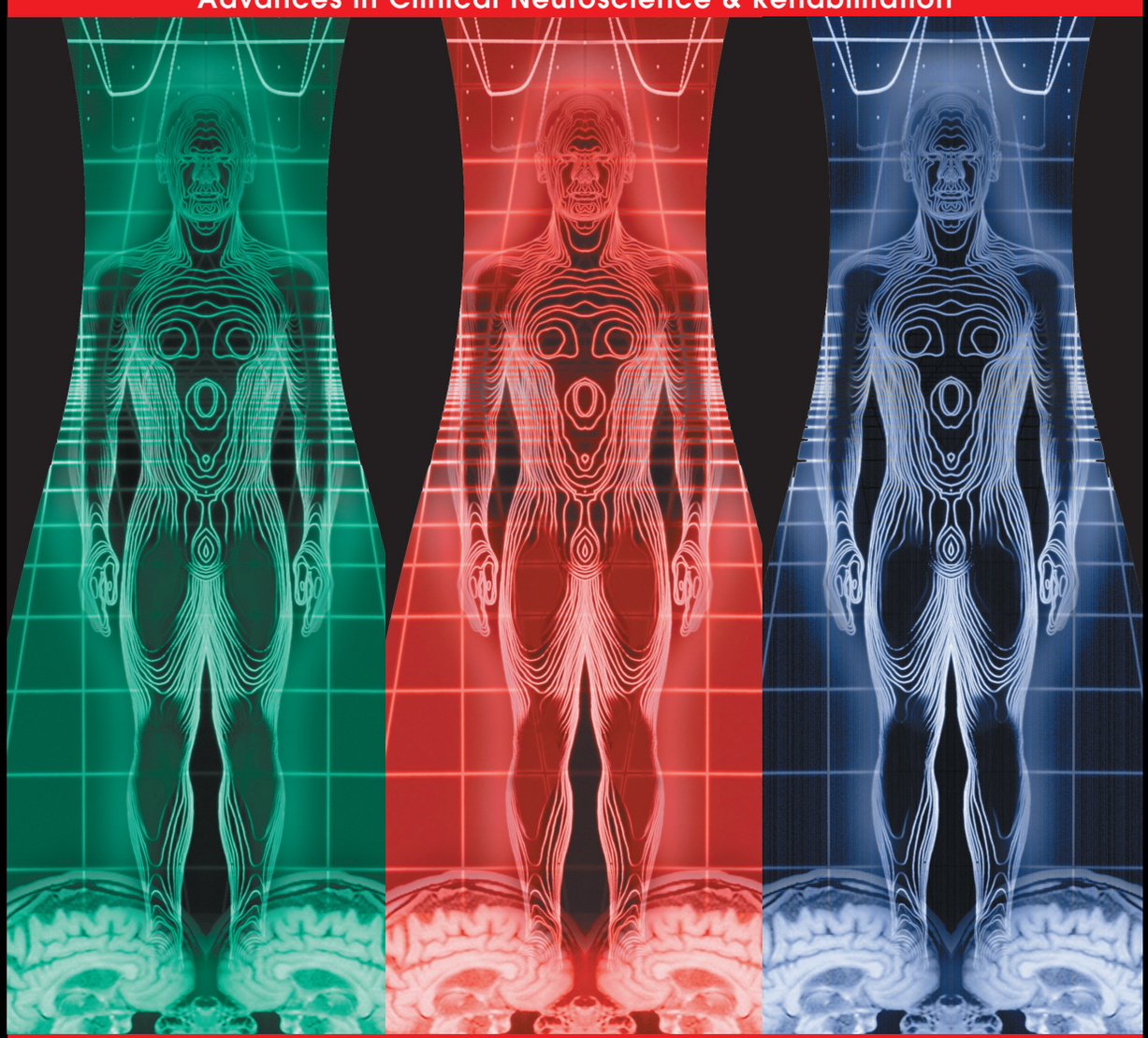
ISSN 1473-9348 Volume 1 Issue 6 January/February 2002

ACNR

Advances in Clinical Neuroscience & Rehabilitation



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

Review Article: The Diagnosis of Variant Creutzfeldt-Jakob Disease

Rehabilitation Article: Driving cortical plasticity to improve swallowing performance after dysphagic stroke

Management Topic: Convulsive status epilepticus

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Neuroimaging has proved to be both sensitive and highly effective in detecting dopaminergic dysfunction in Parkinsonian Syndromes. It can help establish the truth of the disorder when clinical features are incomplete or contradictory.

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Dosage and Administration: DaTSCAN is a 5% (v/v) ethanolic solution for intravenous injection and should be used without dilution. Clinical efficiency has been demonstrated across the range of 111-185 MBq; do not use outside this range. Appropriate thyroid blocking treatment must be given prior to and post injection of DaTSCAN. SPECT imaging should take place 3-6 hours after injection of DaTSCAN. DaTSCAN is not recommended for use in children or adolescents. For use in patients referred by physicians experienced in the management of movement disorders. See SPC.
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Marketing Authorisation number: EU/1/00/135/001
Basic NHS price: £420
Date of Preparation: July 2000
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† Benamer H *et al*. Accurate differentiation of Parkinsonism and Essential Tremor using visual assessment of ^{123}I-FP-CIT SPECT imaging: the ^{123}I-FP-CIT Study Group. Movement Disorders 2000;15:503-510

contents

january/february 2002

This issue of ACNR marks the end of our first year and we would like to thank all our many contributors as well as thank all the readers for their encouraging comments and kind words. We have been very grateful to all those who have tirelessly reviewed the journals and written the excellent series of articles with a minimum of prompting. We are always keen for new ideas and thoughts so do let us know if there are topics you want reviewing or areas of neuroscience and rehabilitation that we are neglecting.

In this issue we have a review of new variant CJD by Andrea Lowman and James Ironside. This disease continues to generate much interest at all levels of medical science, from those involved with molecular mechanisms of neuronal dysfunction to those concerned with public health. Amongst other things, this article highlights the invaluable service of the national CJD surveillance unit, without which new variant CJD might easily have been overlooked for years. We also have an excellent article on neuronal plasticity in the rehabilitation section of the journal. The extent to which the adult mature CNS can reorganise itself in the face of injury and disease is a major issue in contemporary clinical neuroscience.

In the regular articles, Mark Manford completes his excellent series on epilepsy with an elegant and practical account of the management of status epilepticus. We must apologise to Mark for the slight slip in the title of his last article - the Management of rational epilepsy should have read the Management of refractory epilepsy, but no doubt more people (if that is possible) were attracted to the article by the unusual title that appeared. In the next year we are fortunate to have Gillian Hall writing on aspects of the peripheral nervous system. We are pleased to welcome Justin Cross, a neuro-radiologist, to add radiological input to the anatomy primer series. We also have our usual selection of conference reports, book reviews and review of the neuroscience literature.

Finally some thanks. I am very grateful to Alasdair for all his help in this first year, and to Mark for his series of articles, David Burn for the conference section, Steve Kirker for organising the rehabilitation topic and Andrew Larner for the book reviews. I would also very much like to thank our industry supporters, without whom we would be unable to bring you complimentary copies of ACNR.

Roger Barker, Editor
AdvancesinCNR@aol.com

PS: By popular request I have sent in a new photograph of myself!

Features

Regulars

ACNR is published by Whitehouse Publishing,
7 Alderbank Terrace, Edinburgh EH11 1SX.
Tel. 0131 477 2335/0777 969 7677, **Fax.** 0131 313 1110
E-Mail. AdvancesinCNR@aol.com
Publisher: Rachael Hansford
Design & Production: Barbara Newton
Printed by: Stephens & George Magazines, Tel. 01685 388888.

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Presentation

Glatiramer acetate 20mg powder for solution with water for injection.

Indication

Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients who have had at least one relapse in the preceding two years before initiation of therapy.

Dosage and administration

20mg of glatiramer acetate in 1 ml water for injection, administered sub-cutaneously once daily. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after.

Children

Not recommended under 18 years of age.

Elderly

No specific data.

Impaired renal function

No specific studies. Monitor renal function during treatment. Consider possibility of deposition of immune complexes.

Contra-indications

Known allergy to glatiramer acetate or mannitol (excipient).

Special warnings and precautions

Subcutaneous use only. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders. Review such patients regularly. Rarely, convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone.

Interactions

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

Pregnancy and lactation

Safety in pregnancy not established. Consider if expected benefit outweighs risk to foetus. No data on excretion in human milk.

Undesirable effects

Injection-site reactions (particularly hypersensitivity, pain, mass, 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 47% on Copaxone and 29% on placebo. Asthenia, nausea, hypertonia, headache infrequently. Rarely, anaphylactoid or allergic reactions and convulsions. Rarely, shifts in white blood cell counts and level of SGOT, no evidence of clinical significance.

Overdose

Monitor, treat symptomatically.

Pharmaceutical Precautions

Store Copaxone in refrigerator (2° to 8°C). May store in refrigerator after reconstitution for up to eight hours.

Legal Category: POM

Package Quantity and Basic NHS Cost

28 vials of Copaxone plus 28 ampoules of water for injection: £510.14. Copaxone administration package, including syringes and needles supplied free of charge.

Product Licence Number

10921/0019

Further Information

Further medical information available on request from Aventis Pharma Limited, 50 Kings Hill Avenue, Kings Hill, West Malling, Kent, ME19 4AH. Other enquiries to: Teva Pharmaceuticals Limited, Barclays House, 1 Gatehouse Way, Aylesbury, Bucks, HP19 8DB.

Date of Review: December 2000.

Date of Preparation: December 2001.

Editorial Board and regular 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 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.

Mark Manford contributes our Epilepsy Management Feature. He has been Consultant at Addenbrooke's Hospital, Cambridge and at Bedford Hospital for 3 years. He was an undergraduate at University College London and trained in Neurology in London at The National Hospital for Neurology and Neurosurgery, Charing Cross Hospital and at Southampton. His special interest is epilepsy and he is closely involved with undergraduate training in neurology. He has co-authored an undergraduate textbook of neurology and is currently working on a guide to epilepsy.

Niall Pender is a member of the editorial board. He is a Neuropsychologist and Clinical Leader of the Neuro-behavioural Rehabilitation Unit at the Royal Hospital for Neuro-disability, London. He is also Neuropsychologist to the Huntington's Disease Unit at the Royal Hospital. In addition he is an Honorary Lecturer in Psychology at the Institute of Psychiatry, King's College. Following degrees in Psychology and Neuropsychology he completed his training in Clinical Psychology at the Institute of Psychiatry. His research interests include cognition in Huntington's disease, behaviour management in brain injury rehabilitation, memory, and visual impairments after brain injury.

Justin Cross is a Consultant Neuroradiologist at Addenbrooke's Hospital, Cambridge. He trained in neuroradiology in Cambridge and Toronto. Current research interests include the imaging of paediatric brain tumours and the use of web-based media for neuroanatomy teaching. He is a supervisor in neuroanatomy at Peterhouse, Cambridge.

The Diagnosis of Variant Creutzfeldt-Jakob Disease

Introduction

Creutzfeldt-Jakob disease (CJD) is a fatal neurodegenerative disorder which is the commonest form of human transmissible spongiform encephalopathy or prion disease. It exists in four forms – sporadic (s), iatrogenic (i), familial (f) and variant (v). The disease results from the deposition of an abnormal form of prion protein (PrP) in the central nervous system. Variant CJD was first recognised in 1996 in the UK (Will *et al* 1996). It was initially suspected that this form of CJD was related to the epidemic of bovine spongiform encephalopathy (BSE) in cattle and it is now widely accepted that exposure to the BSE agent, probably in meat products, is causative (Scott *et al* 1999, Knight 1999).

The diagnosis of vCJD has been continually refined since 1996 and currently relies on the patient fulfilling a set of diagnostic criteria (Table 1). The clinical features are extremely important, as all of the patients so far have had a very characteristic, stereotyped presentation (Zeidler M *et al* 1997a). Although it is a fatal disease, it remains important to make the diagnosis as the patient and family can then be fully informed about the disease and its prognosis, and further unnecessary investigations are avoided. In addition, it is necessary for accurate surveillance and patients may now be eligible for entry into a clinical trial of potential treatment. (DOH Press Release, Korth *et al* 2001).

Making the Diagnosis: Clinical Features

Variant CJD usually presents in a young person with a median age at symptom onset of 27 years (range 12-74). Making the diagnosis requires a high degree of clinical suspicion, as many of the initial presenting features are non-specific. In most cases, the first symptoms are psychiatric and sensory. The most common psychiatric symptom is depression; others reported include withdrawal, aggression, irritability, anxiety, fear, hallucinations and delusions (Zeidler *et al* 1997b, Will *et al* 1999). First rank symptoms and suicidal ideation can also occur. Sensory symptoms are prominent and those commonly reported include pain, paraesthesia, dysaesthesia, numbness, and cold or burning sensations (MacLeod *et al* 2000), most frequently affecting the limbs. They may be asymmetrical or unilateral in distribution and are usually persistent.

