

ACNR

Advances in Clinical Neuroscience & Rehabilitation



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

Review Articles: Neuropathic Pain;
Von Hippel-Lindau Disease: Insights and advances

Management Topic: Approach to the patient with a
movement disorder

Rehabilitation Article: Dasher – an efficient keyboard
alternative




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Impaired renal function

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Contra-indications

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Interactions

No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored.

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Undesirable effects

Injection-site reactions (particularly erythema, hypersensitivity, pain, mass, pruritus, inflammation, oedema) are common and usually mild. An immediate post-injection reaction (one or more of vasodilatation, chest pain, dyspnoea, palpitation, tachycardia) was reported at least once in controlled trials by 41% on Copaxone and 20% on placebo. Other reactions reported from clinical trials with a frequency greater than 1 in 10 include flu-like syndrome, asthenia, back pain, headache, constipation, diarrhoea, nausea, arthralgia, anxiety, depression, dizziness, hypertonia, rash and sweating. Rarely, anaphylactoid or allergic reactions and convulsions. Rarely shifts in white blood cell counts and elevated levels of liver enzymes, no evidence of clinical significance.

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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



Roger Barker is co-editor in chief of *Advances in Clinical Neuroscience & Rehabilitation (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.



Alasdair Coles is co-editor of *ACNR* and contributes our Anatomy Primer. He is a Wellcome Advanced Fellow working on experimental immunological therapies in multiple sclerosis, based at the Dunn School of Pathology in Oxford and Department of Neurology in Cambridge.



Stephen Kirker is the editor of the Rehabilitation section of *ACNR* and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He graduated from Trinity College, Dublin in 1985 and trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.



David J Burn is the editor of our conference news section and Consultant and Senior Lecturer in Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He qualified from Oxford University and Newcastle upon Tyne Medical School in 1985. His MD was in the functional imaging of parkinsonism. He runs Movement Disorders clinics in Newcastle upon Tyne and Sunderland. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.



Andrew Lerner is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.



Alastair Wilkins is Specialist Registrar in Neurology in East Anglia. He trained in Cambridge, Sheffield and London, and has just finished a PhD investigating potential mechanisms of axon loss in multiple sclerosis.

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4th July 2003

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Key note speaker is Professor Meg Morris from Australia, other speakers are from Holland, Belgium and UK

Abstract submissions for poster presentations are invited,
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For more information contact: Alison Marks, HRRU Secretary, School of Health Professions and Rehabilitation Sciences, University of Southampton, Highfield, Southampton. SO17 1BJ. Tel: 023 8059 4791; Email: adm5@soton.ac.uk, **Website:** <http://appde.unn.ac.uk>

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contents

may/june 2003

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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). 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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. Ecthymosis 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: ecthymosis, pupura, injection site haemorrhage, arm pain, muscle weakness, hypertonia and injection site burning. Less frequent: hyperesthesia, arthralgia, asthenia, pain, bursitis, 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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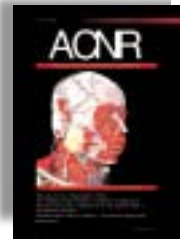
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ACNR is published by Whitehouse Publishing,
7 Alderbank Terrace, Edinburgh
EH11 1SX.

Tel. 0131 477 2335/07989 470278,

Fax. 0131 313 1110

E-Mail. AdvancesinACNR@aol.com

Publisher: Rachael Hansford

Design & Production:

Barbara Newton

Printed by: Stephens & George Magazines,

Tel. 01685 388888.

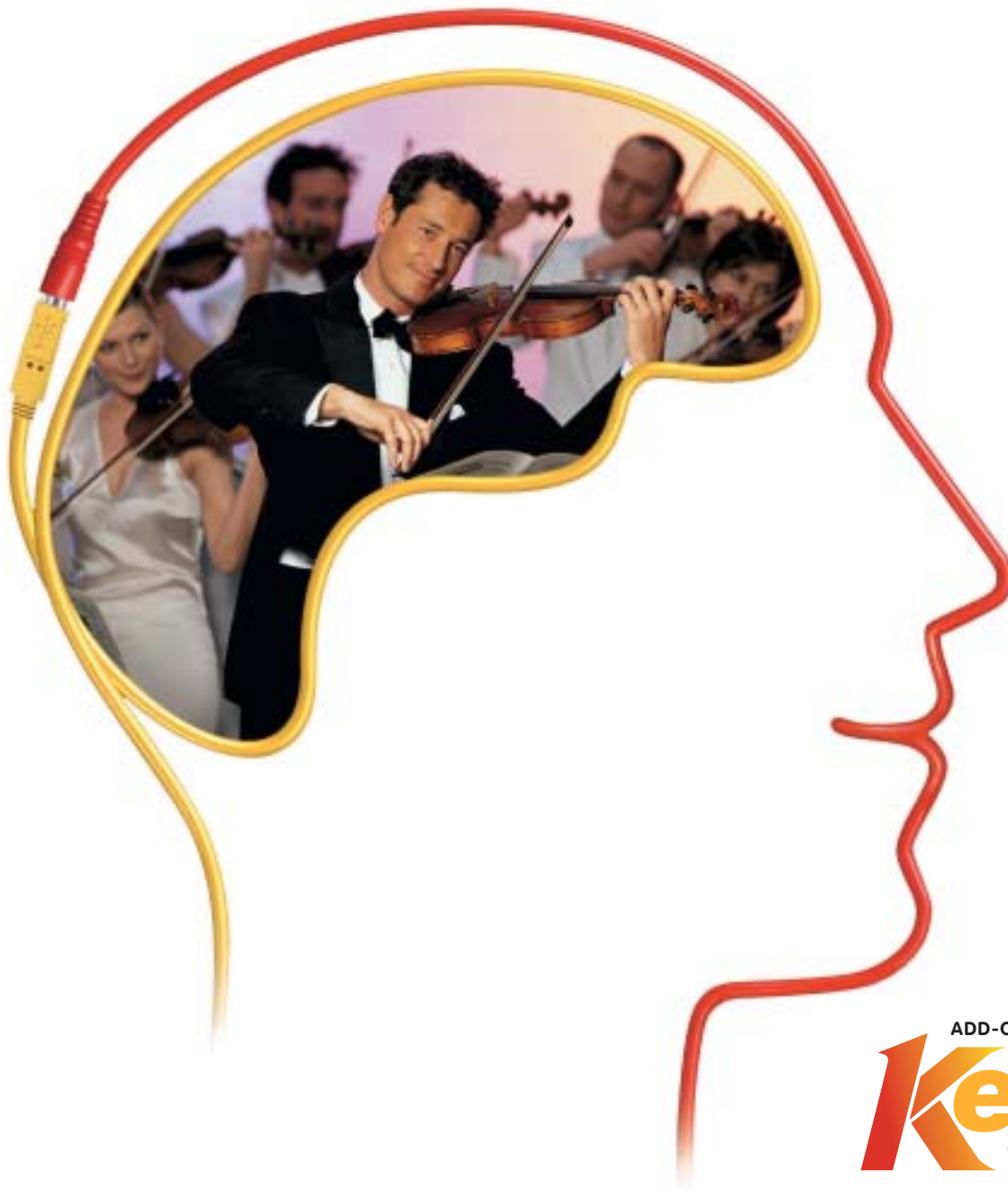
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daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and 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, Watford, 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.





Welcome to a new edition of the ACNR and thanks to everyone that has returned their reader questionnaires and the hundreds of you who have visited the web-site. It is good to know that the journal is popular and being read, both in the UK and internationally.

In this issue we have two contrasting review articles. John Scadding presents a beautiful account of the common problem of neuropathic pain, based on his extensive experience and knowledge of the literature. This article helpfully updates us on the new and emerging concepts in this field, including helpful definitions - so that you should no longer diagnose reflex sympathetic dystrophy but a complex regional pain syndrome (CRPS). Indeed this article explores the pathophysiological mechanism underlying the genesis of pain syndromes and then gives an extremely helpful summary of what is known and not known about therapies for this difficult group of conditions. This is a really helpful practical guide, based on sound scientific principle. This is nicely complemented by one of our reviews on the use of opiates in neuropathic pain.

The second review article is by Professor Patrick Maxwell and Dr Peter Hill on the very rare von-Hippel-Lindau disease. Slightly unusually for ACNR, the authors are renal physicians; their article is helpful in updating us on this syndrome and its aetiology. In this last respect insights from the gene product causing this disease on the cellular response to hypoxia has wide-reaching implications to biology in general including neuroscience - including for example the genesis of dopaminergic neurons from stem cells (see e.g. Studer *et al* (2000) *J Neurosci.* 20(19):7377-83). Thus both these major articles bridge science and medicine, in a way that is the hallmark of this journal.

We embark on a new management topic in this issue, with David Burn giv-

ing us the benefit of his expertise on the approach to a patient with a movement disorder. This will be the first in a series of articles exploring different aspects of this complex field, and will hopefully provide a practical and informed account of the recognition, aetiology and therapeutic options for a range of movement disorders (in a similar fashion to that which we have done previously for epilepsy and muscle disease).

We also have a very exciting rehabilitation topic - Dasher; a novel way of communication. This new device has great potential, and is a reminder of the impact that modern technology can have on the development of better therapies for patients with disability. The article by the inventor of the system, David MacKay, invites you to have a go via the web site (it's free) and then feedback your comments.

Brain McNamara continues his neurophysiological voyage, this time targeting the ulnar nerve. This has the usual Brian common sense approach and is very helpful in distinguishing the site of lesion in this commonly affected nerve.

We also have two historical articles in this issue of ACNR. Andrew Larner takes a different perspective on the work of Edward "smallpox" Jenner and John Pearce guides through an extensive literature on altered awareness in his article on Dreamy States.

So there it is, another issue, which we hope you enjoy and continue to support - but remember we are always keen to hear about suggestions for changes and topics, so don't just sit there and complain: let us know!!

*Roger Barker,
co-editor*

This key meeting aims to consolidate international opinion about the status of DLB and PDD and the relationship between them. An excellent networking opportunity between dementia experts and movement disorders specialists as well as scientists who are working on a common understanding of alpha-synuclein-related disorders. This key event follows two previous successful and influential DLB workshops, the first in Newcastle upon Tyne in 1995 and the second in Amsterdam in 1998.

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Programme Themes

- Clinical features of DLB/PDD - the same or different?
- DLB and PD with dementia - can they be distinguished?
- Neuroimaging
- Can DLB be distinguished from other dementia disorders?
- Molecular Pathology & Genetics I
- Molecular Pathology & Genetics II
- Diagnosis and management clinical workshops
- Treatment strategies
- New science research
- New clinical research

17 - 20 September 2003
Civic Centre
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United Kingdom

Neuropathic Pain

Pain in Neurological Disease

Pain is a frequent symptom of neurological disease. Although there have been improvements in treatment, pain often remains unresponsive to all treatment modalities.

What is Neuropathic Pain?

A limited understanding of underlying pathophysiology, and recent changes in terminology have led to some confusion. The International Association for the Study of Pain (IASP) defines NP as "pains resulting from disease or damage of the peripheral or central nervous systems, and from dysfunction of the nervous system". Originally, NP was used to describe only pain related to peripheral neuropathies, and **central pain (CP)** to lesions of the central nervous system associated with pain. **Neurogenic pain** embraced all causes, both peripheral and central.

The addition of a category of "dysfunction" in the definition of NP allows the inclusion of organic pain states which share the clinical features of NP, but which are not initiated by an identifiable lesion of any part of the nervous system. However, this is a contentious issue; some argue that the "dysfunctional" category should be excluded, on the grounds that there is no initiating neural injury. While it is true that including dysfunctional pain causes difficulties in recognising the limits of NP, exclusion of this important type of pain ignores the clinical reality of the existence of similar pain states, one provoked by neurological damage and the other by damage to non-neural tissues. Creation of a separately defined category of dysfunctional pain is acceptable, as long as it is recognised that there may be pathophysiological mechanisms common to both NP and dysfunctional pain. The debate continues, but from a practical point of view, the current approach to treatment is broadly similar for NP and dysfunctional pain.

The most important of the dysfunctional pain states is

Complex Regional Pain Syndrome (CRPS), formerly known as **Reflex Sympathetic Dystrophy (RSD)**.

Causes of NP

A convenient classification of NP is anatomical, according to the site of initiating nervous system pathology, with an aetiological sub-classification (Tables 1 and 2). A mechanism-based classification is needed, but it is not yet possible to reliably link symptoms and signs to pathophysiology (see Table 4). The development of specific and selective treatments will depend on a mechanism-based classification. For the majority of NP sufferers, the pain will persist lifelong. Co-morbidities (depression, impaired quality of life, employment, domestic issues etc) are very common.

Clinical Features of NP (Table 3)

Patients often find it difficult to describe the quality of NP; it is outside their previous experience of pain. Sensory loss may be mild and overshadowed by **allodynia** (all stimuli producing pain), **hyperalgesia** and **hyperpathia** (delayed perception, summation and painful after-sensation). Rarely, (eg trigeminal neuralgia) there is no demonstrable sensory loss.

There may be signs of **sympathetic dysfunction**, and occasionally dystrophic changes. The onset of pain may be delayed, the commonest example being central post-stroke pain (thalamic), which may start months or years after the initiating stroke.

Pain is often of mixed nociceptive and neuropathic types, for example, mechanical spinal pain with radiculopathy or myelopathy. It is not generally recognised that nociceptive spinal pain can radiate widely, mimicking a root distribution. It can be difficult to identify the dominant pain type and treat appropriately. Such patients require careful examination, imaging and neurophysiological investigation.

Pathophysiology

The pathophysiological properties that are responsible for NP can be broadly categorised into five groups: **ectopic impulse generation** in damaged primary afferent fibres, **fibre interactions**, **central sensitisation**, **disinhibition** (failure or reduction of normal inhibitory mecha-



John Scadding is consultant neurologist at the National Hospital for Neurology and Neurosurgery and Whittington Hospital, London, and Honorary Senior Lecturer at the Institute of Neurology. He is also Associate Dean at the Royal Society of Medicine. As a registrar he worked with PD Wall and PK Thomas, and this kindled a clinical and research interest in mechanisms and management of chronic neuropathic pain.

Table 1

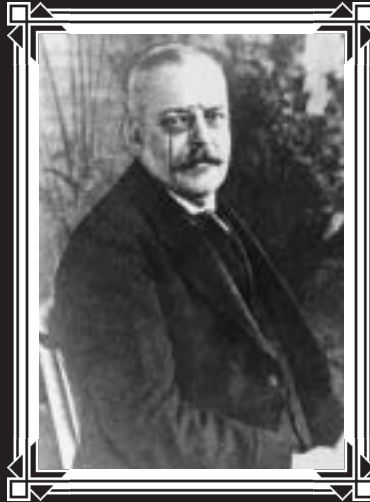
Peripheral Causes of Neuropathic Pain

Mononeuropathies and multiple mononeuropathies		
Trauma: compression, transection, post-thoracotomy, painful scars		
Diabetic mononeuropathy and amyotrophy		
Neuralgic amyotrophy		
Connective tissue disease		
Malignant and radiation plexopathy		
Trench foot		
Borreliosis		
Polyneuropathies		
Metabolic/Nutritional:		
	Diabetic	Cuban neuropathy
	Alcoholic	Tanzanian neuropathy
	Pellagra	Burning feet syndrome
	Beri-beri	Strachan's (Jamaican) neuropathy
	Amyloid	
Drugs/Toxic:	Isoniazid	Thallium
	Cisplatin	Arsenic
	Vincristine	Clioquinol
	Nitrofurantoin	
	Disulfiram	
Infective:	HIV	
	Acute inflammatory polyneuropathy (Guillain-Barre) / CIDP	
Hereditary:	Fabry's disease	
	Dominantly inherited sensory neuropathy / HSN	
Malignant:	Myeloma	
	Carcinomatous	
Idiopathic small fibre neuropathy		

Table 2

Central Causes of Neuropathic Pain

Spinal Root/Dorsal Root Ganglion	
Prolapsed disc	Root avulsion
Arachnoiditis	Surgical rhizotomy
Post-herpetic neuralgia	Tumour
Trigeminal neuralgia	
Spinal Cord	
Trauma including compression	
Syringomyelia and intrinsic tumours	
Multiple sclerosis	
Vascular: infarction, haemorrhage, AVM	
Spinal dysraphism	
Vitamin B 12 deficiency	
HIV	
Syphilis	
Anterolateral cordotomy	
Brain Stem	
Lateral medullary syndrome	Multiple sclerosis
Tumours	Tuberculoma
Syrinx	
Thalamus	
Infarction	Tumours
Haemorrhage	Surgical lesions
Sub-cortical and Cortical	
Infarction	Trauma
AVM	Tumour



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Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration: Adults/elderly;** 5 mg daily which may be increased to 10 mg once daily after at least one month. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. **Children;** Not recommended. **Contra-Indications: Pregnancy.** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Lactation:** Excretion into breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may

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

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



Table 3

Clinical Features of Neuropathic Pain

Abnormal pain quality: burning, stabbing, raw, gnawing, sickening
 Poorly localised, sometimes diffuse
 Paroxysmal pains common
 Immediate or delayed onset after injury
 Pain intensity altered by emotion and fatigue
 Sensory impairment usually in an anatomical distribution
 Associated allodynia, hyperalgesia and hyperpathia
 Vasomotor and sudomotor changes
 Associated dystrophic change in a minority of patients

nisms), and **plasticity** (degenerative and regenerative changes associated with altered connectivity). Table 4 summarises these properties. It is beyond the scope of this short article to discuss pathophysiology in detail, but some important points include:

1. The mechanisms of NP are substantially different to those of nociceptive pain.
2. Novel impulse generators develop at various sites, and these are not stimulus-dependent.
3. In peripheral nerve, it has been shown that ectopic impulse generation (EIG) develops as a result of the expression of abnormal sodium channels. This can be modified by neurotrophic growth factors (a potential target for new treatments).
4. Abnormal chemical sensitivities develop in damaged primary sensory neurons, notably to catecholamines. Whilst this can be readily demonstrated in experimental preparations, the clinical relevance remains uncertain.
5. Degenerative and then regenerative changes in the spinal cord may lead to aberrant connectivity, and possibly a permanently reorganised, irreversible state.
6. Damage at one level in the nervous system may lead to secondary pathophysiological changes at more rostral levels. This has important implications when targeting treatments for NP.

