacy of amantadine alone and in combination with other antiparkinsonian drugs. Most of these trials took place in the early 1970s. More recently, the use of amantadine has focused upon the treatment of levodopa-induced motor fluctuations and dyskinesias.

This article will summarise the evidence available for the use of amantadine in PD and other movement disorders.

## Mechanism of action

Amantadine hydrochloride is a tricyclic amine that is well absorbed orally and is excreted largely unchanged in the urine. It has several proposed mechanisms of action.

- It acts on the pre-synaptic membrane, enhancing the release of dopamine and inhibiting its reuptake.<sup>2</sup> In vitro, however, the latter effect occurs only with high doses and is therefore thought to be unlikely to contribute to its clinical efficacy.<sup>3</sup>
- Post-synaptically, amantadine acts directly on the dopamine receptor, and up regulates D2 receptors in vivo.<sup>4</sup> This may be due to amantadine-induced hypersensitivity of dopamine receptors, which has been demonstrated in rats, although the effects were only transient.<sup>5</sup>
- It has antimuscarinic properties.<sup>6</sup>
- Amantadine has antiglutamatergic properties, via non-competitive antagonism of NMDA receptors.<sup>7</sup> In 6-hydroxydopamine lesioned rats, systemic and intrastriatal injection of a NMDA antagonist can reverse or prevent the changes in motor response that occur with sustained levodopa treatment.<sup>8</sup> Furthermore, potent, competitive, non-subunit selective NMDA receptor antagonists reduce the severity of levodopa-induced dyskinesias in non-human pri-

mates with MPTP parkinsonism.<sup>9,10</sup> These and other observations suggest that NMDA receptor sensitisation may be a key event in the genesis of levodopa-induced dyskinesias.

- Amantadine may have immunomodulatory properties. It restored the production of interleukin-2 (IL-2), which is defective in PD patients.<sup>11</sup> IL-2 levels did not correspond to clinical improvement so the significance of these findings is uncertain.
- One study has shown that amantadine was an independent predictor of improved survival in PD.<sup>12</sup>

## Symptomatic control of Parkinson's disease

Although many trials have assessed the efficacy of amantadine versus placebo for the treatment of motor impairment in PD, the majority were undertaken in the 1970s and suffer from poor methodology or small patient numbers. A Cochrane review in 2002 described six randomised controlled trials that used amantadine as either mono- or adjunctive therapy in PD. Although all reported beneficial effects for amantadine, it was concluded that the evidence available was insufficient to draw any firm conclusions.

## Monotherapy

Initial open label or unblinded studies did not show any consistent results and are difficult to analyse.<sup>13,14</sup> Randomised, double-blind crossover trials are summarised in Table 1. Most trials showed mild beneficial effects of amantadine but follow up periods were too short to comment on long term effects of the drug.

## Adjuvant therapy

Amantadine has been trialled in PD as adjuvant therapy to levodopa and anticholinergics. As with monotherapy, poor methodology limits the interpretation of the results, but some of the more robust trials are summarised in Table 2.



**Dr Naomi Warren** qualified from Newcastle University in 1997. She is a Specialist Registrar in Neurology in the Northern Region. However, she is currently taking time out from the training programme to undertake an MD looking at neurochemical abnormalities in Progressive Supranuclear Palsy.



**David J Burn** is the Editor of ACNR's conference news section and Consultant and Reader in Movement Disorder Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He runs Movement Disorders clinics in Newcastle upon Tyne. Research interests include progressive supranuclear palsy and dementia with Lewy bodies.

**Table 1: Monotherapy randomised, double-blind crossover trials**

Author/Date	Type of trial	Number of PD patients in trial	Intervention	Outcome	Comments
Mawdsley C et al 1972 <sup>15</sup>	Double-blind crossover (4 weeks)	42	Amantadine v placebo	Initial Improvements not maintained at 4 weeks	Some patients had non-idiopathic PD. Patients allowed to chose which drug to continue
Fahn S et al 1975 <sup>16</sup>	Double-blind crossover (4 weeks)	23	Amantadine v placebo	70% improvement in patients on amantadine	Did not present data from placebo arm
Butzer JF et al 1975 <sup>17</sup>	Double-blind crossover (4 weeks)	30	Amantadine v placebo	12% improvement	Some patients had non-idiopathic PD. 3 patients also on anticholinergic treatment
Cox B et al 1973 <sup>18</sup>	Double-blind crossover (6 weeks)	27	Amantadine v levodopa	No improvement in amantadine group	Some improvement when amantadine used in second arm
Parks JD et al 1974 <sup>19</sup>	Double-blind crossover (8 weeks)	15	Amantadine v benzhexol v amantadine + benzhexol	15% improvement in symptoms and not separated for each drug alone, 40% with combined treatment	Some non-idiopathic PD were included in analyses

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**Table 2: Amantadine as adjuvant therapy. ADL – Activities of daily living**

Author/Date	Type of trial	Number of patients in trial	Intervention	Outcome	Comment
Bauer RB et al, 1974 <sup>20</sup>	Randomised double-blind crossover (6 weeks)	48	Amantadine v placebo in patients taking anticholinergics	Improvement in timed tests in 10% of patients	Included some patients with non-idiopathic PD
Jorgensen PB et al, 1971 <sup>21</sup>	Randomised double-blind crossover (3 weeks)	149	Amantadine v placebo in patients taking anticholinergics	Functional improvement in 56% patients. Most benefit in most severely affected patients	Included some patients with non-idiopathic PD
Rinne UK et al, 1972 <sup>22</sup>	Double-blind, non-randomised crossover (4 weeks)	38	Amantadine v placebo in patients taking anticholinergics	60% showed improvement in disability and parkinsonism	Included some patients with non-idiopathic PD
Barbeau A et al, 1971 <sup>23</sup>	Randomised double-blind crossover (8 weeks)	54	Amantadine v placebo in patients taking anticholinergics	Significant improvement in disability and impairment	Included some patients who had undergone stereotactic brain surgery
Forssman B et al, 1972 <sup>24</sup>	Randomised double-blind crossover	27	Amantadine v placebo in patients taking anticholinergics	Significant improvement in parkinsonism and functional status	Included some patients who had undergone stereotactic brain surgery
Walker JE et al, 1972 <sup>25</sup>	Randomised double-blind crossover (6 weeks)	42	Amantadine v placebo. Anticholinergics were stopped in all but 6 patients	64% v 21% improvement in ADLs, but of little statistical significance	No withdrawals
Silver DE et al, 1971 <sup>26</sup>	Randomised double-blind parallel (mean 35 weeks)	50	Amantadine v placebo in patients taking their usual medication (mostly anticholinergics)	Improvement in parkinsonism peaking at 2-3 months	Gradual tapering of effect, but maintained up to 7 months
Fehling C et al, 1973 <sup>27</sup>	Randomised double-blind crossover (2 months)	30	Amantadine v placebo in patients continuing with other therapy (levodopa and anticholinergics)	Significant improvement in PD scores, marginal improvement in functional ability	9 patients withdrew
Savery F et al, 1977 <sup>28</sup>	Randomised double-blind crossover (18 weeks)	42	Amantadine v placebo in patients taking levodopa	Improvement in all but 2 patients, in symptoms and functional activities	
Millac P et al, 1970 <sup>28</sup>	Double-blind, non-randomised parallel (3 months)	32	Amantadine v placebo in patients then started on levodopa	No significant difference in symptoms or examination and no difference in dose of levodopa needed	Included some patients with non-idiopathic PD
Callaghan N et al, 1974 <sup>29</sup>	Open label	31	Amantadine v levodopa v both	Levodopa treatment superior + no benefit when amantadine added	Included some patients with non-idiopathic PD
Muller T et al, 2003 <sup>30</sup>	Open label (4 days)	31	Intravenous amantadine in patients on pre-existing PD therapies	Improvements in motor symptoms and peg insertion but not hand tapping	No control group

The lack of high quality clinical trials limits conclusions which can be drawn as to the efficacy of amantadine in improving motor symptoms of PD. Variable results are seen when amantadine is used in addition to levodopa although there appears to be some benefits when added to anticholinergic therapies. The studies were all very short and there was some suggestion of tachyphylaxis occurring over longer treatment duration. Interestingly, in one trial those patients with most severe disease seemed to derive the greatest benefit.<sup>21</sup>

In our practice we rarely use amantadine as monotherapy, but occasionally find it useful as adjunct therapy to dopamine agonists to delay the need to start levodopa.