Other neurological symptoms and definite neurological signs appear a mean of six months later, although mild cognitive impairment is occasionally present from the onset. Diagnosis prior to this may be difficult. Ataxia, involuntary movements and cognitive problems commonly occur. Patients characteristically develop a movement disorder, often appearing restless and fidgety at first, then developing choreiform movements of the limbs and/or dystonia or myoclonus, which is often more prominent later in the disease course (Will *et al* 2000). vCJD is characterised by its relentless and rapid progression and cognitive impairment quickly progresses to frank dementia. Cortical blindness can occur and primitive reflexes often develop. Dysphagia with subsequent aspiration is common. The terminal stages of vCJD are very similar to sCJD, with progression to an akinetic mute state; however, it has a more prolonged course with a median duration of illness of 14 months (range 6-39), compared with 4.5 months in sCJD.

Authors

Professor James Ironside is Head of the Neuropathology Labs in the CJD Surveillance Unit and Honorary Consultant Neuropathologist in Lothian University NHS Hospitals Trust. He is a member of SEAC, the advisory body to the UK Government on prion diseases, and also a member of the Joint ACDP/SEAC Working Group on TSE and the CJD Incident Panel. He is a member of the WHO Working Group on Reference Materials for TSE Diagnosis, and has acted as an advisor to the EU and other international bodies. Professor Ironside's main focus of research is in the pathology of human prion diseases, and related diagnostics development. He also maintains an interest in neuro-oncology and is a member of study groups on brain tumours.

Dr Andrea Lowman is a Research Fellow at the National CJD Surveillance Unit, Edinburgh, where she is the first point of contact for referrals of potential cases of CJD throughout the UK. Dr Lowman is a member of the RCP and Association of Neurology Trainees. She is currently writing a thesis on the epidemiology of variant and sporadic CJD for a doctorate of medicine at the University of Edinburgh.

Making the Diagnosis: Investigations

If a diagnosis of vCJD is suspected the individual is usually extensively investigated to ensure that treatable conditions are excluded. The most important investigations are lumbar puncture, magnetic resonance imaging (MRI) and electroencephalography (EEG).

Blood tests are usually normal, although some patients have a mild transient elevation of liver function. Wilson's disease should be excluded with the appropriate tests.

Most patients will have a lumbar puncture, with essentially normal cerebrospinal fluid (CSF). The white cell count should be within the normal range, although CSF protein can be mildly to moderately elevated in 10-15% of sporadic and variant cases. Brain specific protein (BSP) analysis of the CSF can be helpful (Will *et al* 1996b, Green *et al* 2000) with the BSP 14-3-3 elevated in approximately 50% of cases of vCJD; this is a less sensitive test in vCJD than sCJD. 14-3-3 is not a diagnostic or screening test and is only valuable if the patient's clinical picture is generally consistent with CJD. If it is negative, the diagnosis is not excluded. False positive results can occur with bloodstained CSF, high CSF white cell count, recent seizures, traumatic brain injury or stroke, encephalitis or a paraneoplastic syndrome.

MRI of the brain can show specific abnormalities in vCJD that are of diagnostic value i.e. the 'pulvinar sign' which is due to bilateral and symmetrical high signal in the posterior thalamic nuclei (pulvinar region), (Figure 1), (Zeidler *et al* 2000, Collie DA *et al* 2001). In the correct clinical context, this is highly supportive of a diagnosis of vCJD, allowing a case that fulfils the criteria for 'Possible' vCJD to be re-categorised as 'Probable' (see Table 1).

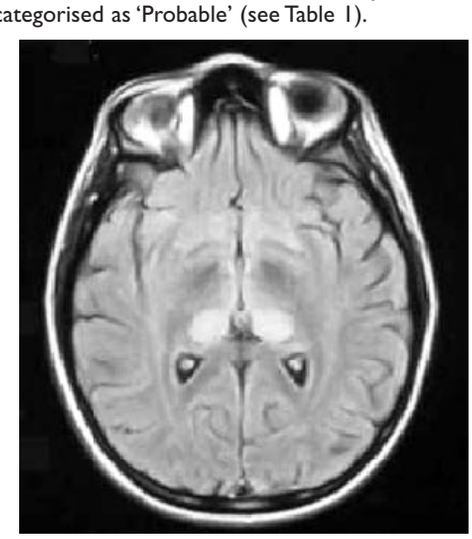


Figure 1: MRI (FLAIR sequence) of brain showing bilateral pulvinar high signal.

Table 1

DIAGNOSTIC CRITERIA FOR VARIANT CJD (Edinburgh 2001)

I	A	Progressive neuropsychiatric disorder
	B	Duration of illness more than 6 months
	C	Routine investigations do not suggest an alternative diagnosis
	D	No history of potential iatrogenic exposure
	E	No evidence of a familial form of TSE
II	A	Early psychiatric symptoms[a]
	B	Persistent painful sensory symptoms[b]
	C	Ataxia
	D	Myoclonus or chorea or dystonia
	E	Dementia
III	A	EEG does not show the typical appearance of sporadic CJD[c] (or no EEG performed)
	B	Bilateral pulvinar high signal on MRI scan (Figure 1)
IV	A	Positive Tonsil Biopsy[d]

DEFINITE: I A and neuropathological confirmation of nv CJD[e]
PROBABLE: I and 4/5 of II and III A and III B
OR I and IV A[d]
POSSIBLE: I and 4/5 of II and III

a depression, anxiety, apathy, withdrawal, delusions
b this includes both frank pain and/or dysaesthesia
c generalised triphasic periodic complexes at approximately one per second
d tonsil biopsy is not recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and MRI does not show bilateral pulvinar high signal
e spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum

In addition, many patients will have an EEG, which is usually non-specifically abnormal. Common abnormalities seen include deterioration in the normal background rhythms, excessive slow wave activity or occasionally excessive fast wave activity. To date, the triphasic complexes seen in sporadic CJD have not been seen in vCJD.

Genetic analysis is important to exclude the presence of a prion protein gene (PRNP) mutation, and to determine the codon 129 status. The PRNP gene has a polymorphic region at codon 129, encoding either the amino acid methionine or valine. All vCJD cases so far tested are methionine homozygous, as are 70% of sCJD patients, but other vCJD genotypes may be identified in the future.

Making the Diagnosis: Pathology

Variant CJD differs form other forms of CJD in that abnormal PrP can be detected in lymphoid tissues throughout the body, including the tonsil. Tonsil biopsy may be considered in specific individuals e.g. those patients who fulfil the diagnostic criteria for 'Possible' vCJD with no 'pulvinar sign' on MRI (Hill *et al* 1999), since a 'positive' tonsil biopsy can change their classification from 'Possible' to 'Probable´ vCJD. For a definite diagnosis to be made, neuropathology remains the gold standard. Cerebral biopsy is rarely performed in life, but may be considered if there is any possibility of an alternative, potentially treatable disease that requires neuropathological diagnosis. The neuropathology of vCJD is characterised by the presence of large amyloid plaques surrounded by spongiform change in the cerebral and cerebellar cortex (Figure 2), and a characteristic pattern on Western blot examination for PrP in unfixed tissue (Ironside *et al* 2000). The neuropathological diagnostic criteria for vCJD are summarised in Table 2.

Differential Diagnosis

This includes other forms of CJD i.e. sporadic, iatrogenic and familial CJD. In the UK, sCJD is the most important differential diagnosis, as it can present atypically and sometimes occurs in younger patients; however, they would not have the typical MRI appearance seen in vCJD, and the distinction can be made definitively at post mortem. In iCJD there is likely to be a history of relevant iatrogenic exposure, and many patients with fCJD have a family history of a similar disorder. If fCJD is a consideration, the patient and their family should be referred for appropriate genetic investigation and counselling. Wilson's disease should be excluded as this can present in a similar way and is potentially treatable. Other diagnoses made in patients classified as at least 'Possible' vCJD include Alzheimer's disease, cerebrovascular disease, limbic encephalitis, cerebral vasculitis and infective encephalitis (Will *et al* 2000).

Variant CJD is a disease that interests many different groups from clinicians and scientists to the media and general public. For accurate surveillance to be maintained it is important to make the diagnosis using the recognised criteria and for all of these patients to be referred to the National CJD Surveillance

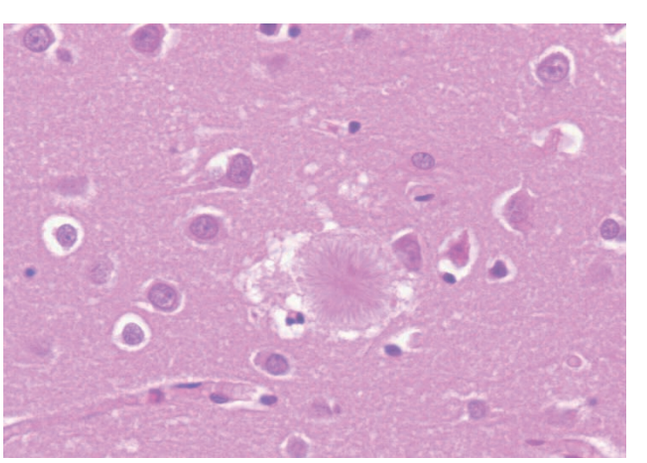


Figure 2. The cerebral cortex in vCJD contains large florid plaques (centre), composed of abnormal PrP. Haematoxylin and eosin stain.

Unit. Many groups are trying to develop a simple diagnostic test that can be used in life, and with the advent of potential treatment for this disease, it is inevitable that diagnosis of all forms of CJD will take on new significance in the future.

Table 2. Diagnostic neuropathological features of vCJD

Cerebral and cerebellar cortex: in H&E sections (Figure 2)	Multiple florid plaques
	Numerous small cluster plaques in PrP stained sections
	Amorphous pericellular and perivascular PrP accumulation
Caudate nucleus and putamen:	Severe spongiform change
	Perineuronal and axonal PrP accumulation
Posterior thalamic nuclei and midbrain:	Marked astrocytosis and neuronal loss
Brainstem and spinal cord:	Reticular and perineuronal matter
PrP accumulation in grey	
PrP accumulation in lymphoid tissues throughout the body	
Predominance of di-glycosylated PrP in Western blot on central nervous system and lymphoid tissues	

Correspondence Address

Andrea Lowman MRCP or James W Ironside FRCPath,
National CJD Surveillance Unit, Western General Hospital, Edinburgh EH4 2XU. Tel: 0131 537 1980, Fax: 0131 537 3056

References:

- Collie DA, Sellar RJ, Zeidler M *et al* (2001) MRI of Creutzfeldt-Jakob Disease: *Imaging Features and Recommended MRI Protocol.* Clinical Radiology 56: 726-39.
- Green AJE, Thompson EJ, Zeidler M *et al* (2000) *Raised concentration of brain specific proteins in patients with sporadic and variant* CJD. Journal of Neurology, Neurosurgery and Psychiatry, 69: 419.
- Hill AF, Butterworth RJ, Joiner S *et al* (1999) *Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples.* Lancet, 353: 183-9.
- Ironside JW, Head MW, Bell JE, McCArdle L, Will RG.(2000) *Laboratory diagnosis of variant* Creutzfeldt-Jakob disease. Histopathology 37: 1-9.
- Knight R (1999) *The relationship between new variant CJD and BSE.* Vox Sanguinis, 76: 203-8.
- Korth C, May BCH, Cohen FE, Pruisiner SB (2001) *Acridine and phenothiazine derivatives as pharmacotherapeutics for prion disease.* Proceedings of National Academy of Science USA, 98: No. 17, 9836-9841.
- MacLeod MA, Knight R, Stewart G, Zeidler M, Will RG (2000) *Sensory features of vCJD.* Journal of Neurology, Neurosurgery and Psychiatry, 69: 413-414.
- Scott MR, Will R, Ironside J *et al* (1999) *Compelling transgenic evidence for transmission of bovine spongiform encephalopathy prions to humans.* Proceedings of National Academy of Science USA, 96: 15137-42.
- Will RG, Ironside JW, Zeidler M *et al* (1996a) *A New Variant of Creutzfeldt-Jakob Disease in the UK.* Lancet, 347: 921-5.
- Will RG, Zeidler M, Brown P *et al* (1996b) *Cerebrospinal Fluid Test for New Variant Creutzfeldt-Jakob disease.* Lancet, 348: 955.
- Will RG, Stewart G, Zeidler M, MacLeod MA, Knight RSG (1999) *Psychiatric features of new variant Creutzfeldt-Jakob disease.* Psychiatric Bulletin, 23: 264-7.
- Will RG, Zeidler M, Stewart G (2000) *Diagnosis of New Variant Creutzfeldt-Jakob disease.* Annals of Neurology, 47: 575-82.
- Zeidler M, Stewart GE, Barraclough CR *et al* (1997a) *New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests.* Lancet, 350: 903-7.
- Zeidler M, Johnstone EC, Bamber RWK *et al* (1997b) *New variant Creutzfeldt–Jakob disease: psychiatric features.* Lancet, 350: 908-10.
- Zeidler M, Sellar RJ, Collie DA *et al* (2000) *The pulvinar sign on Magnetic Resonance imaging in variant Creutzfeldt-Jakob disease.* Lancet, 355: 1412-8.
- The Department of Health Press Release: reference 2001/0424, 17th September 2001

Convulsive status epilepticus

Mark Manford

Definition

- Status epilepticus is seizures occurring continuously or recurrently for at least **thirty minutes** without recovery. Convulsive status epilepticus (CSE) is immediately **life-threatening.**

Epidemiology of status epilepticus

- **The population incidence** of CSE is 180-280 per million.
- The **age-related** incidence of CSE follows a U-shaped curve, reflecting the incidence of epilepsy as a whole.
- CSE is **commoner in males** at all ages.
- **Recurrence** of CSE is common only in children under 5 years old.
- Status epilepticus is the **first presentation** of epilepsy in 12% of patients.

