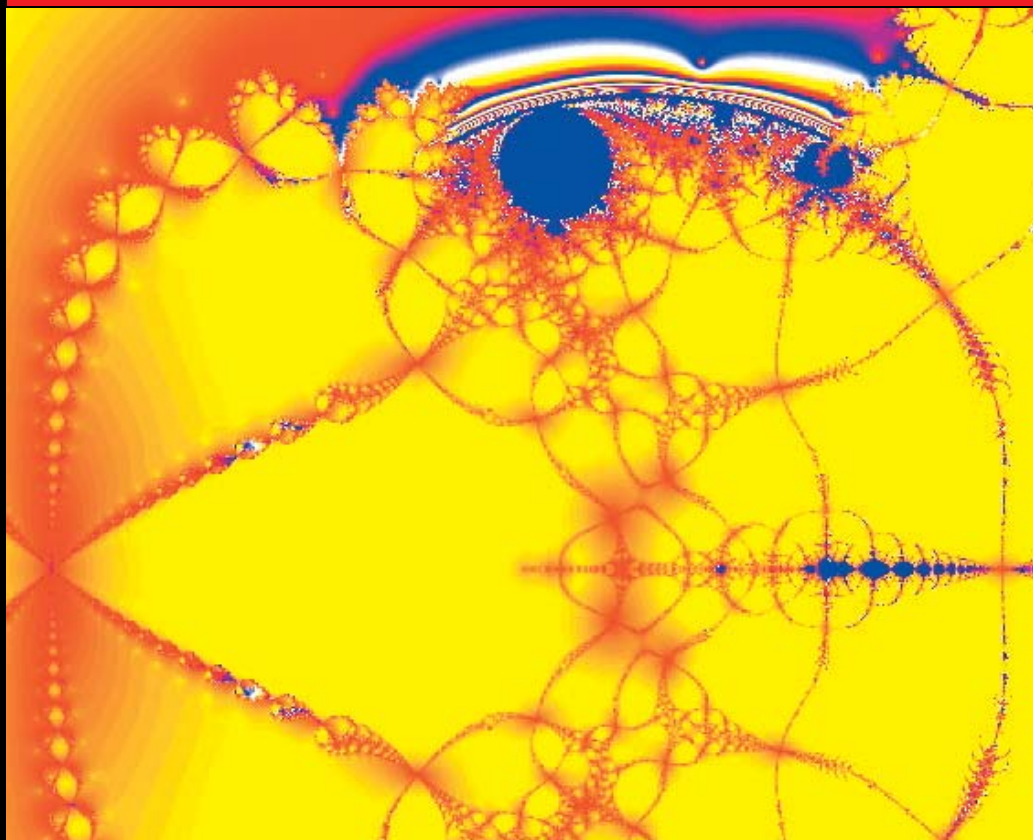


# ACNR

Advances in Clinical Neuroscience & Rehabilitation



journal reviews • events • management topic • industry news • rehabilitation topic

**Review Articles:** The Genetics of Basal Ganglia Disorders;  
Korsakoff's syndrome

**Management Topic:** Chorea - Diagnosis and  
Management

**Rehabilitation Article:** Voice Control of Environmental  
Control Systems



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Date of Review: December 2001.

Date of Preparation: August 2002.

### References:

1. Johnson KP *et al. Multiple Sclerosis* 2000; 6: 255-266.
2. Neuhaus O *et al. Neurology* 2001; 56: 702-708.
3. Comi CG *et al. Annals Neurology* 2001; 49(3): 290-297.

## Editorial Board and contributors



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## International editorial liaison committee

We are delighted to announce that *ACNR* now has editorial representatives in Austria, Germany and Norway. We would like to thank Professor Nils Erik Gilhus, Professor Hermann Stefan and Dr Klaus Berek for taking on this role, and welcome them to the team.



**Professor Klaus Berek**, Austria: Since 1999, Dr Berek has been Head of the Neurological Department of the KH Kufstein in Austria. He is a member of the Austrian Societies of Neurology, Clinical Neurophysiology, Neurological and Neurosurgical Intensive Care Medicine, Internal and General Intensive Care Medicine, Ultrasound in Medicine, and the ENS.



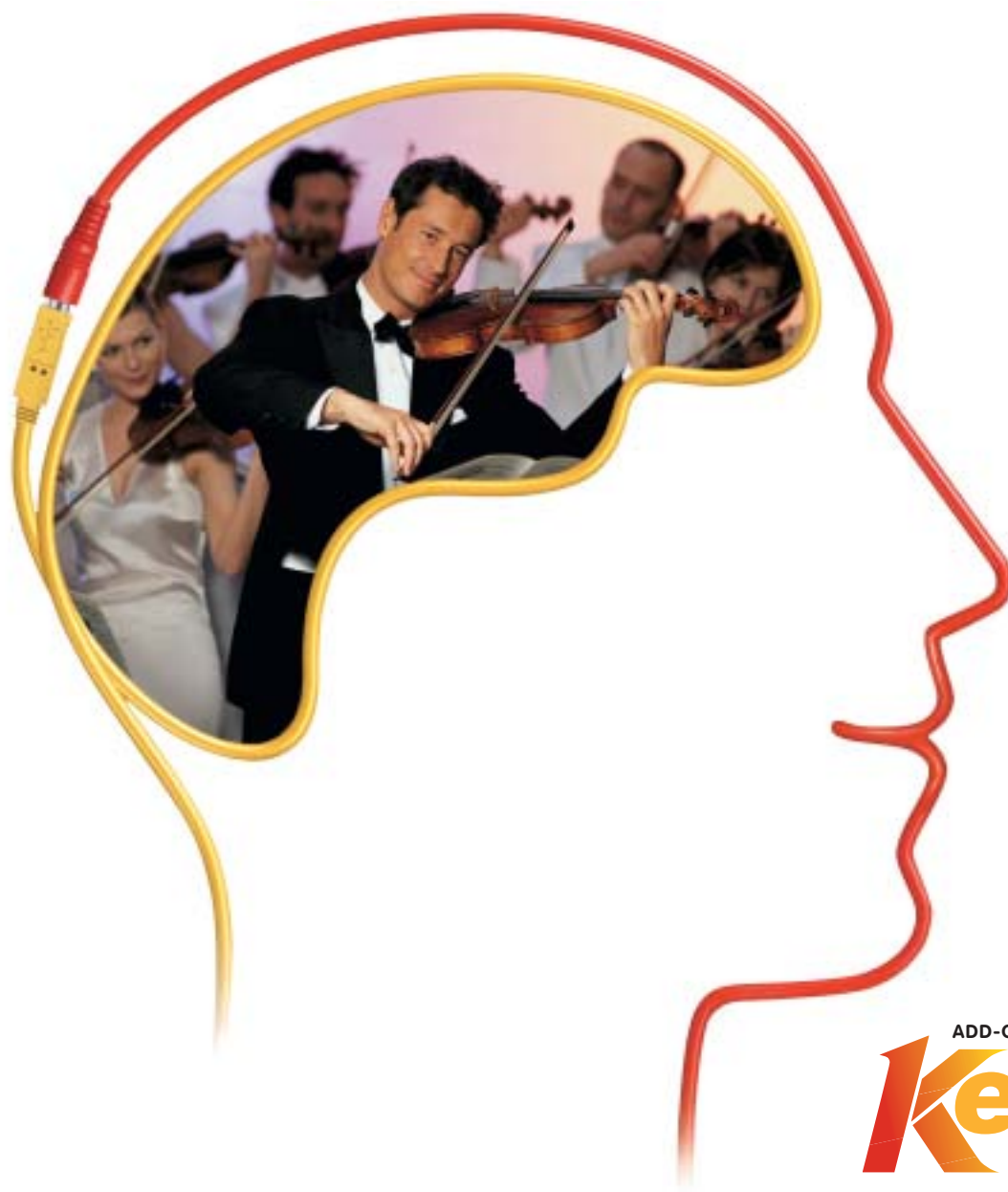
**Professor Hermann Stefan**, Germany: Professor Stefan trained in neurology, psychiatry, neuropathology, and epileptology at the University Bonn. He is Professor of Neurology/Epileptology in the Department of Neurology, University Erlangen-Nürnberg, and specialises in the treatment of epilepsies, especially difficult to treat types of epilepsy and presurgical evaluation, including Magnetic source imaging (MEG/EEG) and MR-Spectroscopy.



**Professor Nils Erik Gilhus**, Norway: Professor Gilhus has been Professor of Neurology at the University of Bergen and Haukeland University Hospital since 1987. He is Research Dean at the medical faculty, and Chairman for the Research Committee of the Norwegian Medical Association. He chairs the scientist panel of neuroimmunology, European Federation of Neurological Societies (EFNS), is a member of the EFNS scientific committee, the World Federation of Neurorehabilitation council, and the European School of Neuroimmunology board. His main research interests are in neuroimmunology and neurorehabilitation.

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daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy 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 tablets: EU/1/00/146/004. 500 mg x 60 tablets: EU/1/00/146/010. 1,000 mg x 60 tablets: EU/1/00/146/024. **NHS price:** 250 mg x 60 tablets: £29.70. 500 mg x 60 tablets: £49.50. 1,000 mg x 60 tablets: £94.50. **Further information is available from:** UCB Pharma Ltd., 3 George Street, Walford, Hertfordshire WD18 0UH. Tel: 01923 211811. medicaluk@ucb-group.com  
**Date of preparation:** March 2003.

**Reference:** 1. Cereghino J et al. Neurology 2000;55(2):236-242.



UCB-K-02-28



In this issue there is an emphasis on movement disorders, which is no bad thing in my book. We begin with a superb review article on the genetics of basal ganglia disorders by Patrick Chinnery and David Burn. This lays out in a clear fashion the genes underlying Parkinson's disease and dystonia as well as discussing some of the more recently discovered conditions - including the neuroferritinopathy described first by this group. The authors go on to discuss the importance of recognising the different genetic disorders of the basal ganglia and suggest that it may be better to "think of the genetics of neurological systems, rather than clinical features or syndromes".

The theme of genetic disorders of the basal ganglia is taken up in the management section, in which I discuss the approach to patients with chorea including Huntington's disease. I hope this sets out in a useful and pragmatic fashion the many causes, and appropriate treatment, of chorea. It is by no means complete but I hope of some help. To highlight the way this field is moving forward there are a number of reviews in the journal section on chorea.

The second review article is on Korsakoff's syndrome. This rare com-

plication of chronic alcohol abuse is much talked about but rarely seen, so we are very fortunate to have the contribution of Mike Kopelman and Mireia Pujol, world leaders on this topic. The article is written from experience and contains a wealth of insight. I am sure you will find this a great short review of this fascinating topic.

The rehabilitation article has taken as its theme the use of voice control as a means of operating a range of electronic devices. This is a fascinating and sophisticated area of support for patients with a range of disabilities, and is surely an area that will evolve rapidly in the years to come. Finally, Brian MacNamara, in his inimitable way, disentangles the confusion in all of our minds about that mysterious ailment: the tarsal tunnel syndrome.

As always, please get in touch if you have a suggestion for a topic ACNR should review. There are myriad facets of neuroscience we could look at. After all: "If the brain were so simple we could understand it, we would be so simple we couldn't" [Lyllal Watson].

Roger Barker, Co-editor

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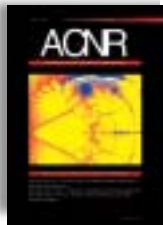
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Neuro-membrane is an Engineer-Artist abstract visualisation of the electrical fields surrounding a neurotransmitter attractor in the area of the synaptic cleft. The form originates from a chaos equation captured at timed iterations. A version of this image appears on the MS Society website, [www.mssociety.org.uk](http://www.mssociety.org.uk)

Richard Stickney is an MS Patient based in the US, with a computer lab and an animation studio. He has written artificial intelligence programs and made custom animation models for everyone from Boeing, BAe, Airbus to Pratt and Whitney rocket engines, and is happy to offer his services to non-profit or funded research efforts. Richard says, 'As long as I am able I will give my time and experience to neurological disorder research.' Contact him at [Stick4013@aol.com](mailto:Stick4013@aol.com)

The MS society is the UK's largest charity dedicated to supporting everyone whose life is touched by MS. It provides respite care, a freephone MS Helpline, specialist MS nurses, funds around 70 vital research projects in the UK and a wide range of information including an award winning website.



## Features

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### 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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**Note:** If changes in AED medication are to be made they should be completed before conception. \* The UK Pregnancy Register (0800 389 1248) is collecting prospective data on the effects of all AEDs in pregnancy. Please phone for information or to register a patient.  
\*Crawford P et al. Seizure 1999; 8: 201-217  
**Date of preparation:** July 2003  
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PEACE OF MIND

## Review Article

# The Genetics of Basal Ganglia Disorders

It is remarkable to think that only fifteen years ago we knew practically nothing about the genes involved in Parkinson's disease (PD) or dystonia. Over the last decade there has been a flurry of publications describing new genetic loci associated with familial PD and different familial dystonia syndromes. Causative DNA mutations have been identified in some instances (for example, the recently identified *DJ-1* gene at the *PARK7* locus<sup>1</sup>, table 1). As in other areas of neurogenetics, these exciting findings have raised many more questions, providing us with tantalising clues about the underlying mechanisms behind rare autosomally inherited forms of a disease that may have broader relevance for more common sporadic cases.

### The *PARK* lot

The first gene to be identified was found in the now famous Italian-American Contursi kindred. An early onset, rapidly progressive, L-dopa responsive phenotype was linked to chromosome 4q21-q23 (*PARK1*)<sup>2</sup>, and subsequent work identified an alanine to threonine substitution at codon position 53 of the  $\alpha$ -synuclein gene (*A53T*)<sup>3</sup>. The same mutation has also been found in Greek kindreds with a similar clinical presentation, while a second  $\alpha$ -synuclein gene mutation has been found in a German family (*A30P*)<sup>4</sup>. This work provided the first direct evidence of a genetic link for PD, and it led to the identification of  $\alpha$ -synuclein protein in Lewy bodies from patients with sporadic PD, providing further insight into the general disease mechanism in PD<sup>5</sup>.  $\alpha$ -synuclein gene mutations are, however, an exceptionally rare cause of PD in the general population<sup>6,7</sup>.

The second locus, *PARK2*, is a more common cause of PD. The locus was identified in 13 Japanese families with autosomal recessive young-onset parkinsonism (6q25.2-27), and subsequent work identified a range of different deletions and point mutations in a novel gene called *Parkin*<sup>8,9</sup>. *Parkin* mutations have been found in 77% of patients developing parkinsonism in their first two decades, but only 3% of patients developing symptoms between the ages of 30 and 45 years<sup>10</sup>. An even smaller proportion of later-onset cases have mutations in the *Parkin* gene<sup>11</sup>. *Parkin* functions as an E3 ubiquitin ligase that may be involved in the ubiquitin-proteasome system<sup>12</sup>, an essential cellular pathway for the degradation and recycling of unwanted proteins. An intriguing finding is that *Parkin* interacts with  $\alpha$ -synuclein<sup>13</sup>, suggesting there may be common mechanisms for various forms of genetically determined PD, and that these may be relevant to the late-onset sporadic PD. This is supported by recent work identifying a mis-sense mutation in the ubiquitin hydrolase *L1* (*UCH-L1*) gene in a German family with autosomal dominant PD<sup>14</sup>. *UCH-L1* is also involved in same ubiquitin-proteasome pathway<sup>14</sup>.

Familial parkinsonian syndromes have also been linked to a number of other genetic loci, and at the last count we reached *PARK 10* (Table 1). Most loci have only been implicated in one or a few families, and their real impact will only be realised after the identification of the underlying gene allows large-scale mutational screening in carefully defined clinical cohorts. There are subtle differences in the clinical phenotype and neuropathology of these different genetic disorders (Table 1).

PD genetics has also been tackled from other directions. There have been two genome-wide genetic linkage studies designed to identify new PD loci in co-affected sib-pairs<sup>14</sup>, or in families with multiply affected members<sup>15,16</sup>. These studies have implicated additional genetic loci in familial

PD, and further work is underway to try and characterise the responsible genes. It may transpire that certain loci are only implicated in specific clinical subgroups of the disorder<sup>17</sup>.

An alternative strategy has been to look for an association between known genetic polymorphisms in candidate genes and PD (*i.e.* sequence variations in the general population in genes hypothesised to be of relevance to the pathogenesis of PD). Although there have been many reported associations (reviewed in<sup>18</sup>), relatively few have been reliably replicated. There are a number of possible reasons for this lack of consistency, but the most likely explanation is that most of the studies were under powered and that the associations are spurious (false positive, or type I errors)<sup>19-21</sup>. Two recent association studies deserve mention. In the first<sup>22</sup>, 20 single nucleotide polymorphisms in 18 candidate genes were studied in 232 PD patients and 249 normal controls. Homozygosity for the V66M polymorphism of the brain-derived neurotrophic factor (BDNF) was more frequent in PD than in controls. This is of potential relevance, since previous studies have demonstrated reduced concentrations of BDNF in the nigra of PD patients, and this growth factor has also been shown in open pilot studies to be effective in improving parkinsonian symptoms. In the second study, a collection of polymorphisms of mitochondrial DNA (mtDNA) were associated with a reduced risk of PD in a large cohort of 609 PD cases, particularly in women<sup>23</sup>. This is intriguing because there are various strands of evidence linking mitochondria with PD<sup>24,25</sup>, and this study provides a potential genetic link. However, it would be unwise to draw firm conclusions before these results have been substantiated by others.

### The *DYT* collection

Dystonia can be divided into primary, dystonia-plus, hereditary degenerative and secondary forms. Primary dystonias are phenotypically "pure" and are generally thought to have a genetic origin<sup>26</sup>. Dystonia-plus syndromes include dystonias with other neurological features such as myoclonus and parkinsonism. Hereditary degenerative forms occur in degenerative diseases where dystonia may be a prominent feature but is not always present. Secondary dystonias result from acquired disease, for example infections, brain trauma and cerebrovascular disease.