### Amantadine to treat dyskinesias in Parkinson's disease

In 1998, a double-blind placebo-controlled crossover study (3 weeks each arm) found amantadine reduced dyskinesia severity, induced by intravenous levodopa, by 60% without altering the antiparkinsonian effect of levodopa.<sup>31</sup> Eighteen patients were included in the trial and four withdrew due to side effects, notably confusion and hallucinations. In a follow up study one year later the anti-dyskinetic effect of amantadine was maintained (56%),<sup>32</sup> although this study was of an unusual design and patient numbers were small. Two further double-blind placebo controlled crossover studies included 24 and 11 patients and reported reductions in dyskinesias of 24%<sup>33</sup> and 50%<sup>34</sup> respectively with oral amantadine. A total of three patients withdrew from these studies. Only one of the three studies included a wash out period between treatment arms<sup>34</sup> so the potential for a carry over effect exists. An open label study of 21 PD patients with no control group found intravenous amantadine followed by oral treatment reduced dyskinesias from 2.5 to 1.3 hours per day.<sup>35</sup> In another open label study of 26 patients amantadine improved dyskinesias by approximately 70% at 3 weeks.<sup>36</sup> This beneficial effect was maintained over an average follow up period of 6.5 months. Intravenous amantadine given on two consecutive days also improved dyskinesias by 50% in nine PD patients.<sup>37</sup> A more recent double-blind placebo controlled study of oral amantadine in 40 patients demonstrated a 45% reduction in dyskinesias in the first month which was not maintained at three to eight months.<sup>38</sup> Five patients withdrew due to side effects. Eleven patients suffered rebound dyskinesias on withdrawal of the drug, two resulting in febrile reactions and confusion.

Two trials have assessed the effect of amantadine on motor fluctuations as secondary outcomes. One reported beneficial effects, with significant reduction in off times,<sup>31</sup> while the other found no difference.<sup>34</sup>

Although most trials have suffered from methodological problems, the overall trend suggests that amantadine is useful for the short term treatment of dyskinesias while little is known of its long term efficacy and patients may become tolerant to the drug. A Cochrane review in 2003 concluded there was insufficient evidence to determine the effectiveness of amantadine in treating levodopa-induced dyskinesias.

Our practice in patients with dyskinesias, unresponsive to conventional measures such as reduction of levodopa, is to start amantadine at 100mg in the morning and increase to 100mg twice a day thereafter. Occasionally an extra 100mg needs to be added at lunch time, but we rarely exceed 300mg per day, and would not use the drug in patients with a history of visual hallucinations or neuropsychiatric problems.

### Dose of Amantadine in clinical studies

In most studies a daily dose of 200mg or 300mg of amantadine was used. One study used only 100mg<sup>27</sup> and another used up to 400mg.<sup>31</sup> It is difficult to assess if higher doses produced more side effects, and there is no data on whether an increase in dose may improve the long term efficacy of amantadine.

### Side effects and adverse reactions

The side effects of amantadine appear to be mild and transient, most commonly livedo reticularis, dizziness, anorexia and blurred vision. This resulted in few patient withdrawals. However, confusion and hallucinations can be problematic, particularly in the elderly PD patient.<sup>39</sup> Toxic levels of amantadine can occur in patients with renal insufficiency as the drug is excreted largely unchanged in the urine.<sup>40</sup>

Withdrawal of amantadine can lead to an encephalopathy, acute delirium, neuroleptic malignant syndrome and motor deterioration.<sup>21,41,42</sup> Three patients with a mean age of 73 years developed acute confusion, disorientation and paranoia on stopping long-term treatment of amantadine.<sup>43</sup> Reinstating the drug restored baseline status. It is noteworthy that all three had a previous history of cognitive impairment and transient hallucinations.

### Patients' characteristics

The mean age of patients in most trials was 60-66 years, but with a wide range (29 to over 80 years of age). There is little evidence to determine whether the age or gender of the patient has any overall effect on treatment response. Disease duration also varied widely between trials, being an average of seven to nine years in the motor treatment trials and over ten years in the dyskinesia trials.

**Table 3: The use of amantadine in our clinical practice**

Use in our clinical practice	Comment	Dose	Caution
Treatment of motor symptoms - monotherapy	Rarely used	100 - 300mg in divided daily doses	Avoid in patients with a history of hallucinations or psychiatric symptoms. Avoid sudden withdrawal
Treatment of motor symptoms - adjunct therapy	May be useful as adjunct to dopamine agonists, as levodopa delaying agent	100 - 300mg in divided daily doses	
Treatment of dyskinesias	Useful if dyskinesias problematic after reduction of dopaminergic therapies	100 - 300mg in divided daily doses	
Other akinetic-rigid syndromes	May be useful as adjunct or alternative to levodopa	100 - 300mg in divided daily doses	



### Amantadine in other akinetic-rigid disorders

There is very limited data available for the efficacy of amantadine in other akinetic-rigid disorders, and well designed clinical trials are needed. Often, in the absence of response to other treatments (particularly levodopa) amantadine is used. Anecdotally, patients may improve with treatment and deteriorate on discontinuation, but whether amantadine provides true clinical benefit remains questionable.

### Multiple System Atrophy (MSA)

In the only placebo controlled trial of amantadine (200mg daily) in 30 patients with MSA-C (previously known as the olivopontocerebellar type of MSA), the drug produced significant improvements in reaction and movement time over three to four months.<sup>44</sup> Two other studies have reported improvements in reaction and movement times with amantadine but they had either no placebo group<sup>45</sup> or only an "untreated" group for comparison.<sup>46</sup>

### Progressive Supranuclear Palsy (PSP)

Three retrospective reviews of treatment in PSP have considered amantadine. Marginal benefit in symptoms (parkinsonism and dystonia) in very few patients were reported in all.<sup>47-49</sup> In the only autopsy confirmed report,

two of five patients improved with amantadine but three patients had shown deterioration.<sup>49</sup>

### Other akinetic-rigid syndromes

There is one case report of a patient with corticobasal degeneration showing improvement in praxis with amantadine, which was reproducible on retesting.<sup>50</sup> There are no reports of its use in vascular parkinsonism.

### The use of Amantadine in our clinical practice

Due to the lack of well designed clinical trials for the benefits of amantadine in PD and other akinetic-rigid disorders, clinical practice is often based on personal experience. The use of amantadine in our own practice is summarised in Table 3.