Complex Regional Pain Syndrome (CRPS)

CRPS is the name now given to reflex sympathetic dystrophy (RSD) and causalgia (Table 5). The term RSD implied a pathogenic role for the sympathetic nervous system that is no longer tenable.

The current definition of CRPS is clinical, and the limits are not clearly drawn (Table 6). As with NP, a mechanism based definition is obviously needed, but is not yet possible.

CRPS is divided into type 1, which includes conditions caused by tissue injury other than peripheral nerve (the majority of cases), and type 2, in which the syndrome is provoked by major nerve injury. The latter corresponds to causalgia, though strictly speaking, causalgia merely means burning pain, and thus denotes a symptom rather than a disease. For the moment, however, the IASP approved terminology makes CRPS type 2 and causalgia one and the same.

The nosology of these conditions is a matter of ongoing debate; the difficulties in finding agreed terms emphasises the limited understanding of their pathophysiology.

The causes of CRPS are listed in Table 7.

Clinical Features and Pathophysiology of CRPS

The common clinical features of CRPS are shown in Table 8. These may vary over time in an individual patient. Not all patients develop dystrophic changes.

The pathogenesis of CRPS is probably heterogeneous;

Table 4

Pathophysiology of Neuropathic Pain

1. Peripheral Nerve

Ectopic impulse generation - EIG (abnormal sodium channel expression)

Increased by:	Decreased by:
mechanical stimulation	local anaesthetic
noradrenaline / adrenaline	alpha receptor blockers
	axon transport blockers
ischaemia	corticosteroid
warming-myelinated fibres	carbamazepine
cooling-unmyelinated fibres	phenytoin

2. Dorsal root ganglion

EIG

3. Spinal Nerve Roots

EIG

4. Central Nervous System

Central sensitisation

Dorsal horn neuron "wind up": NMDA receptor mediated
 Prostaglandin and nitric oxide synthesis in dorsal horn neurones

Disinhibition

Deafferentation of dorsal horn cells: bursting discharge
 Reduced spinal inhibitions: surround, segmental, descending brain stem
 Reduced insular cortex inhibition in central pain

Plasticity

Neurotransmitter excitotoxicity: cell death
 Post-synaptic receptor up-regulation

Altered Connectivity

Inappropriate regeneration (Growth Associated Protein expression)
 Reorganised state

Rostral Effects

Altered physiology at rostral levels resulting from caudal lesions

there is evidence of a noradrenergic sympathetic influence on the development of pain, both with and without nerve injury. Chronic inflammatory processes contribute in CRPS type 1; microangiopathic changes have been found in limbs amputated from CRPS sufferers, and anti-inflammatory treatment may help early in the course of the disease. Secondary central sensitisation is an important component of the pain.

Psychological factors have often been suggested in the pathogenesis of CRPS. Patients with conversion disorder and factitious illnesses can present with symptoms closely resembling CRPS. The severe pain of CRPS, with loss of function, produces anxiety and depression in many patients, but there is no evidence that secondary psychological factors developing early after an injury predispose to CRPS.

Prospective studies indicate an incidence of CRPS of about 1-2% after fractures (type 1 CRPS), and 1-5% after peripheral nerve injury (CRPS type 2).

Diagnostic Limits of CRPS

There are no diagnostic tests for CRPS, which is a clinical diagnosis. One of the problems with the current defining diagnostic criteria for CRPS is establishing the limits of the diagnosis. This is at present a matter of clinical judgement, and not surprisingly, opinions differ in relation to individual patients. Three-phase isotope bone scans are frequently abnormal in CRPS, but a normal scan does not exclude the diagnosis.

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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. 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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. 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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. P899510103.



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Table 5

Complex Regional Pain Syndrome (CRPS) Previously Described Syndromes

Reflex Sympathetic Dystrophy (RSD)
Causalgia
Post-traumatic sympathetic dystrophy
Algodystrophy
Sudeck's atrophy
Post-traumatic vasomotor syndrome
Shoulder-hand syndrome

Table 6

Definition of Complex Regional Pain Syndrome (CRPS)

CRPS describes a variety of painful conditions that usually

- follow injury
- occur regionally
- have a distal predominance of abnormal findings
- exceed in both magnitude and duration the expected course of the inciting event
- result in marked impairment of motor function
- are associated with oedema, abnormal skin blood flow, or sudomotor activity in the region of the pain at some time during the course of the illness

(International Association for the Study of Pain, 1999)

Table 7

Causes of Complex Regional Pain Syndrome

Peripheral Tissues

Fractures and dislocations
Soft tissue injury
Fasciitis, tendonitis, ligament strain
Arthritis
Deep vein thrombosis
Prolonged immobilisation of a limb

Peripheral Nerve

Peripheral nerve trauma
Post-ganglionic brachial plexus lesions

Dorsal Root

Post-herpetic neuralgia
Spinal nerve root lesions
Brachial plexus avulsion

Central Nervous System

Myelopathies, particularly trauma
Head injury
Cerebral infarction/haemorrhage
Cerebral tumour

Viscera

Abdominal disease
Myocardial infarction

Idiopathic

No identifiable provoking cause

Treatment of Neuropathic Pain

NP due to a compressive lesion may be completely relieved by surgery, particularly if there has been little damage.

However, there may be severe continuing NP with relatively minor damage (eg root compression). For the majority of patients with NP, the realistic goal of treatment, undertaken in a multidisciplinary pain clinic, is partial analgesia, and an improvement in functional status.

The modalities of treatment used for NP are listed in Table 9.

Local and Regional Treatments

In some circumstances, local measures may be sufficient, but many patients will also require systemic drugs.

In the presence of severe allodynia, treatment may not be tolerated in the affected area, but applied in adjacent areas, these measures may be helpful.

Topical local anaesthetic applications are often partially effective in allodynia. Topical capsaicin, which initially stimulates, then desensitises afferent C fibres, is helpful in a minority of patients; many find the initial burning pain intolerable.

A successful local anaesthetic block, for example to a painful scar, may be repeated, combined with corticosteroid which can increase the duration of pain relief, possibly by reducing EIG (see Table 4).

Since Leriche reported that causalgia could be dramatically relieved by surgical sympathectomy, temporary blocking or permanent interruption of the noradrenergic sympathetic efferent supply has become an accepted treatment for causalgia and other post-traumatic neuralgias, for CRPS, and for some CP.

Temporary partial analgesia lasting hours or days is commonly observed, and a small number of patients seem to benefit from repeated blocks over long periods. However, controlled trials have not shown significant benefit from any type of sympathetic blockade.

Electrical Spinal Cord and Deep Brain Stimulation

Spinal cord (dorsal column) stimulation (SCS) may be helpful in patients with pain due to major limb injury, CRPS affecting a limb, plexopathies, thoracic or post-herpetic neuralgia, and occasionally, thoracic myelopathies. The commonest indication is lumbar disease with spinal pain, persistent root pain and arachnoiditis (the majority of whom have had at least one operation). The mode of action is thought to be activation of dorsal horn and possibly thalamic gating mechanisms.

SCS can provide lasting useful analgesia in a minority of patients with NP, but in many, the duration of analgesia is only weeks or months, due either to technical factors, or changing physiology.

The principal indication for deep brain stimulation, targeting a number of sites in the thalamus, is severe central post-stroke pain. As with SCS, the analgesic effect may be short-lived.

Systemic Drugs

The quality of trials of systemic drugs for NP has undoubtedly improved in recent years, and several systematic surveys help to guide treatment. The number needed to treat (NNT) statistic, defined as the number of patients needed to treat to produce one patient with 50% pain relief, is commonly used in these meta-analyses. However, this statistic masks variability in trial design and methodology, pain measures (including quality of life measures), and duration of treatment. Table 10 lists systemic, local and spinally administered drugs found to have an analgesic effect in NP, with NNTs where it is possible to calculate these. Excluding trigeminal neuralgia, the two leading treatments for NP are amitriptyline / nortriptyline, and gabapentin. Amitriptyline has multiple sites of action; one possible mechanism in NP may be a facilitation of the descending serotonergic analgesic pathway from the brain stem to the dorsal horn. Gabapentin has an action on voltage dependent calcium channels in spinal cord interneurons.



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On withdrawing, taper off treatment over a period of 2-3 weeks. **Drug Interactions:** Antiepileptics that induce hepatic enzymes enhance the metabolism of tiagabine (plasma concentrations of tiagabine may be reduced by a factor of 1.5-3). **Pregnancy and Lactation:** Not recommended. **Side Effects:** dizziness, tiredness, nervousness, tremor, diarrhoea, concentration difficulties, depressed mood, emotional lability, slowness in speech. Recurrence of behavioural problems. Rare cases of non-convulsive status epilepticus, hallucination, delusion, bruising and visual field defects. **Legal category:** POM. **Marketing Authorisation Numbers:** Gabitril 5 mg: PL 16260/0009, Gabitril 10 mg: PL 16260/0010, Gabitril 15 mg: PL 16260/0011. **Basic NHS Price:** Gabitril 5 mg, 100 tablets, £45.37. Gabitril 10 mg, 100 tablets, £90.74. Gabitril 15 mg, 100 tablets, £136.11. **Marketing Authorisation Holder:** Cephalon UK Limited. **Date of preparation:** October 2002. Gabitril and Cephalon are registered trademarks. Full prescribing information, including SmPC, is available from Cephalon UK Limited, 11/13 Frederick Sanger Road, Surrey Research Park, Guildford, Surrey UK GU2 7YD, Medical Information Freefone 0800 783 4869 (ukmedinfo@cephalon.com).

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Opioids are considerably less effective in NP than in nociceptive pain, but the previous dogma that opioids are without effect in NP has been modified in view of new evidence from controlled trials. In patients with severe intractable NP, a trial of opioid therapy (controlled release morphine or fentanyl patches) is justified when other treatments have failed.

Reports of relief of post-herpetic neuralgia with intrathecal methyl prednisolone require confirmation.

Surgery for NP

NP results from damage to the nervous system, and that includes surgical trauma, even carefully placed lesions designed to relieve pain. Anterolateral cordotomy leads to contralateral analgesia, and this produces short-term analgesia. But when performed for pain of non-malignant origin, a proportion of patients will develop NP in the distribution of the lesioned tract, months or years

later. The same applies to surgical lesions of peripheral nerve, root or spinal cord, advocated for the relief of chronic pain. Thalamotomy, with lesions at various sites, often produces short duration analgesia. Thus, therapeutic lesioning for NP are now considered obsolete by most authorities.

Psychological Treatment

Patients with intractable NP are frequently depressed, and may benefit from antidepressant drugs. Behavioural measures, and pain management programmes are helpful for many patients, both as adjunctive treatment and as the sole treatment, when all other physical measures have failed.

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Table 8

Clinical Features of Complex Regional Pain Syndrome

Inflammatory:	pain colour change temperature change limitation of movement exacerbation by exercise oedema	
Neurological:	allodynia hyperpathia incoordination tremor	involuntary muscle spasms paresis pseudoparesis
Dystrophic:	skin nails	muscle bone
Sympathetic:	hyperhidrosis changed hair and nail growth vasomotor abnormalities	

Table 9

Treatment Modalities for Neuropathic Pain

Topical:	local anaesthetic capsaicin
Local:	transcutaneous electrical stimulation (TENS) acupuncture thermal (heat, cold) vibration massage
Blocks:	somatic of nerve, plexus, root sympathetic of ganglia, or regional guanethidine
Central stimulation:	spinal cord stimulation (SCS) deep brain stimulation (DBS)
Spinal drugs:	epidural or intrathecal (local anaesthetics, opioids)
Systemic drugs:	see Table 10
Surgery:	decompression
Psychological:	behavioural measures, pain management programmes
Rehabilitation	

Table 10

Drug Treatment of Neuropathic Pain: Controlled Trials

Drug/Route	Condition	Efficacy	
Systemic: Tricyclic antidepressants	PHN	+ NNT=2.3	
	DPN	+ NNT=3.0	
	NP	+	
	HIVN	-	
	SSRI: paroxetine	DPN	+ NNT=6.7
citalopram	CPSP	-	
	Carbamazepine	TN	+ NNT=2.6
Phenytoin	DPN	+	
	CPSP	-	
	Gabapentin	PHN	+ NNT=3.7
Mexiletine	DPN	+ NNT=3.2	
	DPN	+/- less than 50% analgesia	
Baclofen	TN	+	
	Fentanyl	NP	+
	Oxycodone	PHN	+
	Dextromethorphan	DPN	+
	CPSP	-	
Phentolamine	NP	+/-	
	Topical	lignocaine	PHN
capsaicin		PHN, DPN	+
non-steroidal anti-inflammatories		PHN	+
epidural clonidine		NP/CRPS	+
intrathecal methyl prednisolone		PHN	+
regional guanethidine		CRPS	-
intranasal calcitonin		CRPS	+/-

Abbreviations: PHN = post-herpetic neuralgia. DPN = painful diabetic neuropathy. NP = neuropathic pain. HIVN = painful HIV neuropathy. CPSP = central post-stroke pain. TN = trigeminal neuralgia. CRPS = complex regional pain syndrome. NNT = number needed to treat.

Von Hippel-Lindau Disease: Insights and advances

Background and History

Von Hippel-Lindau disease is an inherited cancer syndrome associated with retinal and central nervous system (especially cerebellar) haemangioblastomas. Although rare it is scientifically important as it has recently given fascinating insights into how cells adapt to changes in oxygen supply. The disease was first described in 1904 by von Hippel when he described multiple retinal angiomas, but it was not until 1924 that the Swedish pathologist Lindau linked retinal angioma with CNS haemangioblastomas and the visceral manifestations.¹

The syndrome has an incidence of approximately 1 in 50000 and is inherited as an autosomal dominant condition² with a high penetrance rate such that 95% of cases present by the age of 60.³ It typically presents around the third decade of life although it can be much earlier.² The underlying gene was mapped to chromosome 3 in 1988 and was isolated in 1993⁴, and is small with only 3 exons, and is highly conserved in evolution as the same gene is found in *C.elegans*. The clinical syndrome is only caused by mutations in the VHL gene, and the detection of the mutation or deletion has been found in all families studied to date.⁵

The VHL gene encodes for a protein (pVHL) which consists of 213 amino acids,⁴ and is a tumour suppressor protein. It requires both copies to be inactive before any problems arise and in the inherited syndrome one defective copy is present in the germline. A second acquired mutation occurs at the somatic level and it is only when the second gene inactivation takes place that susceptible target organ tumours develop - an example of Knudson's 2 hit model for tumourgenesis.

Clinical management

The clinical syndrome of VHL disease was classified in 1964.¹ The diagnostic criteria for classical VHL disease (Type 1, 2A or 2B) are 2 or more haemangioblastoma or a single haemangioblastoma and a visceral manifestation. If there is a positive family history for VHL, just one clinical manifestation permits the diagnosis. More recently, phaeochromocytomas alone (type 2C) and autosomal recessive polycythaemia (type 3) have been recognised.^{6,7} (See Table 1).

Table 1

Classification of von Hippel-Lindau disease, the clinical characteristics, genetic abnormality and the effect on HIF regulation

Type	Mutation	Clinical Manifestations	Effect on HIF regulation	Transmission
1	Typical deletion or truncation	Haemangioblastoma Renal cell carcinoma Low risk phaeochromocytoma	Abolished	Autosomal dominant
2A	e.g. Tyr 112 His	Haemangioblastoma Phaeochromocytoma Low risk renal cell carcinoma	Abolished	Autosomal dominant
2B	e.g. Arg 167 Gln	Haemangioblastoma Phaeochromocytoma Renal cell carcinoma	Abolished	Autosomal dominant
2C	e.g. Leu 188 Val	Phaeochromocytoma	Unaffected	Autosomal dominant
3	Arg 200 Typ	Chuvash Polycythaemia	Slightly impaired	Autosomal recessive

Haemangioblastomas

The most common and early feature of VHL are CNS haemangioblastomas and retinal haemangioblastomas. They occur in up to 80% of VHL patients³, with the CNS tumours most frequently located in the cerebellum followed by the spinal cord, although they can occur rarely in the cerebral hemispheres. Haemangioblastomas are benign and do not metastasise and symptoms are due either to their mass effect or haemorrhage. The tumours are frequently cystic, with the cysts growing more rapidly than the underlying tumours⁸ (see Figure 1) and are best managed symptomatically with surgery or radiosurgery.

Retinal haemangioblastomas are histologically indistinguishable from CNS lesions and around 60% of VHL patients have them during their lifetime.⁹ They are often multiple and occur in the peripheral region of the retina and are entirely treatable (for example by laser photocoagulation) which is important in preventing blindness¹⁰.

Renal cysts and neoplasms

The risk of developing clear cell renal cell carcinoma with VHL is greater than 70% during a lifetime and is the most common cause of death¹¹. The tumours are frequently multiple and unlike haemangioblastomas have malignant potential. Surgical intervention is usually nephron sparing to delay the need for dialysis and if the lesions are less than 3cm in size then they are usually monitored, since growth is very variable and metastasis appears not to occur below this threshold¹².

Phaeochromocytomas: About 10% of VHL patients develop a phaeochromocytoma during their lifetime¹¹. Of recent interest is the finding that some mutations are associated with the development of phaeochromocytomas but not haemangioblastomas or clear cell renal cell carcinoma (Table 1).