Autosomal dominant early-onset idiopathic torsion dystonia (ITD) was linked to chromosome 9q34 in Ashkenazi Jews (*DYT1*)<sup>27</sup>. The underlying gene defect is a deletion of three base pairs (CAG) in the *Torsin A* gene<sup>28</sup>, and it has arisen many times on different genetic backgrounds (that is to say, all affected individuals are not related to a single common founder individual)<sup>29</sup>. *DYT1* idiopathic torsion dystonia has a reduced penetrance (30-40%) and usually begins before 26 years of age in one limb, becoming generalised over a few years<sup>30</sup>. Other forms of familial dystonia have been mapped to different forms of dystonia with different inheritance patterns (Table 2). At the last count there were fifteen *DYT* loci. Some of these disorders have only been described in single families (for example, *DYT4*, or whispering dystonia in an Austrian family<sup>31</sup>), or ethnic groups (for example, *DYT6*, in Mennonite families<sup>32</sup>), but others seem much more common (for example, *DYT11*, or alcohol responsive myoclonic dystonia<sup>33,34</sup>). There is considerable variation in the clinical phenotype of these disorders and there may be additional neurological (e.g. *DYT3*<sup>35</sup>, *DYT12*<sup>36</sup>) or psychiatric (e.g. *DYT1*<sup>34</sup>) features.



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
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## Review Article

### Late-onset cystic degeneration of the basal ganglia

We recently described a dominantly inherited movement disorder in a large family from Cumbria in the northwest of England due to an adenine insertion at position 460-461 in the ferritin light polypeptide gene (*FTL*)<sup>37</sup>. Serum ferritin levels were low in the presence of normal serum iron, transferrin and haemoglobin levels, and we suggested the name “neuroferritinopathy” for this disease, providing a direct link between a primary disorder of iron storage metabolism and a late-onset neurodegenerative movement disorder<sup>37</sup>.

Looking back through the case notes of affected individuals it is clear that different family members had been labeled with a range of different diagnoses. Some family members developed a late-onset asymmetric akinetic-rigid syndrome resembling PD, and were started on L-dopa with some improvement. Others presented with a focal onset lower-limb dystonia in teenage years which gradually involved other limbs, becoming generalised within a decade (similar to *DYT1* dystonia), while one branch of the family developed generalised chorea in mid adult-life and was thought to have had Huntington’s disease (diagnosed clinically in the pre-molecular era)<sup>37</sup>. Brain imaging in affected individuals revealed basal ganglia cavitation (Figure 1), confirmed at autopsy. Neuronal loss was accompanied by the formation of neuroaxonal spheroids, with intraneural and extraneural iron deposition<sup>37</sup>. Recent genetic studies have shown that all of the UK patients descend from a common founder<sup>38</sup> - but the whole range of movement disorders has been documented in this one family.

### *PARK* and *DYT* – never the twain shall meet?

We all recognise the rigid or “Westphal” variant of Huntington’s disease presenting in early adult life, and many of us look for biochemical markers of Wilson’s disease in patients with young onset parkinsonism or dystonia. On closer scrutiny it is clear that many of the *PARK*s have dystonia as a prominent feature (Table 1), and many of the *DYT*s have parkinsonism (Table 2). For example, what appears to be the most common monogenic form of parkinsonism – mutations in the *Parkin* gene at the *PARK2* locus - characteristically presents with a lower limb dystonia that melts away with L-dopa<sup>39</sup>, and many *Parkin* patients were understandably mis-diagnosed as having dopa-responsive dystonia (DRD or *DYT5*)<sup>40</sup>. This has profound implications for the patient because L-dopa is an effective long-term treatment for patients with DRD, but causes profound early motor fluctuations in patients with *Parkin* mutations<sup>40</sup>. If we look at DRD/*DYT5* in more detail, many families have individuals who present with parkinsonian features in late adult life<sup>41,42</sup>. Since this disorder responds to L-dopa *par excellence*, not surprisingly this leads mis-diagnosis. There are many more examples, such as X-linked dystonia parkinsonism (*DYT3*)<sup>35</sup>, pallidopyramidal degeneration with supranuclear upgaze paresis and dementia (*PARK9*, Kufor-Rakeb syndrome)<sup>43</sup>, or rapid onset dystonia parkinsonism (*DYT12*)<sup>43</sup> which links to the same chromosomal region as neuroferritinopathy (19q) but is genetically distinct (Curtis, unpublished observations).

Unfortunately the problem does not stop there. Patients with other neurogenetic disorders may present with *DYT* or *PARK* phenotype. For example, spinocerebellar ataxia type 2 (*SCA2*) may present with L-dopa responsive parkinsonism<sup>44</sup>, and there is the well-recognised clinical overlap between DRD/*DYT5* and autosomal dominant hereditary spastic paraparesis<sup>45</sup>.

### Is this just semantics?

At this point we run the risk of irritating some readers. Who cares what the name is, and why not just leave that to the laboratory scientists? Unfortunately it is not that simple. Clinical classification is fundamentally important to patient management, molecular diagnostics and research. Not surprisingly, many review articles by experts in the field restrict their content to home territory, and a reader new to the genetics of dystonia may be left with an incomplete picture of inherited parkinsonian syndromes with prominent dystonia (there are, however, a few notable recent exceptions, for example<sup>46-48</sup>). On the research side, the mis-classification of individuals can lead to spurious or unexplainable results, and samples sent to the molecular diagnostic lab labelled “teenage onset lower limb dystonia” may not be tested for *Parkin* mutations. The report may come back negative (for *DYT1*), leading to an incorrect interpretation.

### How can we solve this problem?

In time, all of the underlying mutations at the *PARK* and *DYT* loci will be identified, and it is likely that there will be a re-classification of these disorders based upon gene function rather than clinical phenotype (for example, as we have seen in mitochondrial DNA disorders). This has its own problems, of course, particularly if the phenotype is diverse – but at least it will ensure that we have an accurate list of genes that are implicated in a particular clinical syndrome. This approach will hopefully facilitate the identification of common molecular pathways in disease. In the short term, it may be better to think of the genetics of neurological systems, rather than clinical features or syndromes. In this way, we would think about inherited movement disorders, or basal ganglia disorders, rather than *DYT* or *PARK*. Naturally, there will be overlap with other systems (such as the pyramidal tracts, or cerebellum and connections), but the predominant system that is involved, whether it be clinically or pathologically, should form the basis of the classification.

Finally, we must make sure that scientists and clinicians work together – both in research and in clinical practice. This will help to advance our understanding of the genetics of movement disorders, elucidate the most important disease mechanisms and facilitate the development of fundamental new treatments.

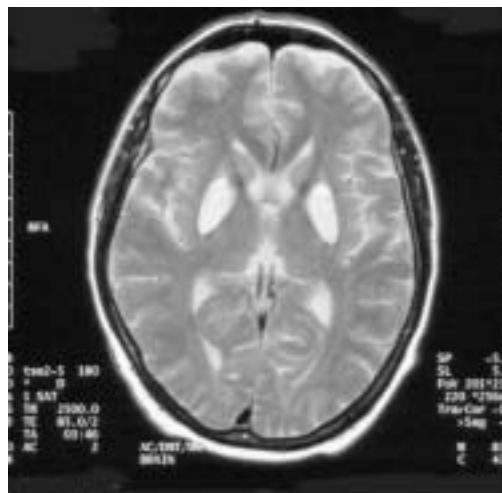


Figure 1. Cystic degeneration of the basal ganglia in a patient with neuroferritinopathy (axial T2 weighted image, with thanks to Dr Alan Coulthard).

Table 1. Genetic loci linked to parkinsonism.

Locus	Chromosomal region	Mutations	Phenotype
<i>PARK1</i>	4q21-q23	$\alpha$ -synuclein	Autosomal dominant early onset rapidly L-dopa responsive progressive parkinsonism.
<i>PARK2</i>	6q25.2-27	<i>Parkin</i>	Autosomal recessive early-onset parkinsonism beginning with focal lower limb dystonia. Responds to L-dopa but treatment leads to early disabling dyskinesias.
<i>PARK3</i>	2p13	?	Autosomal recessive. Onset in middle age. Good L-dopa response. Cognitive impairment noted.
<i>PARK4</i>	4p	?	Autosomal dominant early onset rapidly progressive parkinsonism with good L-dopa response. May only cause a postural tremor.
<i>PARK5</i>	4p	<i>UCH L1</i>	Begins with a tremor. Good treatment response to L-dopa.
<i>PARK6</i>	1p36-35	?	Autosomal recessive. Early onset, benign course with prominent tremor. Good response to L-dopa but early dyskinesias.
<i>PARK7</i>	1p36	<i>DJ-1</i>	Autosomal recessive early onset, benign course, may be dystonia. Good response to L-dopa.
<i>PARK8</i>	12p11.2-q13.1	?	Autosomal dominant. Onset in early middle age. Good response to L-dopa.
<i>PARK9</i>	1p36	?	Parkinsonism with pyramidal features, supranuclear gaze paresis and dementia in a consanguineous Jordanian family (Kufor-Rakeb syndrome).
<i>PARK10</i>	1p32	?	Susceptibility locus for late onset parkinsonism found by genome-wide linkage.

Table 2. Genetic loci linked to dystonia.

Locus	Chromosomal region	Mutations	Phenotype
<i>DYT1</i>	9q34	CAG deletion in <i>TorsinA</i>	Autosomal dominant early-onset dystonia beginning in a limb and rapidly spreading. Oppenheim's dystonia (see text for a more detailed description).
<i>DYT2</i>	(unconfirmed)	?	Autosomal recessive in Gypsies.
<i>DYT3</i>	Xq13.1	?	Lubag disease. Individuals of Philippine origin. Rapidly progressive neurodegenerative syndrome with treatment unresponsive parkinsonism.
<i>DYT4</i>	?	?	Autosomal dominant whispering dysphonia in a single large Australian family.
<i>DYT5</i>	14q22.1	<i>GCH1</i>	Segawa's syndrome. Dopa-responsive dystonia with diurnal variation.
<i>DYT6</i>	8p21-p22	?	Autosomal dominant, only in Mennonites, mixed phenotype (focal or generalised).
<i>DYT7</i>	18p	?	Autosomal dominant with reduced penetrance. Late onset in German families.
<i>DYT8</i>	2q	?	Autosomal dominant paroxysmal non-kinesogenic dystonia.
<i>DYT9</i>	1p	?	Autosomal dominant episodic choreoathetosis with spasticity.
<i>DYT10</i>	16p11	?	Autosomal dominant paroxysmal kinesogenic dystonia.
<i>DYT11</i>	7q21	<i>SCGE</i>	Autosomal dominant alcohol responsive myoclonus-dystonia.
<i>DYT12</i>	19q	?	Autosomal dominant rapid onset parkinsonism-dystonia.
<i>DYT13</i>	1p36.32-p36.13	?	Autosomal dominant dystonia in a large non-Jewish family not linked to <i>DYT1</i> .
<i>DYT14</i>	14q13	?	Autosomal dominant dopa-responsive dystonia in a German family not linked to the <i>GCH1</i> gene.
<i>DYT15</i>	18p11	?	Autosomal dominant alcohol responsive myoclonic dystonia not linked to other loci in a large Canadian kindred.

## Review Article

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## Review Article

# Korsakoff's syndrome

### Introduction and history of the Wernicke-Korsakoff syndrome

The Korsakoff syndrome is defined as a disproportionate impairment in memory, relative to other aspects of cognitive function, resulting from nutritional (thiamine) depletion. Relatively small neuropathological lesions give rise to a severe amnesic syndrome. The neurochemical processes involved and the precise specification of the nature of the memory deficit remain topics of intense investigation.

Korsakoff (1887, 1889 a, b) described a syndrome of characteristic memory disturbance, witnessed in "not less than thirty" cases of chronic alcohol abuse, as well as 16 patients in whom alcohol had not played a role. He did not make any specific reference to Wernicke's syndrome, which had been described in 1881, but mentioned a prodromal state. Memory disturbance occurs in a setting of clear consciousness and characteristically "the memory of recent events...is chiefly disturbed", but in some cases memories "of the long past" (up to 30 years earlier) were also affected. Korsakoff emphasised the variability in the severity of the disorder and how events could be remembered "but not the time when they occurred". Confusion of "old recollections with present impressions", jumbled in temporal sequence, resulted in confabulation.

### The neuropathology

There are petechial haemorrhages, endothelial proliferation, focal areas of parenchymal necrosis, demyelination, gliosis and variable degrees of neuronal loss in the paraventricular and peri-aqueductal grey matter, cerebellum, and the walls of the third and fourth ventricle. The mammillary bodies and the thalamus are among the sites commonly affected. Similar changes are sometimes found in post mortem studies of subjects with a history of alcohol abuse but lacking a Wernicke-Korsakoff diagnosis during life. The latter group show cortical atrophy, acute or "active" pathological changes (haemorrhages, endothelial proliferation), but more commonly chronic "inactive" changes (necrosis, gliosis). Gross atrophy, reduced neuron count, and increased hydration of the frontal lobes are commonly observed in alcoholic subjects at autopsy, particularly those with a diagnosis of Wernicke-Korsakoff syndrome.

The precise location of the lesions responsible for the amnesia is controversial. The balance of the more recent evidence appears to suggest that the critical areas in memory formation are a circuit comprising the hippocampus, entorhinal and perirhinal cortex, mammillary bodies, mammillo-thalamic tract and the anterior nucleus of the thalamus. Variable degrees of atrophy of brain tissue is a consequence of chronic alcohol abuse, even in the absence of Wernicke's encephalopathy (Kril and Halliday, 1999), therefore changes in cellular density should be interpreted with some caution. Harding *et al* (2000) compared the brains of 5 alcoholic patients with Wernicke's encephalopathy who did not develop profound amnesia ('Wernicke only') with those of 8 patients who became severely amnesic ('Korsakoff'). They found that neurodegeneration of the mammillary and medial dorsal thalamic nuclei was substantial in both groups, but that neuronal loss in the anterior (principal) thalamic nuclei was found consistently only in the Korsakoff

group. This suggested that damage in the anterior thalamus is critical for the development of amnesia, a finding consistent with some studies of thalamic infarction (von Cramon *et al*, 1985).

### Neurochemistry of the Korsakoff's syndrome

Disorientation and confabulation show a favourable response to thiamine therapy in very early Korsakoff cases (Bowman *et al*, 1939). The onset of symptoms, which included mental changes in 78% of cases and loss of recent memory in 61%, generally occurred after 6-14 weeks, similar to beriberi but before the symptoms of other vitamin deficiencies. The combination of thiamine deficiency and the direct neurotoxic action of alcohol may be required to produce a persistent memory loss (Freund, 1973; Butters & Cermak, 1980) and the response to treatment seems to be determined by the aetiology, the age of the patient (Tallaksen *et al*, 1993), the abruptness of the onset and the rapidity with which treatment is instituted. Moreover, alcohol reduces both the absorption of thiamine and the activity of the enzyme which converts it to its active form. Transketolase is an enzyme which requires thiamine pyrophosphate (TPP) as a co-factor. A hereditary abnormality of transketolase metabolism might predispose some alcoholics to the Korsakoff syndrome (Blass & Gibson, 1977). TPP, the active form of thiamine, appears to be involved in DNA synthesis as well as three enzymatic reactions which are essential for glucose metabolism and neurotransmitter production (Witt, 1985). The metabolic heterogeneity of different brain regions might explain why some areas are more vulnerable to thiamine depletion than others. Six neurotransmitter systems are affected by thiamine depletion, whether by reduction of TPP-dependent enzyme activity, or by direct structural damage, and four of these neurotransmitters, acetylcholine, glutamate, aspartate and gamma-aminobutyric acid (GABA), are directly related to glucose metabolism.

### Neuro-imaging studies

There is ventricular enlargement with sulcal widening in alcoholics, usually worse in Wernicke-Korsakoff patients. Research studies indicate a significant correlation between sulcal widening and overall cognitive impairment, especially frontal sulcal enlargement. Jacobson and Lishman (1987) found that the degree of third ventricular enlargement, which presumably reflects thalamic and hypothalamic pathology, correlates significantly with the severity of memory impairment, and Kopelman *et al* (2001) found significant correlations between MRI measures of thalamic volume and anterograde memory performance. Colchester *et al* (2001) found significantly reduced thalamic volumes on MRI in Korsakoff patients with evidence also of mammillary body atrophy, whereas the temporal lobes, hippocampi and parahippocampal gyri did not differ significantly from healthy controls. These findings contrasted with the MRI results in another group of amnesic patients who had underlying temporal lobe pathology, secondary to herpes encephalitis. Reed *et al* (2003) reported white matter hypermetabolism on fluoro-deoxy-glucose PET with relative hypometabolism in the diencephalic and medial frontal grey matter.



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Professor Michael D Kopelman is Professor of Neuropsychiatry in the University of London and Honorary Consultant Psychiatrist based at St Thomas's Hospital, London. He is President-elect of the British Neuropsychological Society and a founder member of the Memory Disorders Research Society. He has a particular interest in memory disorders, and he has published widely in the scientific and clinical literature on various forms of amnesia.

“The reason why some alcoholic subjects are more vulnerable to thiamine depletion and to developing the characteristic lesions is still poorly understood.”