### Conclusions

Amantadine appears to improve dyskinesias in the short term in PD but it is unknown how long these beneficial effects are sustained. It probably also has a mild benefit on the motor symptoms of PD but is far less potent than levodopa. Amantadine should be used with caution in patients with a history of confusion or hallucinations. The dearth of information available for PD and other akinetic-rigid syndromes highlights the need for more robust clinical trials of this pharmacologically interesting drug.

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## EDITOR'S CHOICE

## Generation of prions in a test tube

Prion diseases are a group of fatal neurodegenerative disorders, including Creutzfeldt Jakob disease, which exist in sporadic, genetic or acquired forms. They are characterised by the accumulation of PrP<sup>Sc</sup>, a misfolded form of the host prion protein. It is thought that PrP<sup>Sc</sup> acts as a template for the conversion of PrP<sup>C</sup> to its disease-associated conformation. The exact nature of the infectious agent of prion disease has been a hotly debated topic in the field. A widely accepted theory, "protein-only hypothesis", states that the agent is solely proteinaceous. However some believe that other agents, such as nucleic acids, maybe involved in the conversion of PrP<sup>C</sup> to PrP<sup>Sc</sup>. Recent work by Nobel prize-winner Stanley Prusiner lab lends further support to the "protein-only hypothesis". They demonstrated that intracerebral inoculation of a recombinant prion induced neurodegeneration in mice, which overexpressed a fragment of PrP (amino acids 89-231) sixteen times above its normal levels. The recombinant prion was produced by expression of a truncated mouse PrP (89-231) in E.Coli. This material was purified and then polymerised into amyloid fibrils. The mice injected with PrP amyloid developed neurological dysfunction at 380 to 660 days post-inoculation, whilst the control mice remained healthy at 670 days. To demonstrate the infectious nature of the recombinant prion, the brain extracts from sick recombinant PrP mice were shown to successfully transmit disease to wild-type mice. Prusiner claims this work is convincing evidence that prions are infectious proteins and that PrP<sup>C</sup> alone is necessary and sufficient for infectivity. However, experts in the field are wary of jumping to such conclusions. John Collinge from the Institute of Neurology, London, has found that mice over-expressing PrP by 10 times wild-type levels can spontaneously develop prion disease. Moreover, the Prusiner study only involved a small number of animals. The ultimate proof of the "protein-only hypothesis" would be to use recombinant PrP to induce prion disease in wild-type mice expressing normal levels of PrP. Until this has been accomplished, the contribution of an exogenous agent in prion propagation cannot be ruled out. - *LMS, SJT*

Legname G, Baskakov I, Nguyen HB, Riesner D, Cohen FE, DeArmond SJ, Prusiner SB.

*Synthetic Mammalian Prions*

SCIENCE

2004;305:673-76.

## PARKINSON'S DISEASE: Pinky, Parky, DJ and regular Lewy Bodies

★★★ RECOMMENDED

In May this year, Nicholas Wood's group published a Science paper defining a new mutation in three families with recessive parkinsonism, which they called PINK1, bringing to four the number of genes causing mendelian inherited parkinsonism: PARK1 (alpha-synuclein), parkin, DJ-1 and PINK1. Labs all over the world reached for the PINK-1 primers and got cracking... By the September issue of Annals, there were four papers on parkinsonism and PINK-1. An Italian group looked at 100 of their sporadic early-onset (less than 50 years old) Parkinson's patients and found 7 with missense mutations in PINK-1. A Japanese group found 6 out of 8 of their familial parkinsonism families had PINK-1 mutations. And a Spanish group describe one case of early onset parkinsonism with the PINK-1 mutation. In the most important study, the Wood team genotyped SNPs of PINK-1 in 576 cases of regular Parkinson's disease and 514 controls, finding no evidence that PINK-1 variants predispose to Parkinson's disease. The picture that emerges is that PINK-1 mutations cause a recessive inherited form of parkinsonism that is rather similar to the parkin and DJ1 diseases: young onset, a slow course, dystonia at onset and a good response to levodopa. -*AJC*

Valente EM et al.

*Hereditary early-onset Parkinson's disease caused by mutations in PINK1.*

SCIENCE

2004;304:1158-60.

Valente EM et al.

*PINK1 mutations are associated with sporadic early-onset parkinsonism.*

ANNALS OF NEUROLOGY

2004;56:336-41.

Healy DG.

*The gene responsible for PARK6 Parkinson's disease, PINK1, does not influence common forms of parkinsonism.*

ANNALS OF NEUROLOGY

2004; 56:329-35.

Hatano Y et al.

*Novel PINK1 mutations in early-onset parkinsonism.*

ANNALS OF NEUROLOGY

2004;56:424-7.

Rohe CF et al.

*Homozygous PINK1 C-terminus mutation causing early-onset parkinsonism.*

ANNALS OF NEUROLOGY

2004;56:427-31.

## EPILEPSY: Ictal stuttering

In this study, 230 adult patients were identified who met the criteria of seizures which were recorded with monitoring, who had a single diagnosis of epilepsy or psychogenic non-epileptic seizures (PNES) and did not suffer learning disability or interictal stuttering. 117 had PNES (17 male) and 113 had epilepsy (55 male). Ten had ictal stuttering (2 male). These patients often gesticulated in their seizures as if they were trying hard to speak but were unable to. They often struggled with the first part of the word: "ye.. ye.. ye.. yes". After the seizure some patients would suddenly give a burst of fluent speech that had they had been unable to express during the seizure. All these patients had non-epileptic seizures. On psychological profiling, these patients had even more tendency to conversion symptoms than the remainder of the PNES group. This symptom adds to those that are useful in the diagnosis of PNES versus epilepsy, along with post-ictal tearfulness. Of course, the holy grail of the differentiating symptom between epilepsy and PNES will forever remain elusive but the fun is in the quest. Studies from 10 years ago showed a misdiagnosis rate of 20% for epilepsy in many clinics. With increasing awareness, I wonder how we are doing now? - *MRAM*

Vossler DG, Haltiner AM, Schepp MS, Friel PA, Caylor LM, Morgan JD, Doherty MJ.

*Ictal stuttering. A sign suggestive of psychogenic non-epileptic seizures.*

NEUROLOGY

2004;63:516-19.

## PARKINSON'S DISEASE: are new neurons really formed in the substantia nigra?

One of the current goals of cell biology is to stimulate the endogenous stem cells that reside in our brains to repair the degenerating or damaged brain. It is now generally accepted that new neurons are formed even in the adult mammalian brain in the subventricular zone around the lateral ventricles and in the dentate gyrus of the hippocampus. However, there is considerable

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debate about whether neurogenesis persists into adulthood outside these regions, or whether, given appropriate stimulation, it could be induced. Thus considerable interest followed the report by Zhao et al that they had identified neurogenesis in the adult mouse substantia nigra: might it be possible to induce these cells to replace the lost dopaminergic neurons in Parkinson's disease (PD)? The initial report suggested a much slower rate of cell generation than that seen in the hippocampus, but none the less the authors suggested that it would be sufficient to regenerate the entire population of nigral dopaminergic neurons throughout the lifespan of a mouse. Furthermore, in line with the lesion-induced neurogenesis seen in other brain regions, they reported increased nigral dopamine neuron generation after a partial lesion with MPTP (demonstrated by double labelling dividing dopaminergic cells with tyrosine hydroxylase, TH, and the thymidine analogue BrdU). However, in response to this article Frielingsdorf et al reported that they could not identify new dopaminergic neurons in the adult rodent substantia nigra (rat or mouse) either in normal animals or in hemi-Parkinsonian 6-hydroxydopamine-lesioned animals (a commonly used alternative to MPTP to model PD in rodents). They even failed to find convincing evidence of TH/BrdU double labelled cells after administration of brain-derived neurotrophic factor that has been shown to enhance neurogenesis in other regions of the rat brain. Other groups have failed to demonstrate the generation of new nigral dopaminergic neurons using different techniques, although they have identified dividing cells that co-express BrdU with markers of the glial cell lineage. Thus the jury is out. - *AW Michell*

**Frielingsdorf H, Schwarz K, Brundin P, Mohapel P.**

*No evidence for new dopaminergic neurons in the adult mammalian substantia nigra.*

PROCEEDINGS NATIONAL ACADEMY OF SCIENCES  
2004;101:10177-82.