Pancreatic Lesions: These are usually limited to cysts and any symptoms are secondary to local compression. In some cases non-secreting pancreatic islet cell tumours occur¹³.

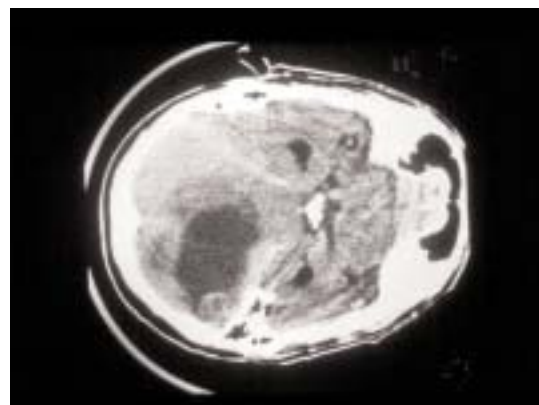


Peter Hill is a Wellcome Trust Clinical Research Fellow in Renal Medicine at Imperial College London, Hammersmith. He graduated from University College London in 1995 and was a SHO in London. He was a Specialist Registrar in Nephrology in Oxford between 1999 and 2003 and is currently at the Hammersmith investigating the role of Hypoxia Inducible Factor in renal disease.



Patrick Maxwell is Professor of Nephrology at the Hammersmith Hospital Campus of Imperial College London. He has worked on oxygen sensing and erythropoietin gene regulation for over 10 years in Oxford, moving to Imperial in 2002.

Figure 1. CT scan on head showing a haemangioblastomas in the cerebellum.



Epididymal Cysts: These are found in around 30-40% of male VHL patients and are benign¹⁴.

Endolymphatic Sac Tumours: These have only been recently recognised as a manifestation of VHL. Up to 10% of VHL patients have these slow growing tumours arising from the petrous-temporal region. They can be frequently bilateral and invasion locally results in deafness or disturbed balance¹⁴.

Clinical management: This is based on regular monitoring of affected or at risk individuals (ie unknown genetic status). It needs to include annual indirect ophthalmoscopy, screening for pheochromocytoma, abdominal imaging for clear cell renal cell carcinoma and neurological evaluation.

Science

Observations that this rare disease is associated with very vascular tumours has provided major insights into the way cells respond to oxygen. When pVHL was first discovered it had no known function, but is now recognised that it regulates Hypoxia Inducible Factor-1.

Hypoxia Inducible Factor (HIF) is a transcription factor that responds to changes in oxygen tensions and influences expression of a large number of target genes. The short-term changes include altering glucose uptake and metabolism and more chronic adaptive changes, include increasing angiogenesis and erythropoiesis. (Figure 2)

The alpha unit of the HIF complex is regulated by oxygen. In low oxygen tensions (hypoxia) the HIF complex is activated and results in increased gene transcription. Under normal oxygen tensions HIF- α is rapidly degraded. Following hydroxylation of HIF- α , pVHL binds to it acting as a ubiquitin E3 ligase which leads to the destruction of HIF by the proteasome after ubiquitination¹⁵. (Figure 2)

The initial step of hydroxylation is carried out by Prolyl Hydroxylase (PHD) enzymes¹⁶. The PHD enzymes use oxygen, and the reaction rate responds to the concentration of molecular oxygen. Additional regulation of HIF- α involves hydroxylation of a different part of HIF by another enzyme, FIH-1, (Factor Inhibiting HIF) which prevents the HIF complex binding other transcription factors. So enzymatic hydroxylation is acting as an 'oxygen sensor'. In the presence of oxygen it turns HIF off both by enabling capture of VHL and preventing it interacting with transcriptional co-activators.

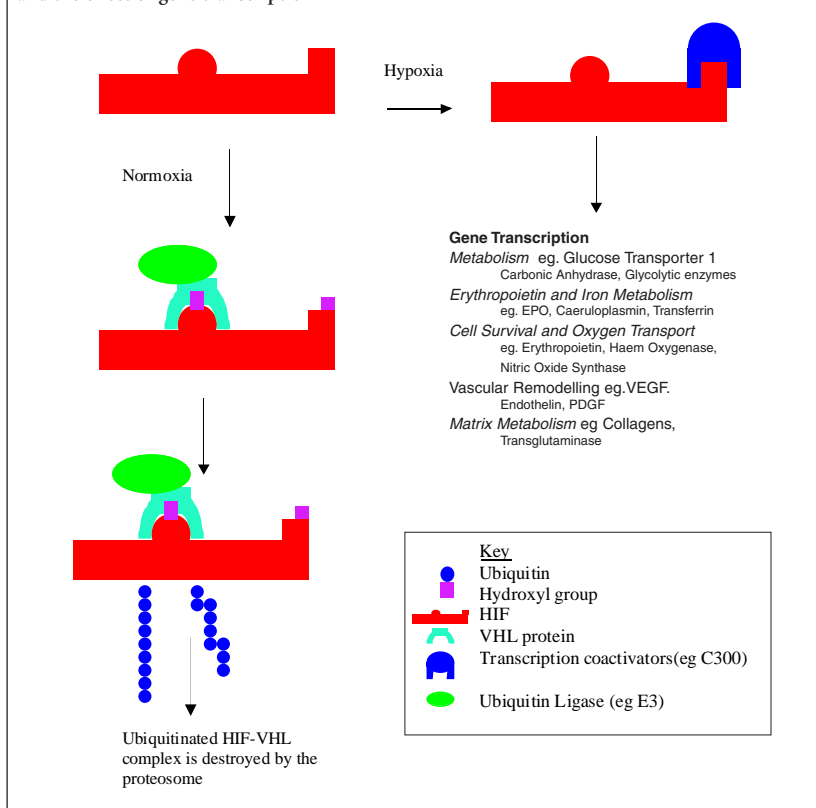
When cells lose VHL function, HIF is constitutively stable and activates target genes such as angiogenic growth factors, explaining the angiogenic phenotype.

Summary

The rare hereditary cancer syndrome VHL is associated with multiple vascular and cystic tumours. These are caused by a germline mutation in VHL followed by somatic inactivation or loss of the second copy of the gene. The protein product of VHL inhibits the accumulation of hypoxia inducible factor and its target genes under normoxic conditions. Manipulation of the HIF-VHL system may lead to new therapies. In the treatment of cancer if the HIF system can be switched off, the production of VEGF and other growth factors involved in tumour growth can be reduced and may aid conventional therapies.

In ischaemia augmenting the activation of HIF may provide benefit.

Figure 2. The pathway of HIF activation and destruction according to oxygen concentration and the effect of gene transcription



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Correspondance to:

Dr Peter Hill, Renal Section, Department of Medicine, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN

Dreamy states

Dreamy states are well known as brief aberrations of awareness and of altered thought and cognition that are a commonplace normal experience. But they also occur in a variety of psychological states and as Hughlings Jackson described, in epileptic attacks deriving from the temporal lobes. Jackson's many papers contain unparalleled richness of clinical description, now seldom cited. This account provides no original material, but seeks to reproduce some of his most important observations, including the unique wealth of personal experiences from one particular doctor-patient.

The Arabian physician and surgeon Abulqasim who served the Caliph of Cordova during the tenth century, recorded examples of hallucinations experienced by epileptics¹. One patient described was a boy,

"... suffering from the same disease who told me that it seemed to him that a black woman came towards him having over herself a small leather garment and when she approached him he immediately fell down."

Antonius Guainerius² of the University of Pavia from 1412-1413 wrote,

"I myself have seen a certain choleric youth who said that in his paroxysms he always saw wonderful things, which he most ardently desired to set down in writing."

Intellectual Aura

It was not until the latter part of the nineteenth century, that Hughlings Jackson recognised such strange symptoms as elements of the epileptic attack.

"It is not very uncommon," he wrote³ "for epileptics to have vague and yet exceedingly elaborate mental states at the onset of epileptic seizures... The elaborate mental state, or so-called intellectual aura, is always the same, or essentially the same, in each case. 'Old scenes revert.' 'I feel in some strange place.' 'A dreamy state.'"

Jackson reported two varieties (ref 3, p.295)⁴:

1. *dreamy states without actions, the dream remembered, and*
2. *actions more or less elaborate, but no mental state during his actions, nor does he remember what he has done."*

The French physicians J Falret, A Voisin, Armand Trousseau and Th Herpin were familiar with these dreamy states, but they described them as intellectual auras, a term Jackson disliked.

"dreamy states consisting of scenes or experiences remembered from the past. A 37-year-old man had attacks that began with an olfactory sensation. He said that he began to think of things years gone by, — 'things from boyhood's days.'"

Jackson recognised that in focal attacks post mortem disclosed "coarse" diseases of the brain, glioma, syphiloma, abscess, and that the site of such lesions could be inferred from the onset of the fit. This was an important step in rational cerebral localisation deduced from clinical signs. His lucid and minute descriptions embraced the diverse intellectual, psychic, dreamy states, sensory, motor, and

aphasic contents of various types of seizures, as well as the several post-epileptic states⁵.

A second patient also had attacks that started with an olfactory sensation, then visual hallucinosis:

"The next thing was his 'dreamy state.' He seemed to actually see large buildings, which he had once seen; it might be that he seemed near a church, close to its wall. In the last attack, he 'saw' certain alms houses, all in a moment 'saw' that building and could actually see the clock. The things he 'saw' seemed of a natural colour."

Jackson described⁶ the sense of strangeness, unreality, *jamais vu*, a dreamy state, and *déjà vu*. He observed a sense of fear and panic and in some, strange unpleasant smells and tastes that he thought derived from the uncus of the temporal lobe. He recorded visual hallucinations, often well formed, so that the subject could recount complex scenes³. An initial rising sense of warmth or discomfort in the stomach constituted the epigastric aura. Importantly Jackson said that the aura is itself the initial symptom of the seizure.

Gower's⁷ too, described several cases with elaborate visual and auditory "warnings". Among them was a patient who saw "beautiful places, large rooms, etc.," and heard at the same time "beautiful music."

Jackson's dreamy states and intellectual auras

The comprehensive account of epilepsy with "dreamy state" was published⁸ in 1888. Case 5, Jackson introduces as, "a very important case. It is of a highly educated medical man, who reports it himself..."

"I first noticed symptoms which I subsequently learnt to describe as petit-mal when living at one of our universities, 1871. I was waiting at the foot of a College staircase, in the open air, for a friend who was coming down to join me. I was carelessly looking round me, watching people passing, etc., when my attention was suddenly absorbed in my own mental state, of which I know no more than that it seemed to me to be a vivid and unexpected 'recollection' — of what, I do not know. My friend found me a minute or two later, leaning my back against the wall, looking rather pale, and feeling puzzled and stupid for the moment. In another minute or two I felt quite normal again, ... I could give no distinct account of what had happened, or what I had 'recollected'."

"During the next two years a few similar but slighter attacks occurred, involving mental states which struck me as like to the first and to each other..."

"In 1874 I first had a haut-mal, preceded by the mental condition I had felt in petits-maux, ... I will attempt to describe the features which I think were common to all, or nearly all."

"Mental condition" — *In a large majority of cases the central feature has been mental and has been a feeling of Recollection, i.e. of realising that what is occupying the attention is what has occupied it before, and indeed has been familiar, but has been for a time forgotten, and now is recovered with a slight sense of satisfaction as if it had been sought for. The recollection is always started by another person's voice, or by my own verbalised thought, or by what I am reading and mentally verbalise; and I think that during*



Dr John Pearce was Senior Consultant Neurologist at Hull Royal Infirmary from 1967 until 1992. He has been Emeritus Consultant Neurologist since 1992. He has written a variety of books on Dementia, Headache, Migraine, Parkinson's disease, and Medical History.

the abnormal state I generally verbalise some such phrase of simple recognition as, 'Oh yes — I see', 'Of course — I remember', etc., but a minute or two later I can recollect neither the words nor the verbalised thought which gave rise to the recognition. I only feel strongly that they resemble what I have felt before under similar abnormal conditions. I re-enter the current of normal life, as a rule, quickly — sometimes, as far as I can judge from my own movements or other people's evidence, within ten or fifteen seconds; I have found myself just after a petit-mal at a London Railway Booking Office, meaning to go to K — , and asking without hesitation for 'Second return to — to — that school, don't you know —' (or some such words) and being a good deal startled at my forgetfulness.

"A petit-mal has two or three times come on when I have been reading poetry aloud — the line I am reading or just going to read seems somehow familiar, or just what I was trying to recollect, though I may have seen or heard it before. I recognise my morbid condition and stop, though I have generally sense enough to finish the line or even sentence, and remain silent for a minute or so; I have made several rude attempts to go on writing, and have kept four or five specimens of what I have written. ... My impression at the time that I was writing was that the words and sense were quite reasonable, and that I had kept within very familiar and prudent limits of expression. I had found, I thought, just the words I was seeking for. A minute or two later I could see that some of the words were grotesquely mal à propos, though I think the grammatical forms of sentence were always preserved. I could not trace any undercurrent of thought or recollection from which the irrelevant words had come.

" **Physical conditions.** —...At the onset I can rarely notice any physical change in myself, my attention being chiefly occupied with my mental condition; but once or twice when I have been standing near a mirror I have noticed pallor of the face, and I have learnt from others that this is common, and that my eyes have a somewhat staring vacant look as if they were not directed to anything near me, or indeed taking notice of anything particular. In this condition I am told, and in fact occasionally remember, that I often say 'yes', with an air of complete assent to any remark made to me, whether it is a pertinent answer or not; and further, that I occasionally make a slight half-vocalised sound, whether addressed or not. This latter, I have been told, is somewhat like a modified and indistinct smacking of the tongue like a tasting movement, and is generally accompanied by a motion of the lower jaw, and sometimes by some twitching of the muscles round one or both corners of the mouth or of the cheeks, but by no sense of taste in my recollection.... I also never notice myself, but learn from others, that sometimes, specially if sitting, I give one or two light stamps on the floor with one foot; and in the only cases where this has been accurately observed it has been with the right foot.

"With the returning normal consciousness I generally feel some superficial flush over the skin, especially over the face, and a slightly quickened and more thumping heart-beat which does not go beyond causing me very slight malaise ...

" The petits-maux have not been accompanied or followed by hallucinatory sensations of sight, sound, taste, smell, or feeling. There has been, I think, no loss of balance. I well recollect in 1878 running across a Swiss glacier, and jumping across many small crevasses when the initial stage of 'aura' came on, and a reflection shot through my mind, that if ever I was likely to pay dearly for the imprudence of going on, it would be then. But I had insufficient control to stop myself and felt no fear, but only a slight interest in what would happen. I went through the familiar sensations of petit-mal with such attention as I had to give concentrated on them, and not on the ice, and after a few minutes regained my normal condition without any injury. I looked back with surprise at the long slope of broken ice I had run over unhurt, picking my way, I know not how, over ground that would normally have been difficult to me. In the same way a petit-mal when I was playing lawn tennis did not in the opinion of my adversary make my strokes or judgment of pace and position of balls to be struck any worse than normal. I had no recollection of the strokes during a minute or two....

He recalls four fascinating episodes in detail; I quote the first and fourth:

"(1) In October 1887 I was travelling along the Metropolitan Railway, meaning to get out at the fourth station and walk to a house half a mile off. I remember reaching the second station, and I then recollect indistinctly the onset of an 'aura', in which the conversation of two strangers in the same carriage seemed to be the repetition of something I had previously known — a recollection, in fact. The next thing of which I have any memory was that I was walking up the steps of the house (about half a mile from the fourth station), feeling in my pocket for a latch-key. I remembered almost at once that I had had a petit-mal coming on at the second station, and was surprised to find myself where I was. I recollected that I had meant to reach the house not later than 12.45, and had been rather doubtful in the train whether I should be in time. I looked at my watch and found it within a minute or two of 12.45... I had no memory of anything since the second station some ten or twelve minutes previously. I imagine that I had carried out my intention automatically and without memory.

... "(4) A fourth occasion is perhaps worth record. I was attending a young patient whom his mother had brought me with some history of lung symptoms. I wished to examine the chest, and asked him to undress on a couch. I thought he looked ill, but have no recollection of any intention to recommend him to take to his bed at once, or of any diagnosis. Whilst he was undressing I felt the onset of a petit-mal. I remember taking out my stethoscope and turning away a little to avoid conversation. The next thing I recollect is that I was sitting at a writing-table in the same room, speaking to another person, and as my consciousness became more complete, recollected my patient, but saw he was not in the room. I was interested to ascertain what had happened, and had an opportunity an hour later of seeing him in bed, with the note of a diagnosis I had made of 'pneumonia of the left base.' I gathered indirectly from conversation

that I had made a physical examination, written these words, and advised him to take to bed at once. I re-examined him with some curiosity, and found that my conscious diagnosis was the same as my unconscious — or perhaps I should say, unremembered diagnosis had been. I was a good deal surprised, but not so unpleasantly as I should have thought probable."

Jackson's descriptive analysis⁸ of the mental state during attacks described by this patient is remarkable. The patient recognised his "recollections" as different from normal memories, being much more vivid and more "satisfactory," but, at the same time, was dimly aware of their fictitious character, indicating some preservation of consciousness, thus resulting in the "mental diplopia" characteristic of the dreamy state. The persistence, during attacks, of performances such as finding his way in a perilous path on a Swiss glacier or, even more surprisingly, to make a correct diagnosis by physical examination of pneumonia of the left base strongly suggests that disturbances of memory rather than of consciousness were the major components of the ictal automatism. Jackson suggested that some of the apparent lack of awareness was the result of concentration of attention on inner feelings. This emphasises that assessment of awareness and responsiveness are not sufficient to characterise the state of consciousness. The tongue smacking and twitching of perioral muscles indicate involvement of the temporal lobes in the epileptic discharge.