DR. ALOIS ALZHEIMER

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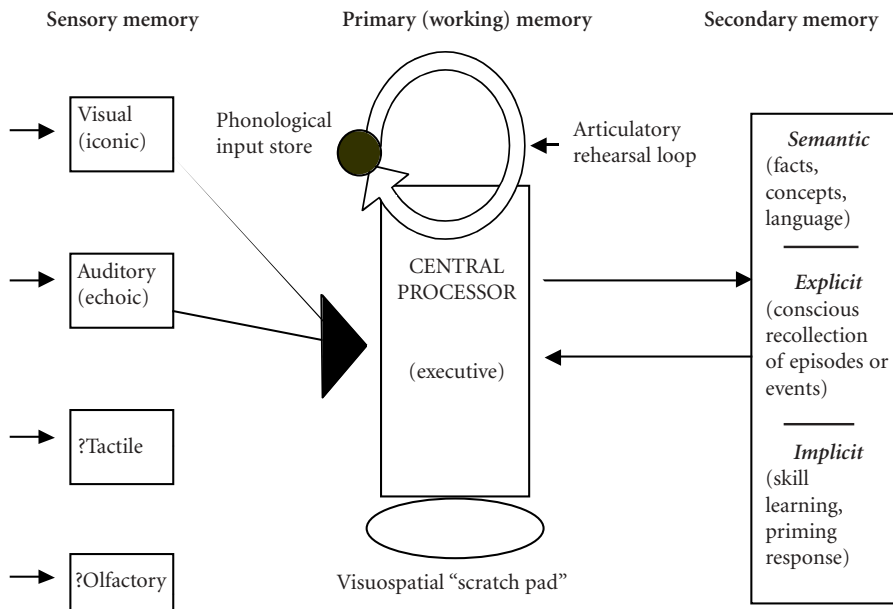


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# Review Article

## Neuropsychology of the alcoholic Korsakoff syndrome

FIGURE 1. Current concepts in memory research.



Jacobson and Lishman (1987) reported a variable degree of impairment on a standard IQ test in alcoholic brain damaged patients indicating a continuum between patients with disproportionate impairment of anterograde memory and those with a more generalised cognitive decline (alcoholic dementia). There is also considerable evidence of frontal lobe or "executive" dysfunction in Korsakoff patients and various aspects of their memory complaints may be related to this.

There are many investigations showing that performance on span tests (verbal and non-verbal) is preserved in the Korsakoff syndrome. Performance on short-term forgetting tasks is much more variable on both verbal and non-verbal tasks. Some authors have postulated that this variability in performance is correlated with the degree of frontal lobe dysfunction and others have argued that these impairments are correlated with left-hemisphere and right-hemisphere cortical atrophy respectively, as measured on CT scans.

The explicit component of secondary memory refers to consciously aware memories for events or episodes. Korsakoff patients have a severe deficit in acquiring such explicit memories, but their problem does not seem to result from accelerated forgetting of previously acquired memories (at least on testing of recognition memory). Implicit memory refers to learning of which the subject is not consciously aware. It encompasses simple conditioning tasks, the acquisition and retention of perceptuo-motor skills (procedural memory) and priming, which refers to the facilitation of a particular response to cues by an earlier stimulus. Korsakoff patients show preserved implicit memory. The implicit memory system is mediated by cortical structures (priming) and/or subcortical

TABLE 1. Neuropsychology of Korsakoff's syndrome.

<b>Primary/ working memory</b>	Relatively intact (span test, "short term" forgetting)
<b>'Psychological' encoding</b>	
Semantic	Deficits probably insufficient to account for amnesia
Contextual	Deficits incidental to amnesia rather than core feature?
'Complex associations'	Currently under investigation
<b>'Physiological consolidation'</b>	Difficult to assess in man
<b>Retention/storage/forgetting/ retrieval</b>	Intact if learning accomplished Deficits secondary to encoding/consolidation
<b>Priming/procedural learning (Skills)</b>	Preserved
<b>Retrograde amnesia</b>	Extensive impairment (25 years or more with temporal gradient)

structures (procedural memory), distinct from the impaired explicit memory system, mediated by limbic-diencephalic structures. There is also some evidence of preserved affective or evaluative memory responses, possibly mediated by amygdaloid circuitry.



Semantic memory is a conglomerate term referring to knowledge of language, concepts, and well-rehearsed facts. Korsakoff patients show relative preservation of performance on semantic memory tests compared with Alzheimer or other dementia patients. However, they are often impaired at speeded tasks such as verbal fluency, and they usually fail to learn the names or definitions of words which have come into the language since the onset of the disorder.

Each memory type can have a retrograde and/or anterograde component. There is clearly extensive retrograde memory loss in the Korsakoff syndrome, extending back to 25-30 years. This loss includes memory for public or semantic information, facts about their own life, and autobiographical memory for incidents or events from the patient's past. All these aspects of retrograde memory show a temporal gradient, with relative sparing of the most distant memories, and the gradient is significantly steeper than that seen in dementing patients. The patients show a pronounced improvement on recognition memory testing for this "old" material, indicating a retrieval component to the disorder.

It is rare for florid and spontaneous confabulation to persist beyond the initial confusional Wernicke stage; it is likely to result from disorganised and disinhibited retrieval of memories and associations and, if persistent, it is associated with frontal lobe (rather than diencephalic) pathology. Table 1 summarises the pattern of preserved and impaired memory processes in the Korsakoff syndrome.

### Conclusion

The Korsakoff syndrome is characterised by prominent memory and new learning impairment whilst other cognitive functions remain relatively intact. This clinical picture can be preceded by Wernicke's syndrome, but coma and an insidious onset are alternative initial manifestations of the disorder. The characteristic neuropathology is sometimes found at autopsy in alcoholic subjects who have never been diagnosed during life. The main lesions are in the periventricular and periaqueductal grey matter, and lesions in the thalami and mammillo-thalamic tracts and mammillary bodies damage neuronal circuitry which is known to be critical for memory formation. There has been controversy regarding the relative importance of these structures: Harding *et al* (2000) have recently indicated that neurodegeneration of the anterior principal nucleus of the thalamus is the only consistent lesion differentiating Korsakoff patients from others with Wernicke's encephalopathy. Neuro-imaging and autopsy studies have corroborated that cortical atrophy, particularly in the frontal lobes, is also present in many cases. The reason why some alcoholic subjects are more vulnerable to thiamine depletion and to developing the characteristic lesions is still poorly understood. Neuropathological studies indicate a severe deficit in anterograde explicit memory with intact or relatively well-preserved working memory, priming, procedural memory and the rate of long-term forgetting (at least on recognition memory testing). Whilst structural lesions and/or neurochemical deficiencies involving the limbic-diencephalic circuits produce anterograde amnesia, other factors, such as a retrieval deficit perhaps associated with frontal lobe atrophy, may account for the severe retrograde memory loss.

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## Anatomy Primer

# The Tibial Nerve and Tarsal Tunnel Syndrome

The term 'heartsink' has with good reason fallen out of fashion, however I must admit to a certain sense of dread when some cases arrive at the EMG clinic. Number one in my dread list is the phrase 'please exclude tarsal tunnel syndrome'. This diagnosis is often the last resort of orthopaedic surgeons and podiatrists when trying to explain painful feet. Unfortunately tarsal tunnel syndrome is rare, and the electrophysiological assessment tricky. So this month I will share my woes by reviewing the anatomy of the tibial nerve at the ankle and briefly reviewing the clinical features of tarsal tunnel syndrome.

Derived from L4-S3 nerve roots, the tibial nerve is the larger of the two terminal branches of the sciatic nerve. It leaves the popliteal fossa between the heads of the gastrocnemius and supplies all muscles in the posterior compartment of the legs (Table 1). The tibial nerve descends in the median plane of the fibula, deep to the soleus. At the ankle the tibial nerve descends towards the foot and runs posterior to the medial malleolus under the flexor retinaculum. This flexor retinaculum forms the tarsal tunnel, which also contains the tibial artery, the flexor hallucis longus tendon, the flexor digitorum longus tendon and tibialis posterior tendon. Passing out of the tarsal tunnel, the nerve then divides into four branches (Figure 1). Two of these, the medial and lateral calcaneal nerves are purely sensory and supply sensation to the heel of the foot. The other two branches, the medial and lateral plantar nerves innervate the intrinsic muscles of the foot (Table 1) and provide sensation to the medial and lateral sole respectively. The medial nerve supplies the first three toes and sometimes the fourth toe, while the lateral nerve supplies the little toe and sometimes the fourth toe (Figure 2). Proximal tibial mononeuropathy is quite rare and almost always occurs as a result of trauma directly to the nerve or injury to the tibial fibres in the sciatic nerve trunk.

### Tarsal Tunnel Syndrome

Tarsal tunnel syndrome is analogous to carpal tunnel syndrome occurring as a result of compression of the tibial nerve under the flexor retinaculum. On rare occasions the nerve may be compressed by mass lesions in the tarsal tunnel or by local trauma as a result of injury to the ankle. Patients may present with perimalleolar pain or burning pain or paraesthesia in the feet. There are generally not a lot of physical signs although wasting of intrinsic foot muscles may sometimes be seen. It is my

experience however that most patients with this constellation of symptoms and physical signs turn out to have either a polyneuropathy, a radiculopathy, lumbosacral plexopathy or local orthopaedic problem.

### Electrophysiological Assessment

In proximal tibial neuropathy the aim is firstly to distinguish if the tibial nerve only is involved or whether there is lumbosacral plexus or sciatic nerve involvement. Assessment therefore should include nerve conduction studies from both tibial nerve and ipsilateral common peroneal and sural nerves. Electromyography is then the most useful means of obtaining anatomical localisation. If there is denervation in the tibial-innervated hamstrings then the lesion is proximal to the popliteal fossa, if there is gastrocnemius and soleus denervation then the lesion is proximal to the ankle. In tarsal tunnel syndrome there may be slowing of distal tibial motor conduction. Nerve conduction studies should therefore be performed on both the symptomatic and contralateral ankle. You can also perform studies on the medial and lateral plantar nerves to assess sensory nerve conduction. This is an unreliable sign as the responses are sometimes absent in normals, the sign is only useful if a response is obtained on the asymptomatic side and there is a reduced or absent response on the symptomatic side. Patients should also be assessed for polyneuropathy or plexopathy so I always check a sural and common peroneal response in the asymptomatic limb.

Table 1

Muscular Branches of the Tibial Nerve below the knee

Branches in the Leg
Plantaris
Soleus
Gastrocnemius
Tibialis Posterior
Flexor Hallucis Longus
Branches in the Foot
Abductor Hallucis
Abductor Digiti Quinti Pedis

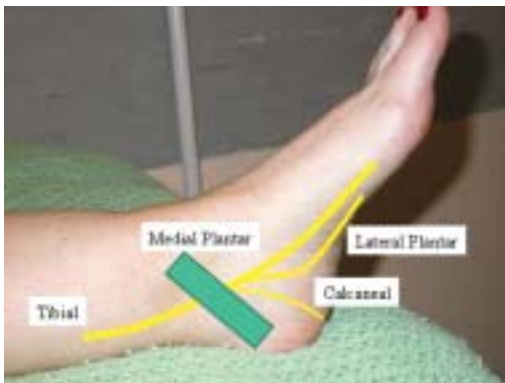


Figure 1: Medial view of the ankle showing the pathway of the tibial nerve through the tarsal tunnel and the terminal branches of the tibial nerve.



Figure 2: Plantar view of the foot showing the sensory distribution of the sensory branches of the tibial nerve.



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# Chorea- Diagnosis and Management

**Definition:** a continuous flow of irregular, jerky, and explosive movements, that flit from one portion of the body to another in random sequence. Each muscle contraction is brief, often appearing as a fragment of what might have been a normal movement, and quite unpredictable in timing or site. Sometimes it can occur with other movement disorders so that it is not uncommon in HD, for example, to see patients in which the chorea and dystonia merge to give the appearance of "hanging chorea". The best way to detect chorea is often to ask patients to do something and look at the limbs carefully – thus one can see finger flicking with walking and irregular movements in the arms and legs with rhythmical hand tapping tasks.

Chorea is seen in a large number of conditions (see Table), but the commonest cause outside the L-dopa treatment of PD is Huntington's disease. However there are a number of non-inherited conditions in which chorea can occur and it is important to screen for these as they may be treatable. A figure summarising the approach to chorea by age and cause is given in figure 1, with the more common causes summarised below.

**HUNTINGTON'S DISEASE (HD)** is a rare, dominantly inherited, relentlessly progressive disease, usually of middle life, characterised by chorea, cognitive decline leading to dementia and psychiatric disorders. It affects about 1 in 10,000 and is the result of an abnormal CAG triplet repeat in the gene coding for huntingtin on chromosome 4. The abnormal expansion of the CAG repeat in HD (>36 repeats) causes a new gain of function in the mutant huntingtin which leads to neuronal dysfunction and death, although the pathogenic pathway underlying this is still not fully understood. The brain is generally atrophic, with conspicuous damage to the cerebral cortex and corpus striatum, where there is loss of nerve cells and reactive gliosis without inflammatory changes associated with extensive neurotransmitter changes.

The onset is typically insidious in middle life, usually between the ages of 30 and 50 years and can be with motor, cognitive and/or psychiatric symptoms and signs. The initial symptoms are frequently those of a change in personality and behaviour, but chorea may be the first sign of the illness. At this stage the patient often retains insight, fully aware of what is in store based on their experiences with affected relatives. Serious depression is common and suicide is a risk and erratic behaviour at work or in society may lead to psychiatric referral. As the disease progresses, cognitive deficits become more pronounced and chorea more severe with walking, speech, and the use of the hands all becoming impaired. As the disease progresses, many patients develop increasing rigidity and akinesia, with reduction of the chorea. Finally the patient becomes bed-ridden with marked weight loss and death occurs on average about 15-20 years from the onset. In younger patients with juvenile HD (defined as disease onset before the age of 21 years) the patient more often presents with behavioural and cognitive problems and an akinetic-rigid parkinsonian syndrome (the Westphal variant), with epileptic fits and little in the way of chorea.

Despite the wide spectrum of clinical manifestations of Huntington's disease, the diagnosis is now straightforward with genetic testing - although this needs to be undertaken sensitively and with the help of trained geneticists.

However in some cases the characteristics of the disease are not overtly manifest and a history is not available, which can mean that the diagnosis is overlooked (see Table). This is especially the case if the family history appears negative because of the early death of the parents.

There is currently no cure for HD but drugs that target the dopaminergic striatal network can be used to treat the movement disorder, and this includes tetrabenazine and sulpiride as well as the newer atypical neuroleptic drugs such as risperidone and olanzepine. However careful consideration needs to be given as to the need to use anti-choreiform drugs as they produce side-effects and the patient is often not especially troubled by the movement disorder. In some cases though these drugs may be as useful in treating some of the psychiatric symptoms of HD as much as the movement disorder. Other drugs may also be required for their psychiatric symptoms including selective serotonin/noradrenergic reuptake inhibitors for depression and carbamazepine, lamotrigine and sodium valproate as mood stabilisers. In younger akinetic patients there may be some value in trying levo-dopa for their parkinsonian syndrome, although the benefits are often slight and poorly sustained. In all cases HD patients benefit from regular follow-up with close attention being paid to their drug therapies along with their support in the community.

More recent experimental therapies for HD have included the use of neurotrophic factors, such as ciliary neurotrophic factor (CNTF); non-specific neuroprotective therapies (e.g. co-enzyme Q) and fetal striatal neural allotransplantation. As yet the efficacy of any of these therapies remains unproven.

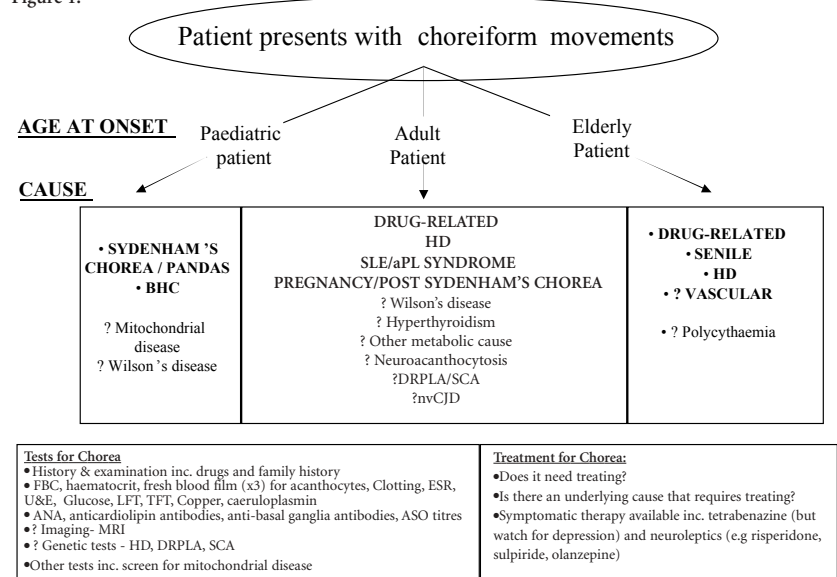
Predictive testing programmes are now available for at risk individuals, provided by a multi-disciplinary team specialised in this condition.

**SYDENHAM'S CHOREA** (St. Vitus dance) is seen as a consequence of streptococcal infection, but nowadays is part of the controversial PANDAS (Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection) which is associated with obsessive-compulsive disorders and anti basal ganglia antibodies.



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

Figure 1.



Most cases of Sydenham's chorea occur between the ages of 7 and 15 years of age and are usually gradual in onset, but may be abrupt. The initial symptoms are often psychological, with irritability, agitation, disobedience, and inattentiveness with a confusional state occurring in about 10 per cent of patients. Generalised chorea then appears and may worsen for a few weeks with speech involvement although in about a fifth of cases the chorea may be predominantly unilateral, and in severe cases is accompanied by flaccidity and subjective weakness (chorea mollis). Although cardiac disease may be found, the child usually has no fever or other manifestations of rheumatic fever.

The chorea and psychological disturbance slowly recover over 1 to 3 months, rarely up to 6 months, but can recur. Those who have suffered one or more attacks of Sydenham's chorea are at particular risk of developing chorea in adult life during pregnancy (CHOREA GRAVIDARUM), or when exposed to drugs such as oral contraceptives, digoxin, or phenytoin.