**Zhao M, Momma S, Delfani K, Carlen M, Cassidy RM, Johansson CB, Brismar H, Shupliakov O, Frisen J, Janson AM.**

*Evidence for neurogenesis in the adult mammalian substantia nigra.*

PROCEEDINGS NATIONAL ACADEMY OF SCIENCES  
2003;100:7925-30.

### PERIPHERAL NERVE: Lewis-Sumner and all that

It is easy to forget that our taxonomy of the inflammatory peripheral neuropathies is actually quite recent: CIDP being defined in 1982 (by Dyck) and multi-focal motor neuropathy with conduction block being recognised in 1988 (Parry & Clarke). There has been much jostling of immune-mediated neuropathies between these two since. Lewis, Sumner, Brown & Asbury introduced a difficult entity in 1982: an asymmetrical neuropathy mainly affecting the arms, with multifocal conduction block. Sadly the eponymists could only cope with the first two authors... and those preferring descriptive names have caused much confusion... but seem to be settling now on "multifocal acquired demyelinating sensory and motor neuropathy". This old-fashioned piece of descriptive neurology, a case series of 23 patients with Lewis-Sumner neuropathy, comes out of the Salpêtrière. There is little surprising, as much learned from the 50 odd cases in the previous literature is confirmed: initial symptoms start in the arms in 70%, with distal muscle wasting in 50%; there was cranial nerve involvement in 25%; CSF protein is normal in 70%; and conduction block was usually found in the forearms; anti-GM1 antibodies were absent. The important point is that 33% of patients benefited from oral steroids in contrast to the dogma that multifocal motor neuropathy with conduction block is steroid-resistant. 50% of patients responded to IVIG... so you lumpers could – I suppose – just give all your immune-mediated neuropathies IVIG. I can hear finance departments groaning up and down the land... - *AJC*

**Viala K, Renie L, Maisonobe T, Behin A, Neil J, Leger JM, Bouche P.**

*Follow-up study and response to treatment in 23 patients with Lewis-Sumner syndrome.*

BRAIN  
2004;127:2010-7.

### PARKINSON'S DISEASE: What's UPSet in PD?

The aetiology of Parkinson's disease (PD) remains unknown in the majority of cases but the recent identification of various genetic forms of Parkinsonism has pointed towards problems in the ubiquitin-proteasome system (UPS). It is in this context that this new study of McNaught et al is interesting. In this study adult rats were given chronic peripherally delivered inhibitors of the proteasome, following which they developed abnormalities akin to that seen in patients with PD. These abnormalities included behavioural motor problems with evidence of dopamine loss and pathology across a range of nuclei known to be affected in PD, which includes the formation

of inclusion bodies similar to the Lewy body that characterises PD. Furthermore, it also raises the question as to what is it in patients with PD that causes proteasome inhibition, presumably something in the environment. This is of course not a new idea, and once we start to think of this we remember similar scenarios with agents such as MPTP in the 1980s and more recently rotenone. Whether UPS inhibition will take us to heart of what causes PD in the clinic, remains unproven, but watch this space. - *RAB*

**McNaught KP, Perl DR, Brownell A-L, Olanow CW.**

*Systemic exposure to proteasome inhibitors causes a progressive model of Parkinson's disease.*

ANNALS OF NEUROLOGY  
2004;56:149-62.

### PARANEOPLASTIC: Ma, what does it look like?

★★★ RECOMMENDED

In this paper Dalmau and colleagues report their findings in 38 patients with anti-Ma2 antibody associated encephalitis, and as is common with their work the data is extensive and helpful, both in its breadth and depth. 38 patients (24M;12F) with a median age of 64 years were identified, of which two-thirds presented with their neurological symptoms ahead of their tumour diagnosis (most commonly germ cell tumours) and only in 4 was no tumour identified. 34 of the patients presented with symptoms of limbic, diencephalic or brainstem dysfunction with the remaining 4 cases having a cerebellar or spinal cord/plexus presentation, and in nearly all cases the neurological disorder was monophasic. These neurological problems commonly occurred with cranial imaging abnormalities – 23 out of 33 with an initial MRI scan and 2 out of 7 having CT scans – typically in the medial temporal lobes, midbrain and thalamus/hypothalamus. CSF was abnormal in 25 out of 32 cases with increased protein and pleocytosis (5-113 cells) being the commonest abnormalities, with normal glucose and oligoclonal bands in the majority of cases where they were tested. A third of the patients improved with treatment, which was immunological with or without chemotherapy; 3 patients made a complete recovery. The 40% of patients who also had additional anti-Ma1 antibodies did less well. Pathological findings in 4 patients were as to be expected, with typically florid inflammation. This paper is a comprehensive account of a relatively rare condition, and makes the points that paraneoplastic conditions can take many forms and finding the primary tumour can be difficult. However, in the young male patients with odd encephalitic/brainstem presentations, it would be worthwhile checking for these antibodies and examining the testes, whilst in older patients it may be the first presentation of a lung cancer. - *RAB*

**Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, Saiz A, Meneses P, Rosenfeld MR.**

*Clinical analysis of anti-Ma2-associated encephalitis.*

BRAIN  
2004;127:1831-44.

### NEGLECT: "Undercover" testing for unilateral neglect

★★★ RECOMMENDED

Visual neglect is commonly tested using cancellation tests in which the subject is asked to put a pen mark through targets that are randomly spread over a page. Subjects with neglect fail to cancel targets, especially missing those on the contralesional side of the page. Such behaviour relates to impaired performance in daily living tasks. It has been proposed that spatial working memory deficits can contribute to the neglect syndrome and so in conventional cancellation tests the pen marks made can cue subjects to search a little further. If so, cancellation tests using invisible marks may be more revealing. This has proved to be the case in a study comparing cancellation performance on tests done with ink and, as the authors put it, "undercover", using carbon paper. 23 successive cases, (average age 66 years), with suspected neglect performed a cancellation task using visible and invisible marks. Neglect of contralesional targets was more pronounced with invisible marks. Indeed about half of the subjects only showed neglect in the undercover version. This more sneaky undercover test may prove to be a very useful predictor of neglect behaviour, especially in borderline cases. However three quarters of all strokes occur in people over 65 years. It remains to be seen if elderly stroke patients can understand the more abstract undercover task and if performance is reliable. - *AJT*

**Wojciculik E, Rorden C, Clarke K, Husain M, Driver J.**

*Group study of an "undercover" test for visuospatial neglect: invisible cancellation can reveal more neglect than standard cancellation.*

J NEUROLOGY NEUROSURG PSYCHIATRY  
2004;75:1356-58.