Uncinate Epilepsy

In Jackson's case 5., the patient's use of the terms *petit mal* and *haut mal* would not be accepted as temporal lobe or uncinata attacks in modern epileptology, but they plainly reflect his complex partial and major generalised fits. Importantly, Jackson believed that the dreamy state was not an aura but an integral part of the attack.

"Of the patient's slight seizures we may learn much, of the severe ones without warning, very little that is definite... there may be a defect of consciousness only; and there may be 'over-consciousness' ('dreamy state')."

By 1888 he had seen about 50 such cases, some of which had come to autopsy study. He was impressed by the lesions often seen in the uncus and therefore adopted the term uncinata epilepsy. In *Neurological Fragments*¹¹ he describes the now familiar hallucinations of taste and smell, the epigastric aura and lip smacking:

"I have several times drawn attention to what I will now call a group of cases of epilepsy— cases in which there is at the onset of the paroxysms a crude sensation of smell or of taste or in which there are movements of chewing, smacking of the lips, and sometimes spitting, etc. These movements are the indirect, the "reflex," consequences of an epileptic discharge of gustatory elements of the cortex. In some cases of this group there is a warning by what is known as the epigastric sensation..."

Normal or physiological dreamy states

Many notable, literary figures have written of their own comparable experiences. It is unlikely that these are all examples of uncinata epilepsy. But the border is often hazy between epilepsy and these strange psychogenic reminiscences, associative feelings, apprehensions of remote and

mystic experience - dreamy states. In an engaging if Ciceronian essay, Crichton-Browne expounded on many examples of autobiographical descriptions. They are, he states,

"rents in conscious life through which glimpses of the supraconscious may be obtained. The description given is that they are indescribable. Exceedingly diverse in character,...concerned with those ultimate idea — space, time, matter, motion or relativity — which are beyond the domain of certain knowledge and, according to Herbert Spencer, unthinkable."

He compares them to the "nebulous and voluminous thoughts" provoked by nitrous oxide inhalation, but these, he says, "have never in them any tinge of fear or alarm". Indeed, he relates that dreamy states when mingled with fear have ultimately merged into epilepsy. We now recognise dreamy states with vivid distortions of sound and vision in hypnagogic hallucinations, psychoses and drug-induced states. For example, dopaminergic medications frequently induce vivid dreams. Crichton-Browne concluded that dreamy states "tarnish for a time the brightness of the brain and reduce the powers of resistance of those who suffer from them..."

He cited Tennyson's Early Sonnets:

*"As when with downcast eyes we muse and brood,
And ebb into a former life or seem,
To lapse far back in some confused dream
To states of mystical similitude;..."*

Tennyson was probably epileptic and Crichton-Browne gives his history. But were these musings physiological daydreams, imaginative reminiscences, or the consequence of seizure activity, as Crichton-Browne believed?

Another famous case was a medical man seen by Jackson (ref 3. pp. 388-9) under the pseudonym of Quaerens (the seeker). He reported similar minor altered consciousness with 'bemazement' in himself. Quaerens quoted Tennyson, Coleridge and Dickens in relation to his own *déjà vu* experiences.

Hughlings Jackson also quotes from David Copperfield: "We have all some experience of a feeling which comes over us occasionally, of what we are saying and doing having been said or done before, in a remote time — of our having been surrounded, dim ages ago, by the same faces, objects, and circumstances — of our knowing perfectly what will be said next, as if we suddenly remembered it."

Experimental dreamy states

In the 1940s and '50s, Wilder Penfield, at the Montreal Neurological Institute, artificially elicited "dreamy states" by cortically stimulating the lateral temporal neocortex, the anterior hippocampus or the amygdala in conscious epileptic patients before their surgical resections. During these experiments, the patients experienced "experiential illusions." These illusions involved an alteration, sometimes subtle, of the person's relationship to his or her environment, as well as emotional response. In contrast to psychotics, they remained aware that their altered interpretation was an illusion. A friend's voice may sound remote, or a well-known living room may appear unfamiliar, but the meaning is preserved, the voice does not become depersonalised, nor does the living room lose its identity. Penfield observed that even those patients describing feelings of unreality state that they know at the same time what reality is. Mullan and Penfield¹⁶ classified these illusions into four groups:

1. Auditory illusions accompanied by the perception that sounds were louder or clearer, fainter or more distinct, nearer or farther away;
2. Visual illusions where things seemed clearer or blurred, nearer or farther away, larger or smaller; fatter or thinner;
3. Illusions of recognition where present experience seemed familiar, strange, altered or unreal; and
4. Illusions of emotion consisting of feelings of fear, loneliness, sorrow or disgust.

Many patients experienced the emotion as part of the seizure described as dread or a feeling of impending doom; in others, the emotion may, as Dostoyevsky described, be pleasant or euphoric. Déjà vu and forced, vivid memories, embarrassment, alterations of behaviour, and sexual automatisms may all accompany various dreamy states in temporal lobe epilepsy. A schizophrenic type psychosis complicates a significant minority of patients, but is beyond the remit of this discussion. Structural abnormalities are now being revealed in epilepsy with increasing frequency by modern static and dynamic brain imaging techniques.

Conclusion

Dreamy states arise in normal subjects, those with intense phobic anxiety and in a variety of psychoses and drug induced states. The diagnosis of the cause rests more on the temporal evolution, and associated neurological feature than with the actual content of the experience.

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Correspondence to:

Dr JMS Pearce
304 Beverley Road, Anlaby East
Yorks HU10 7BG
Tel & Fax: 01482-654165
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EEG has an important role in the diagnosis of epilepsy. However, results need to be carefully interpreted in the context of the clinical data. This course is aimed at Consultants Paediatricians and Paediatricians in training, and aims to highlight the role of EEG in epilepsy management. Cost - £80

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For further information please contact the Marketing Department on 01342 831 337/237 or email training@ncype.org.uk. Further information and an online booking form is also available from our website at www.ncype.org.uk/resource_centre.htm



The National Centre for Young People with Epilepsy

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by June 6th, 2003. An extended version of this diary is available on our website at www.acnr.co.uk

2003

May

EFNS Academy for Young Neurologists

9-14 May, 2003; Stare Splyav, Czech Republic
Ing. Magda Dohnalova,
Tel/Fax. +420 2 6716 3563,
E. efnas@fnkv.cz

Psychosocial Impact on Illness, Disability & Medicine
12 May, 2003; Cardiff, Wales
Tel. 020 7290 3856,
E. wales@rsm.ac.uk

MS Frontiers 2003
14-15 May 2003; Birmingham, UK
www.msociety.org.uk/news_events/conferences

Psychosocial Aspects of Epilepsy
15 May, 2003; Lingfield, UK
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338,
E. klaird@ncype.org.uk,
www.ncype.org.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
16 May, 2003; Widnes, UK
Sam Loughran,
E. Sam_loughran@hotmail.com,
Tel. 0151 420 7619

Evolving MS Services
16 May 2003; Newcastle, UK
www.msociety.org.uk/news_events/conferences

The Society of Neurological Surgeons 2003 Annual Meeting
18-20 May, 2003; Cincinnati, US
David G Peipgras, Tel. 001 507 284 2254, Fax. 001 507 284 5206,
E. piepgras.david@mayo.edu

2nd World Congress of Physical & Rehabilitation Medicine - ISPRM
18-22 May, 2003; Prague, Czech Republic
Congress Secretariat
Tel. +972 3 9727500,
Fax. +972 3 9727555,
E. physical@kenes.com

European Conference on Shaken Baby Syndrome
19-20 May, 2003; Edinburgh, UK
Tel. Marilyn Sandberg, 001 801 627 3399,
E. msandberg@mindspring.com

4th Parkinson's Disease Nurse Specialist Association National Conference
19-20 May, 2003; Birmingham, UK
www.pdnas.org.uk or
E. stella.smith@stgeorges.nhs.uk

Basic Neurophysiology
19 May, 2003; London, UK
Neurosurgery Courses Assistant,
RCSE, Tel. 0207 869 6335,
Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Sleep & wakefulness: medico-legal aspects of sleep

19 May, 2003; London, UK
Tel. 0207 2903941,
E. anke.muller@rsm.ac.uk

Clinical Neurophysiology
20 May, 2003; London, UK
Neurosurgery Courses Assistant,
RCSE, Tel. 0207 869 6335,
Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

MS Trust Study Days
21 May, 2003; London, UK
Tel. Catherine Thornley on 01462 476704.

Neurophysiology
21-22 May, 2003; London, UK
Neurosurgery Courses Assistant,
RCSE, Tel. 0207 869 6335,
Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

8th Euroacademia Multidisciplinary Neurotraumatologica
21-24 May, 2003; Graz, Austria
E. hans.trithart@klinikum-graz.at

8th Annual Meeting of Rehabilitation in MS
22-25 May, 2003; Montana, Switzerland
Tel. +41 27 485 62 28,
E. quadrimed.ch@freesurf.ch

Neurology for Neurosurgeons
22-23 May, 2003; London, UK
Neurosurgery Courses Assistant,
RCSE, Tel. 0207 869 6335,
Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

5th World Congress on Brain Injury
23-26 May 2003; Stockholm, Sweden
E. info@internationalbrain.org or
Tel. 001 703 683 8400 ext 101

The Spectrum of Multiple Sclerosis Care
28 May - 1 June, 2003; San Diego, US
Tel. 001 201 837 0727 x 122,
E. RVRazon@aol.com

3rd International Conference Emotions & Brain
28-31 May, 2003; Lisbon, Portugal
Fax. 351 217 515 571,
E. emotions.brain@ulusofona.p or
francisco.esteves@ulusofona.pt

15th International Congress on Parkinson's Disease
30 May-3 June, 2003; Beijing, China
Fax. 86 1 065 123 754,
E. xvcpd@chinamed.com.cn

10th European Federation of Endocrine Societies Postgraduate Clinical Endocrinology Course
29-31 May, 2003; Riga, Latvia
Tel. 37 17 085 014, Fax. 37 17 820 020, E. endocrinology@latviatours.lv

XVII Iberoamerican Congress of Otoneurology
31 May-4 June, 2003; Madrid, Spain
Fax. 34 915 195 085,
E. ibotoneu@intercom.es

June

Advances in Molecular Mechanisms of Neurological Disorders
1-4 June, 2003; Warsaw, Poland
Prof Katarzyna A Nalecz,
Tel. +48 226 686 216,
Fax. +48 226 686 544,
E. knal@nencki.gov.pl

RCPLive: Multiple Sclerosis
4 June, 2003; Internet based
See www.rcplive.ac

10th Annual Conference on Neurobehavioural Rehabilitation in Acquired Brain Injury
5-6 June, 2003; Hamilton, Canada
Fax. 905 385 3339,
E. jlambert@hhsc.ca

5th Neurology Registrar Study Weekend
6-8 June, 2003; Birmingham, UK
E. info@theabn.org

Biennial Symposium of the International Evoked Response Audiometry Study Group
8-12 June, 2003; Tenerife, Canary Islands
Tel. +34 922 670 181,
Fax. +34 922 670 191,
E. congresos@viajesmencey.es

EPTA Continuing Professional Development Conference
9-11 June, 2003; Lincoln, UK
E. nigel.hudson@phnt.swest.nhs.uk

Balance 2003
9-11 June, 2003, UK
Tel. Jane Burgney 02380 592288,
E. jbb@isvr.soton.ac.uk

Affective, Behaviour and Cognitive Disorders in the Elderly
10-21 June, 2003; Bologna, Italy
G&G International Congress,
Fax. +36 06 503 3071,
E. congressi@gegcongressi.com/abcde

13th Meeting of the European Neurological Society
14-18 June, 2003; Istanbul, Turkey
AKM Congress Service, Clarastrasse 57, PO Box CH 4005, Basel, Switzerland.
Tel. +41 616 867 711,
Fax. +41 616 867 788,
E. info@akm.ch

6th Meeting of the European Neuro-Ophthalmology Society
15-18 June, 2003; Goteborg, Sweden
Bertil Lindblom, Tel. +46 313 433 253, Fax. +46 313 412 904,
E. bertil.lindblom@neuro.gu.se

6th International Symposium on Paediatric Pain
15-19 June, 2003; Sydney, Australia
DC Conferences,
Tel. 0061 2 9439 6744,
E. mail@dcconferences.com.au

7th OSET International Congress
16-20 June, 2003; Egmond aan Zee, The Netherlands
www.oset2003.org

5th National Memory Clinic Conference
17 June, 2003; Birmingham, UK
Sponsored by Eisai Ltd
Tel. 0115 937 1289,
Fax 0115 937 1281

79th Annual Meeting of the American Association of Neuropathologists
18-23 June, 2003; Orlando, US
Dr Joseph Parisi, Tel. 001 507 284 3394, Fax. 001 507 284 1599,
E. aanp@mayo.edu

Mayo Clinic Brain Injury Conference
20 June, 2003; Rochester, US
Fax. 001 507 284 2509,
E. cme@mayo.edu

North West Nurses Epilepsy Forum (Learning Disabilities)
20 June, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

12th European Conference on Clinical Hemorheology
22-26 June, 2003; Varna, Bulgaria
Fax. +3592 707498,
www.12ECCHE.primasoft.bg,
E. biorheo@imbm.bas.bg

6th International Neuromodulation Society World Congress
22-29 June, 2003; Madrid, Spain
Fax. 001 415 567 2534

MS Trust Study Days
25 June, 2003, Llandudno, UK
Tel. Catherine Thornley on 01462 476704.

MS Trust Chatrooms - Sexual problems/pregnancy
23 June, 2003; Internet based
www.mstrust.org.uk

International League Against Epilepsy Annual Scientific Meeting
26-28 June, 2003; Manchester, UK
Tel. 01691 650290,
Fax. 01691 670302,
E. denise@conference2k.com

What's New in Neurological Emergencies?
27 June, 2003; London, UK
Tel. Lulu Ho on 020 7290 2987,
E. a8e@rsm.ac.uk

University of Munich Epilepsy Course
27-29 June, 2003; Munich, Germany
Fax. +49 89 7095 6691,
E. petra.wagenbuechler@nro.med.uni-muenchen.de

7th World Congress on Sleep Apnea
29 June-2 July, 2003; Helsinki, Finland
Fax. 358b 956 075 020,
E. congrex@congrex.fi

Brain 03 & BrainPET 03
29 June-3 July, 2003; Calgary, Canada
Tel. 001 403 210 9397,
Fax. 001 403 220 7054,
E. brain03@brain03.org

Society for Research in Rehabilitation Summer Meeting
30 June-1 July, 2003; Nottingham, UK
Mrs Ann Hughes, Tel. 0115 8404 798,
E. ann.hughes@srr.org.uk

ECNR Seventh Cycle - Second Course: Base of the Skull
June 2003; Otranto, Italy
Dr Cosma Andreula, Servizio di Neuroradiologia, Tel. 0039 080 5592330, Fax. 0039 080 5247441,
E. Andreula@tin.it

July

EPTA Summer Scientific Meeting
July 2003, TBC; London, UK
E. nigel.hudson@phnt.swest.nhs.uk

European Board of PRM Posture & Movement Analysis Course
1-11 July, 2003; Marseille, France
PRM Dept, www.mediterranee.univ-mrs.fr/esm

1st Scientific Conference of the Association of Physiotherapists in Parkinson's Disease (APPDE)
4 July, 2003; Southampton, UK
Alison Marks, Tel. 023 80549 4791, Fax. 023 8059 4792,
E. adm5@oton.ac.uk

East Midlands & Trent Falls Symposium
4 July, 2003; Nottingham, UK
Tel. 0115 962 7758,
Fax. 0115 962 7937,
E. gostell@ncht.trent.nhs.uk

FEBS 2003 meeting on Signal Transduction
4-8 July, 2003; Brussels, Belgium
Professor J E Dumont, Tel. +32 2 555 41 35, Fax. +32 2 555 46 55,
E. cleclere@ulb.ac.be

ISAN 2003: Advancing Autonomic Neuroscience after the Genome
4-8 July, 2003; Calgary, Canada
Dr Joseph Davison, E. jdavison@ucalgary.ca,
Fax. 001 403 283 328.

Learning Disabilities - Focus on Research
7-8 July, 2003; Tel. Susan Hooper on 0115 924 9924 x 42329, or Janet O'Flynn on 0115 924 9924 x 44085

Techniques & Applications of Molecular Biology
7-10 July, 2003; Coventry, UK
Fax. 02 476 523 701,
E. charlotte.moonan@warwick.ac.uk

Vocational Rehabilitation in Long Term Conditions
9 July, 2003; Leeds, UK
Tel. 0113 3055086, E. adele.archer@lcmhst-tr.northy.nhs.uk

CNS 2003: The Annual Computational Neuroscience Meeting
6-10 July, 2003; Alicante, Spain
Chris Ploegaert, E. cp@bbf.uia.ac.be,
www.neuroinf.org/CNS/cns2003

1st International Symposium on CNS Germ Cell Tumors

Our Symposium welcomes basic researchers, pathologists, radiologists, oncologists, psychologists, neurosurgeons, and anyone involved in clinical activities for CNS germ cell tumor patients. The three major objectives of the Symposium are:

- > To demonstrate basic scientific data to facilitate better understanding of the nature of the tumors.
- > To demonstrate and evaluate the clinical treatment results.
- > To facilitate and enable establishment of standard therapeutic protocols.

**September 17-19, 2003
Kyoto, Japan**



For further information, please contact the Secretariat at: The First International Symposium on CNS Germ Cell Tumors, c/o Convex Inc., Ichijoji Bldg., 2-3-22 Azabudai, Minato-ku, Tokyo 106-0041, Japan. Tel: +81-3-3589-3355, Fax: +81-3-3589-3974, E-mail: GCTsympo@convex.co.jp, Homepage: <http://www.gctsympo.com/gctsympo/index.html>

Sponsored by: The Japan Brain Foundation; The Pediatric Brain Tumor Foundation of the United States; The Diabetes insipidus Foundation, Inc.; The Japan Society for Neuro-Oncology; The Children's Cancer Association of Japan

Association of British Neurologists Spring Meeting

2-4 April, 2003; Cardiff, UK

A fine venue in the centre of Cardiff, train station and hotel within walking distance, no parallel sessions to tax our ability to make decisions, and the sun was shining; all the ingredients of a refreshing and helpful conference, and so it proved to be.