Treatment is for the chorea in HD, but it is normal for the child to be given a course of antibiotics (typically penicillin) for the underlying streptococcal infection. The efficacy of immunosuppressive therapies in this and PANDAS is not known.

ANTI-CARDIOLIPIN ANTIBODIES as part of the phospholipid syndrome or SLE are also associated with chorea and are worth looking for, because if present the patient responds to anti-coagulants and immunosuppressant therapies. Other treatable causes such as THYROTOXICOSIS and POLYCYTHAEMIA are said to cause chorea and worth excluding along with other metabolic causes (see table 1). In elderly patients there is the disputed entity of SENILE CHOREA which can look like the chorea of HD, but it is not associated with other symptoms or signs and the genetic defect of HD.

Finally there a host of other rare conditions that are worth considering, although most of these causes cannot be treated and one is left treating the chorea symptomatically.

HEMIBALLISM refers to wild flinging or throwing movements of one arm and leg and like those of chorea, are irregular in timing and force, but predominantly involve the large proximal muscles of the shoulder and pelvic girdle. They can be seen in Sydenham's chorea but more typically occur in the elderly hypertensive and/or diabetic patients as a result of a stroke involving the subthalamic nucleus, although lesions at other anatomical sites can cause this movement disorder. It may appear as the hemiplegic weakness improves with thalamic pain, although in other patients the hemiballism appears abruptly without weakness or sensory deficit and its intensity varies from mild to such a severity as to cause injury and to require treatment.

Hemiballism due to stroke usually gradually remits spontaneously over 3 to 6 months, but when treatment is needed it is typically with haloperidol or tetrabenazine although occasionally interventional neurosurgery for this condition is required and may be of benefit.

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**Table: Commonest and/or most important causes of chorea**

- Hereditary -**
  - Autosomal dominant**  
Huntington's disease  
Spinocerebellar ataxias inc. SCA3 and DPRLA
  - Autosomal recessive**  
Neuroacanthocytosis: Genetic disorder with mutations in CHAC gene on 9q21 presents typically in early adulthood with a movement disorder typically chorea and orofacial dyskinesias along with a motor neuropathy, epileptic fits, cognitive decline and psychiatric symptoms.  
Wilson's disease
  - Other**  
Mitochondrial disease  
Benign hereditary chorea (BHC); a rare condition that presents before the age of 10, gets worse over the next decade then improves and stabilises without any other neurological problems developing.
- Drug induced**  
Neuroleptics  
Anti-convulsants  
Anti-PD medication  
Oral contraceptive (often with a history of previous Sydenham's chorea)
- Toxins**  
Carbon monoxide poisoning
- Metabolic**  
Hyperthyroidism  
Pregnancy  
Hyper/Hypoglycaemia  
Electrolyte disturbances
- Infection**  
Sydenham's chorea/PANDAS  
nvCJD
- Immunological**  
Systemic Lupus Erythematosus/  
Anti-phos pholipid syndrome  
? PANDAS
- Vascular**  
Infarction  
Polycythaemia  
Post pump chorea in children: seen in children who have undergone bypass surgery with hypothermia. It normally resolves spontaneously but can persist in some cases.
- Tumours**
- Trauma**  
Cerebral palsy  
Acquired
- Age related**  
Senile chorea
- Paroxysmal**
- Psychogenic**

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**MIRAPEXIN<sup>™</sup> (pramipexole) Abbreviated Prescribing Information.** Before prescribing see Summary of Product Characteristics. **Presentation:** Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing 0.125mg, 0.25mg and 1mg respectively of pramipexole salt (dihydrochloride monohydrate). **Uses:** 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: The daily dosage is administered orally with water in equally divided doses three times per day. Initial treatment: Titration of dose from 0.264mg base (0.375mg of salt) per day, doubling the dose every 5-7 days, to a daily dose of 1.08mg base (1.5mg salt), if a further dose increase is necessary the daily dose should be increased by 0.54mg base (0.75mg salt) at weekly intervals up to a maximum dose of 3.3mg base (4.5mg salt) per day. NB The incidence of somnolence is increased at doses higher than 1.5mg (salt)/day. Maintenance treatment: The individual dose should be in the range from 0.264mg base (0.375mg salt) to a maximum of 3.3mg base (4.5mg salt) per day. It is recommended that the dosage of levodopa is reduced during both the escalation and the maintenance treatment with Mirapexin, dependent upon individual response. Treatment discontinuation: Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.54mg of base (0.75mg of salt) per day until the daily dose has been reduced to 0.54mg of base (0.75mg of salt). Thereafter, the dose should be reduced by 0.264mg of base (0.375mg of salt) per day. Renal impairment: Consult the Summary of Product Characteristics for information on revised dosage schedules. Hepatic impairment: Dose adjustment in patients with hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications, Warnings etc:** **Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings:** In patients with renal impairment a reduced dose is recommended (see above). Hallucinations are a known side-effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur. Mirapexin has been associated with somnolence and, uncommonly, sudden sleep onset. Patients who have experienced somnolence and/or an episode of sudden onset of sleep must refrain from driving or operating machines, until such recurrent episodes and somnolence have resolved. Furthermore a reduction of dosage or termination of therapy may be considered. In advanced Parkinson's disease, in combination with levodopa, dyskinesias can occur during the initial titration of Mirapexin. If they occur, the dose of levodopa should be decreased. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In cases 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 pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules, such as cimetidine and amantadine, may interact with pramipexole resulting in reduced clearance of either or both drugs. Reduction of the pramipexole dose should be considered when these drugs are administered concomitantly with Mirapexin. While increasing the dose of Mirapexin it is recommended that the dosage of levodopa is reduced and the dosage of other anti-Parkinsonian medication is kept constant. Due to possible additive effects, caution is advised when patients are co-prescribed Mirapexin with other sedating medication or alcohol. Co-administration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** The effect on pregnancy and lactation has not been investigated in humans. Therefore, Mirapexin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Similarly, Mirapexin should not be used during breast-feeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, dizziness and peripheral oedema occurred more often than with placebo. More frequent adverse reactions in combination with levodopa were dyskinesias. These adverse events tend to decrease or 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/emetic measures may be required. **Basic NHS Cost:** 0.088mg x 30 £10.00, 0.18mg x 30 £20.00, 0.18mg x 100 £66.67, 0.7mg x 30 £63.67, 0.7mg x 100 £212.24. **Legal Category:** POM. **Marketing Authorisation Holder:** Pharmacia Enterprises S.A., 6, Circuit de la Foire Internationale, L-1347 Luxembourg, G.D. Luxembourg. **Marketing Authorisation Number:** Mirapexin 0.088mg x 30 tablets EU/1/97/051/001; Mirapexin 0.18mg x 30 tablets EU/1/97/051/003; Mirapexin 0.18mg x 100 tablets EU/1/97/051/004; Mirapexin 0.7mg x 30 tablets EU/1/97/051/005; Mirapexin 0.7mg x 100 tablets EU/1/97/051/006. Further information is available from Pharmacia Ltd, Davy Avenue, Milton Keynes, MK5 8PH, UK. Tel: 01908 661101. **Date of preparation:** April 2003. **References:** 1. Shannon KM, Bennett JP Jr, Friedman JH et al. Neurology 1997; 49: 724-728. 2. Barone P, Bressman S. Poster presented at 53rd Annual American Academy of Neurology, May 5-11, 2001 Philadelphia, Pa. 3. Parkinson's Study Group. JAMA 2000; Vol 284, No.15: 1931-1938. P8995/01/03.

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## Rehabilitation Article

### Voice Control of Environmental Control Systems

Lothian's Electronic Assistive Technology provides Environmental control equipment to enable people with special needs to control electrical/electronic equipment within their homes.

At present there are 57 such installations of environmental control equipment within the Lothian region. Most of the equipment fitted uses a scanning method for the selection of options from a display panel. Voice control is also an option and at present there are five installations of voice based environmental control equipment in Lothian, the first of which took place four years ago.

Voice recognition has been available as a method of computer control for a number of years. There are two main producers, IBM and Dragon Systems. Both require a head worn microphone and a microcomputer and have the advantage of adapting to changes in the user's voice. It is possible to use this software for environmental control by fitting an infrared transmitter to a microcomputer or wheelchair mounted laptop computer. However the former would contrast with the trend within environmental control towards portable compact equipment and the latter would result in reduced reliability because the laptop computer, due to its hard drive, is more prone to damage caused by vibration than a dedicated environmental control unit.

Our experience with voice based systems has been with the Sicare Pilot (figure 1). The Pilot is a compact voice operated unit that can be clamped to the user's wheelchair or positioned on an overbed table. Two models are available, one that transmits infrared only and another that transmits radio signals as well. The Pilot includes a database of standard infrared codes and can, if an additional IR box is purchased, learn the codes for standard infrared remote controls. The Pilot has a built in microphone or alternatively a small external microphone can be fitted. A small LCD screen provides visual indication and a built in speaker enunciates the command just recognised. The Pilot can be operated with one or two switches, as a backup method to voice control.

Figure 1.



The Pilot utilises a menu tree structure of commands (see figure 2). This tree structure is constructed during installation with commands being classified into branches associated with different devices e.g. TV, telephone, intercom etc. Infrared signals are then assigned to each command by either selecting from a database of infrared signals or training the Pilot with infrared signals from the user's remote controls. Voice profiles are then linked to each command by training the Pilot with the user's voice.

Figure 2.



The tree structure is necessary to maximise recognition reliability so at any stage in its use the Pilot is looking for the user to utter one of a few commands in the active branch of the menu, and not looking for the full vocabulary. The Pilot can store a maximum of 64 voice profiles but the tree structure makes it possible to reuse particular voice profiles within different contexts. For example the numbers 0, 1, 2, 3 can be used both within the telephone and TV branches of the menu making the Pilot's memory the limitation on the maximum number of commands. The manufacturer states that they have configured a Pilot with 410 commands and noted that less than 50% of available memory was used.

Fixed display scanning environmental control units such as the Steeper Fox and Gewa Prog have a maximum number of commands of 62 and 161 respectively. This is less than the Pilot but sufficient for most users. Alternatively the SRS 100, a scanning environmental control unit with a LCD screen could be considered. This device, because of its dynamic display, has a maximum number of commands limited only by its memory. The manufacturer states that the SRS 100's maximum number of commands is 2500.

#### Criteria for selecting voice control

- 1) Users must have a reliable repeatable voice.
- 2) Users must have a sufficiently good memory to memorise the Pilot's menu tree structure.
- 3) The user's level of disability should probably exclude other simpler options. The Pilot is approximately 2.5 times the cost of the Gewa Prog or Steeper Fox so initial and replacement costs will be significantly greater. Also, a number of follow up visits may be required, in the weeks immediately after installation, to retrain problem voice profiles. These follow up visits obviously represent a cost in terms of staff hours.
- 4) It's helpful if the user has a good motivation to work with technology. One reason is to fully exploit the functionality offered by the Pilot but also a high level



Colin Geggie is a Clinical Bioengineer responsible for Lothian Primary Care NHS Trust's Electronic Assistive Technology Service based at Rehabilitation Engineering Services (RES), Eastern General Hospital, Edinburgh. His areas of work include environmental control equipment, special controls for powered wheelchairs, and special switches and interfaces for communication aids and microcomputers. He has also been involved in RES's upper limb prosthetic development programs.

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# Rehabilitation Article

## Botox® Abbreviated Prescribing Information

**Presentation:** Vial containing 100 units (U) *Clostridium botulinum* type A neurotoxin complex (900kD). **Indications:** Symptomatic relief of blepharospasm, hemifacial spasm, idiopathic cervical dystonia (spasmodic torticollis) and severe axillary hyperhidrosis. Focal spasticity - dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients (two years or older) and wrist and hand disability due to upper limb spasticity associated with stroke in adults. Safety and efficacy in the treatment of blepharospasm, hemifacial spasm, idiopathic cervical dystonia, or focal hyperhidrosis in children has not been demonstrated. **Dosage and Administration:** See Summary of Product Characteristics for full information. Reconstitute with sterile unpreserved normal saline (0.9% sodium chloride for injection). BOTOX® doses are not interchangeable with other preparations of botulinum toxin. **Blepharospasm:** Inject using a 27-30 gauge needle. Initially, 1.25-2.5 U injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Subsequently, the dose may be increased up to two-fold. Initial dose should not exceed 25 U per eye. Total dose should not exceed 100 U every 12 weeks. **Hemifacial spasm:** Treat as for unilateral blepharospasm (as above). Inject other affected facial muscles as needed. **Cervical dystonia:** Inject using a 25, 27 or 30 gauge needle (for superficial muscles) or 22 gauge (deeper musculature). Tailor dosing to individual patient based on the head and neck position, location of pain, muscle hypertrophy, body weight and response. Do not inject sternocleidomastoid muscle bilaterally. Maximum total dose usually not more than 200 U. **Hyperhidrosis of the axillae:** Inject using a 30 gauge needle. Inject 50U intradermally to each axilla, evenly distributed in multiple sites 1-2 cm apart. **Paediatric cerebral palsy:** Inject using a 23-26 gauge needle into the medial and lateral heads of the affected gastrocnemius muscle. Recommended total dose: 4 U/kg. Divide dose between two limbs if injected on same occasion. Repeat dose not more frequently than every two months. **Focal spasticity associated with stroke:** Inject using a 25, 27 or 30 gauge needle (superficial muscles) or longer needle for deeper musculature. Multiple injection sites may facilitate more uniform contact with the innervation areas of the muscle, especially in larger muscles. Tailor dose and number of sites based on size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness. **Contra-indications:** Known hypersensitivity to any constituent. Generalised disorders of muscle activity (e.g. myasthenia gravis). Concomitant use with aminoglycoside antibiotics or spectinomycin. Bleeding disorders of any type, anticoagulant therapy and whenever there is any reason to avoid intramuscular injections. Pregnancy or lactation. **Warnings/Precautions:** Relevant anatomy and changes due to prior surgical procedures must be understood prior to administration. Extra caution with injection sites close to structures such as the carotid artery and pleural apices. Do not exceed recommended dosages and frequencies of administration. Adrenaline and other anaphylactic measures should be available. For intramuscular injection and in the treatment of hyperhidrosis for intradermal injections ONLY. **Blepharospasm:** Reduced blinking following injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with Vllth nerve disorders. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid areas to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. **Cervical Dystonia:** Limiting dose into the sternocleidomastoid muscle to less than 100 U may decrease the risk of dysphagia. **Hyperhidrosis of the axillae:** Consider secondary causes of hyperhidrosis to avoid symptomatic treatment without the diagnosis and/or treatment of underlying disease. **Focal Spasticity associated with paediatric cerebral palsy and stroke:** Not intended as a replacement for the usual standard of care regimens. Not likely to be effective in improving range of motion at a joint affected by a fixed contracture. **Interactions:** Effect may be potentiated by aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission e.g. tubocurarine-type muscle relaxants. Polymyxins, tetracyclines, lincomycin and muscle relaxants should be used with caution. **Adverse Effects:** Side effects may occur from misplaced injections temporarily paralysing nearby muscle groups. Excessive doses may cause paralysis in muscles distant to the injection site. **Blepharospasm:** Most commonly-reported: ptosis, lacrimation and irritation (including dry eye and photophobia), lagophthalmos. Ectropion, keratitis, diplopia and entropion reported rarely. Ectymosis occurs easily in the soft eyelid tissues. One case of angle-closure glaucoma. **Cervical dystonia:** Dysphagia, pain and soreness at the injection site and local weakness reported frequently. Less frequent: bruising at injection site, general weakness, malaise, nausea. Rare: drowsiness, numbness, stiffness, diplopia, ptosis, headache, dyspnea, fever, flu syndrome. Possible: neck weakness/instability head tremor, dysphonia, dry mouth, allergic reactions. **Axillary hyperhidrosis:** Perceived increase in non axillary sweating. Weakness of arm reported uncommonly. **Cerebral palsy:** Falling, leg pain, leg (local) and general weakness. Leg cramps, fever, knee pain, ankle pain, injection site pain, lethargy. **Focal upper limb spasticity:** Commonly reported: ecchymosis, pupura, injection site haemorrhage, arm pain, muscle weakness, hypertonia and injection site burning. Less frequent: hyperesthesia, arthralgia, asthenia, pain, buritis, dermatitis, headache, injection site hypersensitivity, malaise, nausea, paresthesia, postural hypotension, pruritus, rash, incoordination, amnesia, circumoral paresthesia, depression, insomnia, peripheral oedema, vertigo. **Basic NHS Price:** £128.93. **Marketing Authorization Number:** 0426/0074. **Marketing Authorization Holder:** Allergan Ltd, Coronation Road, High Wycombe, Bucks HP12 3SH. **Legal Category:** POM. **Date of preparation:** February 2003. Further information is available from: Allergan, Coronation Road, High Wycombe, Bucks HP12 3SH.

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of user participation is required both during voice training and also afterwards when it's necessary to highlight any problem voice profiles.

- 5) Familiarity with voice control methods is useful but not essential. People who are already using voice control for computer use appear to take readily to the Pilot.
- 6) A strong aversion to any additional equipment may make the Pilot a good choice. One Pilot user, who had suffered a high level spinal injury, explained that he didn't want to have a switch positioned near his head as he felt this was the only part of him that was not disabled. The Pilot could be recommended for people who express this view at it results in a discreet solution with minimal equipment.

## Reliability

From our experience the Sicare Pilot would appear to be reliable if care is taken during voice training and during the setting up of the Pilot each day. During voice training there are five passes through the list of commands. The documentation recommends that each of these five passes be done at different times of day. This may present difficulties for those fitting the device because it is more time efficient for voice training to be done within a fixed time slot.