## **PARKINSON'S: Ergot derived dopamine agonists – What should we do?**

It is well established that ergot derivatives can cause fibrosis of a variety of structures and hence their cautious use in conditions such as migraine. In Parkinson's disease there are four ergot derived dopamine agonists – namely bromocriptine, lisuride, pergolide and cabergoline – which are widely used both in the UK and abroad. In the BNF there is a clear warning about the fact that these drugs “have been associated with pulmonary, retroperitoneal and pericardial fibrotic reactions” which is followed by some rather vague advice on what should be done in the assessment and monitoring of patients on these agents. It is on this background that a series of new papers have emerged highlighting the fibrotic potential of these drugs, which has raised questions about the frequency and severity of such reactions and how we can best prevent and/or detect these side-effects. In the history of PD such stories about side-effects with commonly used drugs are not uncommon – for example, selegiline and tolcapone were both associated with major adverse effects only to re-emerge as acceptable therapies at a later time. Clearly though attention must be paid to such reports and in one of the most recent editorials in *Movement Disorders*, Oliver Rascol and colleagues try to help with a series of suggestions. So what should we do as prescribing clinicians? I think, note the data, and be aware of these problems and be pragmatic – thinking of this with the breathless PD patient for example. I think it is premature to shift our patients away from these drugs, given the efficacy that many patients report with these agents and the paucity of data on this topic using large cohorts of unselected patients. - *RAB*

Van Camp G, Flamez A, Cosyns B, Weytjens C, Muyldermans L, Van Zandijcke M, De Sutter J, Santens P, Decoodt P, Moerman C, Schoors D.

*Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease.*

LANCET 2004;363(9416):1179-83.

Rascol O, Pathak A, Bagheri H, Montastruc JL.

*New concerns about old drugs: Valvular heart disease on ergot derivative dopamine agonists as an exemplary situation of pharmacovigilance.*

MOVEMENT DISORDERS 2004;19(6):611-3.

Horvath J, Fross RD, Kleiner-Fisman G, Lerch R, Stalder H, Liaudat S, Raskoff WJ, Flachsbarth KD, Rakowski H, Pache JC, Burkhard PR, Lang AE. *Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists.*

MOVEMENT DISORDERS 2004;19(6):656-62.

Agarwal P, Fahn S, Frucht SJ.

*Diagnosis and management of pergolide-induced fibrosis.*

MOVEMENT DISORDERS 2004;19(6):699-704.

## **BRAIN INJURY: Effects of interactive strategy modelling on problem-solving**

It is well established that traumatic brain injury (TBI) often results in problems in executive function, one aspect of which is usually considered to be problem-solving. These problems are known to underlie some of the difficulties experienced by people with TBI in selecting from alternatives when solving problems and interacting appropriately with other people. This failure often contributes to the bizarre conversations that take place, founded on shared misperceptions of situations. Studies of the effectiveness of specific remediation techniques are relatively rare. This is not a study, it has to be said, of therapy for problem-solving in everyday life, which might present fairly major methodological barriers. On the other hand, it offers support for the use of a specific technique – Interactive Strategy Modelling Technique (ISMT) with TBI clients living in the community. The primary assessment was structured around a modified form of the twenty questions game, which is gaining in popularity as a rapid means of identifying strategies for problem-solving. Twenty participants were assessed before and after training, which involved teaching participants to use meta-cognitive strategies for narrowing down alternatives, via both explanation and practice. Learning effects were accounted for statistically. As a group, the participants made significant improvements on measures of the number and style of questions. In particular, the number of plain guesses across the group dropped from 104/326 to 38/525. Given the tendency of TBI clients to make impulsive behavioural and conversational choices, techniques to encourage inhibition and reflection are much in demand. The study did not set its sights high in terms of ecological validity but does represent another step in the search for ways to address the complex problems experienced by people with TBI in dealing with everyday life. - *R Body*

Marshall RC, Karow CM, Morelli CA, Iden KK, Dixon J & Cranfill TB. *Effects of interactive strategy modelling on problem-solving by persons with traumatic brain injury.*

APHASIOLOGY

2004;18:8:659-73.

## **MIGRAINE: Left sided migraineurs display augmented parasympathetic activation when compared to right sided migraineurs**

Evidence from lesion studies, stimulation studies and the Wada procedure has provided evidence that parasympathetic function is predominantly mediated by the left hemisphere and sympathetic by the right. Avnon et al have presented evidence that left sided unilateral migraineurs display augmented parasympathetic activation when compared to right sided migraineurs. They studied 15 patients with left sided and 15 patients with right sided migraine, but no non-migraineurs. Soapy water was instilled into the patient's eyes (the same results were obtained with each eye) to elicit the trigemino-parasympathetic reflex, measured by forehead vasodilation, and somato-sympathetic reflex, measured by digital vasoconstriction. Photoplethysmography pulse sensors were placed on each subject's forehead and index finger. This sensor consists of a light source and photo detector and detects changes in arterial blood volume by measuring changes in light reflection through tissues, such that maximal readings occur during end diastole and minimum readings during systole. Heart rate response to stimulation was also recorded. Forehead vasodilation and bradycardia ie a parasympathetic response, was greater in left sided versus right sided migraineurs both during and between migraine attacks. There was no difference between the two groups in digital vasoconstriction. Several reasons were considered for this difference in parasympathetic response. Pain scores were similar between two groups so altered pain perception and processing is unlikely to account for the difference. Antidromic release of vasoactive substances was considered unlikely, as forehead vasodilation was bilateral ie not a local effect. Digital vasoconstriction was the same between the two groups, thus altered sympathetic responses are unlikely to account for the difference. The authors postulated that the ipsilateral hypothalamus may play a role in augmented parasympathetic responses to stimulation, based on animal work and human functional MRI and PET imaging data. - *WP*

Avnon Y, Nitzan M, Sprecher E, Rogowski Z, Yarnitsky D.

*Autonomic asymmetry in migraine: augmented parasympathetic activation in left unilateral migraineurs.*

BRAIN

2004;127:2099-108.

## **MULTIPLE SCLEROSIS: Assessing muscle strength and motor fatigue**

Reliable tests to measure muscle strength and motor fatigue will enable physiotherapists and other clinicians to gauge how a person responds to ongoing therapy or treatment. Weakness and fatigue are characteristic symptoms of Multiple Sclerosis. Knee dynamometry is often used to measure muscular torque thereby enabling quantification of muscle strength and motor fatigue. Typically a patient is asked to extend or flex their leg against a hydraulic lever and required to hold this position while the applied force is measured. Muscle strength is measured over five seconds, whereas fatigue is calculated from the force-time curve over longer durations. Carried out in Finland, this small study tested the reliability of measuring isometric torque and a new fatigue index in 28 volunteers with mild-moderate MS. Repeated measurements of isometric torque in knee extension or flexion were gathered and indices of muscle fatigue were calculated. Subjective fatigue was recorded using the Fatigue Severity Scale. Measurements were repeated one week later. Isometric torque measurements assessed maximum muscle strength and areas under the force versus time curve provided the basis for calculating motor fatigue. Maximal isometric torque was reliably measured using the knee dynamometer. The authors conclude that their new index (calculated using the time of peak muscle strength as the starting point) is a reliable measure of motor fatigue in MS patients. They point out that previous indices include the rise to maximal strength (ie non-fatiguing time) in the calculations or omit the initial 5 seconds (where in MS fatigue may start). Interestingly, the subjective questionnaire data did not correlate well with the quantitative measures of motor fatigue. This underlines the importance of helping patients and clinicians communicate subtleties effectively. Developing objective and subjective measures in tandem would help to support this. - *LAJ*

Surakka J, Romberg A, Ruutiainen J, Virtanen A, Aunola S and Mäentaka K. *Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index*

CLINICAL REHABILITATION

2004;18:652-59.