The format was traditional and began on Wednesday afternoon with a lively educational symposium on difficult consultations. In the evening symposium Professor Nick Wood brought us up-to-date with the genetics of Parkinson's Disease with an impressive and wide-ranging lecture. Thursday was enriched by Professor Steve Dunnet's lecture on the current status of cell transplantation for neurodegenerative diseases. The society was honoured that Professor Peter Harper accepted honorary membership and we were privileged to hear his superb lecture on Myotonic Dystrophy on Friday.

Professor Warlow interrogated the clinical aspects of the clinicopathological conference and Dr Jim Neal presented the pathological findings of merantec endocarditis in a lady who had a low grade ovarian carcinoma.

The evening reception on Wednesday was in Cardiff Castle. The conference dinner on the Thursday evening was in the National Museum of Wales. The Society was addressed by Mr Richard Mills, Consultant ENT Surgeon and his rousing address was followed by a recital by the Blaenavon Male Voice Choir.

The platform presentations and posters were of a high standard and strict time-keeping allowed adequate time for questions and discussion.

I have selected some of the presentations and attempted to summarise them below. It is not possible to describe all of the presentations but I know that the hosts were very grateful to all those who contributed to the scientific sessions.

1. Early risk of recurrent stroke by aetiology sub-type: implications for stroke prevention. Lovett, Oxford.

Analysis of data on 1670 patients suggests that recurrent stroke risk varies significantly between sub-types; patients with stroke due to large artery disease had the highest odds of recurrence at both 7 and 30 days suggesting that this group requires early preventative treatments.

2. Diffusion weighted magnetic resonance imaging in acute ischaemic stroke: pathophysiological insights with quantitative positron emission tomography (PET). Guadagno, Cambridge.

A 53 year-old patient was imaged 7-9 hours following stroke onset with back-to-back DWI and quantitative PET mapping of cerebral blood flow and cerebral metabolic rate of oxygen. The study demonstrated for the first time that the DWI lesion can contain still viable tissue and, therefore, may not represent a core of irreversibly damaged brain.

3. Oligodendrocytes produce neurotrophic and axonotrophic factors in vitro Wilkins, Cambridge

Using rat neurones cultured in oligodendrocyte-conditioned media or control media, soluble factors released by oligodendrocytes were shown to increase axonal survival in culture which may have important implications in determining the causes of axonopathy in multiple sclerosis. Characterisation of neurotrophic factor production by oligodendrocytes may lead to therapeutic strategies to prevent irre-

versible axon loss in late stages of the disease.

4. Quantification of walking mobility in multiple sclerosis using an ambulatory activity monitor: a pilot study. Pearson, Cardiff

The mobility of 12 MS patients and 14 volunteers was assessed with ambulatory monitoring which allows unobtrusive counting of every step over prolonged periods. Strong correlations were demonstrated with commonly used indices of mobility in MS and the face validity of counting every step over many days may lead to such methodology becoming a gold standard for measurement of actual – rather than claimed or derived – walking mobility.

5. Gastrostomy tubes for MND in Scotland: frequency, timing and survival. Swingler, Dundee and Belfast

Patients with motor neurone disease who underwent endoscopic gastrostomy were identified from the Scottish MND Register between 1989 and 1998. 142 PEG episodes were identified with a mean age of 66.8 years at insertion with a mean disease duration of 24 months. Median survival from PEG insertion was 146 days but the 1 month mortality post-gastrostomy was 25%. Gastrostomy did not appear to confer a survival advantage.

6. Meeting the Association of British Neurologists guidelines: provision of 24 hour acute neurology care by neurologists. Carroll, Plymouth

Derriford Hospital provides a 24 hour neurology on take service to a population of 500,000 with the equivalent of four consultants, three SpR's and four SHO's with a 37 bed ward. Admissions to the department were analysed prospectively over a 3 month period. Currently each SpR spends 18 hours per week involved in the care of acute admissions. Meeting the ABN guidelines will require an increase in neurology bed provision to at least 15.2 per 100,000 population with the equivalent of three consultant sessions (11 hours per week).

7. Cerebrovascular disease and the failure of elimination of amyloid β from the ageing and Alzheimer brain: implications for therapy. Weller, Southampton and Newcastle

In this study thromboembolic occlusion of penetrating cortical arteries was associated with complete block of elimination of amyloid β along perivascular drainage channels and the development of severe capillary amyloid angiopathy. This suggests that cerebrovascular disease is a major factor in the failure of clearance of amyloid-beta from the ageing and Alzheimer brain.

Dr Tom Hughes, Consultant Neurologist, University Hospital of Wales and Rockwood Hospital, Cardiff.



National Museum of Wales where the conference dinner was held



Cardiff Castle, the venue of the evening reception

55th Annual Meeting of the American Academy of Neurology

29 March – 5 April, 2003; Honolulu, Hawaii

The 55th Annual Meeting of the AAN coincided with the International Spam Festival (Spam – spiced ham). 7200 delegates registered but the Iraqi war and fear of SARS took their toll and well under that number actually attended.

The scientific programme, as usual was held mainly on Tuesday, Wednesday and Thursday while the bulk of the education programme took place on Sunday, Monday and Friday. There was an extensive choice of nearly 200 teaching sessions ranging from breakfast and after dinner seminars to all day sessions. It seemed to me that the teaching programme was virtually identical to the previous meeting I attended in Denver. The scientific programme comprised 1300 platform or poster presentations out of a total of 2600 submitted. It was a bit disappointing that about one in five posters was withdrawn. However, there was no shortage of interesting material presented.

The Oxford group presented data on the clinical characteristics of ten myasthenic patients with MuSK (muscle specific tyrosine kinase) antibodies. Anti-MuSK antibodies are seen in about 40% of patients with seronegative generalised myasthenia gravis (but not in pure ocular myasthenia). These patients were all female and they tended to have weakness of neck (particular neck extension), shoulder and respiratory muscles with little ocular involvement. The response to pyridostigmine was variable while thymectomy and azathiopine were ineffective. All patients however responded well to plasma exchange but no comment was made about response to ivIg. This important paper therefore gave useful information about the clinical characteristics of these patients and also their different responses to treatment.

The Parkinson's Disease study group reported further on the Elldopa trial. This was set up to see if L-Dopa influences the rate of progression of Parkinson's Disease. Three hundred and sixty one patients were enrolled with early Parkinson's Disease who did not require symptomatic therapy. They were allocated in a double blind fashion, to either placebo or three different dosing regimes of L-Dopa. Regular assessments were made during the study and after forty weeks, treatment was withdrawn with the final assessment two weeks later. Patients treated with L-Dopa showed a dose dependent clinical effect based on the UPDRS scores and this persisted two weeks after treatment was withdrawn. Neuro-imaging was carried out in 142 patients with the striatal dopamine transporter

being assessed by Beta CIT uptake measured by SPECT. The percentage decline of Beta CIT uptake in the striatum was significantly more pronounced in the L-Dopa groups than the placebo group. These rather contradictory findings clearly need further investigation; there remains continuing concern about the harmful effects of long term L-Dopa treatment.

There were not surprisingly a number of papers on West Nile virus infection which has been gradually spreading across the USA over the last few years. This is a mosquito born viral infection which usually causes a sub-clinical illness. However there is a wide spectrum of neurological presentations which include meningoencephalitis with or without focal deficits, lumbosacral plexopathy, Guillain-Barre like illness and a cerebellar syndrome. I am unaware of any cases in the UK but we need to bear this infection in mind in patients with acute neurological problems who have recently been abroad.

My own area of interest is in epilepsy and there were some interesting papers. One study followed up twelve patients with refractory epilepsy and evidence of mesial temporal sclerosis who declined surgery. These patients had repeat MRI scans with volume measurements after an interval of 2.5-5.2 years. Three patients became seizure free while nine remained intractable. A significant decline in ipsilateral hippocampal volume occurred only in patients who had continuing seizures while there was no change on the contralateral side. This would suggest that continuing seizures cause progressive hippocampal atrophy. Perhaps we should give more thought to repeating MRI scans on patients with continuing seizures who have focal EEG changes and either normal or minimally abnormal MRI scans.

I am not a golfer myself but I was interested in a study of six professional and seven amateur female golfers who were asked to mentally execute their pre-shot routine to a target pin and then to imagine their appropriate swing. They underwent functional MRI during these mental activities and some interesting differences emerged. The volume of brain activated in professional golfers was smaller in all active regions and amateur golfers activated a number of additional areas. These included the limbic system and amygdaloid complex, basal forebrain and basal ganglia. The authors concluded that the neural networks in professional golfers was more focused suggesting a more specialist and efficient network whereas the amateur golfers activated other areas involved in learning and emotional expression. I will pass this vital information to my golfing neurological colleagues although I suspect they will say (as they are all male) that this has something to do with the peculiarities of the female golfing brain.

Honolulu itself is a pleasant uncommercialised city with a fascinating array of flora which include a variety of palm trees, the delicate Monkey Pod trees, Hibiscus (the state flower of Hawaii), bougainvillea, ginger plants and various ferns. I did not of course have time to go on a submarine excursion nor a helicopter tour as I was too busy extracting pearls of information from the conference. My surfing instructor however did tell me that I would need at least another fourteen days to be able to 'do it standing up;' I have my doubts. The trouble is that I will be 105 when the next AAN meeting is held in Hawaii.



Venue: Hawaii Convention Centre



Honolulu sunset

Picture: Chuck Painter

*Peter Cleland, Consultant Neurologist,
Sunderland Royal Hospital*

Dasher – an efficient keyboard alternative

Dasher is a text-entry interface driven by continuous two-dimensional gestures, delivered, for example, via a mouse, touch screen, or eyetracker; the user writes by steering through a continuously expanding two-dimensional world containing alternative continuations of the text, arranged alphabetically. Dasher uses a language model to predict which letters might come next and makes those letters easier to write. The language model can be trained on example documents in almost any language, and adapts to the user's language as she writes. Dasher is free software.

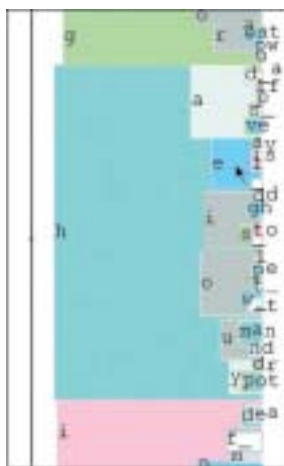


Figure 1. A screenshot of Dasher when the user starts writing hello. The shelf of the alphabetical 'library' is displayed vertically. The space character, ' ', is included in the alphabet after z. Here, the user has zoomed in on the portion of the shelf containing messages beginning with g, h, and i. Following the letter h, the language model makes the letters a, e, i, o, u, and y easier to write by giving them more space. Common words such as had and have are visible. The pointer's vertical co-ordinate controls the point that is zoomed in on, and its horizontal coordinate controls the rate of zooming; pointing to the left makes the view zoom out, allowing the correction of recent errors.

How Dasher works

Imagine writing a piece of text by going into the library that contains all possible books, and finding the book that contains exactly that text. In this way, writing can be turned into a navigational task. What is written is determined by where the user goes. In Dasher's idealised library, the 'books' are arranged alphabetically on one enormous shelf. When the user points at a part of the shelf, the view zooms in continuously on that part of the shelf. To write a message that begins 'hello', one first steers towards the section of the shelf marked h, where all the books beginning with h are found. Within this section are sections for books beginning ha, hb, hc, etc.; one enters the he section, then the hel section within it, and so forth.

To make the writing process efficient we use a language model, which predicts the probability of each letter's occurring in a given context, to allocate the shelf-space for each letter of the alphabet, as illustrated in figure 1. When the language model's predictions are accurate, many

successive characters can be selected by a single gesture. With Dasher, it is easy to spell correctly and hard to make spelling mistakes.

Potential of Dasher for rehabilitation

The user steers using any convenient pointing system. The simplest is an ordinary mouse attached to an ordinary PC. Using a mouse, typical novice users reach a writing speed of 25 words per minute after 60 minutes of practice, and expert users can write at 35 words per minute. Some disabled users prefer using a roller-ball or trackpad to control the mouse. Dasher can also be driven more directly using a computer with a touch-screen; an elegant and cheap communication solution for rehabilitating patients who cannot speak might be to use Dasher on a Pocket PC (videos are on the Dasher website, www.inference.phy.cam.ac.uk/dasher/). Dasher does not need great pointing precision.

For users who cannot point using a conventional mouse or touchscreen there are two ways in which Dasher can be used hands-free with a PC. The cheapest solution (about £150) is a head mouse: a reflective dot is attached to the user's head (or whatever piece of anatomy they wish to move) and a small camera tracks the dot to control the mouse. For severely paralysed people, the direction of gaze can be tracked using an eyetracker (£2000 upwards). After 60 minutes' practice, novice users can drive Dasher using an eyetracker at a speed of about 15 words per minute; expert users can write at 25 words per minute. Not only is this speed much faster than alternative hands-free systems such as on-screen keyboards; Dasher users make far fewer spelling mistakes. Furthermore, whereas staring at on-screen buttons is exhausting, navigating through the Dasher landscape is a natural activity for the eyes, comparable to driving a car.

The future of the Dasher project

Dasher was created by David MacKay and David Ward in the Physics department of the University of Cambridge. The project is supported by the Gatsby charitable foundation. Dasher currently works on PCs running Windows or GNU/Linux and on Pocket PCs; other computer platforms should be supported soon. Over the next year we aim to enhance Dasher for disabled users. Version 3.2 will feature a steering method for users who have only one dimension of motor control rather than two.

Most users find Dasher is quick to learn, just like a video game - 'attack of the killer alphabets', it's been called. We encourage you to try it out (it's free!) and send us your feedback.

www.inference.phy.cam.ac.uk/dasher/



David MacKay is a Reader in the Department of Physics at Cambridge University. He obtained his PhD in Computation and Neural Systems at the California Institute of Technology. His interests include machine learning, reliable computation with unreliable hardware, the design and decoding of error correcting codes, and the creation of information-efficient human-computer interfaces.



Figure 2. Dasher can be driven by eyetracker or by pointing on a touchscreen, as well as with a regular mouse.

Correspondence to:
David MacKay, Fax. 07092
115587, E.Mail.
mackay@mrao.cam.ac.uk

The Ulnar nerve

Before digging in for an EMG clinic I like to take a sneaky look at the referral forms, it gives me some idea whether I will be diverting to golf course on the way home or rushing to beat closing time. If there is one request that makes my heart skip with joy it is 'please exclude ulnar neuropathy'. Ulnar nerve conduction studies are technically easy to perform and can often provide an accurate localisation of the presenting symptoms, so this issue I will briefly review the anatomy of the ulnar nerve and the neurophysiological approach to ulnar neuropathy.

Anatomy

The Ulnar nerve is derived in most instances exclusively from the C8/T1 nerve roots although sometimes there is a minor C7 component. Nearly all ulnar fibres arise in the lower trunk of the brachial plexus and pass through the medial cord, the terminal extension of which is the ulnar nerve. It is worth remembering that a large portion of the median nerve and the medial antebrachial cutaneous nerve also arises from the medial cord. The ulnar nerve runs down the medial aspect of the arm, and there are no significant branches in the arm. At the elbow the nerve passes into the groove between the medial epicondyle and

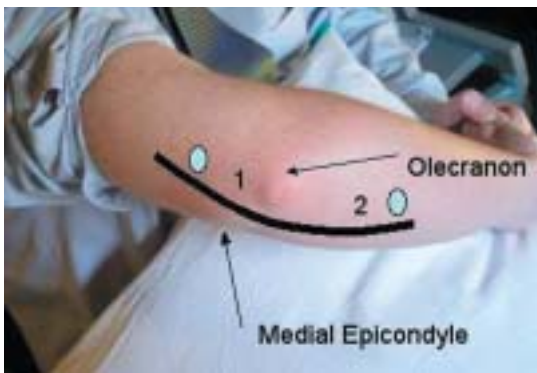


Figure 1: Anatomy of the ulnar nerve at the elbow, the ulnar nerve passes over elbow in the groove between the olecranon and the medial epicondyle, the ulnar groove (1). The nerve then enters the nerve under the aponeurosis between the two heads of the flexor carpi ulnaris (cubital tunnel).

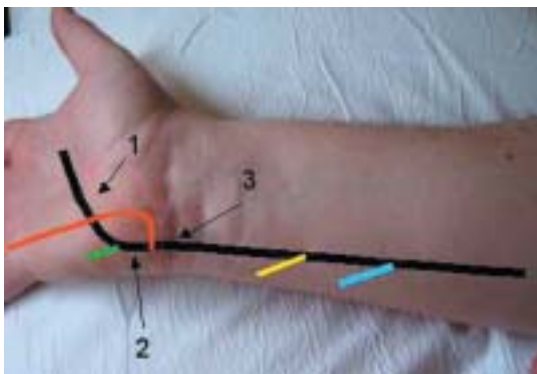


Figure 2: Anatomy of the ulnar nerve at the elbow, the branches are the dorsal ulnar cutaneous sensory (blue), the palmar cutaneous sensory (yellow), hypothenar motor (green) and the digital sensory (red), the trunk of the nerve in the hand continues as the deep palmar motor branch. The clinical features depend on the site of compression. At site 1 there is wasting of intrinsic hand muscles with sensory sparing and sparing of the hypothenar eminence, at site 2 there is involvement of the hypothenar eminence with sensory sparing, at site 3 there is sensory involvement of the digits sparing the palm.

olecranon process, the ulnar groove. Just beyond the groove the nerve runs under a tendonous arch formed by the two heads of the flexor carpi ulnaris muscle. This arch is commonly referred to as the cubital tunnel but is more correctly called the humeral-ulnar aponeurosis (HUA) (Figure 1). Muscular branches to the flexor carpi ulnaris muscle and the ulnar portion of flexor digitorum profundus are found at this site. The ulnar nerve then passes down the medial forearm with the next important branch being the dorsal cutaneous sensory branch just proximal to the wrist. This nerve supplies sensation to the dorsal medial hand and digits, whilst at the ulnar styloid there is a palmar cutaneous branch that supplies the palmar aspect of the hand. Finally the ulnar nerve passes into the hand through Guyon's canal. The proximal wall of Guyon's canal is formed by the pisiform bone; the distal wall by the hook of hamate; the floor is formed by a combination of the thick transverse carpal ligament and the hamate and triquetrum bones and finally the roof is formed loosely but at the outlet is narrowed by a ligament running from the pisiform bone to the hamate. The branches in Guyon's canal are shown in figure 2. The muscles supplied by the nerve are outlined in table 1.