## Factors to Maximise Reliability

- 1) During training make the five passes through the command list with different levels of background noise.
- 2) Use the small clip-on microphone to make the Pilot less susceptible to background noise. Note the position and orientation of the microphone during voice training and ensure that the user has this information so carers can set the microphone up similarly each day.
- 3) Maximise the phonetic difference between commands. For example use "Dial Out" instead of "Dial" in order to include more syllables.
- 4) Structure the menu tree to minimise the number of commands within each branch. This is especially important for more safety-critical commands.

## Reliability for Safety-Critical Functions

There is some concern about using voice control for safety-critical commands e.g. to call for help via alarms. Our experience with the Pilot leads us to conclude that occasionally the user may have to repeat commands. This is especially the case when significant background noise is present, e.g. when the hi-fi is playing when it may be necessary for the user to wait for a lull in the sound before proceeding.

The risks have to be weighed up in each case in order to establish if backup switches are required. If there are factors that increase the risk in the event of a problem e.g. the user requiring a ventilator, then backup switches should be provided. For community alarms where assistance is being sought from a carer outwith the immediate home environment then, similarly, it would be wise to consider backup switches. We would also have serious concerns about voice control being used for the control of electrically tilting armchairs where there is a risk of injury to the user.

## Acknowledgement

The author would like to thank Sandy McCallum and Philip Bain. Both use the Pilot and provided many valuable comments and suggestions during the writing of this article.

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## BSRM summer meeting: Exercise, Brain Repair and punting down the Cam

10-11 July, 2003; Cambridge, UK

The meeting was held at the beautiful location of St. John's College in the centre of Cambridge. The organisation was immaculate as usual.

Exercise in health and illness was the theme of the first day. Professor Tom Storer from UCLA was the first speaker and he gave a very clear introduction to exercise prescription. Most of the UK rehabilitation specialists leave the details of the exercise prescription to physiotherapists. However, the clarity of the presentation and the special focus he gave on the different methods to determine the intensity of the exercise and the ways to assess its outcome probably made the whole subject less intimidating. Prof. Storer stressed the need for valid and objective measurements such as metabolic markers in the assessment phase and prescription, whilst simple measures such as heart rate or psychometric measures could be used to monitor progress. Dr Kathy Speed from Addenbrooke's Hospital then talked about the importance of exercise in the elderly population. She emphasised the importance of exercise in this group to tackle the problems associated with deconditioning and sarcopenia.

Following that, Professor Chris Cooper talked about exercise as a therapeutic modality that has dose dependent characteristics. He used pulmonary rehabilitation as a framework for his talk. The basic principle is to identify a lower threshold for exercise intensity that elicits a clinically meaningful and measurable response. It was very useful to hear of the new guidelines from The American Society of Sports Medicine for aerobic exercise for healthy individuals, particularly that the frequency now recommended is 5 or 6 days a week and not just 3 days, as it used to be. I was disappointed to hear that exercise for less than 2 days a week is useless. The duration of each session should be at least 30 minutes and the intensity should be between 55% to 95% of maximum heart rate.

Dr Kate McGlashan then presented the results from her research on the value of exercise in chronic stroke patients. In that study 20 chronic stroke patients showed improvement in mobility after having aerobic exercise training on a treadmill or static bike. The improvement in mobility was maintained at 6 months follow up. These encouraging results were consistent with the literature and gave some food for thought regarding the different ways to organise such a service. As most of the speakers stressed the safety of exercise after excluding serious cardiac pathology, it was felt that health clubs could probably offer such a service in the future.

Mr Tim Theologis, an orthopaedic surgeon from Oxford, talked about his experience in using gait analysis for the assessment of patients with cerebral palsy. The main take home message is that the principal value of the analysis is to test a hypothesis already formulated by the clinician and either acceptance or rejection of the hypothesis will lead to a specific intervention. It is unjustified to ask for a gait analysis just to understand what the problem is. The presentation was a real surgeon's lecture, clear and to the point.

Dr Alison Sansome, a Cambridge Paediatrician, talked about the use of botulinum toxin in the management of spasticity in children with cerebral palsy. She gave very good tips especially regarding the dosage and potential complications. Dr Turner-Smith, Reader in Rehabilitation Engineering at KCL, rounded up the day with a presentation that explained the principles of the ICES programme (Integrated Community Equipment Services) which

should improve the provision of assistive technology in the UK.

Professor David Menon from The Wolfson Brain imaging centre in Cambridge started the second day with an overview of the value of the new imaging methods such as PET and MR spectroscopy scans in increasing our understanding of the immediate sequelae of brain injury. Nevertheless, it will still be some time before these tests become widely available to guide more adventurous interventions. At the moment, maintaining normal physiology, especially blood perfusion, together with keeping the patient's temperature down are the main management strategies for the acute head injury patient.

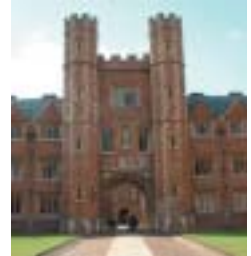
This talk was followed by a fascinating account of the mechanogrowth factor (MGF) by Professor Geoffrey Goldspink. He presented the recent work of his team in the Royal Free Hospital. Professor Goldspink went through the steps in identifying MGF and its potential to play an important role in the management of muscle diseases. That was followed by ACNR's Editor in Chief Dr Roger Barker who took us on a journey through the highs of cell replacement therapies with the promise from studies in the lab and animal models, to the lows of the modest successes in clinical trials with occasional catastrophes, as the media likes to call them. Dr Aileen Ho, a neuropsychologist working with Dr Barker in the Cambridge Brain Repair Centre, then presented her preliminary results from a study using human striatal foetal tissue to repair the damaged striatum in patients with Huntington's Disease. The preliminary results were encouraging and the presentation was followed by a lively discussion about the ethics and future of cell therapy.

The second session of the last day is traditionally devoted to biomechanics and prosthetics. Professor Alan Wing from Birmingham presented some elements of his current research in behavioural neuroscience which dealt mainly with motor control and rehabilitation of the motor function of the brain damaged. That was followed by an interesting talk by Dr Carol Fraser, recently retired from the Occupational Therapy Department at Addenbrookes, who described how upper limb amputees actually used their prostheses, and emphasised how functional dress or cosmetic limbs can be, and how often patients do not actively use their "functional" terminal devices.

*Tarek Gaber,  
Consultant in Rehabilitation Medicine,  
Leigh Infirmary*



Rajiv Hanspal (left), BSRM President and Emlyn Williams (right), at the meeting.



Venue: St. John's College in Cambridge

# Conference Report

## ENS 2003

14-18 June, 2003; Istanbul, Turkey

### **ACNR prize for the best gene at the ENS: CACNA1A**

Michel Ferrari, from Leiden, gave an animated talk (including racy pictures of his family firm's products) on this gene on chromosome 19. It encodes the main alpha unit of the neuronal calcium channel, which is involved in the modulation of the release of neurotransmitters including monoamines, acetylcholine, glutamate and substance P. What could not be expected is the extraordinary diversity of diseases caused by mutations in CACNA1A. Most people will be aware of its association with familial hemiplegic migraine, spinocerebellar ataxia 6 and episodic ataxia type 2. But it seems that its dysfunction also causes generalised epilepsy and, most bizarre of all, a syndrome of delayed cerebral oedema after minor head injury. How can we possibly make sense of that? When the human genome project estimated that the number of genes was only 30,000, rather less than previous guesses, there was some disappointment that human genetics was not as complex as had been imagined. But if each of those genes is half as complex as CACNA1A, we are in for a long haul.

### **ACNR prize for the most provocative poster at the ENS: protective autoimmunity against MPTP toxicity**

This is not an entirely novel story, but the context is interesting. Michal Schwarz and colleagues at the Weizmann Institute have shown before that autoreactive anti-myelin T cells improve the functional outcome of optic nerve crush injury and have postulated the concept of protective autoimmunity. In this poster, from Warsaw, EAE was induced in animals by myelin oligodendrocyte glycoprotein and then, 6 days later, MPTP was given. This toxin causes selective depletion of dopaminergic cells in the substantia nigra. In the MOG treated animals, MPTP caused less dopamine depletion, less glial reaction and reduced striatal inflammatory cellular infiltration. Extrapolating from this: perhaps idiopathic Parkinson's disease is less frequent amongst patients with multiple sclerosis (for which there is no evidence as far as I am aware)? Or can neurodegenerative diseases be treated by inducing autoimmunity?

### **ACNR prize for the best virus at the ENS: Epstein-Barr virus in multiple sclerosis**

The nature of the oligoclonal bands in CSF has long been studied without clear conclusions. Hemmer's group, in Marburg, have taken the subject further by applying some technical wizardry to the CSF of 15 multiple sclerosis patients and 5 controls. They ran the CSF against a protein array, comprising 35,000 cDNA inserts from a human foetal brain library, and found four proteins that selectively bound CSF oligoclonal bands from MS patients. They demonstrated intrathecal synthesis of antibodies against these proteins and, by substitutional analysis, identified the binding epitopes in two of these proteins. These peptide sequences matched two motifs from the Epstein Barr virus, namely BRF2 and EBNA1. These are both located close to each other and use the same promoter. They went on to show higher CSF and serum BRF2 and EBNA1 peptide and protein immunoreactivity in 150 multiple sclerosis patients compared to 90 controls. What does this mean? Well the traditional interpretation is that Epstein-Barr might cross-react with a myelin peptide. However an alternative possibility is that the EBV acts as a B cell mitogen increasing B cell turnover in a non-antigen specific way and hence boosting antibody production, thus increasing the likeli-

hood of an anti-myelin antibody escaping tolerance and causing multiple sclerosis.

### **ACNR prize for the best prognosis at the ENS: cervical dissection**

As we increasingly recognise cervical dissection as a cause of stroke, so we face the question more and more: how likely is it to happen again, Doc? This study, presented on behalf of the *Multicentre Survey on Natural History of Cervical Artery Dissection Group (!)* followed 459 patients with such a dissection for an average of 30 months. In that time, 0.9% (4 patients) had a recurrence, of whom 2 patients had an associated stroke, and only one had a recurrence in the same vessel. All very reassuring.

### **ACNR prize for the most exciting drug at the ENS: antisense therapy in myasthenia gravis**

This really is a fabulous study, from a collaboration between Manchester and Jerusalem, into the treatment of that paradigmatic disease, myasthenia gravis. The teams treated 16 patients with EN101, an antisense oligodeoxynucleotide that binds selectively to AChE mRNA preventing its translation into protein. Or at least, that is what it does *in vitro*. As the drug was given orally in this trial, the sensible prediction would be that EN101 would be degraded long before it got anywhere near a neuromuscular junction. Regular anti-cholinesterase inhibitors were stopped 12-18 hours before instituting EN101 for three days. In 15/16 patients, this led to a clear deterioration in strength, followed by a marked improvement when EN101 was introduced. Of course, trial purists will immediately say this was a placebo effect, as there was no blinding and no control arm. Nonetheless, it is a really exciting approach. Antisense technology is taking off in all disease areas, particularly since 1998 when the FDA approved Vitravene® for HIV-induced cytomegalovirus eye infection.

### **ACNR prize for the most bizarre disease at the ENS: quail eater's disease**

It seems that, from time to time, people from Mediterranean countries will eat quail and get rhabdomyolysis. Two such patients presented themselves to the University of Milan, with CKs of 33,981 and 10,500, normal EMG and normal muscle biopsy. The Italian myologists have carefully probed the mechanism of this curious illness. The usual molecular suspects of muscle disease were examined and found to be normal. But Western blot analysis of the muscle showed a reduced expression of calpain-3. Mutations in the gene encoding calpain-3 cause Limb-Girdle Muscular Dystrophy type 2A. The quail eaters had normal calpain-3 genes, so presumably something about the quails had interfered very specifically with calpain-3. The presenters were asked if quail muscle contained calpain-3. This stumped them. They had not looked. Tut tut.

This solves another mystery. You will remember the Israelites received all that manna from heaven. After a while they got fed up with it and wanted meat. God was annoyed with them. The story is told in Numbers, 11: "Now a wind went out from the LORD and drove quail in from the sea..... All that day and night and all the next day the people went out and gathered quail.... But while the meat was still between their teeth and before it could be consumed, the anger of the LORD burned against the people, and he struck them with a severe plague."

*Alasdair Coles  
ACNR, Co-editor*



If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 313110 or E-Mail: AdvancesinCNR@aol.com by October 6th, 2003. An extended version of this diary is available on our website at www.acnr.co.uk

2003 September

**European Association of Neurosurgical Societies 2003 Congress**  
7-12 September, Lisbon, Portugal  
Fax. 351 218 473 746, E. stephanie.garfield@virgin.net  
**British Aphasiology Society Biennial International Conference**  
8-10 September, 2003; Newcastle, UK  
Tel. Sue Franklin 0191 222 8859, E. s.e.franklin@ncl.ac.uk  
**IPCA 2003; Workshop on Information Processing in Cells & Tissues**  
8-11 September, 2003; Lausanne, Switzerland  
Christof Teuscher, Tel. 0041 21 693 66 30, Fax. 0041 21 693 37 05  
**4th National Conference on Falls & Postural Stability**  
9 September, 2003; London, UK  
Hampton Medical Conferences, Tel. 020 8977 0011, Fax. 020 8977 0055, E. hmc@hamptonmedical.com  
**European Regional Meeting of the Cognitive Science Society - EuroCogSci2003**  
10 September, 2003; Osnabruck, Germany  
Tel. +49 541 969 4830, Fax. +49 541 969 6229, E. eurocogsci03@uos.de  
**MS Trust Study Days**  
10 September, 2003, Penrith, UK  
Tel. Catherine Thornley on 01462 476704.  
**2nd Cambridge Update in Neuro-Critical Care**  
11-12 September, 2003; Cambridge, UK,  
Mrs M Archibald, Tel. 01223 217060, E. mal0001@medschl.cam.ac.uk or arun.gupta@addenbrookes.nhs.uk  
**11th Congress of the International Headache Society**  
13-16 September, 2003; Rome, Italy  
Tel. +31 20 6793218, Fax. +31 20 6758236, E. IHC2003@lgce.nl  
**British Sleep Society 15th Annual Scientific Meeting**  
14-16 September, 2003; Cambridge, UK  
E. martin.king@papworth.nhs.uk or bssoffice@huntingdon52.freereserve.co.uk, Fax. 01487 840618  
**XV International Congress of Neuropathology**  
14-18 September, 2003; Turin, Italy  
Newtours spa, Via San Donato 20, 50127 Florence, Italy, Tel. 0039 055 33611, Fax. 0039 055 336 1250, E. icnp2003@newtours.it  
**Epilepsy Nurse Association Annual Conference**  
15-16 September, 2003; London, UK  
Christine Morley, Tel. 01482 617635, E. christine.morley@herch-tr.nhs.uk  
**Neuro-Behavioural Rehabilitation in Severe Brain Injury: Challenging Behaviour & Complex Neuro-Disability**  
16 September, 2003; London, UK  
Tel. 020 8780 4500 x 5236, E. conferences@rhn.org.uk  
**6th Annual Advanced Rehabilitation Course, University of Nottingham**  
16-19 September, 2003; Nottingham, UK  
Tel. 0115 924 9924 x 42378, E. Janet.o'flynn@nottingham.ac.uk

**IFCN/AAEM International Congress**  
16-20 September, 2003; San Francisco, US, E. saadkins@aaem.net  
**Central Nervous System Infections**  
17 September, 2003; Liverpool, UK  
Emily Thompson, tel. 0151 298 2999, E. mnt@gnc.u-net.com  
**1st International Symposium on CNS Germ Cell Tumors**  
17-19 September, Kyoto, Japan  
Fax. 81 49 294 4955, E. rnishika@saitama-med.ac.jp  
**British Society of Neurological Surgeons**  
Autumn Scientific Meeting  
17-19 September, 2003; Cardiff, Wales  
E. admin@sbn.sfn.freereserve.co.uk  
**19th Congress of ECTRIMS**  
17-20 September, 2003; Milan, Italy  
Professor Dr Giancarlo Gomi, Tel. +390 2 2643 2881, Fax. +390 2 2170 2881, www.akm.ch/ectrims2003, E. info@akm.ch  
**12th Nordic Meeting on Cerebrovascular Diseases**  
17-20 September, 2003; Oslo, Norway  
Tel. +47 22561930, Fax. +47 22560541, E. stroke@congrex.no  
**35th Annual General Meeting of the European Brain & Behaviour Society**  
17-20 September, 2003; Barcelona, Spain  
http://seneca.uab.es/ebbs-2003/  
**International Society for Neuronal Regulation Annual Conference**  
18-21 September, 2003; Houston, US  
Tel. 001-361-949-8428, Fax. 1-361-949-8881, E. amh@stx.rr.com  
**International Association of Biomedical Gerontology Congress**  
19-23 September, 2003; Cambridge, UK  
Aubrey de Grey, E. ag24@gen.cam.ac.uk  
**North West Nurses Epilepsy Forum (Learning Disabilities)**  
19 September, 2003; Widnes, UK  
Sam Loughran, Sam\_loughran@hotmail.com, Tel. 0151 420 7619  
**Signalling Processes & Structures in Nervous System in Health & Disease**  
19-20 September, 2003; Dresden, Tel. +49 03916713088, Fax. +49 03916713097, E. georg.reiser@medizin.uni-magdeburg.de  
**16th Congress of the European College of Neurophysiopharmacology**  
20-23 September, 2003; Prague, Czech Republic  
E. secretariat@ecnp.nl  
**MSIF 2003 International Conference**  
20-24 September, 2003; Berlin, Germany  
E. dmsg@dmsg.de, www.dmsg.de  
**16th ECNP Congress 2003**  
20-24 September, 2003; Prague, Czech Republic  
E. ecnpreg@congrex.nl  
**Putting the SIGN Guideline for Epilepsy into Your Practice**  
24 September, 2003; Glasgow, UK  
Olivia Marks-Woldman, Tel. 0141 427 4911, E. omarks-woldman@epilepsyscotland.org.uk  
**31st Congress of the European Association of Geriatric Psychiatry**  
25-27 September, 2003; Wroclaw, Poland  
Tel. +48 71 784 1565, Fax. +48 71 784 1571, E. eag@psych.am.wroc.pl