## **EPILEPSY: A shocking pain in the neck**

Vagus nerve stimulation (VNS) has become increasingly popular as a treatment for epilepsy in the USA and more centres in the UK are also undertaking or planning to undertake the procedure. It involves inserting electrodes

around the left vagus nerve (supposedly less cardiac efferent fibres than the right) attached to a stimulator box. The box may work in one of two ways. It delivers regular pulses or it can be activated by an external device to give a pulse, for example if the patient senses the onset of one of their seizures. It is hypothesised that the pulses desynchronise cerebral rhythms and prevent build-up of pathological synchronised epileptic activity. Like all new treatments for refractory epilepsy, it was initially licensed for use in focal epilepsy and it is now being explored in other syndromes. In this study 16 adults were treated. Eight were diagnosed with idiopathic generalised epilepsy and eight with symptomatic generalised epilepsy. The aetiology of these symptomatic cases is not mentioned. Where a patient had more than 500 per month of one seizure type, the number was recorded as 500. The headline result is of a 43% reduction in seizures, but one has to go deeper into the results to work out what is going on. Am I naïve in thinking that it is the authors' job to get a calculator out and it should not be left up to the reader? If the conventional response rate of a 50% seizure reduction is used as in drug trials then the number of patients achieving this result is 37.5%, disappointing compared to most drug trials, and one has to remember that there is no placebo arm. Sixteen patients had 45 different seizure types between them ie between 2 and 4 each. Only 5 patients had more than 50% reduction in more than one seizure type. Hidden within this are some dramatic results with reductions in tonic seizures from 90 to 2, from 300 to 90 and from 210 to 12 in 3 patients in the study period. Three patients had atonic seizures and 2 had near complete cessation, a very useful benefit, given the morbidity of falls associated with these seizures. In fact only myoclonic seizures showed a reduction that was statistically significant. Patients with both idiopathic and symptomatic epilepsies seemed to show similar results. The results suffer from the usual statistical problems of small sample size and skewed results by a few patients with enormous numbers of seizures and an impressive result. Perhaps it doesn't matter that there are no useful selection criteria but as someone brought up on rigorous work-up for epilepsy surgery, this makes me uncomfortable. The results are modest but these patients are desperate and VNS seems to be safe, if expensive. I suspect that only history will judge if this is a passing fad. - **MRAM**

**Holmes MD, Silbergard DL, Drouhard D, Wilensky AJ, Ojeman LM.**

*Effect of Vagus nerve stimulation on adults with pharmacoresistant generalised epilepsy syndromes.*

**SEIZURE**

2004;13:340-45.

## **EPILEPSY: childhood epilepsy**

In this study the authors recruited 466 children with new onset epilepsy. This was about 75% of the number of children expected from previous epidemiological studies to develop epilepsy in the recruitment period. Follow-up was nearly complete; eight died and 5 were lost to follow-up. The primary outcome measure was terminal remission at 5 years, which is the duration of seizure freedom at 5 years since onset. They divided children into bands according to duration of remission at 5 years: 5years (14%), >4years(27%), 3-4 years (14%), 2-3 years (9%), 1-2 years (12%), <1year (ie not in remission, 24%). About 25% achieved terminal remission within 2 months of onset. The authors performed a multivariate analysis to identify the factors which predicted refractoriness. Factors relating to the seizure syndrome were the only ones which predicted a poor outcome at a level of  $P < 0.001$  and included infantile spasms, myoclonic and atonic seizures; and focal epilepsy (except the idiopathic group). Unclassifiable epilepsy was associated with a significantly better prognosis than other groups. A wide variety of other factors were not related to refractoriness, including gender, age at onset, other seizure types neurological signs, EEG, imaging, family history and history of febrile convulsions. They had previously reported this cohort at 2 years follow-up and found only 6% of patients with good control at 2 years deteriorated to poor control at 5 years. Generally the outcome at 5 years was predictable from the two year data although 25% improved from 2 to 5 years. This is an observational study and treatment cannot be assessed in a scientific fashion. However, 388 (86%) children received medication; 206 a single therapy. 46% achieved a remission greater than one year, 19% with two drugs and 9% with three or more. At 5 years only 161 were still using medication. This study confirms the view that most childhood epilepsy can be well controlled and is a benign condition but that focal epilepsy and certain rarer syndromes are more refractory. Overall, most children can expect their condition to be self-limiting. - **MRAM**

**Arts WFM, Brouwer OF, Boudjewin-Peters AC, Stroink, H, Peeters EAJ, Schmitz PIM, van Donselaar CE, Geerts AT.**

*Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood.*

**BRAIN**

2004;127:1774-84.

## **ALZHEIMER'S DISEASE: donepezil treatment**

★★★ **RECOMMENDED**

The acetylcholine esterase inhibitors (donepezil, rivastigmine and galantamine) represent the only specific treatment modality for that overwhelmingly common condition, Alzheimer's disease. Although approved by the National Institute of Clinical Excellence, there remains a great deal of uncertainty about their value in real clinic populations over the medium- to long-term. This independent, large, multicentre trial with broad inclusion criteria and follow-up for five years provides important, if disheartening, insights. It confirms the modest cognitive improvements reported by other, usually less rigorous, trials and documents continued efficacy of donepezil over two years. The key message, however, is that the primary outcome measures of time to institutionalisation and 'disability' (by the Bristol activities of daily living scale) did not differ significantly between the placebo and treatment groups. The many secondary endpoints, including carer-related indices, were similarly unimpressive. A run-in phase with its own randomisation is adopted as a prelude to the main randomisation and ongoing trial. Patients not completing the run-in did not proceed to the main trial; drop-out from long term follow-up was thereby kept to a minimum whilst retaining data on early intolerance. Although adverse events are noted to have occurred a little more frequently among those receiving donepezil, few details are given. A criticism of the trial is that far fewer patients were actually included than had originally been envisaged (500 v. 2-3000). The explanation offered was that the poor availability of donepezil throughout the NHS from 2001 limited recruitment; this is rather unconvincing given that the trial started in 1998. Perhaps more centres were needed. The eventual size of the sample gave a power of 90% to detect a delay to institutionalisation of 6 months. The conclusion that 'donepezil ... benefits (are) below minimally relevant thresholds' is very forthright. It is difficult to imagine the withdrawal of these agents without alternatives being available. None, however, would disagree that the acetylcholine esterase inhibitors scarcely begin to address the need for effective treatment in Alzheimer's disease. - **RDD**

**Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P; AD2000 Collaborative Group.**

*Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial.*

**LANCET**

2004;363:2105-15.