Aetiology of status epilepticus

- In patients with a **previous history** of epilepsy, treatment failure is the commonest cause of CSE. **Risk factors** include symptomatic seizures, especially lesions of the frontal lobes and mental handicap.
- In ***de novo* cases** head injury, hypoxia, metabolic disturbances and cerebrovascular disease are common at all ages.

Mortality and morbidity of status epilepticus

- The overall **mortality** of status epilepticus is approximately 23% but is **strongly age dependent.** Under age 15 it is less than 10%, from age 16-59 mortality is about 13% and over the age of 60 it is 38%.
- The incidence of **new neurological deficits** after convulsive status is 9% of survivors in childhood.
- The **cause** of status epilepticus is the main determinant of outcome.
- The **duration** of status epilepticus is another major factor.

Stages of convulsive status epilepticus

1. **Prestatus** is a phase of escalating seizures lasting hours to days, which commonly precedes status epilepticus.
2. **Early status** is the first 30 minutes of CSE. The metabolic consequences of status are contained by homeostatic mechanisms.
3. **Established status** occurs from 30-60 minutes when homeostatic mechanisms start to fail.
4. **Refractory status** lasts over one hour and persists despite first line treatments. There is a high risk of hypoxic-ischaemic brain damage.
5. **Subtle status** may emerge if the seizures are maintained for hours. Convulsive motor activity gradually declines in amplitude and extent. Coma deepens and the motor manifestations may become limited to just twitches around the eyes or mouth. The diagnosis is easily missed at this stage and the mortality is 65%.

Management of convulsive status epilepticus

1. **Standard first aid.**
2. **Diagnosis** of the seizure disorder. Epileptic seizures are difficult to differentiate from **psychogenic non-epileptic seizures** (PNES) and the two types may co-exist in the same patient. About 80% of patients with convulsive status epilepticus respond to first line treatment on arrival in hospital. Around half the remainder have PNES mimicking status epilepticus.
    - **Ictal EEG** is diagnostic but is rarely available acutely.
    - **Incongruous clinical signs** point to PNES the whole clinical picture needs to be included to make a diagnosis (table 1).
    - **Hypoxia** is rare in attacks with a psychological cause.
    - **If in doubt** treat as epilepsy and seek specialist advice.
3. **Investigation of the cause**
    - A **serious cause** is likely if CSE is the first presentation of epilepsy.
    - **All cases** should have blood for blood count, electrolytes, renal function, liver function, glucose, calcium, magnesium, AED levels, arterial blood gases and urine for toxicology. **All *de novo*** cases should have a brain scan and if normal, a CSF examination. Patients with **known epilepsy** should also undergo these investigations unless they recover to normal with treatment within 2 hours.
4. **Treatment of status epilepticus** (figure)

Prestatus

- Aggressive treatment of prestatus may **prevent status** from ever occurring. In patients with known epilepsy an escalation of seizures is readily recognisable and a **benzodiazepine** may stop a seizure cluster from evolving into status. If the **patient is alert** between seizures, use **oral clobazam** 10-20mg daily for 2-3 days. If the seizures are very close together or the **patient is drowsy**, use parenteral benzodiazepines, which may cause respiratory depression.
- Urgent AED blood levels may help decide whether the problem is due to treatment failure.

Stopping status epilepticus

- A **benzodiazepine** aborts status in about 80% of cases and the main risk is 10% of respiratory depression.
- **Lorazepam** is the drug of choice. It works as fast as diazepam but the rate of relapse of status is much lower: 55% at 24 hours, compared to 50% at 2 hours for diazepam.
- **Phenobarbital** 15-20mg/Kg used alone has similar efficacy to lorazepam in adults and lasts longer but may cause slightly more hypotension.
- **Paraldehyde** is an irritant drug and is difficult to use but has the advantage of rarely causing respiratory depression.

Keeping seizures away

- **Reinstitute AED** if status is due to AED withdrawal and the relevant drug can be given as a loading dose.
- Otherwise **IV phenytoin** 15-18mg/Kg can be infused slowly with cardiac monitoring. Mild local reactions/phlebitis are common and severe local reactions (purple glove syndrome) or cardiac depression are recognised. Fosphenytoin (phenytoin prodrug) is as effective, does not cause local reactions and cardiac effects are reduced. It can be given IV or IM.
- **IV phenobarbital** is effective but causes more respiratory depression when used after a benzodiazepine.
- **IV valproate** may also be given at therapeutic doses but is less fully evaluated.

Refractory status lasting more than one hour despite appropriate intravenous therapy should be suppressed by general anaesthetic in an intensive care unit.

- **Barbiturate anaesthesia** with phenobarbital or thiopental is the standard. This is best guided by **simultaneous EEG** until the EEG evidence of seizures disappears or the EEG shows the pattern of "burst suppression". **After 12 hours** of seizure suppression, anaesthesia can be lightened. The patient is monitored for the return of electrographic or clinical

seizure activity that may necessitate repeat anaesthesia.
- **Propofol** is also widely used although theoretically proconvulsant in low doses. It has a much shorter half-life, allowing more rapid weaning, although there may be some accumulation. It is contraindicated in children under 16.

Treating the complications of seizures

- There are numerous systemic complications of status epilepticus (table 2).
- Many of these complications **reverse spontaneously** on cessation of seizures if treatment is sufficiently early in the condition.
  1. **Respiratory depression** is common especially in advanced status.
  2. **Pyrexia** with leukocytosis is common and may lead to a presumptive diagnosis of infection. If in doubt, investigate with blood cultures, neuroimaging and CSF examination.
  3. **Oliguric renal failure** due to dehydration, seizure-induced myoglobinaemia and hypotension can be avoided with adequate intravenous fluids.

Catches in status epilepticus

- PNES mimicking status epilepticus.
- Giving a benzodiazepine and failing to give another AED.
- Inadequate AED loading doses.
- Delay in anesthesia
- Missing subtle status epilepticus.
- Failing to diagnose the cause of status epilepticus, including AED withdrawal.

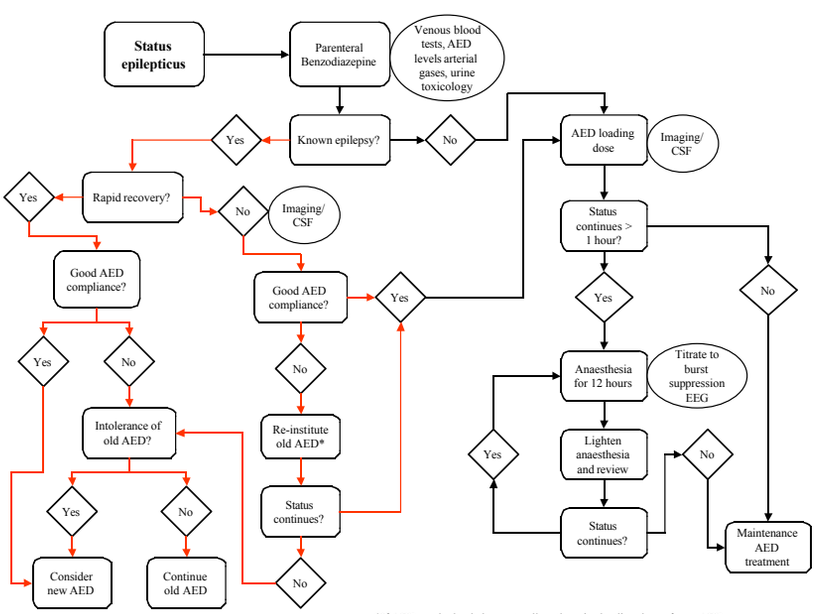
Table 1. Differentiation of status epilepticus and psychogenic non-epileptic seizures

Clinical signs	Epilepsy	Non-epileptic seizures
Seizure activity	Continuous or well-defined attacks are usual	Continuously fluctuating motor activity
Seizure variability	Usually stereotyped	Often variable
Eye deviation	Where present, fixed to one side	Always looks away from examiner
Tongue biting	Major injuries to sides of the tongue	Minor injuries to the tip of tongue
Cyanosis	Common	Rare, but patient may look purple from straining
Self-protection	No attempts at self protection	Patient may withdraw from noxious stimuli
Pattern of motor activity	Tonic with limb jerking commonest	Truncal and pelvic movements commonest
Responsiveness of motor activity	Activity continues independent of external stimuli	Activity is altered by external stimuli, often more violent when attempts are made at restraint

Table 2. Systemic complications of status epilepticus

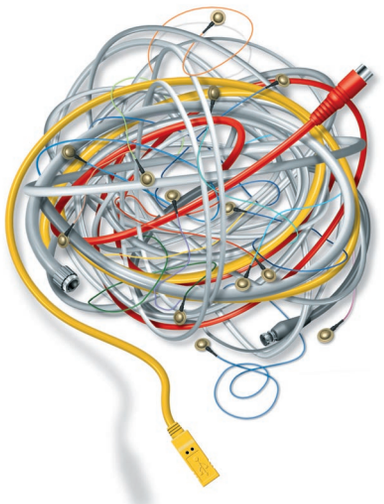
Metabolic	Hypoglycaemia, hyperkalaemia, myoglobulinaemia leading to acute renal failure, respiratory and metabolic acidosis, dehydration, inappropriate antidiuretic hormone secretion
Autonomic	Pyrexia and hyperpyrexia, hypertension or hypotension, cardiac arrhythmia, urinary retention or incontinence
Haematological	Leukocytosis, disseminated intravascular coagulopathy
Others	Trauma including intracranial, aspiration pneumonia, venous thrombosis, pressure sores

Figure. A scheme for the management of status epilepticus, illustrating the crucial differentiation of patients into de novo cases and those with known epilepsy.



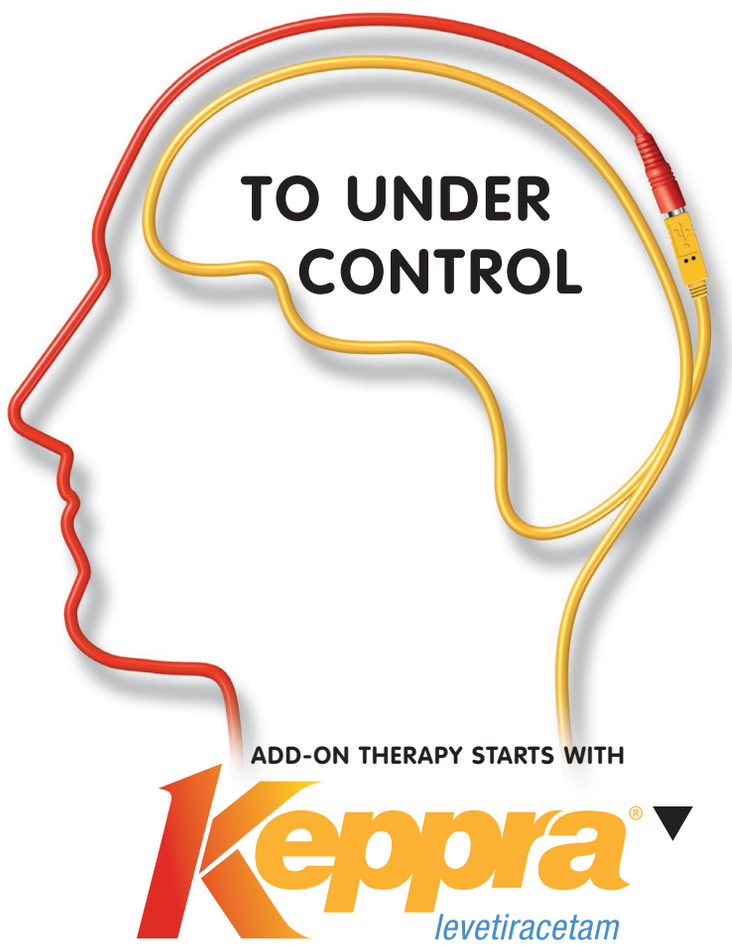
*If AED can be loaded parenterally, otherwise loading dose of new AED.

ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS



FROM UNCONTROLLED...