**Sexual Wellbeing, Relationships, Responsibilities and Reproductive Health for People with Learning Disabilities: You and Your Body**  
26 September, 2003, UK  
Tel. 020 7290 3934, E. learning-disability@rsm.ac.uk  
**8th World Congress of Biological Psychiatry**  
28 September - 3 October, 2003; Buenos Aires, Argentina  
Tel. 54 11 43 42 32 16, Fax. 54 11 43 31 02 23, E. congrete@congressint.com.ar  
**Epilepsy Action Meeting**  
30 September, Wales, UK  
Epilepsy Action, Tel. 0113 210 8800, E. rwood@epilepsy.org.uk

October

**ABN Autumn Scientific Meeting**  
1-3 October, 2003; Glasgow, UK  
E. karen.reeves@theabn.org  
**Eurospine 2003**  
1-4 October, 2003; Prague, Czech Republic  
www.eurospine2003.cz/  
**Hope For the Wounded Brain - RSM Presidential Address**  
2 October, 2003; London, UK  
Tel. 020 7290 2984, E. cns@rsm.ac.uk  
**National Tremor Foundation 2003 Conference**  
3 October, 2003; Chester, UK  
Tel. 01708 386399, Fax. 01708 378032, E. tremorfoundation@aol.com  
**XIth World Congress of Psychiatric Genetics**  
4-8 October, 2003; Quebec, Canada  
CHUL Research Centre, RC-9800, 2705 boul Laurier, Sainte-Foy, Quebec, Canada. Fax. 001 418 654 2753, E. psygen2003@crchul.ulaval.ca, www.psygen2003.ca  
**2nd Emirates Neuroscience Conference**  
4-9 October, 2003; Dubai, UAE  
tel. +971 4 2666416, Fax. +971 4 2666894, E. jiqbal49@emirates.net.ae  
**Panamerican Congress of Neurology**  
8-12 October, 2003; Santiago, Chile  
Tel. +56 2 232 9347, Fax. +56 2 231 9287, www.soc-npsnc.l  
**Management of Childhood Epilepsy**  
9 October, 2003; Lingfield, UK  
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338, E. klaird@ncype.org.uk, www.ncype.org.uk  
**New Directions in Dementia**  
9 October, 2003; Liverpool, UK  
Tel. 01517 269002, Fax. 01517 268228, E. joanna@evensis.com  
**Opioids Update & Combination Therapy for Nociceptive and Neuropathic Pain**  
10 October, 2003; London, UK  
Dr M Hanna, Tel. 0207 346 3632, Fax. 0208 325 6473  
**25th International Epilepsy Congress**  
12-16 October, 2003; Lisbon, Portugal  
Tel. +353 1 4097796, E. +353 1 455 4648, E. Info@epilepsycongress.org  
**Commissioning of Services for Complex Neurological Disorders**  
14 October, 2003; London, UK  
Tel. 020 8780 4534, E. klandrews@rhn.org.uk, www.rhn.org.uk/institute  
**MS Trust Study Days**  
15 October, 2003, Peterborough, UK  
Tel. Catherine Thornley on 01462 476704.

**Understanding the Genetic Causes of Learning Disability**  
15 October, 2003; Dundee, UK  
Tel. 020 7290 3934, E. Learning-disability@rsm.ac.uk  
**7th Annual Conference - Recent Advances in Brain Injury Rehabilitation**  
15 October, 2003; London, UK  
Tel. 020 8510 7970, Fax. 020 8510 7318  
**Alzheimer's Disease - Dementia Care in an Ageing Society**  
15-17 October, 2003; Kyoto, Japan  
Tel. +81 75 823 6544, Fax. +81 75 823 6545, E. adiconference@alzheimers.org.jp  
**18th Congress of SOFMERR**  
16-18 October, 2003; Lille, France  
Tel. 02 51 464848  
**North West Nurses Epilepsy Forum (Learning Disabilities)**  
17 October, 2003; Widnes, UK  
Sam Loughran, Sam\_loughran@hotmail.com, Tel. 0151 420 7619  
**EPTA Autumn Scientific Meeting**  
17-18 October, 2003; Manchester, UK  
E. nigel.hudson@phnt.swest.nhs.uk  
**ACTRIMS**  
19 October, 2003; California, USA  
Tel. 001 212 476 0465, Fax. 001 212 499 0741, E. actrims@nmss.org  
**Emotions 2003, The (Non) Expression of Tilburg**  
19 October, 2003; Netherlands  
E. Emotions2003@tilburguniversity.nl  
**ANA Annual Meeting**  
19-22 October, 2003; San Francisco, US  
Tel. 952 545 6284, Fax. 952 545 6073, E. lorijanderson@msn.com  
**Rehabilitation Medicine, Community Services & Assistive Technology**  
21 October, 2003; London, UK  
E. enquiries@empowernet.org  
**European Paediatric Neurology Society Congress**  
22-25 October, 2003; Taormina, Italy  
E. taormina2003@hotmail.com  
**3rd International Course on Carotid Angioplasty and other Cerebrovascular Interventions**  
23-25 October, 2003; Frankfurt am Main, Germany  
Fax. 49 6 106 770 384, E. nkoebke@convents.biz  
**10th Annual Meeting of the American Society of Neurorehabilitation**  
23-26 October, 2003; Tucson, USA  
www.asnr.com/meeting/10th.htm  
**Vascular Dementia**  
23-26 October, 2003; Prague, Czech Republic  
Kenes International, PO Box 50006, Tel Aviv 61500, Israel. Tel. +972 3 5140018/9, Fax. +972 3 5172484  
**European LIMS Forum**  
27-30 October, 2003; London, UK  
Tel. 01392 250331, Fax. 01392 250332, E. jcates@eurolims.com  
**Developing Epilepsy Services**  
30 October, 2003; Aberdeen, UK  
Epilepsy Action, Tel. 0113 210 8800, E. rwood@epilepsy.org.uk  
**Sexual Wellbeing, Relationships, Responsibilities and Reproductive Health for People with Learning Disabilities: Sexual Rights & Support**  
31 October, 2003, UK  
Tel. 020 7290 3934, E. learning-disability@rsm.ac.uk

**Weekly CME in London**  
31 October-7 November, 2003; London, UK  
Michael Kessler, Tel. 0800 334 6578, Fax. 404 252 2728, E. mk@worldwidecme.com  
**November**  
**MS Trust Annual Conference**  
2-4 November, 2003; Harrogate, UK  
Tel. Katy Simpson on Tel. 020 8772 1551  
**New Neurosurgery for Children**  
5 November, 2003; London, UK  
Tel. RSM on 020 7290 3934, Fax. 020 7290 298, E. makeithe@rsm.ac.uk  
**British Neuropsychological Society Autumn Meeting**  
5-6 November, 2003; London, UK  
E. georgina.jackson@nottingham.ac.uk  
**Persistent Vegetative State**  
6 November, 2003; London, UK  
Tel. 020 7290 2984, E. cns@rsm.ac.uk  
**Brain Injury: The Rehabilitative & Neuropsychiatric Interface**  
6-7 November, 2003; Florida, USA  
Tel. 001 813 903 4844, Fax. 001 813 978 5852, E. frank.walva@med.va.gov  
**Annual Meeting of the Society for Neuroscience**  
8-13 November, 2003; New Orleans, US  
Tel. Jamie Swank, 001 202 462 6688, E. info@sfn.org  
**Creating Symbolised Resources**  
11 November, 2003; Lingfield, UK  
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338, E. klaird@ncype.org.uk, www.ncype.org.uk  
**European Society of Gene Therapy**  
14-17 November, 2003; Edinburgh, UK  
Congrex Sweden AB, Tel. +46 8 459 66 00, Fax. +46 8 661 91 25, E. esgt@congrex.se  
**Advanced Course in the Treatment of Parkinson's Disease & Extrapyramidal Disorders**  
18 November, 2003; Pescara, Italy  
Tel. +39 064 455 618, Fax. +39 064 455 618, E. limpe@interfree.it  
**Parkinson Parkinsonism Dementia: Work in Progress**  
19-21 November, 2003; Pescara, Italy  
Fax. 39 064 455 618, E. limpe@interfree.it  
**Good Practice in Epilepsy**  
20 November, 2003 Birmingham, UK  
Epilepsy Action, Tel. 0113 210 8800, E. rwood@epilepsy.org.uk  
**Living with Thalidomide**  
20 November, 2003; Leeds, UK  
Tel. Linda at the Thalidomide Trust, 01480 474074  
**International Syncope Conference**  
20-22 November, 2003; Newcastle upon Tyne, UK  
E. info@syncope-conference.co.uk  
**North West Nurses Epilepsy Forum (Learning Disabilities)**  
21 November, 2003; Widnes, UK  
Sam\_loughran@hotmail.com, Tel. 0151 420 7619  
**11th Asian-Australasian Congress of Neurology**  
22-26 November, 2003; Singapore  
Dr Balaji Sadasivan, Tel. 657 381 871, Fax. 657 387 691, enquiries@aasns.com  
**Good Practice - Diagnosis and Epilepsy**  
27 November, 2003; Bristol, UK  
Epilepsy Action, Tel. 0113 210 8800, E. rwood@epilepsy.org.uk

**MS Trust Annual Conference - MS: Maintaining the Momentum**  
2nd-4th November 2003, Majestic Hotel, Harrogate, UK Fees: £525 which includes accommodation for Sunday and Monday night inclusive, breakfast, lunch (including Sunday) and refreshments, Sunday & Monday dinner and registration fee.  
Aimed at nurses, health & social care professionals with a special interest in multiple sclerosis.  
Further details: Packer Forbes Communications, Tel: 020 8772 1551, Fax: 020 8772 1552  
E-Mail: MS2003@packerforbes.co.uk



# Courses and Conferences

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## 'MOVEMENT DISORDERS'

Advanced lectures on the broader aspects of the scientific basis of Neurology are being given on WEDNESDAY EVENINGS during the Autumn term 2003. These lectures are for senior and junior clinicians, as well as non-clinical scientists seeking information on new advances in medical research. The first lecture will commence at 5pm; there will be a break for coffee at 5.40pm and the second lecture will commence at 5.50pm. The venue will be the Wolfson Lecture Theatre, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1. **All those interested are invited to attend, free of charge, on production of a valid identity card.**

### WEDNESDAYS

15 October	Tauopathies - Basic (Cambridge) PSP, CBD etc - Clinical (ION, UCL)	Dr Michel Goedert MD,PhD,FRS  Professor A J Lees MD,FRCP
22 October	Alpha synucleinopathies - Basic  PD,DLB, MSA - Clinical (ION, UCL)	Dr Maria Spillantini PhD (Cambridge) Professor N P Quinn MD,FRCP
29 October	The etiopathogenesis of Parkinson's disease  Paroxysmal movement disorders (ION, UCL)	Professor A Schapira DSc,MD,FRCP,FMedSci (Royal Free Hospital, UCL)  Dr K Bhatia MD,DM,MRCP
5 November	The genetics of dystonia  UC Medical School) The pathophysiology of dystonia (ION, UCL)	Dr T Warner PhD,FRCP (Royal Free Hospital &  Professor J Rothwell MA,PhD
12 November	Brain rhythms in movement disorders Surgery for Parkinson's disease and dystonia	Dr P Brown MD,FRCP (ION, UCL) Professor M Hariz MD,PhD (ION, UCL)
19 November	Psychogenic movement disorders  Anti-basal ganglia antibodies and movement disorders	Dr A Schrag MD,PhD (ION, UCL) Dr G Giovannoni PhD,FCP (ION, UCL)
26 November	The genetics of Parkinson's disease Tremors	Professor N W Wood PhD,FRCP (ION, UCL) Professor G Deuschl MD (University of Kiel, Germany) Professor M R Trimble
3 December	Tics and Tourette Syndrome MD,FRCP,FRCPsych  Huntington's Disease	(ION, UCL) Dr S Tabrizi MRCP,PhD (ION, UCL)

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For more information contact Institute of Neurology on  
Tel. 0207 829 8740, Fax. 0207 278 5069,  
E-Mail. j.townsend@ion.ucl.ac.uk

University of Newcastle upon Tyne

## Syncope



www.syncope-conference.co.uk

20-22 November 2003  
Civic Centre  
Newcastle upon Tyne, UK

Organiser: Prof RA Kenny, Dr S Parry

The symposium is particularly targeted to all physicians who encounter the common symptoms of syncope such as those in the field of accident and emergency medicine, geriatric medicine, neurology, general internal medicine, cardiology and orthopaedic surgery.

### Themes:

- Definition, Classification, Epidemiology - House Debate: Who Should Run a Syncope Service?
- Syncope Guidelines
- Diagnosis
- Special Situations through Case Studies
- What's New in Pathophysiology
- Invasive Management
- Syncope and the Non-Cardiologist
- Non-invasive Management

### Invited Speakers:

Prof D Bates	Prof D Chadwick	Dr M Jackson	Dr SW Parry
Dr RS Bexton	Dr A Fitzpatrick	Prof RA Kenny	Dr FE Shaw
Prof JJ Blanc	Dr S Furniss	Prof C Mathias	Dr R Sheldon
Dr JP Bourke	Dr M Gammage	Dr JM McComb	Dr N Sulle
Dr M Brignole	Dr M Griffith	Dr K McLeod	Dr R Sutton
Prof AJ Camm	Prof B Hainsworth	Dr J Newton	Prof W Wellington

For more information please contact:

Syncope Conference, Benchmark Communications Ltd,  
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Tel: +44 (0) 191 241 4523 Fax: +44 (0) 191 245 3802

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www.syncope-conference.co.uk

Homerton University Hospital NHS  
1913 Trust

## RECENT ADVANCES IN BRAIN INJURY REHABILITATION

### Wednesday 15th October 2003

#### Topics include:

- ◆ Relevance of National Service Framework for chronic conditions to the provision of rehabilitation services after brain injury.
- ◆ Contextual rehabilitation: a working model
- ◆ Balance and its modulation after stroke
- ◆ Clinical and neurophysiological aspects of constraint induced movement therapy
- ◆ Genetic influences on outcome after brain injury
- ◆ Development of a simplified version of the multiple errands test for use in hospital settings
- ◆ The assessment of Quality of Life after brain injury
- ◆ Motivational Interviewing after brain injury

Cost: £105

Deadline for applications: 19th September 2003

This course has been awarded 5 CME credits

Applications and enquiries to: Nick Hall, Unit Administrator  
RNRU, Homerton Hospital, London E9 6SR. Tel: 020 8510 7970,  
Fax: 020 8510 7318, E-Mail. Nick.Hall@homerton.nhs.uk

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#### 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 gastro-intestinal 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:** ICN Pharmaceuticals Ltd, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire. RG24 8WD

#### References:

1. Sharma KR. Myasthenia Gravis: a critical review. *IM Intern Med* 1996;August:47-69
  2. Drachman DB. Myasthenia Gravis. *N Eng J Med* 1994;330: 1797-1810
  3. Buckley C. Diagnosis and treatment of Myasthenia Gravis. *Prescriber* 2000;11(Issue 22);107-113
  4. Genkins G et al. Treatment strategies in Myasthenia Gravis. *Ann NY Acad Sci* 1993;681:603-608
- Date of Preparation:** February 2002

## Book Reviews

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

### Greenfield's Neuropathology 7th Edition

The publication of a new edition of Greenfield's, the world's definitive neuropathology reference text, is a great event for a neuropathologist and an important landmark for the whole neuroscience community. The editors, Professor Peter Lantos and Professor David Graham, are to be congratulated on this fine achievement. This is an impressively comprehensive text book with chapters covering the pathology of all types of neurological disorder. Introductory chapters deal with general principles relating to cell biology and cellular pathology of neurons and glial cells. Pathology affecting the brain itself is, on the whole, divided into chapters by the traditional headings of diagnostic category. In addition, there are specific chapters on ophthalmic pathology, the hypothalamus and pituitary gland, the spinal cord and vertebral column, peripheral nerves and diseases of muscle. The editors have carefully chosen multi-author teams for each chapter who represent the pinnacle of knowledge for their specific sections. Not only is the authorship truly global with representation from all parts of Europe, North America, and the rest of the world, but often individual chapters have co-authors who each have a slightly different perspective on the disease process, whether from the angle of neuropathology, clinical aspects, or fundamental neuroscience. Although the main perspective of the book, appropriately, is that of the classic neuropathology, this choice of authorship gives an impressively broad perspective on disease processes. I counted a total of 75 people in the list of contributors to this edition. The role of this text book is not primarily that of a practical diagnostic manual (for example, the tumour chapter does not in all cases contain sections for detailed consideration of differential diagnosis) but rather it impressively manages to provide both a very broad perspective and incredible detail concerning pathological processes affecting the nervous system. The multi-author approach leads to successful integration of fundamental neuroscience, genetics, clinical factors and neuroimaging with the neuropathology.

Who is Greenfield's Neuropathology for? Firstly, it is essential for every neuropathologist to own a copy of

Greenfield's Neuropathology. Others who could benefit immensely from this book are trainees in neuropathology, the clinical neurosciences and general pathology, clinicians managing patients with neurological disease and fundamental neuroscientists whose interests may be in pathobiology, in vitro or animal models of neurological disease.