## **BASAL GANGLIA: The ventral striatum mediates recognition of anger**

The authors postulated that the ventral striatum (VS) is involved in anger recognition, based on previously described observations and animal work. Four patients with lesions of the VS were recruited and compared with four patients with dorsal basal ganglia damage and neurologically normal controls. Baseline IQ and audiometry were performed. Patients completed a number of tasks including visual recognition of emotion, vocal recognition (sounds and prosody of digit spans), and questionnaires pertaining to the personal experience of anger. Patients with VS lesions scored poorly on anger recognition tasks, particularly visual recognition. The authors felt that this was a specific deficit, particularly as it is fear that is lost non-specifically with ageing and non-specific brain injury. One VS patient reported an increased experience of anger, another a reduced experience, and the remaining two reported no change. Scores fluctuated across different questionnaires. The authors postulated that this result could represent an erratic aggression system in patients with VS lesions, and drew parallels with Huntington's disease (HD) patients. Previous studies have shown that disgust perception is particularly impaired in HD patients although anger perception is also impaired. The authors hypothesised that impaired recognition of disgust could result from degeneration in the insula while striatal dysfunction and degeneration could account for impaired recognition of anger. Based on functional MRI studies, it has been postulated that the amygdala, which mediates fear perception, may also be involved in defensive aggression (which is partly fear mediated). The authors concluded that the VS and frontostriatal circuitry is involved with competitive aggression, and acquiring resources, which requires recognition of anger in others. - **WP**

**Calder AJ, Keane J, Lawrence AD, Manes F.**

*Impaired recognition of anger following damage to the ventral striatum.*

**BRAIN**

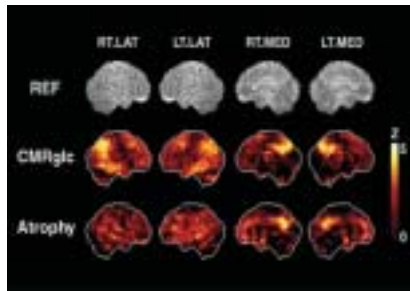
2004;127:1958-69.

## Society of Nuclear Medicine's 'Image of the Year'

For the seventh year in a row, the Society of Nuclear Medicine's 'Image of the Year' award was won by a user of Siemens Medical Solutions imaging equipment. The award was announced at the Society's annual meeting in Philadelphia, Pennsylvania, on June 23.

The University of Michigan, a longtime user of Siemens Medical Solutions PET equipment, won the award in collaboration with Hamamatsu Photonics KK and the University of Washington. The collaborators were cited for their contribution to composite brain image database useful in identifying Alzheimer's disease and other brain disorders.

Alan Heaton, Product Manager at Siemens Medical Solutions, said: "With Siemens users being regular winners, I wouldn't be surprised if the new



TruePoint SPECT-CT is featured heavily in the awards next year because it combines the power of SPECT with the precision of diagnostic multislice-CT, hence, provides superior analysis."

For further information contact Siemens on Tel: 01344 396317 or see [www.siemens.co.uk/medical](http://www.siemens.co.uk/medical)

## Revised Management Guidelines For Migraine & Tension-Type Headache

The British Association for the Study of Headache (BASH) has published the newly revised 2nd edition of its Management Guidelines for all Doctors in the Diagnosis and Management of Migraine and Tension-Type Headache.

The revised BASH Guidelines are available in pdf format, along with an accompanying slide set, at [www.bash.org.uk](http://www.bash.org.uk)

First published in 2001, the guidelines are updated to take account of new medical developments, or the emergence of new and relevant evidence for the management of migraine and tension-type



headache.

These revised Guidelines include an updated section on the use of prophylactic drug intervention for migraine due

to well-established clinical experience with older agents and in light of emerging new evidence for existing agents demonstrating good efficacy in migraine.

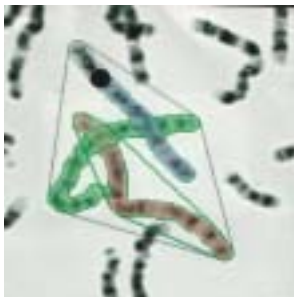
The publication of the revised Guidelines in the new format was sponsored by an unrestricted educational grant from Janssen-Cilag Ltd. The text is entirely the work of BASH.

For more information see [www.bash.org.uk](http://www.bash.org.uk)

## Intelligent Karyotyping From Olympus & Digital Scientific

Olympus has established a partnership with Digital Scientific in the UK to sell and support their karyotyping software. Digital Scientific's software for microscopists engaged in molecular cytogenetics and fluorescence cytology is used in over 500 sites worldwide.

Digital Scientific has developed a specialist system, called SmartType, for brightfield and fluorescence karyotyping. A SmartType workstation includes an Apple iMac computer, digital camera and software. The system examines captured microscope images of stained chromosomes in cells during mitosis and automatically analyses and classifies the chromosomes to provide a



complete karyotype.

The software automatically separates touching and overlapping chromosomes – with the option of manual editing. The chromosome images can be software enhanced, but the original high resolution digital image is always retained. The system classifies the chromosomes for standard banding patterns and can also 'learn' from your samples to improve its automatic classification. Karyotypes from the same or different cases can be compared by display in tabular format.

For more information contact Microscope Marketing Manager, Olympus, Tel: 020 7250 0179, Email: [microscope@olympus.co.uk](mailto:microscope@olympus.co.uk)

## New Journal From Karger

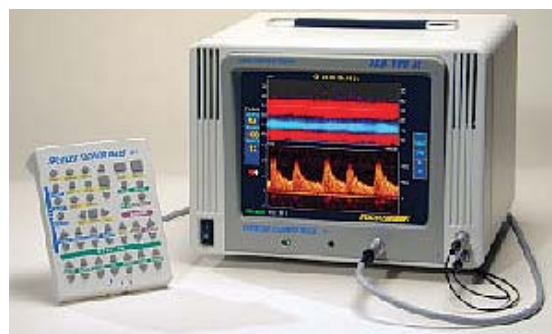
Neurodegenerative Diseases is a bimonthly, multidisciplinary journal for the publication of advances in the understanding of neurodegenerative diseases, including Alzheimer disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and related neurological and psychiatric disorders.



Neurodegenerative Diseases publishes results from basic and clinical scientific research programs designed to better understand the normal functions of genes and proteins involved in neurodegenerative diseases, to characterise their role in pathogenic disease mechanisms, to model their functions in animals and to explore their roles in the diagnosis, treatment and prevention of neurodegenerative diseases. It is our firm belief that successful strategies for novel treatments of neurodegenerative diseases will emerge from the intelligent integration of basic neurobiology with clinical sciences. Therefore, Neurodegenerative Diseases will accept high-quality papers from a broad spectrum of scientific research areas ranging from molecular and cell biology to neuroscience, pharmacology, genetics and the clinical sciences.

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

## Stand-Alone Digital Transcranial Doppler System



Pulse Medical Limited has introduced the Spencer Technologies PMD 100, said to be the world's first stand-alone digital Transcranial Doppler system. It offers Power M-Mode Doppler (PMD), a new modality for Transcranial Doppler monitoring. PMD technology allows both the novice and the expert user to obtain and evaluate flow and embolic information in a way never before available. The system features: Power M Mode colour display and flow velocities, Embolus detection unparalleled by any other device, Comprehensive recording and playback, Bilateral or unilateral configuration, Compact and portable. Applications include: Vascular Diagnosis, Vasospasm Monitoring, intra-operative monitoring, PFO diagnosis and monitoring, Neuro-interventional monitoring. Pulse Medical also supply the Marc 600 Head-frame, one of the most stable fixation devices available.