- Highly effective: up to 4 out of 10 refractory patients had ≥50% partial seizure reduction[1,2,3]
- Excellent tolerability, discontinuation rates not significantly different from placebo[4,5]
- No known drug/drug interactions[6]
- Therapeutic starting dose (500mg bd)



ADD-ON THERAPY STARTS WITH

Keppra® levetiracetam

KEPPRA® Prescribing Information:
Presentation: Keppra 250 mg, 500 mg and 1,000 mg film-coated tablets containing 250 mg, 500 mg and 1,000 mg levetiracetam respectively. **Uses**: Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy. **Dosage and administration:** *Adults and adolescents older than 16 years:* The initial therapeutic dose is 500 mg twice daily which can be started on the first day of treatment. Depending upon clinical response and tolerance the dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. *Elderly:* Adjustment of the dose is recommended in elderly patients with compromised renal function. *Children (under 16 years):* Not recommended. *Patients with renal impairment:* Adjust dose according to creatinine clearance as advised in SPC. *Patients with hepatic impairment:* No dose adjustment with mild to moderate hepatic impairment. In patients with severe hepatic impairment and creatinine clearance <70 ml/min a 50% reduction of the daily maintenance dose is recommended. **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Warnings and special precautions for use:** If discontinuing treatment reduce dose gradually as advised in SPC. **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel) or levels of luteinizing hormone or progesterone. 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:** The most commonly reported undesirable effects are somnolence, asthenia and dizziness. In the pooled safety analysis there was no clear dose-response relationship but incidence and severity of the central nervous system related undesirable effects decreased over time. Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: Very common (>10%): asthenia and somnolence. Common (between 1%–10%): accidental injury, headache, anorexia, diarrhoea, dyspepsia, nausea, amnesia, ataxia, convulsion, depression, dizziness, emotional lability, hostility, insomnia, nervousness, tremor, vertigo, rash and diplopia. **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. **Basic NHS cost:** 250 mg x 60 tablets: £27.00. 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, Herts WD18 0UH. Tel: 01923 – 211811 or e-mail medicaluk@ucb-group.com
Date of Preparation: October 2001.

References:
1. Shorvon S et al. Pooled efficacy and safety data of levetiracetam (LEV) used as adjunctive therapy in patients with partial onset seizures. *Epilepsia* 1999;40,S7:76,abstract B.01.
2. Cereghino J et al. Levetiracetam for partial seizures. Results of a double-blind, randomized clinical trial. *Neurology* 2000;55:236-242.
3. Ben-Menachem E et al. Efficacy and tolerability of levetiracetam 3,000 mg in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 2000;41,10, 1276-1283.
4. Shorvon S et al. Multicenter, double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *Epilepsia* 2000;41,9,1179-1186.
5. Data on file, UCB Pharma Ltd.
6. Patsalos P. Pharmacokinetic profile of levetiracetam: towards ideal characteristics. *Pharmacol Ther* 2000;85(2):77-85.

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SIMPLIFYING SEIZURE CONTROL

Driving cortical plasticity to improve swallowing performance after dysphagic stroke

Author

Dr Shaheen Hamdy is an MRC Clinician Scientist. He qualified from the University of Manchester Medical School in 1990, and took up an MRC Clinical Training Fellowship at the MRC HMBU, Institute of Neurology, in 1996. Following this, he became a Lecturer in GI Sciences at the University of Manchester, Hope Hospital, Salford. Currently, his studies focus on characterisation, modulation and therapeutic application of neuroplasticity within human cerebral cortex in health and after brain injury. He has a specific interest in the human brain gut axis, with much of his work investigating the central neural control of human swallowing and its abnormalities after stroke.

Concepts of neuroplasticity

Central nervous system plasticity refers to the ability of neuronal systems to alter function in response to changes in input, both physiological and pathophysiological[1]. The precise role of neuroplasticity in modelling and remodelling behaviour is still unclear, although over the last two decades a number of studies have improved our understanding both of the mechanisms responsible, and its relationship with injury[2]. These studies have demonstrated that neuroplasticity may be both beneficial, as in recovery of function after cerebral injury[3], and also maladaptive, for instance in the development of pain syndromes, e.g. phantom limb pain after amputation[4]. At present, while there is increasing evidence that neuroplasticity plays a substantial role in centrally remodelling human function after cerebral injury, an understanding of how it relates both to pathophysiology and functional recovery remains limited. Recently, interest has been growing into the potential benefits of experimentally "driving" neuroplasticity in the adult human brain with the long-term goal of improving recovery following injury. A greater knowledge of these processes is thus of fundamental importance in designing interventions which might be functionally relevant to clinical rehabilitation and to favourably alter functional outcome.

Current evidence for driven plasticity

Evidence to support a role for driving neuroplasticity to improve function after cerebral damage comes mainly from animal work[3,5,6]. For example, monkeys who were allowed to recover spontaneously following an ischaemic infarct to hand motor cortex showed a contraction of the remaining undamaged hand area in motor cortex at 4 months post lesion. However in the group which received constraint therapy plus repetitive training post-injury, a net gain of 10% of the hand area was observed when intracortical maaping studies were performed following restoration of manual skills to normal levels (figure 1). It was noted that unimpaired limb constraint alone did not help preserve the hand cortical representation and therefore it was concluded that the physical therapy of repetitive task training was the driving force behind the observed reorganisation. Thus, the available evidence from animal studies suggested a role for physical therapy in driving reorganisation following cortical injury and provided the impetus for human investigations of stroke patients undergoing neuro-rehabilitation programmes. In the case of the latter, Liepert *et al* used transcranial mapping techniques (see below) to examine the cortical effects of a very specific rehabilitative intervention: constraint induced therapy (CIT) for 12 days in a group of 13 chronic (>6 months) stroke patients[7]. This technique involves the immobilisation of the unaffected upper limb in tandem with intense training of the affected limb. Before CIT there were 40% fewer hand active sites in the affected hemisphere versus the unaffected hemisphere, a ratio which was essentially reversed almost immediately post therapy. This effect persisted at 4 weeks and by 6 months the activity between the two hemispheres was essentially equal. These results were also mirrored by the functional scores.

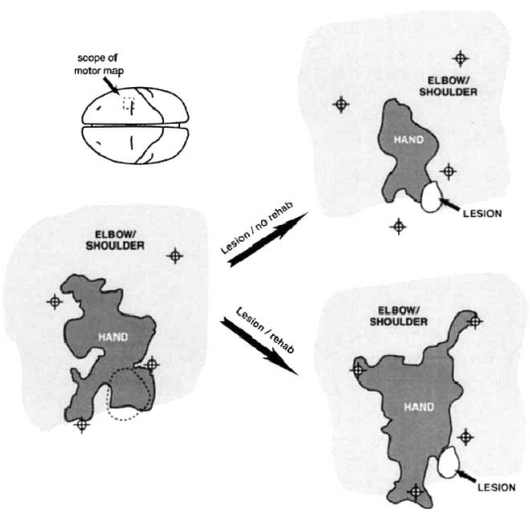


Figure 1: Summary of functional remodelling of the hand representation in the primary motor cortex after a stroke-like injury. Data were derived from hundreds of microelectrode penetrations using microstimulation techniques to determine evoked movements in anaesthetised monkeys. These studies, and others like them, demonstrate that the uninjured tissue adjacent to a cortical injury undergoes functional reorganisation that can be modulated by post injury behavioural training. (Reproduced with kind permission reference 6).

The human swallowing mechanism: the role of the cortex

It is now well established that the cerebral cortex plays an important functional role in the regulation of swallowing (8). While the reflexive component of swallowing depends on swallowing centres in the brainstem, the initiation of swallowing is a voluntary action that involves the integrity of motor areas of the cerebral cortex [9]. In anaesthetised animals, electrical stimulation of either hemisphere can induce swallowing[10]. This might be interpreted as indicating that both hemispheres have an equal role in controlling the swallowing process[10]. Analogous neurosurgical studies of the motor cortex in man[11,12] have usually been confined to one hemisphere, so that a direct comparison with animal data has not been possible. However, these human data show that the locus of cortical control of swallowing lies within and antero-caudal to the face area of primary motor cortex[11].

The problem of dysphagia after brain injury

Injury to swallowing areas of motor cortex and/or their connections to the brainstem will usually result in problems with swallowing (dysphagia). The commonest reason for dysphagia in the UK is now stroke[13]. Up to half of all stroke patients experience dysphagia, which is associated with the life threatening complications of pulmonary aspiration and malnutrition[13,14]. Dysphagia leads to increased length of stays in hospital and greater demands on health service resources[15]. Diagnosing dysphagia in stroke (and other neurological diseases) can be difficult and therefore requires have a high level of clinical suspicion. The pattern of disordered swallowing in stroke is usually a combination of oral and pharyngeal abnormalities[13], typically delayed swallowing reflex with pooling or stasis of residue, reduced pharyngeal peristalsis and weak tongue control, but occasionally oesophageal abnormalities may be apparent. Clinical suspicion of swallowing difficulty should be followed up by a thorough bedside swallowing assessment and where appropriate, videofluoroscopy.

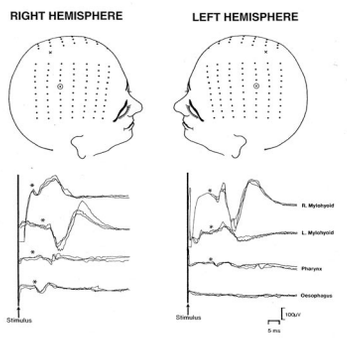


Figure 2: Top: Schematic representations of the sites of stimulation on a scalp grid in relation to the head surface are shown. Bottom: The cortically evoked EMG responses recorded in one normal subject from: right mylohyoid muscle, left mylohyoid muscle, pharynx, and oesophagus, following magnetic stimulation of the right and left hemispheres are shown. The sites of stimulation on the grid from which the EMG responses were obtained are indicated by the open circle. Responses to three stimuli have been superimposed to show reproducibility. An initial stimulus artefact can be seen in the mylohyoid muscles (representing oral musculature) immediately after the stimulus. The response latencies are in the region of 8-10 ms, indicating a rapidly conducting pathway. It is evident, however, that the pharyngeal and oesophageal responses obtained from the right hemisphere are larger than those from the left hemisphere. (* indicates onset of EMG response). Reproduced with kind permission from reference 17).

The swallowing mechanism and transcranial magnetic stimulation

The missing piece of data in these swallowing studies has been lack of information about the normal pattern of cortical projections to swallowing muscles in normal humans. Recently, the technique of transcranial magnetic stimulation (TMS) has been able to fill the gaps in our knowledge. This technique uses a very short, rapidly changing magnetic field to induce electric current in the brain beneath the stimulator. The site of stimulation is less well localised compared to an electrode applied directly to the surface of the brain, so that the effective area of stimulation is larger than that obtained in acute experiments on anaesthetised subjects or animals. However, because of the risk of inducing epileptic seizures in awake subjects, TMS studies usually employ only single shocks given several seconds apart. Following a single stimulus, the EMG response is monitored by recording activity in the pharynx and oesophagus from an intraluminal catheter inserted into the oesophagus[16,17]. The type of response that can be observed is illustrated in figure 2. A single stimulus evokes a simple EMG potential that has a latency of about 8-10 ms, compatible with a fairly direct and rapidly conducting pathway from cortex via brainstem to the muscle. Mapping these projections demonstrates that the various swallowing muscles are arranged somatotopically, with the oral muscles (mylohyoid) lateral and the pharynx and oesophagus more medial. However, the most important finding from a large group of subjects[17] was that in the majority of individuals, the projection from one or other hemisphere tended to be larger than the other, i.e. asymmetric representation for swallowing between the two hemispheres, independent of handedness. It was also observed to be discordant in a pair of identical right handed twins, suggesting little genetic contribution to its development.

Cortical reorganisation and swallowing recovery after stroke

Given sufficient time, many dysphagic stroke patients eventually recover their ability to swallow. However, the mechanism for this recovery, seen in as many as 90% of initially dysphagic stroke patients[14], has remained controversial. In a detailed study of stroke using TMS, both dysphagic and non-dysphagic patients were serially mapped over several months while swallowing recovered[18]. The findings of the study showed that the area of pharyngeal representation in the undamaged hemisphere increased markedly in patients who recovered (figure 3), whilst there was no change in patients who had persistent dysphagia or in patients who were non-dysphagic. No changes were seen in the damaged hemisphere in any of the groups. These observations imply that over a period of weeks, the recovery of swallowing after stroke depends on compensatory reorganisation in the undamaged hemisphere. The situation appears to differ from that in the limb muscles where some TMS studies have indicated that limb recovery after hemiparesis is more likely to result from an increase in the activity of remaining viable cortex in the damaged hemisphere[19]. In such cases, the scope for expansion of a normal connection from the undamaged part of the brain may be a limiting factor in recovery.

Driving reorganisation in human swallowing motor cortex

Given that the intact hemisphere plays an important role in the recovery of swallowing after stroke, then we are provided with an interesting opportunity for studying plasticity of an intact (normal) pathway. Indeed, it could be suggested that any future therapies aimed at enhancing swallowing recovery should be targeted towards manipulating reorganisation on the intact side. One potential candidate for such a therapy might be the manipulation of sensory input to the cortex. Sensory input from the gut not only has a major influence on the activity of brainstem swallowing centres, but also converges onto cortical sensory and motor areas[9]. Furthermore, it has been shown that the excitability of the cortical projection to swallowing muscles can be influenced by stimulation of afferent fibres in the vagal and trigeminal nerves[20]. Single stimuli, used in those studies, had a very short lasting effect, but recent work has shown that prolonged (10 minutes) electrical stimulation of the pharynx, via intraluminal ring electrodes housed on a thin catheter which is then swallowed, can induce changes in cortical excitability that outlast the stimulus by up to 60 minutes[21]. Depending on the frequency used, it appears that pharyngeal stimulation can produce changes in pharyngeal cortex which are either excitatory (1-10 Hz) or inhibitory (20-40 Hz),[22]. Thus, if the excitatory approach could be adopted in dysphagic stroke patients, then it could prove to be a potential mechanism for speeding recovery of function from the intact representation in the undamaged hemisphere.