Like the peroneal nerve at the knee the ulnar nerve's close association with the elbow and superficial pathway render it particularly vulnerable to external compression and trauma in the ulnar groove. The most common cause of an ulnar neuropathy is chronic mechanical trauma, (but see Table 2 for other causes). The nerve may also be compressed under the arch of the HUA giving rise to the 'cubital tunnel syndrome'- term often mistakenly applied to all ulnar neuropathy at the elbow. Ulnar nerve compression at the wrist is less common, however it is always worth bearing in mind as it is often missed or the atrophy of intrinsic hand muscles without sensory involvement is mistaken for a generalised motor neuropathy. The common causes of ulnar neuropathy at the wrist are outlined in table 2.

Clinical Assessment

Ulnar neuropathies often present with progressive weakness or even wasting of intrinsic hand muscles. If there are sensory symptoms they usually involve the ring and little finger. In ulnar nerve compression at the elbow there is weakness of most of the intrinsic hand muscles, this may result in the classic benediction posture, this is essentially due to clawing of the fourth and fifth fingers.



Brian McNamara is Consultant Neurophysiologist at Cork University Hospital. He was SHO and Registrar at Cork University Hospital, and SpR at Addenbrooke's Hospital in Cambridge. His interests include magnetic stimulation, cellular electrophysiology all aspects of clinical neurophysiology.

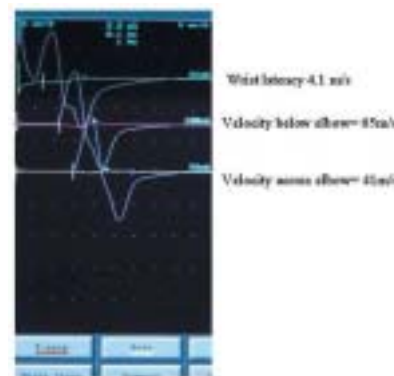


Figure 3: Normal ulnar motor study, this is performed by recording over the hypothenar eminence, and stimulating at the wrist, below the elbow and above the elbow.



Figure 4: Study in ulnar nerve compression at the elbow, note the slowing across the elbow and decrease in amplitude (a normal study is superimposed in gray).

There are also two eponymous signs associated with ulnar neuropathy at the elbow. In Wartenburg's sign the little finger remains in an abducted posture due to weakness of the third palmar interosseus muscle - patients may complain of the little finger getting caught when they put their hand in a pocket. Froment's sign occurs when attempting to pinch an object, because of weakness of the intrinsic hand muscles, the long flexors of the thumb and index fingers are used resulting in a flexed thumb and index finger posture. In compression of the nerve at the wrist the degree of involvement depends on the exact site of compression (Figure 2).

Neurophysiological Assessment

As compression at the elbow is by far the most common cause, the first step is to examine ulnar nerve conduction across the elbow. In compression of the nerve at the elbow there is focal slowing of motor conduction across the elbow segment (at least 10m/s slower than the below elbow segment). This should also be accompanied by a sensory study from the little finger to assess for any sensory axonal loss. If this study is normal it is sometimes worthwhile performing an inching study looking at conduction in 2.5cm segments of the nerve across the elbow, again the principal sign being focal slowing. In compression at the wrist there may be a focal increase in distal latency if the compression occurs before the branch to the hypothenar muscles, sensory studies may be abnormal depending on the site of compression. If these are normal or if there is an ulnar neuropathy without focal slowing then it is worth considering a C8/T1 radiculopathy or lower trunk plexopathy. In a radiculopathy there will be denervation of both the ulnar innervated muscles and abductor pollicis brevis while sensory studies from the little finger and the medial ante-brachial nerve will be normal. In a lower trunk plexopathy there may be denervation with abnormal sensory studies from both the little

finger and the medial ante-brachial nerve. If there is wasting without sensory disturbance it is worth considering compression to the deep palmar motor branch. To test for this, place a needle in the first dorsal interosseous and measure the latency of conduction from the wrist to the muscle. Finally if you still are drawing a blank it is worthwhile testing median conduction across the wrist as carpal tunnel syndrome can sometimes present with sensory symptoms in an ulnar nerve distribution.

Table 1: Muscles innervated by ulnar nerve.

<p>Branches in the Forearm Flexor Carpi Ulnaris Medial Division of Flexor Digitorum Profundus</p> <p>Branches at Wrist Hypothenar Eminence Deep Palmar Motor Branch Palmar Interossei Dorsal Interossei 3rd and 4th Lumbricals Adductor Pollicis Deep head of Flexor Pollicis Brevis</p>
--

Table 2: Causes of Ulnar Neuropathy

<p>Anatomical Compression at Elbow Ganglia Tumours Fibrous Bands Accessory Muscles</p> <p>Chronic Compression at Elbow Trauma and arthritic change Leaning on elbow including the use of crutches Prolonged immobilisation</p> <p>Ulnar Neuropathy at Wrist Trauma Ganglia in Guyons Canal Prolonged external compression eg cycling, power tools, crutches</p>
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Approach to the patient with a movement disorder

The characteristic feature of all movement disorders is an abnormality of the form and velocity of movements of the body. The use of the term “movement disorder” in neurology has become synonymous with basal ganglia disease and extrapyramidal features. Although it is true that many movement disorders arise from pathology within the basal ganglia, disorders such as myoclonus may also arise from other structures. Abnormalities of movement may be the only manifestation of a disease (for example, essential tremor) or may be part of a more widespread neurological disorder (for example, Creutzfeldt-Jakob disease). Basal ganglia disease is also commonly associated with neuropsychiatric symptoms and these may have a greater impact upon the patient and their family than the movement disorder itself. As in all aspects of neurology, it is important not to divorce the disorder of movement from general medical problems, since these may be directly or indirectly related (for example, chorea in systemic lupus erythematosus; myoclonic ataxia in coeliac disease; drug-induced parkinsonism caused by metoclopramide used to treat a hiatus hernia).

Classification & definitions

The key to success in diagnosing and managing these patients is to establish the phenomenology of their movement disorder. Although the broad division of patients into those who move too much (hyperkinetic disorder) or move too little (hypokinetic, or akinetic-rigid disorder) is simple enough, to the inexperienced physician, differentiating jerky dystonia from tremor, or tics from chorea, for example, may not always be straightforward. There may also be a mixed movement disorder present, such as myoclonic dystonia, for instance. Definitions of commonly encountered movement disorders are listed in Table 1. Athetosis (a writhing, sinuous distal limb movement) is a term gradually falling out of use, as these movements are more economically classified as dystonic or choreo-dystonic.

Historical features and examination (Table 2)

When approaching the patient with a movement disorder, the value of a careful history and examination can never be under-stated, even if the diagnosis may seem obvious from the moment the patient first walks in to the consultation room. A videotape recording of the movement disorder may be helpful, particularly in the case of a “compound” or “mixed” problem. It is not uncommon for the rest of the neurological examination to be normal in patients reporting a movement disorder; in other words, “what you see is what you get”. If no problem is apparent, consider whether the complaint is highly action specific (for example a task-specific dystonia) and may therefore have been overlooked on the routine examination (any excuse to get a golf club out in clinic, or even a violin!). Failing this, asking the patient and their family to record a home video-segment when the problem occurs may be very revealing.

Always consider drugs, both past and present, as a potential cause for the movement disorder. Tardive dyskinesias (commonly stereotypic movements, often orofacial in distribution, although a broad spectrum of tardive drug-induced movement disorders, from tics to myoclonus, has been described) may develop after relatively short exposure to an offending dopamine receptor blocking agent (DRBA) but persist for many years. A full list of medications previously taken by the patient should

be obtained from the GP, if necessary. Approximately 80% of drug-induced parkinsonism will resolve within eight weeks of discontinuing a DRBA, although recovery up to 18 months has been reported. If causality is suspected, always check with the hospital drug information service. For example, while DRBAs are well known to cause parkinsonism, a link with agents like amiodarone and cinnarizine, is less widely recognised.

Analysis of the following characteristics (adapted from Kishore and Calne 1997) may assist the diagnosis:

1. Specific distribution: for example, restless legs syndrome (RLS, although this is now known as restless limb syndrome since symptoms may also be reported in the upper limbs as well!) and painful legs and moving toes (PLMT). Parkinson’s disease is typically asymmetric in onset.
2. Specific actions: for example task - specific tremor and dystonia (don’t forget to ask the patient to write or pick up a cup of water if history suggests this might be helpful).
3. Speed: for example-

	slow	intermediate	fast
	parkinsonism, dystonia & dystonic tics	chorea, tremor	myoclonus, myoclonic tics

4. Rhythm: continuous – for example, tremor, PLMT; or intermittent, for example, asterixis (“negative myoclonus”).
5. Relation to posture: for example, orthostatic tremor (presents as unsteadiness when standing still but improved when walking).
6. Relation to sleep: few movement disorders persist during sleep; examples include palatal tremor and segmental myoclonus.



David J Burn is the editor of our conference news section and Consultant and Senior Lecturer in Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He qualified from Oxford University and Newcastle upon Tyne Medical School in 1985. His MD was in the functional imaging of parkinsonism. He runs Movement Disorders clinics in Newcastle upon Tyne and Sunderland. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

Movement	Definition
parkinsonism	a clinical syndrome with bradykinesia as the defining feature, almost always accompanied by rigidity, and often by tremor
dyskinesia	may be applied to any involuntary movement (although often used to refer to drug-induced choreas and dystonias)
tremor	a rhythmical, involuntary oscillatory movement of a body part; may be qualified by addition of a descriptive term (e.g. resting, postural)
chorea	a quick, irregular, semi-purposive and predominantly distal involuntary movement (patient may look “fidgety”)
dystonia	an abnormal movement characterised by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures
ballism	a proximal, high amplitude movement, often violent and flinging in nature; usually unilateral in nature and often resolves through a choreic phase
tic	an abrupt, jerky non-rhythmic movement (motor tic) or sound (vocal tic) that is temporarily suppressible by will power; tics may be simple or complex
stereotypy	purposeless voluntary movements carried out in a uniform repetitive fashion at the expense of other activity (e.g. hand wringing, clapping, mouthing)

7. Relation to voluntary movement: for example – action tremor and action dystonia.
8. Associated sensory symptoms: PLMT, RLS and phantom dyskinesias; tics may be associated with an vague discomfort or unusual sensation in the prodrome before the movement.
9. Suppressibility: volitional in tics (but associated with increasing unease and rebound worsening of tics upon release), by sensory tricks in dystonia (including the “geste antagoniste”) and by activity in rest tremor.
10. Aggravating or precipitating factors: stress and anxiety are of no discriminating value in that they worsen all movement disorders; myoclonus may be worsened by specific stimuli e.g. sudden, loud noise; heavy carbohydrate-containing meals and fatigue may precipitate paroxysmal *non*-kinesogenic dystonia; rapid movement triggering paroxysmal kinesogenic dyskinesia.
11. Ameliorating factors: alcohol may relieve essential tremor and myoclonic-dystonia, sometimes quite dramatically; walking backwards or running may improve a dystonic gait, leading the unwary to suspect a non-organic cause.

Ancillary studies

An increasing range of blood and cerebrospinal fluid analyses, genetic tests, electrophysiological, structural and functional imaging studies exist to supplement clinical acumen. Occasionally, tissue biopsy (including skin, muscle, small bowel, bone marrow aspirate) may even be necessary. These will be dealt with more fully by other articles in this management series. Suffice it to say that establishing the correct phenomenology of the movement disorder is essential as to which ‘line’ of more complex investigations is initiated.

There should, however, be a low threshold to undertaking serum caeruloplasmin estimation, since Wilson’s disease may present with tremors, dystonia or parkinsonism and is eminently treatable. At a cut-off of 0.2g/l, serum caeruloplasmin is a cheap and simple test, although not very sensitive as 5-20% of homozygous carriers will have normal results. Thus, while an abnormal result should prompt further screening (ophthalmological assessment and urinary copper excretion minimum) a normal serum caeruloplasmin level does not fully exclude Wilson’s disease.

Management considerations

Some key general points I try to remember in clinic:

- Treat disability or poor quality of life, *not* recorded impairments
- Remove potentially exacerbating/causative drugs whenever possible
- Always consider underlying depression when there seems to be a marked mis-match between impairment and reported disability
- Patients don’t always volunteer neuropsychiatric features like visual hallucinations; ask!
- Members of the multidisciplinary team generally prefer an early referral
- Never forget the need for genetic counselling and implications for other family members (Gasser 2003)
- If a psychogenic movement disorder is suspected, the patient will be best managed by a formal admission and a staged, multidisciplinary approach

Table 2 Historical and Examination Features to Remember	
History	Time course / functional disability / effect upon quality of life Past medical history, including infections & toxin exposure Musculoskeletal symptoms (e.g. frozen shoulder with early PD) Drug history – past & previous & recreational (need to contact GP?) Alcohol consumption & responsiveness Family history (with pedigree drawn out if necessary) Neuropsychiatric features (plus carer to inform/corroborate) Autonomic symptoms Sleep problems (REM sleep behavioural disorder suggests PD, DLB or MSA)
Examination	Observation during history of (involuntary) movements including excessive sighing (?atypical parkinsonism) Cognitive assessment (subcortical vs cortical problems? – MMSE often insensitive to former, consider verbal fluency test, Luria, go/no-go task) Cardiovascular – lying & standing blood pressure, cool periphery (MSA?) Gait, postural reflexes (pull test) & axia tone Eye movements (especially saccadic speed & latency) & blink frequency Limb examination (include specimen of writing & observe posture) <ul style="list-style-type: none"> • tremors/dystonic posturing (including postural & action) • tone – use reinforcement if in doubt • power & co-ordination • fine finger and rapid alternating movements Reflexes / plantars / primitive reflexes

Table 3 Ten Useful Diagnostic Pointers	
Symptom or Sign	Underlying Conditions to Consider
Tremor of onset over 50	‘Tremor-dominant’ Parkinson’s disease (or possibly dystonic tremor) > essential tremor
Able to carry two cups of tea/pints of beer but unable to do up buttons?	‘Yes’: Parkinson’s disease > essential tremor
Excessive sighing	‘No’: Essential tremor > Parkinson’s disease
Cold, dusky blue hands	Atypical parkinsonism (MSA or PSP)
Sudden, brief dystonic or choreic movements, often unilateral, when patient moves quickly	MSA
Male>>female with early onset motor and / or sensory tics (voluntarily suppressible); ‘magic number’, obsessive-compulsive tendencies	Paroxysmal kinesogenic dyskinesia
Clicking sound in the ear (look in the mouth!)	Gilles de la Tourette syndrome
Jerks precipitated by tapping the “snout” area of the face	Essential palatal tremor (tremor of tensor veli palatine connecting with Eustachian tube)
Personality disorder, dysarthria, asymmetric tremor (tongue tremor?) in late teens-early 20’s	Reticular reflex myoclonus
Inconsistent or incongruous movements, with non-anatomical sensory loss & ‘giving way’	Wilson’s disease
	Psychogenic movement disorder
> = more likely than; MSA = multiple system atrophy; PSP = progressive supranuclear palsy	

Further Reading

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Correspondance to:
E.Mail.
David.Burn@nuth.northy.nhs.uk

Jenner, on the intellect

Surely no medical practitioner can be unaware of the name and work of Dr Edward Jenner (1749-1823). A Gloucestershire country doctor, he pioneered smallpox vaccination, work for which he is rightly adjudged one of the immortals of medical history, and the anniversary of which is still noted.¹ Even the Royal College of Physicians of London, which assiduously excluded him during life, seems prepared to acknowledge him “one of the greatest doctors in history”.² Besides smallpox, some may know of Jenner’s work on the nesting habits of the cuckoo (*Cuculus canorus*), the work for which he was appointed a Fellow of the Royal Society. Few, if any, may be aware that he also had ideas on the classification of the intellectual faculties.

Jenner’s thoughts were published in an article, bearing the long-winded title of:

Classes of the Human Powers of Intellect – Hints for a Classification of the Powers of the Human Mind as they appear in various Descriptions of Men – Examples of Excellence rare – General Division into seven Classes – Difficulty of analysing all the Varieties of Intellect in Individuals

This article [hereafter *Classes of the Intellect*] was first published in the London weekly periodical *The Artist* (no. XIX, Saturday, July 18th, 1807), published by Prince Hoare, foreign secretary of the Royal Academy. Thirteen years later it was reprinted as a pamphlet by the Cheltenham publisher Griffiths, a friend of Jenner’s who was facing financial difficulties in the summer of 1820. The reprint was without any revisions, notwithstanding Jenner’s statement in the original that “I may hereafter treat more copiously” of the subject. Jenner’s first biographer, Baron,³ does not mention the work at all, and more recent biographers, Saunders⁴ and Fisher,⁵ mention it only in passing. In his bibliography of Jenner’s publications, Le Fanu lists it under “Medical Digressions”.⁶ I am unaware of any previous publications devoted to it.