For further information contact Pulse Medical Ltd, 3000 Cathedral Hill, Guildford, Surrey. GU2 7YB, Tel: 01483 243573, Fax: 01483 243501, Email: [sales@pulsemedical.co.uk](mailto:sales@pulsemedical.co.uk) or visit [www.pulsemedical.co.uk](http://www.pulsemedical.co.uk)

## Addenbrookes Hospital Orders Siemens Neuro Imaging X-Ray System

Addenbrookes has ordered a Siemens' AXIOM Artis BA imaging X-Ray for its new neuro angiography room with the aim to improve X-Ray image quality for patients, speed patient workflow and lower radiation doses for patients without compromising image quality.

The AXIOM Artis BA is a universal biplane C-arm system with flexible system architecture for vascular and non-vascular diagnostics and interventions. It provides complete ergonomic system operation in both the examination room and control room and has user

profiles tailored to various clinical applications, such as neuroradiology and universal angiography.

Halina Szutowicz, Superintendent Neuroradiographer from Addenbrookes, said, "We have been using the system for four months now and are very pleased with its performance and superb image quality. This system has increased the speed of our routine examinations and made interventional procedures much more efficient."

For more information Tel. 01344 396317.



In the foreground, left to right: Graham Walker, Senior Regional Sales Manager, Siemens Medical Solutions; Halina Szutowicz, Superintendent Neuroradiographer, Addenbrookes Hospital and Dr Desmond Hawkins, retired Neuroradiologist who is a pioneer of interventional neuroradiology in the UK.

## Cadence™ Defibrillation Electrodes

The Critical Care Division of Tyco Healthcare is a leading manufacturer and supplier of specialised critical care products. It has now introduced the Medi-Trace Cadence defibrillation electrodes, designed to provide maximum adhesion and electrical contact with a conductive adhesive hydrogel.

Cadence electrodes employ gradient technology, so that the silver/silver chloride composition enables a more uniform distribution of current under the electrode during defibrillation, thereby avoiding 'hot spots' and potential skin trauma. Importantly



too, Cadence demonstrates superior radio-transparency in comparison with some other electrodes at normal X-Ray levels.

Cadence electrodes are user-friendly, with colour coded packaging and clear placement diagrams. The latex free foam substrate conforms easily to body contours and is available in both paediatric and adult formats. They connect directly to defibrillator cables without the need for special adapters, and conveniently can be used with OEM equipment, as well as biphasic defibrillators.

## New Treatment for Epilepsy and Peripheral Neuropathic Pain

LYRICA®, a new medicine with analgesic and anticonvulsant properties, is now available in the UK as an add-on therapy in epilepsy for adults with partial seizures, and as an effective and simple option for the early treatment of peripheral neuropathic pain (NeP). Studies have shown that in half of all patients, adding LYRICA® to standard treatment results in at least a 50 per cent reduction in seizures. These studies involved people with epilepsy who had continued to experience seizures whilst taking older anti-epileptic drugs (AEDs).

Consultant Neurologist, Dr John Paul Leach commented, "I see many people with epilepsy whose lives are blighted by uncontrolled seizures. There is a real need for a new treatment that is easy-to-use, well-tolerated and that helps to reduce seizures. LYRICA® offers both impressive sustained reductions in seizures even in those patients that have been previously hard to treat."

For more information see [www.acnr.co.uk/latestnews.htm](http://www.acnr.co.uk/latestnews.htm)



## New Airway Management Brochure

Tyco Healthcare's range of Airway management products is now presented comprehensively in a free, glossy 32-page reference brochure.

The brochure includes: A glossary of technical terms, together with a description of the advantages these features can confer on a procedure; Illustrations of the wide range of products; Features and benefits of each prod-



uct; Ordering information, with sizes; Product specifications.

Product ranges include tracheal tubes, the Lanz and Brandt systems, the Hi-Lo aspiration system, dual lumen ventilation tubes and nasopharyngeal airways, plus a variety of accessories. Products are sterile-packed, latex-free and CE approved, in line with Tyco Healthcare policy.

For a copy of the Airway Management Brochure, or for further information on Tyco Healthcare products, Tel. 01329 224187.

## Certificate of Recognition awarded by The Dystonia Society

Dr Tom Warner, Medical Adviser to The Dystonia Society and Neurologist at London's Royal Free Hospital, has received a certificate of recognition from The Dystonia Society in recognition of his work for the charity over the last 13 years.

"I was delighted and honoured to receive the certificate of recognition. It has been a privilege to work with The Dystonia Society to increase the awareness and understanding of dystonia as a neurological condition amongst the medical profession and general public. The Dystonia Society has achieved a great deal in 20 years through innovative education programmes and the promotion of research" said Dr Warner.

For further information about The Dystonia Society, Tel. 020 7490 5671, or Email: [info@dystonia.org.uk](mailto:info@dystonia.org.uk)

## The SynchroMed® II System From Medtronic®

For the management of severe complex spasticity delivering intrathecal baclofen therapy (ITB™)

**SMALLER:** 30% reduction in size for increased patient acceptance; 20% reduction in weight for enhanced patient comfort; Contoured shape for a better fit with the patient's body.

**SIMPLER:** 20ml and 40 ml reservoirs for more therapy options and for up to 59% fewer refills; Reduced number of implant steps; No need to purge or warm the pump; Redesigned and larger refill port and catheter access port for easier access.

**SMARTER:** "Flex dosing" option to match drug delivery to specific patient needs; Critical therapy data stored in the pump memory; Louder more distinctive alarms;

- Estimated Replacement Indicator (ERI) provides estimate of time to replacement
- Personal Therapy Manager (PTM) option to allow the patient to access physician
- preprogrammed bolus doses for enhanced therapy delivery.

For further information contact Clive Woodard on [clive.woodard@medtronic.com](mailto:clive.woodard@medtronic.com)

# Going solo

A double-blind, randomised trial has shown that Topamax 100 mg is as effective in various seizure types:

- as carbamazepine when it is predominantly selected for partial-onset seizures<sup>1</sup>
- as valproate when it is predominantly selected for generalised seizures.<sup>1\*</sup>



BECAUSE LIFE  
WITHOUT SEIZURES  
IS SO MUCH BETTER\*

\*In a double-blind trial in newly diagnosed epilepsy, 49% of patients taking topiramate 100 mg and 63% of children on topiramate were seizure free for the last 6 months of the study<sup>1,2</sup> †Topamax is indicated as monotherapy in adults and children aged six years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures

**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: 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. Dosage and Administration: Oral: Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. 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. 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. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and requires discontinuation of Topamax and treatment of symptoms. Increased risk of renal stones. Adequate hydration is very important. Food supplement may be required. Interactions: Possible with phenytoin, carbamazepine, digoxin, oral contraceptives and metformin.

Decrease in serum bicarbonate levels. Pregnancy: If benefits outweigh risks. 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, diplopia, headache, hyposensitivity, fatigue, 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 angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis and suicidal ideation or attempts reported rarely. 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: Package Quantities and Prices: Bottles of 60 tablets. 25 mg (PL0242/0301) = £20.02; 50 mg (PL0242/0302) = £36.17; 100 mg (PL0242/0303) = £64.80; 200 mg (PL0242/0304) = £125.83. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.88, 25 mg (PL0242/0349) = £25.32, 50 mg (PL0242/0350) = £41.60. Product licence holder: Janssen-Cilag Limited, Saunderton, High Wycombe, Buckinghamshire HP14 4HJ, UK. Date of text revision: February 2004. APIVER250204.

References: 1. Privitera MD et al. Acta Neurol Scand 2003; 107: 165-175.  
2. Wheless J, Wang S et al. Epilepsia 2001; 42(Suppl 7): (Abstract 1.179).

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