Pharyngeal stimulation in stroke

Despite this observation, there have been few if any direct demonstrations in man that any form of plasticity inducing stim-

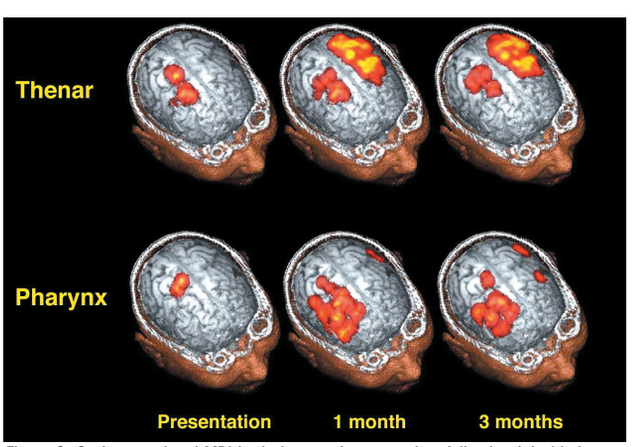


Figure 3: Surface rendered MRI brain images from a patient following left sided hemipsheric stroke. TMS topographic data of the pharyngeal and contralateral thenar muscles have been coregistered. The patient was dysphagic at presentation but recovered and was swallowing safely at 3 months. It is evident that after stroke, the representation of the pharynx in the anterior aspect of the motor cortex and premotor areas expands anterolaterally in the right unaffected hemisphere at both 1 and 3 months, with little change in the affected left hemisphere. In contrast, the representation of the thenar muscles in superior motor cortex increases anteriorly and posteriorly in the affected left hemisphere over time, but remains unchanged in the unaffected right hemisphere. (Reproduced with kind permission reference 18).

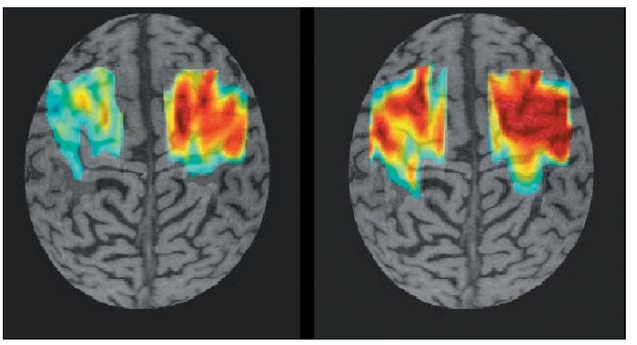


Figure 4: MRI co-registration of pharyngeal motor map in a dysphagic stroke patient after left basal ganglia infarct. Topographic maps were acquired before and 1 hour post-pharyngeal stimulation. Stimuli were applied to individual points on a scalp grid matrix and the responses recorded. A scalp map representing the areas of response for pharynx was then generated and co-registered anatomically with the patient's motor cortices using MRI. After stroke, most of the pharyngeal representation is on the undamaged (right) hemisphere. The greatest changes are also seen in the intact hemisphere after pharyngeal stimulation (Reference 22).

uli produces a measurable improvement in function after cerebral injury. Of relevance, however, the effects of pharyngeal stimulation on swallowing have been recently investigated in acute dysphagic stroke patients[22]. The application of 10 minutes of the excitatory frequency 5 Hz of pharyngeal electrical stimulation at 75% of that maximally tolerated by the patient was used. The stimulation was again applied using the intraluminal catheter swallowed by the patient, and resulted in a long-term (60 minutes) increase in swallowing cortico-bulbar excitability predominantly within the undamaged, with lesser changes in the damaged hemisphere (figure 4). Critically, this was strongly associated with an improvement in swallowing during the same time frame using videofluoroscopy, the gold standard for measuring swallowing performance[22]. Specifically, the swallowing response time reduced, implying a more efficient swallow, and the degree of aspiration lessened. The exciting implication from these results is that that sensory input to the human adult brain can be programmed to promote beneficial changes in plasticity that result in an improvement of function after cerebral injury. Whilst the more long-term (days to weeks) effects of this approach still need to be established, the observations hold great promise for future neuro-rehabilitative strategies.

Correspondence Address

Dr Shaheen Hamdy
Department of GI Science, Clinical Sciences Building, Hope Hospital
Eccles Old Road, Manchester M6 8HD
Tel: 0161 787 4363, Fax: 0161 787 1495
Email: shamdy@fs1.ho.man.ac.uk

Acknowledgements

The contributions of Professor David Thompson, Professor John Rothwell, Ms Maxine Power, Dr Chris Fraser and Dr David Gow are gratefully acknowledged.

References

1. Buonomano, D.V. and Merzenich, M. M. (1998). *Cortical plasticity: from synapses to maps.* Ann. Rev. Neurosci. 21, 149-186.
2. Cohen, L. G., Ziemann, U., Chen, R. G., Classen, J., Hallett, M., Gerloff, C. and Butechisch, C. (1998). *Studies of neuroplasticity with transcranial magnetic stimulation.* J. Clin. Neurophysiol. 15, 305-324.
3. Nudo, R. J. and Milliken, G. W. (1996). *Reorganization of movement representations in primary motor cortex folowing focal ischaemic infarcts adult squirrel monkeys.* J. Neurophysiol. 75(5), 2144-2149.
4. Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., Larbig, W. and Taub, E. (1995). *Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation.* Nature 8(375), 482-484.
5. Nudo, R. J., Wise, B. M., SiFuentes, F. and Milliken, G. W. (1996). *Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct.* Science 272, 1791-1794.
6. Nudo, R. J., Plautz E. J., Frost S. B. (2001). *Role of adaptive plasticity in recovery of function after damage to motor cortex.* Muscle Nerve 24, 1000-1019.
7. Liepert, J., Bauder, H., Wolfgang, H. R., Miltner, W. H., Taub, E., Weiller, C. (2000). *Treatment-induced cortical reorganization after stroke in humans.* Stroke 2000 31, 1210-1216.
8. Martin, R. E. and Sessle, B. J. (1993). *The role of the cerebral cortex in swallowing.* Dysphagia 8, 195-202.
9. Miller, A. J. (1982). *Deglutition. Physiol.* Rev. 62, 129-184.
10. Sumi, T. (1969). *Some properties of cortically evoked swallowing in rabbits.* Brain Res. 15, 107-120.
11. Penfield, W. and Boldery, E. (1937). *Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation.* Brain 60, 389-443.
12. Woolsey, C. N., Erikson, T. C. and Gilson, W. E. (1979). *Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation.* J. Neursurg. 51, 476-506.
13. Gordon, C., Langton Hewer, R. and Wade, D. T. (1987). *Dysphagia in acute stroke.* Br. Med. J. 295, 411-414.
14. Barer, D. H. (1989). *The natural history and functional consequences of dysphagia after hemispheric stroke.* J. Neurol. Neurosurg. Psychiatry 52, 236-241.
15. Smithard, D. G., O'Neill, P. A., Park, C., Morris, J., Wyatt, R., England, R. and Martin, D. F. (1996). *Complication and outcome after acute stroke. Does dysphagia matter?* Stroke 27, 1200-1204.
16. Aziz, Q., Rothwell, J. C., Barlow, J. and Thompson D. G. (1995). *Modulation of esophageal responses to magnetic stimulation of the human brain by swallowing and by vagal stimulation.* Gastroenterology 109, 1437-1445.
17. Hamdy, S., Aziz, Q., Rothwell, J. C., Singh, K., Barlow, J., Hughes, D., Tallis, R. C. and Thompson, D. G. (1996). *The cortical topography of human swallowing musculature in health and disease.* Nat. Med. 2(11), 1217-1224.
18. Hamdy, S., Aziz, Q., Rothwell, J. C., Power, M., Singh, K., Nicholson, D. A., Tallis, R. C. and Thompson, D. G. (1998). *Recovery of swallowing after dysphagic stroke relates to functional reorganisation in intact motor cortex.* Gastroenterology 115, 1104-1112.
19. Turton, A., Wroe, S., Trepte, N., Fraser, C. and Lemon, R. N. (1996). *Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke.* Electroenceph. Clin. Neurophysiol. 101(4), 316-328.
20. Hamdy, S., Aziz, Q., Rothwell, J. C., Hobson, A., Barlow, J. and Thompson, D. G. (1997). *Cranial nerve modulation of human cortical swallowing motor pathways.* Am. J. Physiol. 272, G802-808.
21. Hamdy, S., Rothwell, J. C., Aziz, Q., Singh, K. D. and Thompson, D. G. (1998). *Long-term reorganisation of human motor cortex driven by short-term sensory stimulation.* Nat. Neurosci. 1(1), 64-68.
22. Fraser, C., Power, M., Hamdy, S., Hobday, D., Hollander, I., Hobson, A., Tyrell, P., Williams, S., Rothwell, J., Thompson, D. G. (2001). *Driving Plasticity In Adult Human Motor Cortex Improves Functional Performance After Cerebral Injury.* Clin. Neurophysiol. 112, Suppl. 1, S86.

Delaying the need for levodopa - Mirapexin™ approved as initial monotherapy for Parkinson's disease

Mirapexin™ (pramipexole) has been granted a licence in the UK for use as monotherapy for the treatment of the signs and symptoms of idiopathic early Parkinson's Disease (PD). Newly diagnosed patients can now be managed with Mirapexin™ as initial therapy, thereby delaying the need for levodopa.

One of the goals of PD therapy is to prevent the long-term complications associated with chronic levodopa use. This new licence indication for Mirapexin™ allows specialists to start treatment with Mirapexin™ alone in early PD, thereby delaying the need for levodopa and the onset of complications. This approach fits with current medical opinion, which is in favour of levodopa-sparing. It will also widen the therapeutic options for PD, a condition where the manifestations of symptoms may be highly individualised.

A recent study showed that initial therapy with pramipexole may reduce the risk of developing dopaminergic complications by 55% compared with levodopa over a two year period. In addition, recent data indicates that early PD patients can be successfully managed for at least four years using pramipexole without the need for levodopa.

PD affects around 120,000 people in the UK and is the second most common neurodegenerative disease in adults. It is caused by a progressive deterioration of the nerve cells of the brain that help control movement and is characterised by difficulty in walking, movement and co-ordination. The nature and severity of symptoms, which include tremor, muscle rigidity, slowed motion, shuffling gait and loss of facial expression, vary from patient to patient. There is currently no cure for PD and drug treatment is primarily aimed at controlling the symptoms, thereby allowing patients to lead as normal a life as possible.

Levodopa, which has been available for more than 30 years, is one of the most widely used treatments for the symptoms of Parkinson's disease. However, long-term treatment with levodopa can be associated with complications that can lead to additional disability. These complications include 'on-off' fluctuations where patients fluctuate between periods of relatively good mobility and periods of immobility when they do not respond to medication, and dyskinesias (uncontrollable involuntary movements). Approximately 50-75% of patients experience motor complications within three to six years of initiating levodopa therapy.

Most drug treatments for PD work by restoring dopamine receptor stimulation. They do this either by increasing dopamine levels (levodopa or COMT inhibitors) or mimicking the action of dopamine (e.g. dopamine agonists).

> "Mirapexin™ (pramipexole) has been granted a licence in the UK for use as monotherapy for the treatment of the signs and symptoms of idiopathic early Parkinson's Disease (PD). Newly diagnosed patients can now be managed with Mirapexin™ as initial therapy, thereby delaying the need for levodopa."

Pramipexole is a non-ergot dopamine agonist, which has been approved for monotherapy use in the United States since launch in 1997. Pramipexole is now the most widely prescribed dopamine agonist in the US, and recent guidelines published this year suggest that it is preferable to employ a dopamine agonist, such as pramipexole, as initial symptomatic therapy to reduce the risk of motor complications associated with levodopa.

A randomised controlled trial involving 301 PD patients compared initial therapy with pramipexole with initial therapy with levodopa. The study demonstrated that patients treated with pramipexole had a significantly lower incidence of major motor complications (28% pramipexole vs 51% Levodopa). Also, patients treated with pramipexole had a significantly reduced probability of developing dyskinesias, possibly the most troubling motor complication. Overall, the study showed that initial therapy with pramipexole may reduce the risk of developing dopaminergic complications by 55% compared with levodopa over a two year period.[1]

In addition, recent data indicates that early PD patients can be successfully managed for at least four years using pramipexole without the need for levodopa. The study, which includes 717 patients (one of the largest databases in the world for the long-term follow up of early PD patients initiated on a dopamine agonist), showed that 47% of the patients completing the trial were successfully maintained on pramipexole monotherapy at four years. According to a survival analysis, there is a probability of up to 41% that patients can maintain on pramipexole for more than four years without the need for levodopa.[2]

Pramipexole can also be used as adjunctive therapy and thus help to reduce the complications associated with long-term chronic levodopa use. It therefore offers an alternative treatment option in patients with late stage PD.

For more information contact Pharmacia Ltd on Tel. 01908 661 101, Fax. 01908 603950.