The seventh edition of Greenfield's Neuropathology is presented as two separately bound hard-back volumes with a sewn binding and good quality paper. This is not intended as a pictorial atlas of neuropathology but the images are appropriate in number and include imaging, macroscopic brain appearances, histology and electron microscopy. The paper has a matt surface which makes it easy to get the best from the images in all lighting conditions. A CD is available for purchase at extra cost, which contains all of the images from the book. I cannot recommend this CD too highly. It is a great service to provide the images from Greenfield's Neuropathology in electronic format and I have no doubt that this feature will help to improve the quality of teaching and training in clinical neurosciences throughout the World. The benefits of this feature cannot be overstated. Perhaps it is unfortunate that the written text is not also on the CD. I would imagine that technically it would not have been difficult to add the text to the CD but perhaps there are copyright issues relating to this. It is therefore not possible to search electronically for a term in the whole text but one has to rely on traditional contents and indexing sections, which are adequate.

This new edition of Greenfield's Neuropathology is expensive in the sense that the purchase price, particularly with the CD, is a substantial sum. However, in terms of the human endeavour which it represents and its aesthetic appeal it has to be something of a bargain. With this new edition Greenfield's Neuropathology stamps its authority as the world's definitive text book for neuropathology.

*James AR Nicoll,  
University of Southampton*



Edited by: David I Graham  
and Peter L Lantos  
Publisher: Arnold  
ISBN: 0-340-74231-3  
Price: Two volume set -  
£395.00  
Book/CD-ROM Set -  
£450.00 + VAT

### The Muscular Dystrophies

Developments in molecular biology have provided the average clinician with an overwhelming amount of knowledge about the muscular dystrophies. These conditions have provoked two inspiring decades of groundbreaking research, giving us new tools with which we can fight a vast array of other diseases. While there is an enormous amount of detail on most of the dystrophies, many of us are left with the mere remnants of our undergraduate understanding of this complex range of disorders. What has long been needed is a comprehensive yet readable account of the molecular and clinical features of the dystrophies.

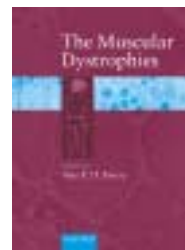
There can be few people as well suited to writing such a textbook on this group of disorders as Professor Emery: with support from a wealth of expertise gathered from around the world, he has attempted the daunting task of producing a piece of work which is accessible to the non-specialist and yet still taxing for the expert.

We should be delighted that he has achieved all of these

aims. The prose is engaging and the layout of the book is logical. Each distinct syndrome merits its own chapter outlining the molecular pathogenesis and clinical features. The book is as comfortable addressing diagnosis, and day-to-day management of the dystrophies as it is assessing wider issues. Surgical treatment of patients with dystrophies merits a chapter, as does past and future potential of gene and cell therapies. Animal models are also covered. Such an approach allows the clinician to dip into the book for relevant information, but also take a look at the wider implications and potential future treatments.

This book will make a useful addition to any hospital library or personal collection. More importantly, it will provide an authoritative and wise voice for anyone interested in the muscular dystrophies.

*JP Leach,  
Glasgow*



Edited by: Alan EH Emery  
Publisher: Oxford  
University Press 2002  
ISBN: 0-19-263291-4  
Price: £79.50

## EDITOR'S CHOICE

## CHOREA

**Molecular mimicry in Sydenham's chorea**

The debate as to the exact mechanism underlying Sydenham's chorea is not known (see this issue page 19). However, the argument has always been that the streptococcal infection triggers antibodies which, by chance, also recognise components of the basal ganglia (so called "molecular mimicry" between host and pathogen). In this recent paper the identity of the offending antibody has been postulated to be against a mammalian lysoganglioside GM1 and N-acetyl- $\beta$ -D-glucosamine which is the dominant epitope of group A streptococcal carbohydrate. However whilst the exact identity of the neuronal epitope recognised by the anti-Streptococcal antibodies is not known, it is clear that these antibodies can bind to neuronal cells (in the form of a neuroblastoma cell line) and activate a calcium/calmodulin dependent kinase (CaM kinase II). How this effects the cellular function or causes the movement disorder and other features of Sydenham's chorea (and/or PANDAS) is not known, but does at least highlight how antibody mediated neurological disease may induce its effects. Thus about 320 years after its original description, Sydenham's chorea continues to generate new research and insight into autoimmune neurological disorders. -**RAB**

Kirvan CA, Swedo SE, Heuser JS, Cunningham MW.

*Mimicry and auto-antibody mediated neuronal cell signalling in Sydenham Chorea.*

NATURE MEDICINE

2003; 9: 914-920

**Benign hereditary chorea and the thyroid gland**

Benign hereditary chorea is an autosomal dominant condition where chorea starts young and progresses little during life. This paper, from Toronto, describes one affected family where chorea had been noted between 6 months and two years, and all were delayed in starting to walk between 2 and 5 years. In most cases there was some progression over time and FDG-PET on four affected members was normal. The report focuses on a mildly affected family member, who died at the age of 59 from leukaemia. At post-mortem, there was mild "fronto-parietal-temporal atrophy" (surely "cerebral atrophy" would have been a simple description!), and microscopically there was some non-specific astrogliosis. This form of chorea is associated with defects in the thyroid transcription factor 1 (TTF-1) gene and sure enough a novel mutation was found in this family, in part of the TTF-1 gene that is highly conserved. The predicted effect of the mutation is to shorten a loop in a stem-loop structure which would probably significantly inter-

fere with protein function.

TTF-1 is a transcription factor, exclusively expressed during embryogenesis and is important for the development of the thyroid gland, lung and pallidum. TTF-1 knockout mice die at birth and have loss of the normal cholinergic tract from pallidum to striatum. One phenotype in man, of a heterozygous mutation in TTF-1, has been described with congenital hypothyroidism, pulmonary abnormalities and choreoathetosis. -**AJC**

Kleiner-Fisman G, Rogaeva E, Halliday W, Houle S, Kawarai T, Sato C, Medeiros H, St George-Hyslop PH, Lang AE.

*Benign hereditary chorea: Clinical, genetic, and pathological findings.*

ANNALS OF NEUROLOGY

2003 Aug;54(2):244-7.

**Proliferating stem cells in Huntington's chorea?**

The role of neural stem cells in the repair of neurological disorders has been a hot topic in recent years, as has the ability of the endogenous neural precursor cell to repair acute CNS damage (see ACNR 2.5 page 25). However the response and role of these latter cells in chronic neurodegenerative conditions has been somewhat overlooked, even though exciting hypotheses in this area have been generated (see for example; Armstrong and Barker (2001) Lancet 358:1174-1176). However a recent paper by Richard Faull's group rectifies this issue by studying the proliferation of CNS cells in Huntington disease brains using the marker, PCNA (proliferating cell nuclear antigen) and double-labelling for markers of neuronal and glial differentiation. In this study they report that with disease progression there is an increase in cell proliferation which may imply increased neural precursor cell turnover and differentiation – an attempt by the degenerating brain to repair itself. This is clearly of great interest and has a number of important implications – not least how such a response is recruited and why it is ineffective in halting disease progression and expression. However, whilst this study shows cell proliferation in the degenerating HD brain, it does not convincingly show that these cells form surviving functional neurons. Indeed much of the proliferation may relate to the ongoing gliosis that is seen in advancing HD. Whatever the interpretation of the results as presented in this paper, this study is stimulating not only to the endogenous stem cell but conceptually to all those working on this and related neurodegenerative conditions. -**RAB**

Curtis MA, Penney EB, Pearson AG *et al.*

*Increased cell proliferation and neurogenesis in the adult human Huntington's disease brain.*

PNAS

2003; 100:9023-9027

**Genetic heterogeneity in Huntington's disease**

## ☆☆☆ RECOMMENDED

Most cases of Huntington's disease (HD) result from CAG trinucleotide repeat expansions in the important transcript 15 (IT15) gene on chromosome 4. However, a HD-like (HDL) phenotype may occur in the absence of such expansions. This study involved samples from 252 patients referred for IT15 gene testing which had proven negative. Sixty of the patients had been seen by movement disorder specialists and were clinically diagnosed as "typical" HD; less detailed clinical characterisation was available for the remaining 192 cases. Mutations were sought in other candidate genes: PRNP, encoding prion protein, an insertion in the octapeptide coding region of which has been associated with the HD phenotype in one family (HDL1); junctophilin-3 (HDL2); TBP, a TATA-binding protein, mutations in which have been identified in autosomal dominant cerebellar ataxia (SCA17); and DRPLA.

Two cases showed CTG repeat expansions in JPH3, both individuals were of African origin. Two cases showed CAG/CAA repeats in TBP, both of French origin. No CAG expansions in the DRPLA gene were identified and no insertions in the octapeptide coding region of the PRNP gene. All four patients with expansions were from the clinically typical HD group; no mutations were identified in the 192 other cases.

These findings indicate genetic heterogeneity in patients with the HD phenotype. Up to 6% of clinically "typical" HD patients without IT15 CAG expansions may harbour trinucleotide expansions in either TBP or JPH3. -**AJL**

Stevanin G, Fujigasaki H, Lebre A-S *et al.*

*Huntington's disease-like phenotype due to trinucleotide repeat expansions in the TBP and JPH3 genes.*

BRAIN

2003;126(7):1599-1603

**Panel of Reviewers**

**Roger Barker**, Honorary Consultant in Neurology, Cambridge Centre of Brain Repair

**Patrick F Chinnery**, Senior Lecturer in Neurogenetics and Honorary Consultant

Neurologist, University of Newcastle upon Tyne and Newcastle Hospitals NHS Trust

**Alasdair Coles**, Wellcome Advanced Fellow, Dunn School of Pathology, Oxford and Dept of Neurology, Cambridge

**Amanda Cox**, Research Registrar, Addenbrooke's Hospital, Cambridge

**Tom Foltynie**, Neurology Research Registrar, Cambridge

**Richard Hardie**, Consultant Neurologist and Director of Neurorehabilitation, Headley Court Medical Rehab Unit

**Tim Harrower**, SpR in Neurology, Addenbrooke's Hospital

**Lucy Anne Jones**, Research Associate (Cognitive Neuroscience)

**Andrew Lerner**, Consultant Neurologist, Walton Centre for Neurology & Neurosurgery, Liverpool

**Simon J G Lewis**, Honorary Clinical Research Fellow, Cambridge Centre for Brain Repair

**Mark Manford**, Consultant Neurologist, Addenbrooke's Hospital, Cambridge, and Bedford Hospital

**Peter Martin**, Consultant Neurologist, Addenbrooke's Hospital, Cambridge

**Brian McNamara**, Consultant Neurophysiologist, Cork, Ireland

**Wojtek Rakowicz**, SpR Neurology, National Hospital for Neurology and Neurosurgery, London

**Julian Ray**, Consultant Neurophysiologist, Addenbrooke's Hospital, Cambridge and Queen Elizabeth Hospital, Kings Lynn

**Robert Redfern**, Consultant Neurosurgeon, Morrision Hospital, Swansea.

**John Thorpe**, Consultant Neurologist, Addenbrooke's Hospital, Cambridge, and Peterborough

**Ailie Turton**, Research Fellow, Burden Neurological Institute, Bristol

**Andrew Worthington**, Brain Injury Rehabilitation Trust, Birmingham

For more information on joining our panel of reviewers,

E-Mail [AdvancesinCNR@aol.com](mailto:AdvancesinCNR@aol.com) or Tel. Rachael Hansford on 0131 477 2335.

# Journal Reviews

## MULTIPLE SCLEROSIS

### ☆☆☆ RECOMMENDED

#### Myelin antibodies and multiple sclerosis

Thomas Berger and his group in Innsbruck have long been interested in the presence of antibodies in the serum and CSF of patients with multiple sclerosis that react against myelin basic protein and myelin oligodendrocyte glycoprotein. Their research seems to have borne fruit in a clinical study that has made it into the *NEJM*.

A total of 103 patients were studied with a first demyelinating event and typical demyelinating lesions on an MRI brain scan as well as oligoclonal CSF bands. Such patients are likely to have a second demyelinating episode in the future and so become classified as clinically definite multiple sclerosis. In the fifty odd months of follow-up during this study, 65 patients had such a second episode. Of these, 56 (86%) had serum antibodies at presentation to MBP, MOG or both. In contrast, such antibodies were found in only 7 of the 38 (18%) people who did not convert to MS. It turns out that serum anti-MOG antibodies alone generate a relative risk of 32, compared to without antibodies, of developing MS; anti-MOG and anti-MBP antibodies together increase this to 76, but anti-MBP antibodies alone are not associated with an increased risk. The time to first relapse was much quicker for those with positive myelin antibodies (7-14 versus 45 months). At baseline, those patients with serum myelin antibodies had significantly greater numbers of enhancing MRI lesions, however in a Cox-proportional hazards model, the risk of developing MS was significantly associated with anti-myelin antibodies but not active MRI lesion load.

Fascinating results no doubt, and potentially of real usefulness in managing the patient with an isolated demyelinating syndrome. One quibble is that there were no illustrations of the immunoblot technique used to detect the anti-myelin antibodies. Interpretation of these blots is not always easy. In particular, it seems that positive immunoreactivity was judged by the naked eye. This probably ought to be validated by a more objective technique before taking these tests into the clinic. Biologically, we do not yet know whether these anti-myelin antibodies are pathogenic or whether they simply reflect increased tissue damage. Matters are further confused by the ideas of Michal Schwarz and others on the protective effects of anti-myelin antibodies. -AJC  
Berger T, Rubner P, Schautzer F, Egg R, Ulmer H, Mayringer I, Dilitz E, Deisenhammer F, Reindl M.

*Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event.*

NEW ENGLAND JOURNAL OF MEDICINE

2003;349(2):139-45.

## EPILEPSY

### Anticonvulsants... like rabbits from a hat

With a bewildering array of drugs at our disposal, we like to think that with evidence-based practice, training and long clinical experience we can select exactly the right anti-epileptic drug to suit the patient sitting in front of us. Well think again! The authors studied 26 patients in an open-labelled trial of clobazam as first-line therapy over 24 weeks. Only 25 were available at follow-up, of whom 16 were seizure-free. The patients were not entirely typical of UK practice; 5 had ring-enhancing lesions on CT, presumably neurocysticercosis. These all became seizure-free but then these lesions may frequently spontaneously regress anyway. Two of four others with complex partial seizures were well controlled and both patients with juvenile myoclonic epilepsy were well controlled.

The dose of clobazam ranged from 20-80mg daily with a mean of 27mg. 16% of patients were sedated but generally not severe, although one suspects that the patient on 80mg was too fast asleep to complain. This is a small and short study and of course clobazam is particularly prone to habituation effects which may cause late relapse in a higher proportion of patients than more conventional monotherapy drugs. However, on the face of it this study shows remarkably similar efficacy to just about every other monotherapy study in the history of epilepsy – about 60% seizure-free and somewhat better at generalised than focal seizures. This supports Professor Martin Brodie's hypothesis that you could choose a drug from a hat and get more or less the same results in terms of efficacy. Don't tell that to the patients but perhaps the SANAD study will help us restore our mystique. -MRAM  
Mehndiratta MM, Krishnamurthy, Rajesh KN, Singh G.

*Clobazam monotherapy in drug naïve adult patients with epilepsy.*

SEIZURE

2003;12:226-228

## Photosensitivity & book covers

This is one of those papers drawing your attention with an impressive title verging on neurophilosophy. It then goes on to talk about "phase clustering analysis" (PCI), which is where the head nods, the lids become leaden and theta rhythms appear. But I must struggle on, this may be taking me one step closer to unlocking the meaning of life, the universe and everything. PCI is a term used by the authors to describe the degree of phase synchronisation of the different rhythms of the brain as measured by magnetoencephalography (MEG). The authors stimulated 10 patients with photosensitive epilepsy with stroboscopic stimuli at various frequencies, some of which did and some did not produce a pathological photoparoxysmal response (PPR). On the MEG, they found that gamma region (30-120Hz) harmonics of the stimulation frequency were particularly revealing. When photic stimulation did not produce a PPR the PCI was the same in the gamma region as in the fundamental frequency or in controls. Before a PPR occurred the index was increased, suggesting much greater synchronisation in the harmonics than in the fundamental frequency. The increase in PCI was 85% sensitive and 80% specific in predicting PPR. The changes were widespread and sensitivity was greatest with red and blue flashes, reflecting the greater potential of these stimuli to induce a PPR. Phase synchrony at higher frequencies has been postulated to be important in visual processing and the authors suggest that a loss of normal controls over this process may underlie the PPR.

The authors suggest that on a more practical level the predictive role of the PCI for PPR may be useful in diagnosis without exposing the patient to a risk of triggering a photic induced seizure. This would only be realistic if EEG rather than MEG could be used and the test is proven to have satisfactory sensitivity and specificity in less highly selected patients. So did the paper live up to the title? It certainly told me something I didn't know but I have learned never to buy novels with a picture of a pretty woman on the cover, I should transfer this knowledge to my academic reading. -MRAM

Parra J, Kalitzin SN, Iriarte J, Blanes W, Velis D, Lopes da Silva FH  
*Gamma-band phase clustering and photosensitivity: is there an underlying mechanism common to photosensitive epilepsy and visual perception.*

BRAIN

2003;136:1164-1172.



## Project Grants

Applications are invited for grants to a maximum of £60,000 to undertake basic or clinical research in the UK into the causes and treatment of epilepsy for a period of up to 3 years.

Requests for equipment up to £10,000 can also be submitted.

## Epilepsy Research Foundation Fellowship

Applications are also invited for the Epilepsy Research Foundation Fellowship. The Fellowship is for the personal support of young researchers entering the field, for example those undertaking a 3 year PhD or a 2 year MD. Candidates must be graduates in medicine or one of the allied sciences and should be resident in the UK. The research could be of either a clinical or laboratory nature.

For more information and an application pack please contact Mrs Camilla Young, Research & Information Executive, Epilepsy Research Foundation, PO Box 3004, London W4 4XT. Tel: 020 8995 4781. Applications have to be received by Friday 24th October.