The Artist was, as its name implies, a non-scientific periodical, although it did have a scientific editor, Tiberius Cavallo (1749-1809), who was interested in the therapeutic aspects of electricity. *The Artist* consisted of essays by artists, writers and politicians; Jenner was the only physician to contribute.

Jenner’s paper ran to seven pages, about two thousand words. The classification of intellect, “or, to speak more correctly, of the various degrees of intellectual capacity, which distinguish the human animal”, which Jenner “hinted” at was into seven classes, *viz.*:

- | | |
|-----------------------|---|
| 1. The Idiot: | “the mere vegetative being” |
| 2. The Dolt: | “the weak, silly, poor creature” |
| 3. Mediocrity: | “the large mass of mankind” |
| 4. Mental Perfection: | “From this point Intellect again diverges” |
| 5. Eccentricity: | “I have in this class a very numerous acquaintance” |
| 6. Insanity: | “the most affecting of all conditions” |
| 7. The Maniac: | “the wreck of the mental faculties” |

Although no doubt based on Jenner’s personal observations, *Classes of the Intellect* lacks (and does not pretend to) scientific rigour, or any kind of empirical verification, so unlike the experimental method, learned by Jenner from his mentor John Hunter (1728-1793), which marks

his work on smallpox vaccination (and, for that matter, the nesting habits of the cuckoo). It has been suggested that the article was written as a diversion or distraction, perhaps light-hearted, from the struggle to establish smallpox vaccination which occupied so much of Jenner’s time and energy, and on which subject he was under attack from various critics.^{4,5}

No contemporaneous reaction to the article is recorded. From the vantage of hindsight, it is probable that many of us may recognise from personal experience some verisimilitude in this scheme, and indeed may find some attractions in it. Yet nonetheless it is difficult to disagree with Le Fanu’s analysis of *Classes of the Intellect* as a “slight essay in psychology ... showing a scientific bent to classification, it is little more than a *jeu d’esprit*”.⁶ Fisher calls it “a fair summary of the common eighteenth-century [*sic*] wisdom on mental attributes, elevated slightly by being ordered into classes”.⁵

The nineteenth century saw the origin of many of our currently accepted neuroscientific concepts,⁷ and so it is reasonable to ask how Jenner’s ideas compared with those of the time. The early nineteenth century saw a gradual increase in research interest devoted to the nervous system such that many physiologists saw it as pre-eminent. Moreover, hierarchical views of nature, espoused particularly by adherents of *Naturphilosophie*, popular in the early nineteenth century, envisaged not only a hierarchy of animal forms reaching its apogee in the human body, but also within the human body itself, with the nervous system its apex. The first four of Jenner’s categories seem to form a hierarchy but, as Saunders points out,⁴ the next three seem aberrations from this pattern. This perhaps reflects the difficulties of attempting to conflate physiological variation with pathological aberration.

As Fisher implies,⁵ Jenner’s ideas were perhaps more akin to those of earlier epochs, when the urge to classify was strong, as exemplified in the work of Linnaeus in the eighteenth century and of John Ray in the seventeenth century. Analogies may be seen between Jenner’s classification and the idea of a “Great Chain of Being”, as seen for example in the work of Edward Tyson published on the threshold of the eighteenth century.⁸ Noting the morphological similarities and differences between an “orang-outang” (in fact, a chimpanzee) and man, Tyson conceived a gradation of forms, in which man was placed above brute animals, of which the chimpanzee was his nearest relative, but below the angels. Jenner’s grading may also be seen to span from the sublime to the fatuous.

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Andrew Larner is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

Correspondence to:
Andrew Larner
Walton Centre for Neurology
and Neurosurgery
Lower Lane, Fazakerley
LIVERPOOL L9 7LJ
U.K.
E.mail.
larner-a@wcn-tr.nwest.nhs.uk

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Delirium in Old Age

Delirium is a boundary subject. The fact that no one specialty wholly lays claim to it may be illustrated by the not unfamiliar scenario of interdepartmental friction occasioned by patients who are deemed "psychotic", and hence appropriate for the psychiatric ward, by physicians and surgeons, but considered "organic" by psychiatrists and hence best investigated on a medical ward. It is these polar attitudes that the editors of this slim tome seek to break down.

The diagnosis, pathophysiology, epidemiology, management, and prevention of delirium are discussed. The rich variety of cognitive and behavioural features are emphasised, perhaps reflecting variable aetiology. Diagnosis remains clinical in the absence of diagnostic tests or biomarkers. Rating scales to screen for, and measure severity of, delirium are outlined. Predisposing and precipitating factors are discussed, as is the multifactorial model of pathogenesis which proposes an inverse relation between pre-existing vulnerability and severity of acute insult required to cause delirium. It is clear that much still

remains to be learned about pathophysiology, although it merits the longest chapter in the book: mechanisms already implicated include derangements in neurotransmitters (acetylcholine, dopamine), the hypothalamo-pituitary-adrenal axis, and cytokines. These diverse aetiologies may converge on a "final common neural pathway".

Epidemiological research suggests the incidence of delirium is 5-10% in medical in-patients, and 30% in surgical patients. That delirium may be prevented by proactive intervention has been shown by a trial in the US, which has led to the suggestion that the quality of health care services may be measured by the incidence of delirium. This book concisely summarises a difficult area, and clearly marks out an agenda for change which envisages both better management and prevention of delirium as a priority.

Dr Andrew Larner; Cognitive Function Clinic, WCNN, Liverpool



Edited by: James Lindesay, Kenneth Rockwood and Alastair Macdonald
Publisher: Oxford University Press 2002
Pages: 226
ISBN: 0-19-263275-2
Price: £55.00

Physical Medicine and Rehabilitation Secrets, Second Edition (2002)

This book comes from the tried and tested Secrets® stable and is aimed at many disciplines, from neurorehabilitation to HIV and AIDS rehabilitation, from amputation rehabilitation to performing arts rehabilitation.

The Socratic method of teaching by asking the right questions is not to everyone's taste but underpins much of medical education. To the uninitiated, the format is one of posing a question, and then giving a concise answer. Some of the questions will apply wholly to rehabilitationists in North America, such as the chapter on Legislative Issues, but nonetheless make for interesting reading; the vast majority of the book is applicable to specialists worldwide.

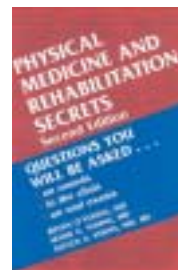
There are 97 succinct chapters with contributions from mainly North American specialists. New chapters include Transplantation Rehabilitation and Developmental Milestones.

Each chapter is followed by a short bibliography drawn from authoritative textbooks and key references are also listed. Occasionally, websites are listed as useful resources. Tables are used where helpful, as are mnemonics. The illustrations are scant, but when used, are clearly labelled. It was nice to see medications described by their generic names first followed by their US brand name; similar books fall into the trap of assuming US proprietary names are known by their entire readership. The index is detailed and easy to use. However, it is not a book that one

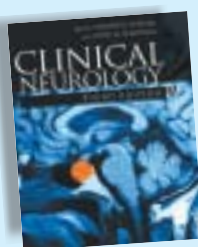
can carry in a white coat and should be used with standard reference textbooks. The book does contain a wealth of information and can serve as a useful revision aid. It contains chapters on basic neuroanatomy and physiology. The Electrodiagnosis section has been enlarged and includes a chapter of questions on radiculopathies. The chapters focusing on traumatic brain injury and spinal cord injury have changed a little since the first edition. I was pleased to see that the chapter entitled Frontiers and Fundamentals in Neurorehabilitation mentioned acetylcholinesterase inhibitors and gangliosides to reflect newer theories and modern practice. I felt that the psychological aspects of neurological rehabilitation especially in spinal cord injury were glossed over and should have been covered in greater depth. The first edition contained chapters on rehabilitation nursing, physiotherapy and occupational therapy; sadly, these weren't included in this edition.

Overall, I would recommend this textbook to anyone in need of a "quick refresher" type of text. It is fairly comprehensive, easy to use, and well priced. It will appeal to trainees in rehabilitation medicine, whose exposure to formal questioning and assessment of their theoretical knowledge may be sporadic.

*Dr Simon Paul (MRCP)
RAF Defence Services Specialist Registrar in
Rheumatology & Rehabilitation*



Edited by: Bryan O'Young, Mark Young and Steven Stiens
Publisher: Hanley & Belfus Inc.
Pages: 626
ISBN: 1-56053-437-0,
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CLINICAL NEUROLOGY Third Edition

Authors: Timothy J Fowler DM FRCP Consultant Neurologist, Maidstone and Tunbridge Wells NHS Trust. Formerly of Kings College Hospital, London, John W Scadding MD FRCP Consultant Neurologist, The National Hospital for Neurology and Neurosurgery, London
£39.99 • 0 340 80798 9 • August 2003 Paperback • c.480 pages • 158 illus

The third edition of this concise but comprehensive textbook follows on from the highly-regarded earlier editions in providing the trainee and general physician with a better understanding of the principles of neurology. Retaining an emphasis on the core clinical skills of history taking and careful neurological examination, the new edition has been thoroughly revised and updated to take into account new developments in investigation and treatment. Particular areas of enhanced coverage include headache, expanded beyond migraine to cover other presentations, and multiple sclerosis. Completely new chapters discuss the increasing role of neurogenetics in the understanding and treatment of neurological disease, the importance of pain and its management and neurological complications associated with respiratory intensive care.

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EDITOR'S CHOICE

The first human PM study of the amyloid- β peptide vaccination cases

Regular readers of this section of ACNR will have seen our previous reports of the exciting animal studies that showed vaccination with amyloid- β peptide caused resorption of amyloid plaques in animals models of familial Alzheimer's; and then the disappointing –but intriguing – news that human trials of this approach were brought to a premature end by the unexpected development of meningo-encephalitis in some of the cases. This report, from Roy Weller's group in Southampton, is the first account of the pathology of one of these patients. She was a 72 year old woman with a five year history of Alzheimer's disease. She received five doses of the vaccine, AN-1792 (Elan), over 36 weeks with no clinical benefit. Six weeks after the last dose she became drowsy, feverish, ataxic and with worsening cognitive scores. 11 months later she died of a pulmonary embolus. Her brain makes for fascinating study. For the vaccine clearly worked at clearing the amyloid plaques and, just as in the animal models, probably through the scavenging of microglia in which A β immunoreactivity was found. However, as expected, the characteristic tangles, neuropil threads and amyloid angiopathy of Alzheimer's disease were all unaltered. Furthermore, and quite unlike the animal results, there was a CD4+ T cell meningitis and invasion of the cerebral white matter by macrophages. Quite what had got these cells excited is a mystery. But the conclusion is that perhaps, by going back to the drawing board and giving the vaccine a tweak or two, these cellular reactivities could be abolished whilst retaining the potential beneficial effects. Of course, the question then will be: does the vaccine do anything for the dementia? -AJC

Neuropathology of human Alzheimer [sic] disease after immunization with amyloid- β peptide: a case report.

Nicoll JAR, Wilkinson D, Holmes C, Steart P, Markham H, Weller R
NATURE MEDICINE
2003; 9: 448-52

PAIN

☆☆☆ RECOMMENDED

A poppy for your pain

It is gospel that opioids do not help in the treatment of neuropathic pain. John Scadding's article in this issue of ACNR mentions that this view may not be altogether correct. Here is the evidence, in a prominent article in the New England Journal of Medicine from the Pain Clinical Research Centre in San Francisco. 81 patients were randomised to low (0.15mg) or high dose (0.75mg) capsules of a μ -opioid, levorphanol. (The authors felt that a placebo-controlled trial for pain was inappropriate). Patients could taper the dose up themselves, up to a total of 21 capsules a day for four weeks, before weaning themselves off. The high dose ended up as three times the low dose (8.9 v. 2.7mg). Patients had peripheral neuropathy, focal nerve lesions, multiple sclerosis, incomplete spinal cord injury, postherpetic neuralgia and central pain from strokes or focal brain lesions. The primary outcome measure was a visual analogue scale of pain, which was reduced by both doses of levorphanol compared to baseline; but the high dose group reduced the pain significantly more (36 v. 21%). This level of pain reduction is equivalent to that achieved in trials by antidepressants and gabapentin. Levorphanol was least effective, and least well tolerated, for focal central lesions. It did rather better in patients with peripheral lesions, and best of all in those with multiple sclerosis. The most common adverse effects (which lead to withdrawal in 35% of those on the high dose) were a dry mouth, itchy skin, increased sweating and a feeling of drunkenness. So it may be reasonable to consider using an opiate in your patients with neuropathic pain, except perhaps those with pain caused by focal brain lesions, warning them that a third risk developing intolerable side-effects. -AJC

Oral opioid therapy for chronic peripheral and central neuropathic pain.
Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D.
NEW ENGLAND JOURNAL OF MEDICINE
2003 348 (13) 1223-32

MULTIPLE SCLEROSIS

Multiple sclerosis: a forgetful disease

Christian Confavreux, Professor of Neurology in Lyons, has done one simple thing very effectively: since 1957, he has systematically recorded basic clinical data on patients in his multiple sclerosis clinic. And over the last five years or so, his diligence has been rewarded with a string of landmark studies. This is no exception. By April 1997, he could draw on information from 2021 patients, of whom 1562 had a relapsing-remitting course at onset. This exhaustive paper, only really suitable for a weighty journal like *Brain*, follows in the tradition of the London Ontario natural history studies of multiple sclerosis. It focuses on the prognostic value of events early in the clinical course of multiple sclerosis, which is important as treatment is advocated at increasingly earlier stages. The take home messages are:

- The French love azathioprine! In 1997 (before the penetration of β FN into France) 49% of this group had received a disease-modifying agent; in 91% of cases this was azathioprine.
- It takes 11, 23 and 33 years, on average, for someone with relapsing-remitting multiple sclerosis to reach the disability points of first having difficulty with mobility (EDSS 4.0), requiring one stick to walk (6.0), and requiring a wheelchair (7.0). The equivalent figures for those with primary progressive multiple sclerosis are 0, 7 and 13 years.
- In those with relapsing-remitting course from onset, the time from onset to EDSS 4.0 was longer in women, those with a higher relapse frequency in the first five years, onset at an early age, optic neuritis as a first presentation, a complete recovery from the first episode and a longer interval between first and second episode of multiple sclerosis. None of these variables affected the time to EDSS 4.0 in those with primary progressive multiple sclerosis.
- Once patients had reached a fixed disability level of EDSS 4.0, their subsequent time to further levels of irreversible disability was completely unrelated to any of these variables.

"This indicates that when a detectable threshold of irreversible disability has been reached, the disease enters a final common pathway, where subsequent progression of disability becomes a seemingly self-perpetuating process amnesic to the clinical history of the disease." Understanding

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the different biologies of the initial phase of multiple sclerosis, so influenced by this or that clinical variable, and its forgetful later phase is critical. -AJC

Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process.

Confavreux C, Vukusik S, Adeleine P.

BRAIN

2003; 126: 770-82

REHABILITATION

Reduction of oro-facial hypersensitivity in brain injury

Increased hypersensitivity in and around the mouth is common following severe traumatic brain injury. It can be difficult to break the vicious circle consisting of negative reactions to attempts to maintain oral hygiene, decreased sensory stimulation and further reduced oral tolerance. Given the rather crucial role of the mouth in both eating and communication this is a problem that has received relatively little attention.

This single case study reported a successful controlled management programme in a 56 year old man whose oral intolerance, at 10 months post-injury, was leading to marked deterioration in oral hygiene. The stability of the patient's problems suggested that an ABA research design would potentially demonstrate any gain from focused intervention.

Measures included duration of tolerance to touch by different stimuli (e.g. oral sponge, toothbrush) in the four quadrants of the mouth and recording of associated negative reactions (e.g. facial grimacing, reflex biting). Treatment was carried out in 24 sessions of 15 minutes over 2 weeks. The programme used stimulation moving from distal structures (hands and shoulders) towards proximal structures, combined with passive mobilisation of facial muscles.

Touch tolerance increased to the designated ceiling level post-treatment. Negative reactions reduced after intervention, though a return of negative reactions was seen for the right teeth surfaces. Functionally, the reduction in hypersensitivity allowed for full maintenance of oral hygiene. No change in status was recorded on other functional measures, suggesting that experimental changes were not due to general spontaneous neurological improvement.

It is not clear from the article why such desensitisation measures could not be undertaken until 10 months after the injury, but this situation could conceivably arise in a variety of service settings. This small study demonstrates that improvements can be made at a relatively late stage and also encourages similar careful recording of interventions at a clinical level - RABody

Treatment of oro-facial hypersensitivity following brain injury.

Gilmore R, Aram J, Powell J, Greenwood R.

BRAIN INJURY

2003; 17; 347-354

Should post-polio patients exercise?

A recent study by Chan *et al*, illustrates a growing trend in neurophysiology towards monitoring and guiding rehabilitation strategies. Post-polio patients are reliant on their surviving motor units to perform daily activities, and whilst intact motor neurons have a remarkable ability to reinnervate and compensate for deficits, through axonal sprouting, there is a limit to this rehabilitative mechanism. Of particular concern is the question that strength training may overwork the surviving neurons leading to a further decline in their precious numbers. This Canadian team performed a randomised control trial, in which, post-polio patients (10) either underwent a moderate strength-training program or were followed up as controls. A small group of healthy elderly subjects were also randomised and trained in a similar manner. Baselines neurophysiological measurements were applied to the thumb muscles and included maximum voluntary contraction (MVC), voluntary activation index (VAI, based on supra-maximal electrical stimulation of hand nerves during MVC, which will generate an additional twitch if voluntary activation is deficient), and motor unit number estimates (MUNE) utilising surface EMG. Patients with very low MUNE were excluded from the study. Exercise involved a 12 week graded resistance training regime with safeguards against the risk of overuse. The above parameters were measured 4 weekly and a significant increase in strength (MVC) was seen in both healthy elderly controls and even more so in the post-polio patients ($P < 0.05$). Reassuringly MUNE did not appear to change, whilst modest increases in VAI suggest that the increase in strength may have a central

component. The conclusion has to be that moderate exercise is good for post-polio patients that do not have a severely depleted motor neuron pool. Ideally, this research needs to be followed up in more patients over a longer period of time, to see if the benefits are retained and whether adaptive mechanisms differ depending on the particular muscles exercised. -JLR

Randomised control trial of strength training in post-polio patients.