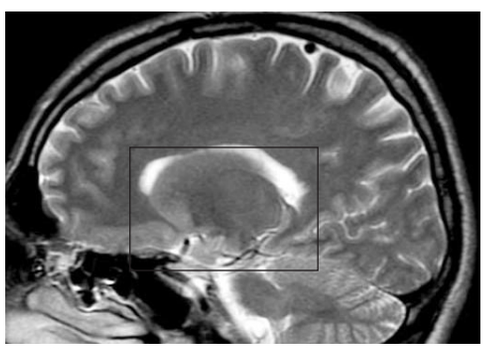
References

1. Parkinson Study Group (PSG) (2000) 'The CALM-PD [Comp-arison of the Agonist Pramipexole vs. Levodopa on Motor Complications in Parkinson's Disease] Trial', JAMA 284: 1931-38.
2. Barone P., Bressman S. & Musch, B., 'Pramipexole (PPX) Without Levodopa (LD) As Early Treatment For Parkinson's Disease (PD): A Long-Term Follow-Up Of 717 Patients', presented at 14th Int'l Congress on Parkinson's Disease, Helsinki, Finland, July 29, 2001.
3. IMS Xponent data – Jul 01
4. Olanow, CW, Watts, RL, & Koller, WC (2001) 'An algorithm (decision tree) for the management of Parkinson's Disease: Treatment Guidelines', Neuology 56(Suppl 5): S1-S5

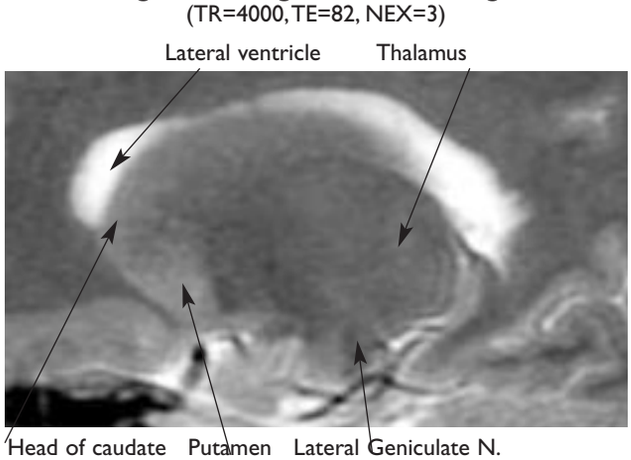
The Basal Ganglia

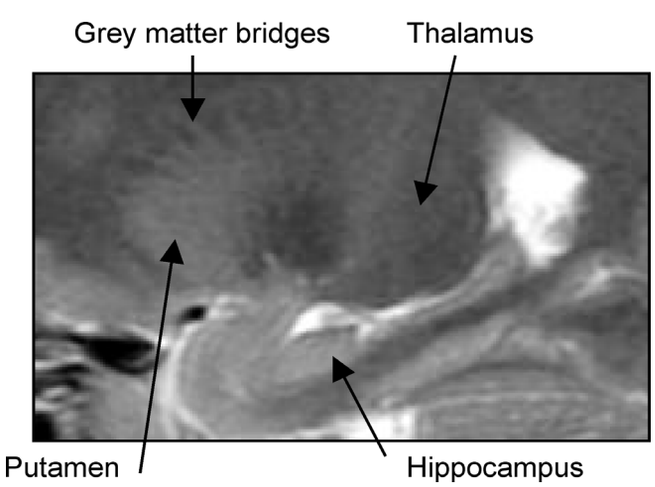
Alasdair Coles and Justin Cross

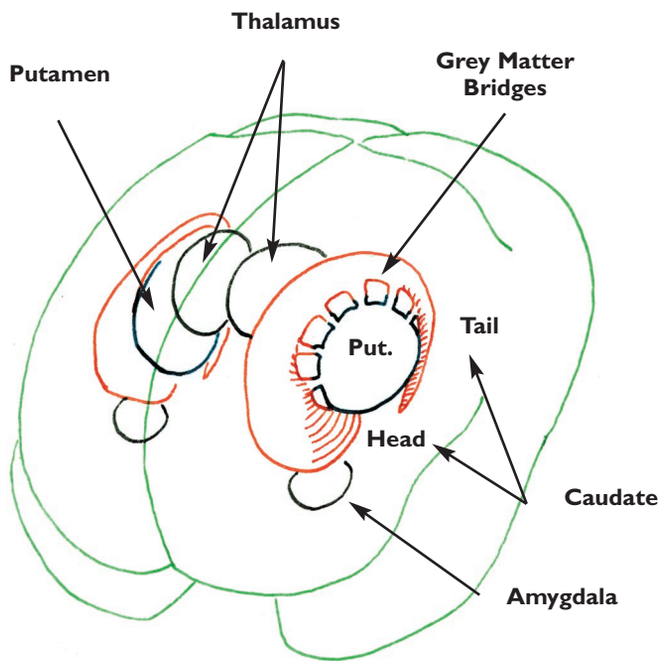
The Basics. The term basal ganglia usually means those deep grey nuclei that are involved in the higher control of movement and cognitive processes and includes the putamen and caudate, and perhaps also the subthalamic nucleus and the substantia nigra. Cells within the basal ganglia have complex properties, responding for instance to sensory stimuli only when a movement results, or firing just before a joint is moved. The basal ganglia are therefore best seen as converting highly processed sensory information into a motor programme. This is reflected in the pathology of the basal ganglia which give rise to complex movement disorders such as Parkinson's disease, Huntington's chorea and the dystonias.



Sagittal T2 weighted FSE MR images
(TR=4000, TE=82, NEX=3)



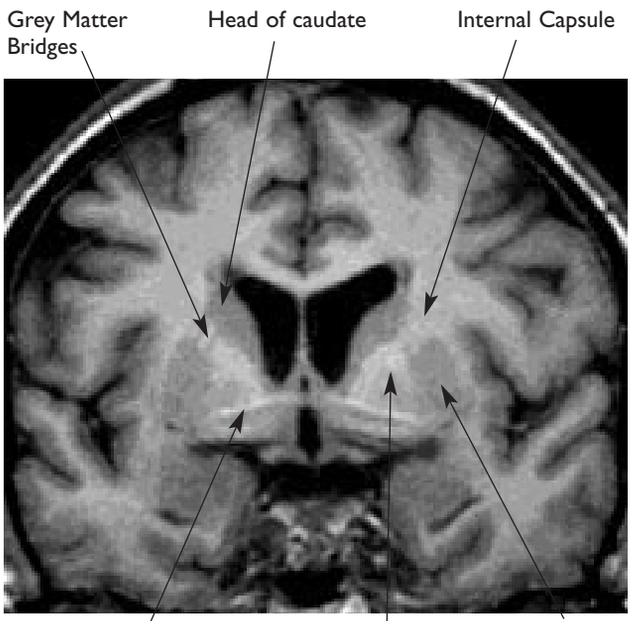




Development & Terminology. The **caudate, putamen, claustrum** and **amygdala** have similar origins. But, as the claustrum is rather obscure and the amygdala is better thought of as part of the Papez circuit, only the caudate (Latin: tail) and putamen (Latin: shell) are considered part of the basal ganglia. They are called collectively the **neostriatum**, as they derive from neocortical cells around the lateral ventricle. They are really one structure, having very similar histology, separated by the internal capsule, and connected by grey bridges, giving the striped appearance that led to the name **corpus striatum**. The globus pallidus (Latin: pale body), or pallidum, is phylogenetically more ancient, arising from the developing diencephalon and so is referred to as **paleostriatum** (paleo = ancient). The **lentiform,** or lenticular, nucleus is a convenient term to describe the putamen and pallidum as they appear to form one lens-shaped mass, but it is not a functional unit.

The caudate. The **head** of the caudate forms the lateral wall of the frontal horn of the lateral ventricle and merges inferiorly with the putamen. The **body** begins at the level of the foramina of Munro and forms part of the floor of the body of the lateral ventricle. It is separated from the thalamus by the caudothalamic groove which transmits the stria terminalis and the thalamostriate vein. The **tail** continues from the body of caudate at the posterior thalamus and follows the contour of the lateral ventricle forming part of the roof of the temporal horn. The tail is slender and poorly visualised on MRI. It terminates in the amygdala.

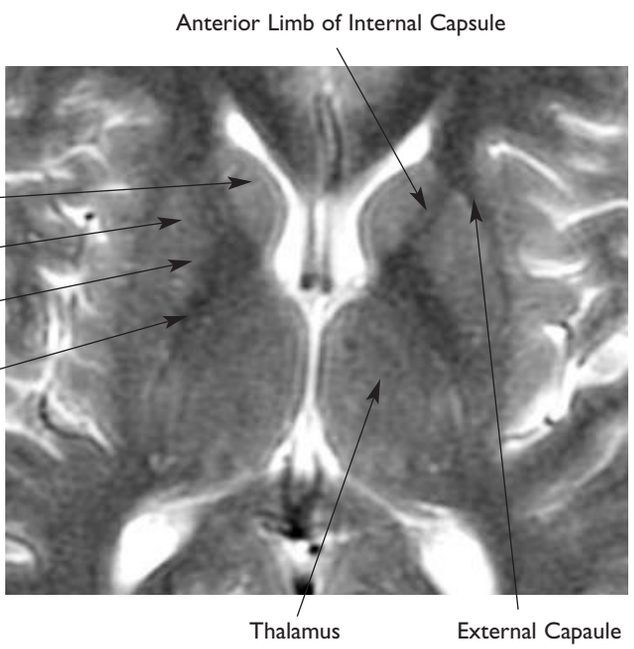
Neuroradiological Anatomy



Coronal Gradient Echo MR image at the level of the anterior commissure
(TR=19.2, TE=4.2, TI=450, NEX=1)

The lentiform nucleus (putamen and pallidum) is surrounded medially by the internal capsule and laterally by the external capsule. It is divided by a thin vertical plate of white matter into the medial globus pallidus and lateral putamen. The globus pallidum is more heavily myelinated than the putamen and is therefore slightly hyperintense on T1WI and hypointense on T2WI, merging with the adjacent internal capsule. Functionally, the globus pallidus has internal and external components, however, these cannot be resolved on imaging.

Axial T2 weighted FSE MR image at the level of the foramina of Munro
(TR=6000, TE=100, NEX=2)



Imaging of the Basal Ganglia

Perivascular (Virchow-Robin) spaces measure up to 1.5 cm in diameter and are commonly seen in the basal ganglia. They arise from enlargement of the CSF-filled sleeves that contain the small perforating arteries. They have no clinical significance, but may be misinterpreted, often for a lacunar infarction. **Calcification of the basal ganglia** is usually idiopathic and without clinical significance. It is better seen on CT; diffuse calcification is seen in 15% of paediatric CT examinations with little relation to clinical symptomatology [1]. There are however multiple underlying causes for basal ganglia calcification: disorders of calcium metabolism (hyper, hypo- and pseudohypo-parathyroidism) to ToRCHS infection, tuberose sclerosis and Cockayne syndrome. **Iron deposition** is normal in the basal ganglia and increase with age. Iron is seen as decreased signal intensity on T2WI and variable signal change on T1WI. Quantitative measurement of T2 shortening may be a useful marker for certain basal ganglia diseases (eg Parkinson's Disease) [2].

Connections of the Basal Ganglia. The putamen and caudate receive input from the whole cortex and the intralaminar nuclei of the thalamus. The output from the basal ganglia is mainly inhibitory, GABAergic, and via the internal segment of the globus pallidus and the pars reticulata of the substantia nigra, to specific brainstem structures and the ventrolateral and ventroanterior nuclei of the thalamus. Projections from here go to the premotor cortex, supplementary motor area and prefrontal cortex. There are two important loops in the wiring of the basal ganglia, put simplistically: a **motor loop**, mediated through the putamen that goes to premotor cortex and supplementary motor area, and a **non-motor loop** that passes through the caudate and projects to prefrontal cortex.

References

1. Kendall B, Cavanagh N (1986). Intracranial calcification in paediatric computed tomography. Neuroradiology 28(4):324-30.
2. Martin WR (2001). Magnetic resonance imaging and spectroscopy in Parkinson's disease. Adv Neurol 86:197-203.

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British Society of Neuroradiology Annual Meeting

12-13 October 2001, Harrogate, UK

The 2001 Annual Meeting of the British Society of Neuroradiology was organised by the Neuroradiology Department of Leeds General Infirmary (Drs. Bonsor, Nelson and Straiton). As usual, it was a very well attended event, with over one hundred neuroradiologists from around the country present.

There were six scientific sessions over the two days of the meeting, covering a wide range of diagnostic and interventional subjects.

In the diagnostic neuroradiology sessions, there was a very stimulating and broad ranging agenda. The use of advanced MR techniques was particularly well represented. Several papers from Queen Square described the application of diffusion and perfusion scanning in the imaging of intracranial haemorrhage and cerebrovascular disease, and the use of advanced diffusion tensor techniques in stroke and tumour imaging was reported by the Cambridge group. Several speakers presented work relating to the use of proton MR spectroscopy: papers from Liverpool and Newcastle reported early work correlating spectroscopic and histological findings in brain tumours, and there was interesting work from Charing Cross describing its application in Alzheimer's disease.