For more information about The Foundation visit our website at [www.erf.org.uk](http://www.erf.org.uk) where, if you wish to be kept informed of our activities, you can register your interest in epilepsy research.



## PARKINSON'S DISEASE

## ★★★ RECOMMENDED

**Slow, slow, quick, quick, slow – auditory cues for walking with Parkinson's disease**

Walking is a major problem for people with Parkinson's disease (PD). They commonly experience difficulty with both temporal and spatial parameters of gait. They may freeze and have difficulty initiating walking or controlling speed; moving very slowly or having involuntary quickening of step, and they often walk with small steps. Therapists have often used extrinsic sensory cues such as lines or obstacles on the floor to help patients with PD to keep walking or to increase stride length. However these visual cues are restricted to therapy or home environment. Auditory cueing using a portable system offers the opportunity for widening the environment in which PD patients can walk. In a study reported in *Clinical Rehabilitation* patients were shown to modulate their cadence (number of steps per minute) with respect to the rate of beat supplied by a pocket sized digital metronome.

The cadence, velocity and stride length of eleven patients with early stage PD were recorded on an electronic walkway within a physiotherapy gym. The patients were all studied after taking their medication. They walked first at their preferred pace and then with the metronome set to 85%, 92.5%, 107.5% and 115% of the mean of preferred pace. The mean velocity and cadence increased relative to baseline values at cue rates of 107.5% and 115% of preferred pace cadence and decreased at the 85% cue rate. Stride length was not affected by the variations in cue rate.

This is a promising and simple aid for walking and as the authors point out, it will be interesting to see if benefits extend to more chronic patients and to environments outside the hospital. –AJT  
Howe TE, Cody FWJ, Ashton VJ, Oldham JA.

*Auditory cues can modify the gait of persons with early stage Parkinson's disease: a method for enhancing parkinsonian walking performance?*

CLINICAL REHABILITATION

2003; 17: 363-367

## COGNITION &amp; MOVEMENT

**Premier planning - an fMRI study**

The dorsal and dorsolateral prefrontal cortex are involved in solving problems requiring effort. These areas are implicated in higher executive processes, being involved in planning and utilising working memory to support complex tasks. The extent to which the areas are involved differs between individuals and in this functional Magnetic Resonance Imaging (fMRI) research, it is demonstrated that individuals who are better than others at solving an electronic "Tower of London" (TOL) planning task have different patterns of brain activation from those who are less effective.

Solving the TOL task involves mental manipulation and a number of other cognitive abilities including planning, working memory and attentional control to work out the most efficient way (minimum number of moves) to recreate a tower of coloured balls from distributed starting positions.

All eleven volunteers showed dorsolateral prefrontal cortex activation which was bilateral as well as other bilateral activations in the anterior and posterior cingulate and parietal regions. However, the six people who performed best on the task were found to have a more widely extended activation in the left dorsolateral prefrontal cortex. The five more standard performers (<70% correct) demonstrated a greater extent of anterior cingulate activation, an area whose function is still debated. It is speculated that differing patterns of dorsolateral prefrontal cortex activation reflect differences in "strategy selection" or "attentional capacity" across performers, and these notions would benefit from further investigation. Studying and comparing activation patterns in clinical populations where executive processes are challenged may help further delineate intact function. –LAJ

Cazalis F, Valabrègue R, Pèlègrini-Issac M, Asloun S, Robbins T W, Granon S

*Individual differences in prefrontal cortical activation on the Tower of London planning task: implication for effortful processing.*

EUROPEAN JOURNAL OF NEUROSCIENCE

2003; 17: 2219-2225

**Think yourself better**

The idea that imagining a motor task has physiological effects on the motor system has recently been demonstrated by a number of authors utilising transcranial magnetic stimulation (TMS). An increase in primary motor cortex excitability during imagery of target muscle contraction, for example, has been shown to decrease motor threshold and increase the amplitude of the motor evoked potential amplitude of the target muscle, compared to rest conditions. However, the relative contributions of supraspinal and spinal changes responsible for this behaviour remains unknown. This study from New Zealand not only supports the notion that the modulation is principally supraspinal, but the temporal effect is also comparable to the actual motor task. Eight subjects had TMS studies performed on 2 hand muscles (APB target muscle, ADM control muscle), whilst alternating randomly between three different conditions; rest, isometric contraction of their thenar muscles (pressing the thumb downwards onto a table), and motor imagery of the same contraction. Performance of the task was performed in time with a metronome (1Hz) allowing analysis division into 'on' and 'off' periods. In both active and imagined motor tasks an increase in MEP amplitude was observed and was significant only during the active 'on' phases ( $P<0.05$ ). The tentative conclusion is that motor imagery and

Web Address	Details
<b>PRODUCT INFORMATION</b> <a href="http://ambion.com">ambion.com</a>	<b>Ambion (Europe) Ltd:</b> The RNA resource from the RNA company. Information, research papers, developments, technologies, protocols, products, and manuals for RNA manipulations.
<a href="http://camb-labs.com">camb-labs.com</a>	<b>Cambridge Laboratories:</b> Information on our range of neurology products and useful backgrounders on various neurological disorders. Links to key neurological organisations and patient associations are provided.
<a href="http://vnstherapy.com/international">vnstherapy.com/international</a>	<b>Cyberonics Europe:</b> Up to date information on Vagus Nerve Stimulation Therapy - the effective and tolerable treatment for refractory epilepsy, includes clinician and patient resources plus contact details for Cyberonics.
<b>PUBLISHERS</b> <a href="http://dunitz.co.uk">dunitz.co.uk</a>	<b>Martin Dunitz Ltd:</b> Part of the Taylor & Francis Group, Martin Dunitz publishes top quality, high level medical books in areas such as cardiology, neurology, psychiatry, oncology and urology.
<a href="http://acnr.co.uk">acnr.co.uk</a>	<b>ACNR magazine:</b> Download free PDF's of articles past and present and link to other sites of interest.
<b>CONFERENCES</b> <a href="http://epdaconferences.org">epdaconferences.org</a>	<b>European Parkinson's Disease Association:</b> 5th European PD Association meeting.

**To list your web site in the Web Browser  
call Rachael on 0131 477 2335.**

## Journal Reviews

actual movement appear to modulate corticospinal activities in similar ways both temporally and spatially. Perhaps we should be using our imagination in neurorehabilitation. -JLR

Stinear SM and Byblow WD.

*Motor imagery of phasic thumb abduction temporally and spatially modulates corticospinal excitability.*

CLINICAL NEUROPHYSIOLOGY

2003; 114; 909-914

### ALZHEIMER'S DISEASE

#### ☆☆☆ RECOMMENDED

#### **Alzheimer's disease: another possible CSF biomarker**

Although clinical criteria for the diagnosis of Alzheimer's disease (AD) may achieve a sensitivity and specificity of around 80%, nonetheless the availability of additional biomarkers remains a research priority. Since there is evidence for a long preclinical phase in AD, which would seem the optimal time to initiate disease-modifying treatment, a biomarker for early diagnosis is particularly desirable.

Having previously demonstrated a decline in sulfatide (ST), a sulphated galactocerebroside of oligodendroglial origin, in AD grey and white matter in an autopsy study, investigators from the Memory and Aging Project at Washington University, St Louis, looked for this compound in CSF using electrospray ionization mass spectrometry. Two groups of volunteers were studied, those with incipient dementia (defined as CDR = 0.5, which probably corresponds to what others describe as "mild cognitive impairment"; n = 20) and normal individuals (CDR = 0; n = 19). A 40% decline in the absolute value of CSF ST was noted in the incipient dementia group, whereas phosphatidylinositol (PI) was unchanged; ST/PI ratio was accordingly lower in the CDR = 0.5 group, and this was statistically significant.

Encouraging as these data are, they will require corroboration. It will need to be shown that the changes are specific to AD, since the ST decline may reflect non-specific axonal damage and degeneration. Other CSF biomarkers for AD have been reported (such as reduced Ab; elevated tau; neuronal thread protein), but have not achieved widespread adoption into clinical practice. For the time being, the jury must be out on the utility of CSF ST as a biomarker for AD. -AJL

Han X, Fagan AM, Cheng H *et al.*

*Cerebrospinal fluid sulfatide is decreased in subjects with incipient dementia.*

ANNALS OF NEUROLOGY

2003;54(1):115-119

### VASCULITIS

#### **Treating vasculitis**

Cerebral vasculitis, often discussed at clinico-pathological conferences, is so rare that few neurologists are comfortable with its management. It

makes sense then to look at how physicians manage systemic vasculitides. Amazingly, the European Vasculitis Study Group has managed to perform an open randomised clinical trial on the maintenance treatment of 144 patients with ANCA-associated vasculitis (Wegener's granulomatosis and microscopic polyangiitis).

All patients were given oral cyclophosphamide (2mg/kg/day for most patients) and a reducing dose of prednisolone (starting at 1 mg/kg/day) for twelve weeks. They were then randomised to receive either continued cyclophosphamide or azathioprine (1.5mg/kg/day). At 12 months after starting treatment, all patients were put onto azathioprine. So the trial was, in effect, of the consequences of early switching from cyclophosphamide to azathioprine: would the benefit in terms of reduced exposure to cyclophosphamide's toxicity be at the cost of earlier return of vasculitis? There was no difference between the groups on any measure: relapse of vasculitis, an index of vasculitis damage, adverse events, renal function or inflammatory markers. -AJC

This all seems pretty clear: switch your vasculitis patients from cyclophosphamide to azathioprine at 12 weeks and they will be no better off. A truly helpful study.

Jayne D and the European Vasculitis Study Group.

*A randomised trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies.*

NEW ENGLAND JOURNAL OF MEDICINE

2003;349(1):36-44.

### PAIN

#### **GABA and your pain threshold**

Ohara's group in San Francisco study pain in rats. They are particularly interested in the *rostral agranular insular cortex* (RAIC) which is one of the few cortical areas consistently activated by painful stimuli. Increasing the concentration of GABA in this area, using vigabatrin or genetic manipulation, resulted in analgesia of the rats' paws that was mediated by increased activity in descending spinal inhibitory pathways. This turns out to be mediated by RAIC neurons with GABA A receptors projecting to the locus coeruleus. On the other hand, RAIC GABA B neurons innervate the amygdala. Selective blockade of GABA B receptors resulted in ipsilateral hyperalgesia.

So the cerebral cortex contains pathways that raise or lower pain thresholds. It may be that chronic pain states are caused by activation of a pain-inducing circuit that includes the amygdala. Inhibiting the amygdala just might be a useful treatment. -AJC

Jasmin L, Rabkin SD, Granato A, Boudah A, Ohara PT.

*Analgesia and hyperalgesia from GABA-mediated modulation of the cerebral cortex.*

NATURE.

2003;424(6946):316-20.

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Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP. Tel. 01865 267154, Fax. 01865 267985.

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Blackwell Publishing, Commerce Place, 350 Main Street, Malden, MA 02148-5018, USA. Tel. 888 661 5800,

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## The Neurometer® CPT/C electrodiagnostic automated sensory nerve conduction threshold (sNCT) device



The Neurometer® CPT/C electrodiagnostic automated sensory nerve conduction threshold (sNCT) device provides painless measures of both large and small fiber mediated sensory function, from the periphery to the CNS. Objective measures bypass cutaneous receptors/end-organs and trophic variations which can confound the clinical evaluation. Both hyperesthesia and hypoesthesia can be rapidly quantified and verified to help guide patient management ( $p < 0.006$ ). This test is useful for the differential diagnosis and monitoring of axonal and demyelinating polyneuropathies, spinal cord impairments, radiculopathies, compressive/focal neuropathies and nerve regeneration. Testing may be conducted from any cutaneous/mucosal site. The painless sensory measures assure high patient compliance for follow-up evaluation.

Additionally, an atraumatic pain tolerance threshold measure permits the evaluation of allodynia. This portable battery operated device may be used at the patients bedside and is not effected by EMFs. There are established norms from 1000's of controls. Over 400 peer reviewed publications and 17 years of routine clinical application.

For further details please contact Neurotechnics on 01844 260777 or E-Mail [info@neuro-technics.com](mailto:info@neuro-technics.com)

## Avonex® prefilled syringe approved in Europe

The EMEA, (European Agency for Evaluation of Medicinal Products), has approved a new Avonex® formulation (Interferon beta-1a) in a prefilled syringe designed to make treatment even more convenient for people with multiple sclerosis (MS). This follows approval of the Avonex® prefilled syringe in the US by the Food and Drug Administration (FDA) earlier this year. Ireland was the first country in the world to launch at the end of July and the UK will follow in September.

Avonex®, the only once-a-week treatment for MS, is now approved in a prefilled syringe which makes it even easier for people with MS to administer. The prefilled syringe formulation will replace the currently available form of Avonex®.

As with the current form of Avonex®, the new formulation is indicated to slow the progression of disability and reduce the frequency of relapses in relapsing remitting forms of MS, including people who have experienced a first clinical episode and who have MRI scans consistent with MS. The new formulation carries the same low rate of neutralising antibodies in patients treated for up to three years.

For further information contact Nina Jones or Emma Robinson at Lowe Fusion Healthcare, Tel. 020 8948 0094.



## Sensation10 in clinical use

The Radiology department at Preston Royal has recently taken into clinical use the latest addition to the Siemens Sensation family, the Sensation 10.

"I am very happy with Sensation 10. The image quality is excellent and little affected by the technically difficult patient. Image post processing is easy to do and allows routine review of the sagittal and coronal data sets. This in turn no doubt enhances diagnostic confidence and accuracy," said Consultant Radiologist, Sue Kearney. "The in-room fluoroscopy has had a major impact on our biopsy practise, with interventional procedures now taking significantly less time. As a result patient tolerance is improved and it is likely that complication rates will be reduced".

As CT is a workhorse of the department it was advantageous that the staff learnt the new Syngo based system quickly and easily. Some staff were familiar due to the identical operating system on the existing MAGNETOM Symphony. As part of a major customer focused initiative Siemens will be introducing CD and Internet based training, through the new Somatom Life website, for customers. This will make new staff familiarisation easier and lead to a quicker understanding of upgraded software for all.

For more information Tel. Siemens on 01344 396156.



Dr Sue Kearney, Consultant Radiologist, on the couch with Senior Radiographers Karen Stevens, and Graham King

## Primus users meet in Cambridge



Judy Carter, Superintendent Radiographer and Sarah Knight, Senior Radiographer Siemens Primus Linac recently enjoyed the second UK user group meeting, held in Cambridge and hosted jointly by Addenbrookes NHS Trust and Siemens Medical Solutions. The meeting gave participants the opportunity to exchange ideas and experiences with other users, and provided a forum for education of both Primus users and Siemens Medical Solutions personnel. Ajit Singh, President of Siemens Oncology Care Systems flew over from the USA to take advantage of the opportunity to learn directly about the unique nature of Radiotherapy in the UK from healthcare professionals. The meeting was well attended by the full spectrum of Primus users, Radiographers, physicists, technicians and medical staff.

Chris Watson, Executive Specialist said, "The great thing about these meetings is the exchange of knowledge and experience between users and Siemens Medical Solutions. We learn as much from them during these events as they learn from us. As radiotherapy is a dynamic and rapidly evolving field we're intending to hold these meetings regularly - to make sure we all have the opportunity to learn from best practice in the field."

For more information contact Siemens on Tel. 01344 396156.

## Synamps<sup>2</sup>, Stim<sup>2</sup> and Scan 4.3 from Neuroscan Compumedics

Neuroscan has launched Synamps<sup>2</sup>, Stim<sup>2</sup> and Scan 4.3. Synamps was hailed as the most powerful amplifier in the world at its launch 1992, and more than 1300 are now used by researchers around the world.

The new Synamps<sup>2</sup> amplifier is said to raise the research standard for electrophysiological amplifiers yet again.

Visit [www.advancedmedicalequipment.com](http://www.advancedmedicalequipment.com) for more information and a complete list of the new and advanced specifications (USB 2.0 interface, 24 bit DataStream, etc). Stim<sup>2</sup> is now completely Windows XP compatible and timing is perfectly synchronised to the recording system. There is a free upgrade to all users of Scan version 4.0 or higher - details are on the website.

Contact Advanced Medical Equipment for more information or a demonstration any of these products. E-Mail. [info@advancedmedicalequipment.com](mailto:info@advancedmedicalequipment.com)



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Imagine if you were in a queue.  
And you suddenly couldn't move.  
And, instead of help you  
got abuse.



You in this bleedin'  
queue or not?

**REQUIP**<sup>®</sup>  
ropinirole

## FIGHTS PARKINSON'S. DEFENDS DIGNITY.

### REQUIP (ropinirole) Prescribing Information

**Presentation** 'ReQuip' Tablets, PL 10592/0085-0089, each containing ropinirole hydrochloride equivalent to either 0.25, 0.5, 1, 2 or 5 mg ropinirole. Starter Pack (105 tablets), £43.12. Follow On Pack (147 tablets), £80.00; 1 mg tablets - 84 tablets, £46.20; 2 mg tablets - 84 tablets, £92.40; 5 mg tablets - 84 tablets, £184.80. **Indications** Treatment of idiopathic Parkinson's disease. May be used alone (without L-dopa) or in addition to L-dopa to control "on-off" fluctuations and permit a reduction in the L-dopa dose. **Dosage Adults:** Three times a day, with meals. Titrate dose against efficacy and tolerability. Initial dose for 1st week should be 0.25 mg t.i.d., 2nd week 0.5 mg t.i.d., 3rd week 0.75 mg t.i.d., 4th week 1 mg t.i.d. After initial titration, dose may be increased in weekly increments of up to 3mg/day until acceptable therapeutic response established. If using Follow On Pack, the dose for 5th week is 1.5mg t.i.d., 6th week 2.0mg t.i.d., 7th week 2.5mg t.i.d., 8th week 3.0mg 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.

POM

**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.

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