Chan K, Amirjani N, Sumrain M, Clarke A, Strohschein F.

MUSCLE AND NERVE

2003; 27: 332-338

☆☆☆ RECOMMENDED

A randomised controlled trial of splinting the hand in brain damaged patients

Frustrated by the development of contractures affecting the hand in hemiparetic patients, many occupational and physiotherapists encourage patients to wear splints at night. The hope is that splints that keep the hand in the 'functional' position over a long period of time will prevent further contracture or even reverse it and result in muscle and tendon lengths that will allow the hand to be functional should recovery after the brain damage occur. The 'functional' position most often used holds the wrist in between 10° and 30° of extension, the fingers slightly flexed and the thumb abducted and in opposition. There has been little in the literature to support this treatment. Splints are expensive and are intrusive to wear in bed. We need to know whether wearing a splint is beneficial and the cost in money and sleep is justified? At last, a good randomised control trial from Australia has been reported, but it may not resolve the question for therapists in many British hospitals.

28 patients admitted to a rehabilitation unit after stroke or brain injury were recruited to the trial. All were given daily upper limb training and stretches as part of their routine therapy. 17 were randomly allocated to the experimental group and wore a static palmar resting splint for up to 12 hours a night for a period of four weeks. The length of wrist and finger flexors were assessed by measuring with a standard force the range of wrist extension with fingers extended. Motor assessment and pain evaluation using an analogue scale were also carried out. The assessments were performed before random allocation, at the end of the 4 weeks of treatment and at a follow up one week later. Assessors were blinded to allocation.

Compliance with wearing the splint was high, but the effects of splinting were found to be non significant and clinically unimportant in this study. However before throwing out the treatment as a waste of time and money it is important to realise the therapy routinely practiced in the rehabilitation in Townsville Hospital, Queensland may have been effective on their own in maintaining muscle length. All of the patients were given training for the upper limb for approximately 30 minutes a day, 5 days a week. In addition they were given two 30-minute stretches, five days a week which placed the wrist and fingers into extension. Prolonged stretching is not routinely practiced in the UK and 30 minutes daily for motor training of the upper limb is very rare. All too often upper limb training is neglected.

It could be that splinting may prevent contractures in hands of patients who are not given such an intensive training and stretching regime. Or perhaps we are putting our resources into the wrong kind of treatment. -AJT

Splinting the hand in the functional position after brain impairment: a randomised, controlled trial.

Lannin NA, Horsley SA, Herbert R, McCluskey A, Cusick A.

ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION

2003; 84: 297-302

TINNITUS

Brain stimulation for tinnitus

Is tinnitus one of those conditions that, like stroke, punches below its epidemiological weight when it comes to publications? Certainly the neurological journals do not seem to be awash with articles, despite the frequency and morbidity of the condition. This may be a little surprising in view of the growing evidence, for example from functional imaging, that higher order processing is important in tinnitus perception, so called "auditory phantom perception".

In this study from Tubingen, patients (n = 14; all right-handed) with

chronic subjective tinnitus of ≥ 1 year duration underwent repetitive transcranial magnetic stimulation (rTMS) at twelve scalp positions (five randomised trials at each position). Stimulus intensity was 120% of individual resting motor threshold (for thumb twitch), delivered at 10 Hz for 3 sec. After each train, the relative change in tinnitus was evaluated with a 5-point self-rating scale. Patients were blinded to the hypothesis of the experiment; controls for the noise and discomfort of rTMS were undertaken. 8/14 patients noted reduced tinnitus ratings immediately after rTMS, and at the group level (ANOVA) there was a significant effect for stimulus location in the left temporal and temporoparietal positions.

These data suggest that a "virtual" temporary lesion to the left temporoparietal region, "jamming" neuronal circuitry, may reduce tinnitus perception. Excess activation of temporoparietal cortex, as suggested by functional imaging, perhaps reflecting maladaptive cortical reorganisation (possibly in Brodmann areas 42, 22, and 21), may be critical to tinnitus perception. Whether a therapeutic role for rTMS may be feasible awaits further studies: one patient in this trial did experience exacerbation of tinnitus for two months. -AJL

Transient suppression of tinnitus by transcranial magnetic stimulation.

Plewnia C, Barthels M, Gerloff C.

ANNALS OF NEUROLOGY

2003;53(2):263-266

EPILEPSY

When is a drug not a drug? When it's a herb

In this study the authors reviewed the literature relating to the use of herbal remedies in the treatment of epilepsy. A resource called *napralert* was particularly useful in obtaining information about herbs. They found a whole spectrum of effects. At one end of the scale Zhenxianling was used as add-on therapy to anti-epileptic drugs (AED) in an open label study of 239 patients and gave >75% reduction in seizures in 66% of patients. This is better than any trial of new AED's that I know of in refractory epilepsy. Zhenxianling is thought to contain peach buds and human placenta amongst its ingredients. Also from China, Qingyangsen roots controlled seizures over 2-9 months in 9 patients for whom standard AED had been unsuccessful and who suffered 4 seizures per month. If ingesting human placenta gives you the heeby-jeebies, even washed down with Chianti, how about cow's urine concoction, a traditional anti-epileptic preparation used widely in Africa? It is the leading cause of drug poisoning in childhood in Western Nigeria resulting in cardiovascular collapse, respiratory depression and CNS depression – not recommended.

At the other end of the spectrum are herbs that may cause seizures. One boy was admitted with status epilepticus after ingesting roots of water hemlock. The authors went on to test the root in animal studies and found it triggered convulsive EEG patterns within 60 seconds of IV injection of the alcoholic extract. Among the things you are more likely to meet for which there is evidence of proconvulsive activity are Ginkgo biloba, borage, marine wormwood oil and oil of evening primrose - surely not, it's so good for you!

Herbal remedies may also interact with AED, for example eucalyptus oil lowers pentobarbitone levels and one to remember: grapefruit juice increases carbamazepine bioavailability and may trigger toxicity.

So, there you have it: drugs are good, bad or toxic and may interact but herbs are natural and they are good for you. Hmmm – I'm off for an invigorating cup of rosehip tea, I don't touch caffeine. -MRAM

Herbal remedies, dietary supplements and seizures.

A Tyagi and N Delanty

EPILEPSIA

2003;44:228-235

People who go bump in the night

My teachers always told me never say never in medicine. Despite this wise counsel I still cling to some beliefs in the hope of certainty in an uncertain world. With this paper, another of my emotional struts crumbles to dust. One of the most difficult diagnostic conundrums is the differentiation of epileptic from non-epileptic seizures. There are few clear rules as epileptic and non-epileptic seizures may have very similar manifestations. One useful one has been that if a patient is truly asleep (EEG verified sleep) at the onset of an attack, then the attack is organic, whether a parasomnia or epilepsy, but alas no longer according to this paper. In 5 patients of 76 with a clinical diagnosis from video-telemetry, the seizures

arose within seconds of arousal or in sleep. In one case the patient interacted immediately with the nurse upon her arrival, terminating the non-epileptic seizure. The attacks were all with prominent motor activity, including opisthotonic posturing, shaking movements of either hand or asynchronous jerking. A niggling doubt remains in my mind whether some of these could have been frontal lobe epileptic attacks, which are often characterised by bizarre motor activity and may have no ictal EEG changes. The more perceptive of you will no doubt attribute this to a feeble mind clinging to preconceptions in the face of evidence to the contrary. I take consolation from the fact that it was only 5 patients in a large series so the rule can be demoted to a clinical pointer, rather than having to be abandoned altogether. -MRAM

Psychogenic, nonepileptic seizures associated with EEG-verified sleep.

Orbach D, Ritaccio A and Devinsky O

EPILEPSIA

2003;44:64-68

Look into their eyes

It is 5pm and you are called to see a patient on the medical ward. She is drowsy and confused. The general physicians have done all the usual tests; there is no intracranial lesion, meningitis, encephalitis, metabolic disturbance or infection and no suggestion of drug overdose. Is she in non-convulsive status epilepticus (NCSE)? Are you going to transfer her that night to the regional centre for an urgent EEG? Current opinion is that delay in managing status may lead to neuronal damage. In this paper the authors sought clinical predictors of NCSE. They asked residents requesting an urgent EEG to fill out a questionnaire for the presence of recent or remote risk factors for seizures, tonic-clonic activity in the current episode, history of epilepsy, mental state/Glasgow coma score, ocular movement abnormalities or subtle motor activity. Ocular movements considered were hippus, nystagmoid jerks, repeated blinking and eye deviation, but not roving eye movements. Forty-eight patients were enrolled, 12 turned out to have NCSE and 36 did not. The proportion of women was greater (2:1) in NCSE compared to 16:20 in non-NCSE. Mean age was 55-60 in both groups. GCS scores in NCSE was 4.5 v 9.2 in other cases, $P < 0.001$ but no single factor predicted the presence of status epilepticus. The presence of both abnormal eye movements and a remote cause of seizures had a sensitivity of 100% with much lower specificity. It is sensitivity that is crucial in a screening test of this kind, you don't want to miss the diagnosis. The number of patients in this study was small and one feels that exceptions are likely to emerge in larger series. Nevertheless, I for one shall look more carefully at the eyes in future. -MRAM

Non-convulsive status epilepticus: usefulness of clinical features in selecting patients for urgent EEG.

AM Husain, GJ Horn, MP Jacobson

JNNP

2003;74:1289-91

COGNITION

☆☆☆ RECOMMENDED

Anticipating a switch. Brain control processes

Humans switch between activities as necessary. This capacity is achieved via "executive control processes". On behavioural paradigms, performance improves as preparation for switching is maximised. Nevertheless there is a performance "cost" on switch trials compared to repeat trials. Switch trials tend to be performed more slowly and less accurately. It seems that however much preparation for switching there is prior to the switch stimulus being presented, some control aspects necessary for switching occur only after the presentation.

Non-clinical, different-gender subjects performed a task switching-"Go/NoGo" behavioural paradigm. High-density event related potentials recorded the brain's activity allowing cognitive processes to be examined with defined timing. An early potential over posterior visual cortex differentiates Go and NoGo trials and occurs about 140-150ms after stimulus presentation. Here, this "Discrimination potential" was used as a readiness measure, presumed to indicate recognition processes drawing on an existing cognitive set. The potential is thought to reflect preparation for a task occurring some time before the relevant stimulus is presented. During repeat trials, the Discrimination potential was robust and the authors concluded that the correct cognitive set had been accessed.

However, during switch trials, the potential was absent. This is proposed to reflect prior processing, different from processing occurring on repeat trials, and evidenced by behavioural measures indicating only partial success. The paper suggests that preparation for switching may not be a separate process but rather the start of competing stimulus-response associations where competition is "resolved during the switch trial".

Showing the benefit of converging methodologies, maybe another experiment would uncover gender differences in task switching. In certain clinical populations switching is excessive and maladaptive to productive behaviour, while in others, maladaptive behaviours perseverate as switching is impaired. Perhaps this model could help explore the brain basis of these dysfunctions and help gauge outcome of rehabilitation interventions. -LAJ

Cognitive control processes during an anticipated switch of task.

Wylie G.R, Javitt D.C and Foxe J.J

EUROPEAN JOURNAL OF NEUROSCIENCE

2003; 17: 667-672

PARKINSON'S DISEASE

☆☆☆ RECOMMENDED

Agonies over agonists...The role of dopamine agonists in early Parkinson's disease

There has always been enormous controversy as to how to best treat the early stages of Parkinson's disease (PD). There were those who have advocated that starting with the most effective drug, namely L-dopa, is the best strategy whilst others have emphasised the use of dopamine agonists, given that they delay the motor complications of drug therapy. Then there was selegiline and its role as a neuroprotective agent. So it is that we now embark on a whole new debate about whether dopamine agonists are neuroprotective - giving more weight to their early use.

This debate has been sparked by the recent claims that the use of both pramipexole and ropinirole reduce the progression of disease as measured using imaging ligands - a way of trying to get around the problems of using rating scales with drug therapies and unknown wash-out periods. These studies have suggested that the rate of loss of dopaminergic striatal signal using either SPECT or PET scanning is less with agonist therapy compared to L-dopa over several years.

These claims are exciting and have massive implications if true and such is their significance that the studies have generated a whole series of articles in Neurology. These articles take various stand-points with respect to the trials, one of which has only been reported in abstract form to date (showing how heated the debate is becoming!). These articles question the validity of these functional imaging paradigms to measure what they claim to be doing, which if true also has far-reaching implications given how much they have become the gold-standard in trials of therapy in PD.

So what should we conclude from all this? Well as with all things to do with first line therapy in PD, I would suggest that we do not rush to conclusions. The results with dopamine agonists are exciting, but further analysis of the data is required, and once the ropinirole study is published

in full then a clearer picture may emerge. Till then I would suggest you continue doing whatever you do with your patients and wait until a consensus appears - assuming of course that one will be reached!!
- RABarker

Wooten GF

Agonists vs Levodopa in PD. The thrill of witha

NEUROLOGY

2003 60: 360-362

Ahlskog JE

Slowing Parkinson's disease progression. Recent dopamine agonist trials.

NEUROLOGY

2003 60: 381-389

Albin RL, Frey KA

Initial agonist treatment of Parkinson disease. A critique.

NEUROLOGY

2003 60: 390-394.

☆☆☆ RECOMMENDED

Dopamine pathways in Parkinson's disease - do they all do the same thing?

The loss of dopamine in the nigrostriatal pathway is the biochemical hallmark of Parkinson's disease and lies at the core of the symptoms and therapy...but what about the other dopaminergic pathways in the brain, what happens to them? Recently there has been interest in the cortical dopaminergic networks, which seem overactive in early PD, although this is lost with disease progression. The reason for this is not known, but it may be that the initial overactivation of the mesocortical dopaminergic pathway represents some global upregulation of all dopaminergic pathways to compensate for the failing nigrostriatal system. However the functional consequences of having such an overactive pathway may be significant, and may explain some of the deficits seen in early PD with cognitive tasks using prefrontal cortical networks (e.g. working memory and probabilistic reversal learning).

In this latest study Brooks and colleagues have extended these observations on central dopaminergic pathways by studying the less well-known dopaminergic nigropallidal pathway. In this study using PET, they showed that in early PD there is increased dopaminergic activity in the nigral projection to the internal (but not external) part of the globus pallidum, an effect that is lost with advancing disease.

The significance of this early compensatory increase is not known, but it may be important in the development of drug induced dyskinesias. Namely the loss of compensation in this pathway leads to the development of these movements, which if true would have far-reaching consequences not only to our understanding of their aetiology but to their treatment especially with novel neurosurgical procedures -RABarker
Plasticity of the nigropallidal pathway in Parkinson's disease.

Whone AL, Moore RY, Piccini PP, Brooks DJ (2003)

ANN.NEUROL.

53:206-213

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For further information please contact Emma Stafford on 01344 741336 or stafforde@bra.boehringer-ingelheim.com

The Bereitschaftspotential



Kluwer Academic/Plenum Publishers has published The Bereitschaftspotential: Movement-Related Cortical Potentials edited by Marjan Jahanshahi and Mark Hallett, ISBN 0-306-47407-7. This 328 page book costs EUR 153 / USD\$ 150/ GBP £96.

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Anti-epileptic may provide pain relief in MS



Results from a new study show that the antiepileptic drug Keppra™ (levetiracetam), in combination with tricyclic antidepressants, anticonvulsant drugs and/or long-acting narcotics, provided some multiple sclerosis (MS) patients improvement in pain and uncomfortable sensations associated with their condition. The study was conducted at the MS Treatment and Research Center of the Yale School of Medicine and presented recently at the American Pain Society's 22nd Annual Scientific Meeting.

"We were interested in studying Keppra™ in combination with more commonly used treatments for neuropathic pain and paresthesias in MS patients. Because of its unique mechanism of action, it can potentially complement other anticonvulsant treatments," said Marco Rizzo, MD, PhD, author of the study and assistant professor at the Yale School of Medicine, New Haven, Conn. "We were impressed to find that Keppra™ was well-tolerated and effective for neuropathic pain and uncomfortable numbness."

For further information Tel. UCB Pharma on 01923 211811.

Prize draw winners

Congratulations to readers who won the following books in the reader survey prize draw:

Handbook of Neurological

Rehabilitation: Douglas Gentleman, Consultant in Brain Injury Rehabilitation, Centre for Brain Injury Rehabilitation, Dundee; B Concannon, CNS Paediatric Epilepsy, Princess Diana Children's Hospital, Birmingham

Diseases of the Nervous System:

Zdenek Ambler, Professor of Neurology,

University Hospital Plzen, Czech Republic

Self Assessment Colour Review of

Clinical Neurology & Neurosurgery:

Andy Watt, Geriatrics SpR, Victoria Infirmary, Glasgow; Rustam Al-Shammi, SpR Neurology,

Western General Hospital, Edinburgh

Current Practice of Clinical

Electroencephalography:

P Ray, SpR, QE Neuroscience Centre, Birmingham

On hearing that he had won Diseases of the Nervous System, Professor Ambler said, "I am really very much looking forward to receiving a copy of this book. It will be a much appreciated addition to our library".

Thank you to everyone who completed our reader survey.

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[®]
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.

Date of preparation: February 2003

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Freephone 0800 221441
Fax 020 8990 4328
customercontactuk@gsk.com

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