Jonathan Gillard who presented one of the three "most outstanding papers"

Various aspects of vascular imaging were presented, with videos of real-time dynamic MR angiography of dural arteriovenous fistulas presented by the Sheffield group, and of dynamic MR venography by the Newcastle department. Experience using spiral CT angiography for the imaging of intra- and extracranial vascular disease from Belfast and Edinburgh was also presented. A particularly novel application of spiral CT angiography was presented from Leeds, with the use of volume rendering technology to produce a highly entertaining virtual flight through the vessels of the circle of Willis as seen from the perspective of a red blood cell.

Several papers were presented relating to interventional neuroradiology. Experience from Oxford using a novel liquid embolic agent for the treatment of intracranial aneurysms was described, and work from Edinburgh using new varieties of coil for aneurysm embolisation was also presented. Preliminary experience using vertebroplasty for the treatment of painful osteoporotic vertebral fractures was presented by the Newcastle group.

Three presentations were made to the presenters of the three most outstanding papers.

Jonathan Gillard (Addenbrooke's) presented a paper entitled 'High resolution MR of carotid atheroma', and described his experience using high resolution sequences (voxel sizes down to 0.24 mm) to characterise plaque morphology and composition, using histopathological examination of carotid endarterectomy specimens as a standard for comparison. He concluded that this technique was a useful tool for the evaluation of plaque morphology and volume.

Alison Jones (a medical student at Royal Hallamshire Hospital) presented work performed in conjunction with the academic MR unit at Sheffield University entitled 'Interpretation of MR images of posterior fossa abnormalities of the fetus in utero and post-mortem'. Ultrafast MR imaging of fetuses with posterior fossa abnormalities was performed in utero, and subsequently in a proportion of these cases post-mortem. MR was

found to be a valuable tool for in utero visualisation of the posterior fossa, a site notoriously difficult for antenatal sonography.

Neil Stoodley (Cardiff) presented a paper entitled 'Pachygyria: what's in a name?', in which he reviewed over fifty cases of lissencephaly and polymicrogyria. He concluded that polymicrogyria is frequently misinterpreted as pachygyria or lissencephaly, an important distinction that should be made because of genetic implications.

There were three invited lectures. Jan Casselman of Bruges is a highly respected neuroradiologist with an international reputation for head and neck imaging. He presented two lectures: 'Imaging of the trigeminal nerve – anatomy and pathology' and 'Imaging of the inner ear and central auditory pathways'. These lectures confirmed Dr Casselman's reputation as a speaker of great verve and skill, and he enlightened his entire audience. He was subsequently awarded the James Bull Medal for his lectures. Jim Meaney of Dublin also presented a lecture entitled 'MR angiography in neuroradiology' in which he described state-of-the-art applications of cranial MR angiography.

The Annual Dinner took place at the Old Swan Hotel. The President of the Society, Dr John Bradshaw of Frenchay Hospital, Bristol, gave the after-dinner speech and announced his retirement from the post after several years' service.

The conference was well organised, and the standard of papers presented was very high. The scientific content of the papers was at least as good as that at American and European conferences, and in many cases better. There was a good mix of subject material, and some excellent and entertaining presentations. There was much catching up with colleagues from around the country, and the Old Swan Hotel was an excellent venue.

Dr Daniel Birchall, Newcastle upon Tyne

Next year's Annual Meeting will take place in Winchester.

Epilepsy Specialist Nurse Association Annual Meeting

17-18 September 2001, Bath, UK

The university had a pleasant feel, but an opportunity was missed for delegates to meet beforehand. The conference proper began with Jim Oates requesting a minute's silence for those who lost their lives in the atrocities in America.

First speaker Sarah McLoud, is a CPN in Birmingham who has worked with Tim Betts. Sarah's main theme was complimentary medicine as applied to epilepsy. In her survey, over 50% of nurses used some form of complimentary medicine in their work, and many workplaces have a policy for such care. Many nurses felt using such therapies helped them maintain their intimate care role. The other topic was Tim Betts' study of related EEG recordings and complimentary therapies. Over 1 million people had some form of complimentary therapy, and 4 out of 10 GPs offer some form.

Professor G Stores, a Developmental Neuro-psychiatrist at Oxford, gave a talk on Epileptic and Non-epileptic nocturnal events covering Parasomnias. These are behavioural episodes that interrupt or are closely associated with sleep, grouped depending on which stage of sleep occurrences were likely to happen. He mentioned both primary and secondary disorders. Some nocturnal frontal lobe seizures may well be confused with repetitive sleep starts, sleep onset hallucinations especially if combined with sleep paralysis. Some secondary conditions were manifestations of psychological and medical conditions and were often confused with epilepsy. Professor Stores produced a good example of a cerebral tumour which had been picked up on a CAT scan but disregarded. Arousal disorders, i.e. sleep walking and night terrors, were discussed with the recommendation that they be properly investigated, with a polysomnography required for correct diagnosis.

Bernie Morris, who works at a tertiary referral centre in Birmingham, dealt with daily aspects of life for the school child and adolescent, taking into account the child's attention span, memory and motor skills whilst considering views, attitudes and moral reasoning. The aim is to provide safety, training, avoidance of absences and communication by producing health and safety policies for teachers and others such as dinner ladies and coach drivers.

Lorraine Lawton gave a quiz to start her talk. The answers raised interesting points, and she emphasised the need for accurate and honest information.

Following lunch the delegates went into their chosen workshops. 'Managing challenging behaviour in epilepsy' was the most popular. The others were 'EEGs unravelled'; 'Managing Status with Midazolam' and 'Audit: How to start'.

The last session was a talk on 'An Overseas Experience' by Lucy Magola, an Epilepsy Specialist Nurse in Malawi. She spoke of starting up a specialist service against a background of traditional beliefs where many sufferers were thought to be possessed, resulting in social isolation. The setting up of a clinic and attendance figures were shown, as was how they coped with the lack of modern AEDs. Lucy showed that slow but positive progress was being made.

On the second day Professor G Castledine, University of Central England, spoke of an 'Agenda for Health', with nurses giving less holistic care due to their increasing specialism. An increased through-put of patients has added pressure, as has the Government setting some difficult-to-reach targets. The various specialist nurses, differences between specialisms, the relationship between specialists and general nurses, and arrangements for professional development were discussed. He finished by discussing the soon to be published set of competencies for the different levels of function for specialists.

The subsequent AGM discussed the name change of the association. This is because there is uncertainty about use of the words 'specialist nurse' in proposed legislation.

In the afternoon, Dr Helen Cox, Wessex Genetics Service, talked about Syndromes of genetic origin in which epilepsy was a major factor. These included Tuberous Sclerosis, Fragile X and Angelman syndrome. This presentation raised questions but also gave hope for the future in reducing such disorders.

Kim Barlow-Miles discussed the NSE's 'Epilepsy Information Service' which provides specialist epilepsy nurse training to an additional listening service and a face-to-face information resource provided by volunteers. It is a confidential listening support service to support professionals who deal with epilepsy. Sharon Harvey then presented the BEA's Accredited Volunteer scheme. This is a complimentary service to that of the NSE. Volunteers are well trained but limitations are well identified.

The final session by Sue Thomas, Nursing, Policy and Practice Advisor to the RCN, was on 'Nurse Prescribing'. This covered a brief history of nurse prescribing, nurse training for qualification and the results on qualifying. Future options were identified, along with the differences between Independent prescribing and Supplementary (Dependent) prescribing. Present legislation and future NHS plans giving the various hypotheses were shown, including the roles and relationships in primary and secondary care. The talk concluded by stating that nurse prescribing is here to stay – it is a positive development in nursing and with good teamwork, networking and peer support it will provide a better service for the patient.

The conference was supported by Neuro-Education in the form of Brian Chappell, the National Manager, who produced certificates of attendance.

Jack Somers, Executive Committee

Next year's conference will be at Sheffield University on the 16th and 17th September, 2002.

Society for Neuroscience 31st Annual Meeting

10-15 November, 2001, San Diego, USA

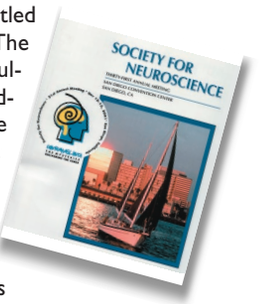
A total of 28,870 delegates attended this meeting, exceeding the previous years total and a testament to the tremendous growth in research activity in neuroscience. The title of the meeting was 'Unravelling the mysteries, delivering the cures,' emphasising the important contribution that basic research is playing towards developing therapies for CNS disorders.

The following were some of my highlights. The main meeting kicked off with a public lecture by T.M. Jessell of Columbia University entitled 'Genes, neurons and circuits: Therapeutic Insights from Neural Development.' Jessell posed the question: How do sets of neurons get organised into neural circuits? He described how neural circuits are critical to brain function and the phases of circuit assembly namely, neuronal identity, axon pathfinding and connectivity. This work used the spinal cord as a model of circuit assembly given its well defined motor output and sensory feedback circuits and the fact that spinal cord is highly conserved in lower organisms. The main part of this lecture emphasised the important interplay between transcription factors and secreted signals in determining the classes of postmitotic cells generated in the spinal cord. For example, the influence a graded concentration of the Sonic Hedgehog protein plays in determining cell fate was particularly interesting. In the latter part of his lecture Jessell suggested some therapeutic interventions for spinal cord injury including the role of transcription factor expression in axonal regeneration in the mature spinal cord. One possibility is to reintroduce genes that are expressed during development in order to increase the regenerative potential of mature spinal cord. It is likely that defects in transcription factors or mechanisms controlling transcription factor expression may underlie some disease conditions. As an example of this Williams syndrome was described which involves deletion of GTF2i. Many challenges still lie ahead in the field of spinal cord regeneration and Jessell among others believes that understanding the development of circuitry will give a real insight into the understanding of mature circuits.

The Pfizer lecture was presented by Christine Holt from the Department of Anatomy, University of Cambridge. Dr. Holt gave an interesting lecture demonstrating how axons find their targets using the retinotectal system of Xenopus as a model. She showed the purposeful and dynamic movement of growth cones using time-lapse video and explained the effects of various factors including Netrin-1 Ephrin-B and Semaphorin 3A in specific domains acting as molecular cues for guiding axons. For example the optic nerve head is rich in Netrin-1 and this acts as a cue for the axon to leave the eye.

As part of a symposium on serotonin-induced neural plasticity R.S. Duman of Yale University School of Medicine showed that cell proliferation in the hippocampus can be increased by 5-HT release and can be decreased by 5-HT depletion. This group also showed that 70-80% of newborn cells in this area are neurons. The number of bromodeoxyuridine labelled cells within the subgranule cell layer of the hippocampus increased following Fluoxetine treatment, indicating increased cell proliferation. Interestingly when this was measured over a time course the increase only became significant after 14 days of treatment, which is consistent with the time course for effects of antidepressant treatment. The response to Fluoxetine was blocked in 5-HT1A knockout mice suggesting that its effects may be specifically mediated by the 5-HT1A receptor. The big question remains whether neurogenesis is directly involved in the pathophysiology and treatment of depression. Further research is required to answer this question.

The Bristol Myers Squibb Presidential Lecture was given by Sangram S. Sisodia of the University of Chicago who discussed the cellular and transgenic approaches to understanding the functions of APP and presenilins in a lecture entitled 'Molecular neurobiology of Alzheimer's disease.' The lecture began with an overview of the disease, the vulnerable neurons and its prevalence and costs worldwide. It was suggested that Aß 1-42 was probably the pathogenic variant in Alzheimer's disease and went on to describe some of the proposed functions of the amyloid precursor protein (APP). The processing of APP through ß, α or γ secretase was described. The relatively recently discovered presenilins (1995) were then outlined. These molecules may prove to be particularly important as FAD-linked presenilin elevates Aß 1-42 peptides in plasma. Two hypotheses were presented, one in which presenilins are γ secretases and the second that presenilin is a co-factor in γ secretase activity. There is much controversy over which hypothesis is correct. Some work was presented implicating the presenilins and their role in modulating calcium function as being important in the selective vulnerability of perforant path cells. The lecture finished with a look to the future and some of the therapeutic approaches and developing treatments for Alzheimer's disease including anti Aß immunotherapy, secretase inhibitors, Aß disaggregation with Cleocinoyl as well as new modalities using NSAIDs or modifying levels of estrogen and cholesterol.



A symposium on animal models and therapeutic strategies in Alzheimer's disease contained several presentations utilising clearance of amyloid-ß by immunotherapy. One novel approach, being undertaken by Bacskai and colleagues at Massachusetts General Hospital in conjunction with Elan Pharmaceuticals, is the monitoring of plaque clearance by immunotherapy in vivo. This was achieved by using fluorescent anti-amyloid antibodies and multiphoton confocal microscopy on the exposed surface of the rat brain.

A previous study has shown that women who participate in estrogen replacement therapy have a lower incidence of Alzheimer's disease. This prompted Levin and colleagues to use an APP overexpressing mouse model to investigate the effects of 17α and 17ß estradiol on Aß concentration and demonstrated that both compounds reduced Aß concentration. In addition, two groups from Washington University in conjunction with Lilly research labs demonstrated CNS and plasma Aß clearance is altered by peripheral anti-Aß antibody and this decreases the Aß burden in a mouse model of Alzheimer's disease.

The pace of research into neurodegenerative diseases is phenomenal, for example there were around fifty separate sessions (poster sessions, slides and symposia) dedicated to Alzheimer's disease. In addition to the scientific sessions a notable presence among the exhibitors was that of the GlaxoSmithKline Neurology Centre of Excellence for Drug Discovery, which is focused on understanding basic mechanisms of neurological disorders and developing therapies for these disorders.

Overall, this meeting once again emphasised the explosion of research activity in neuroscience. Enthusiasm for investigating basic mechanisms, in order to deliver the cures, seems to be at an all-time high. The quality of the speakers underpinned the significance of the meeting and emphasised its international importance. Although the sheer volume of research at this conference is at times overwhelming, it is clear that this is a meeting that should not be missed, especially by anyone intent on keeping up to date with the latest developments in their chosen neuroscience field. Attendance at a large meeting has the added advantage that there are always opportunities to gain knowledge from other areas of neuroscience.

Ian De Souza, The Open University

The 32nd Annual Meeting of the Society for Neuroscience is in Orlando, November 2-7, 2002 - 'In pursuit of the Answers'.

International Psychogeriatric Association 10th Congress

9-14 September, 2001, Nice, France

The Tenth IPA Congress brought together around 2,000 scientists and clinicians in the field of psychiatric disorders in late life. The IPA has members in over 70 countries and is the foremost multidisciplinary organisation concerned with mental health care of elderly people. Membership includes Old Age Psychiatrists, Neurologists, Geriatric Medicine Physicians and those from other disciplines including Psychology, Social Work, Occupational Therapy and Nursing. This congress represented a rich feast of multi-dimensional approaches to some of the major psychiatric problems in late life.

The topics which predominated were the expected ones: more evidence for the efficacy of cholinesterase inhibitors in Alzheimer's disease (with new data on improvements in non-cognitive symptoms, reduced carer stress and improved activities of daily living); sessions on Mild Cognitive Impairment, dementia with Lewy bodies and late life depression and psychosis. A particular feature of the meeting was the excellent quality of the poster presentations, which in terms of scientific content often considerably outweighed those of the oral sessions.

Not that the oral sessions were disappointing, and picking highlights is difficult. In the area of Mild Cognitive impairment, Ron Petersen outlined his groups' view that "amnestic" MCI, which progresses to Alzheimer's disease at a rate of 10-15%/year, is probably just one of many different forms of MCI which require further research. Barry Reisberg described his group's work from New York suggesting that certain types of subjective cognitive difficulties might even define a "pre-MCI" group who were at high risk of subsequently fulfilling MCI criteria. This challenges us to attempt to move detection back to an even earlier level. A European collaborative study investigating the usefulness of SPECT scans in the diagnosis of dementia, reported by Klaus Ebmeier, suggested that amongst inexperienced raters diagnosis could be considerably enhanced by utilising automated methods of scan assessment such as statistical parametric mapping. However, such methods did not improve diagnostic accuracy of experienced raters. Many interesting brain-behaviour correlates were reported, including the relationship between specific neural substrates and personality disturbances; loss of emotional control and amygdala disturbance and apathy and frontal lobe problems. A model of conscientiousness involving frontal lobe function was put forward by J Pochon who argued the central importance of the dorsolateral prefrontal cortex in this regard, as it is the only cortical area to receive sensory messages both from the external world and the internal milieu, as well having a key role in conscious "cognitive" processes. On a similar note, Bruce Miller eloquently outlined the importance of the right frontotemporal regions in self-awareness.

The usefulness of new imaging techniques, such as diffusion tensor imaging for detecting white matter tract pathology, was eloquently demonstrated by Robert Howard. A number of presentations focused on accumulating scientific evidence for widely adopted, but often inadequately researched, use of psychosocial interventions and alternative therapies in dementia. A further update on the Syst-Eur project, which demonstrated that anti-hypertensive treatment produced a 50% reduction in risk of dementia, was reported by F Forette. Continuation treatment with longer follow-up supported a reduction in incidence of dementia by 55%, with evidence that Alzheimer's as well as vascular dementia was reduced. There were several intriguing bits of new data from the poster presentations, such as the suggestion that obesity in late life is a risk factor for Alzheimer's disease and that hypertension is associated with "age associated memory impairment". The important clinical question of whether those with Alzheimer's disease who are non-responders to one of the three cholinesterase inhibitors should be "switched" to another was also addressed by several researchers. Although, unfortunately, no double-blind data was available, the general message appeared to be that switching might well be effective, perhaps more so in those who were intolerant of a cholinesterase inhibitor rather than those who are non-responsive. In terms of maintenance treatment of depression in the elderly, an important study was described by David Wilkinson which showed that recovered depressed subjects were significantly less likely to relapse over a two-year period if lithium was added to their maintenance antidepressant.

Prof. Edmund Chiu (past President) and Prof. Alistair Burns, President as of October 2001.

This brief piece cannot do justice to the presentations - the full programme and abstracts are available at www.ipa-online.org. It is unfortunate that this congress is likely to be best remembered for the terrorist attack in New York which occurred midway through the meeting. While no delegates could really concentrate that afternoon, as the full horror was relayed on large television screens in the congress centre, the IPA board led by President Ed Chiu issued a statement of deep regret and condemnation for the action, but decided to continue the scientific programme as a mark of respect. This difficult but commendable decision was fully supported by delegates.

John O'Brien, Newcastle upon Tyne

The 11th International Congress is in Chicago, USA, 17-22 August, 2003

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 February 8th, 2002.

2002

February

RSM - Neurological Disability in Old Age
12 February, 2002; London, UK
RSM, Tel. 020 7290 2984,
E. fleur.raggatt@rsm.ac.uk

The British Neuropsychiatry Association 2002 Annual Meeting
21-22 February, 2002; London, UK
Gwen Cutmore, BNPA Conference Secretary, Landbreach Boatyard, Chelmer Terrace, Maldon, Essex. CM9 5HT, Tel/Fax: 01621 843334; E-Mail: gwen.cutmore@lineone.net)

March

Practical Paediatric Neurology Study days
Monday 4 - Wednesday 6 March & Thursday 21 - Friday 22 March 2002
Tel 020 7829 8692/ 020 7813 8394, Fax: 020 7831 6902, E-Mail: Courses@ich.ucl.ac.uk

Clinical Electrophysiology of Vision Course
5/6-8 March, 2002; London, UK
E. maggie.lawlor@moorfields.nhs.uk

British Society of Clinical Neurophysiology Scientific Meeting
8 March, 2002; Liverpool, UK
E. secretariat@bscn.org.uk

Brain Awareness Week 2002
12-17 March, 2002; UK
Elaine Snell, Tel. 020 7738 0424, E. elaine.snell@which.net

Immunisation against Alzheimer's and other Neurodegenerative diseases
13 March, 2002; Paris, France
Fondation Ipsen, Tel. 0033 1 44 96 10 10, Fax. 0033 1 44 96 11 99, www.beaufour-ipsen.com

RSM - Neuro-Epidemiology
21 March, 2002; London, UK
RSM, Tel. 020 7290 2984, E. fleur.raggatt@rsm.ac.uk

Degeneration and Regeneration of the Nervous System
21-24 March, 2002; St Moritz, Switzerland
Joachim Weis, Division of Neuropathology, Institute of Pathology, Fax. 0041 31 632 9872, Tel.0041 31 632 3210, E. joachim.weis@pathology.unibe.ch

23rd Advanced Clinical Neurology Course
26-28 March, 2002; Edinburgh, UK
Tel. 0131 537 2082,
Fax. 0131 332 7886,
E. jcc@skull.dcn.ed.ac.uk

April

ABN Spring Meeting
3-5 April, 2002; Oxford, UK
Susan Tann, ABN,
Tel. 020 7405 4060,
Fax. 020 7405 4070,
E. abn@abnoffice.demon.co.uk

3rd World Congress in Neurological Rehabilitation
3-6 April, 2002; Venice, Italy
Aristea, Tel. 0039 06 844 98364,
Fax. 0039 06 844 98332,
E. neurorehab2002@aristea.com

International League Against Epilepsy Annual Scientific Meeting
3-6 April, 2002, Exeter, UK
Conference 2000,
Tel. 01691 650290,
Fax. 01691 670302,
E. denise@conference2000.co.uk

54th Annual Meeting of the American Academy of Neurology
13-20 April, 2002; Denver, USA
Tel. 001 651 695 1940,
Fax. 001 651 695 2791

RSM - Sherrington Memorial Lecture
15 April, 2002; London, UK
RSM, Tel. 020 7290 2984,
E. fleur.raggatt@rsm.ac.uk

IPA European and Mediterranean Regional Meeting
17-20 April, 2002; Rome, Italy
Tel. 001 847 784 1701,
Fax. 001 847 784 1705,
E. ipa@ipa-online.org

5th European Parkinson's Disease Association Conference
22-24 April, 2002; Jerusalem, Israel
Lizzie Graham, Tel 0207 932 1304,
Fax. 0207 233 9226,
E. lgraham@parkinsons.org.uk

British Neuropsychological Society Spring Meeting
April, 2002; London, UK
www.hop.man.ac.uk/bns,
Tel. 0161 275 3401

1st Mediterranean Congress of Neurology
26-28 April, 2002; Limassol, Cyprus
Tel. 00357 5 749919, Fax. 00357 5 749744, E. conwise@cytanet.com.cy

May

RSM - Advances in Management of Epilepsy
2 May, 2002; London, UK
RSM, Tel. 020 7290 2984,
E. fleur.raggatt@rsm.ac.uk

3rd Neurological Cooperation Workshop
2-7 May, 2002; Trest, Czech Republic
Tel. +420 2 67 16 28 14,
Fax. +420 2 67 16 23 77,
E. efns@fnkv.cz

8th European Congress on Epilepsy and Society
3-6 May, 2002; Seville, Spain
Tel. 00353 145 0302,
Fax. 00353 1 409 7814

XIV International Neuro-Ophthalmology Society Meeting
5-8 May, 2002; Buenos Aires, Argentina
Fax. 0054 11 4331 0223,
E. Inos2002@congresosint.com.ar

International Workshop Parkinsonism & Dementia
9-11 May, 2002; Istanbul, Turkey
Tel. ++90 212 293 93 08,
Fax. +90 212 244 12 33,
E.events@vistatourism.com

6th Congress of the European Society for Clinical Neuropharmacology (ESCNP)
14-18 May, 2002; Budapest, Hungary
Tel. 0036 1 311 6687,
Fax. 0036 1 383 7918,
E. Motesz@elender.hu

4th European Federation of Autonomic Societies Meeting
16-18 May, 2002; Athens, Greece
Tel. 0030 1 3634 944,
Fax. 0030 1 3631 690.
E. Info@era.gr

7th Meeting of the European Society of Neurosonology and Cerebral Hemodynamics
26-28 May, 2002; Bern, Switzerland
Tel. 0041 41 767 34 49,
Fax. 0041 41 767 34 00,
E.Neurosonology2002@jacch.jnj.com

13th European Congress of Physical Medicine & Rehabilitation
28-31 May, 2002; Brighton, UK
Melanie Ramsdell, Concorde Services.
Tel. 020 8743 3106,
www.bsrm.co.uk/ec2002

33rd Scandinavian Neurology Congress
29 May-1 June, 2002; Reykjavik, Iceland
Tel. 00354 585 3900,
Fax. 00354 585 3901,
E. Congress@congress.is, www.congress.is

11th European Stroke Conference
29 May-1 June, 2002; Geneva, Switzerland
Tel. 0041 22 33 99 624,
Fax. 0041 22 33 99 621,
E. Esc@mci-group.com

June

International Association of Gerontology: European Section. 6th European Congress of Clinical Gerontology
June 2002; Moscow, Russia
Prof L B Lazebnik, E. Lazebnik@aha.ru

RSM - Advances in treatment of movement disorders
6 June, 2002; London, UK
RSM, Tel. 020 7290 2984,
E. fleur.raggatt@rsm.ac.uk

10th International Symposium on Paediatric Neuro-Oncology
9-12 June, 2002; London, UK
Meeting Makers, Jordanhill Campus, 76 Southbrae Drive, Glasgow, G13 1PP.
E. helen@meetingmakers.co.uk

6th European Headache Congress
17-22 June, 2002; Istanbul, Turkey
Flap Tourism & Organisation, Cinnah Cad. Tel. 0090 312 4420700,
E. Flaptour@flaptour.com.tr

BSCN Paediatric Theme Meeting
21 June, 2002; Oxford, UK
E. E. secretariat@bscn.org.uk

ENS 2002
22-26 June, 2002; Berlin, Germany
Tel. +41 61 686 77 11,
Fax. +41 61 686 77 88,
E. info@akm.ch

7th Euroacademia Multidisciplinaria Neurotraumatologica Congress
26-29 June, 2002; Newcastle upon Tyne, UK
Tel. 0191 273 88 11 22 999,
E. emn2002@ncl.ac.uk

July

ABN one-day joint meeting with RCP
4 July, 2002; London, UK
Susan Tann, ABN,
Tel. 020 7405 4060,
Fax. 020 7405 4070,
E. abn@abnoffice.demon.co.uk

10th International Congress of Neuromuscular Diseases
7-12 July, 2002; Vancouver, Canada
Tel. 001 604 681 5226,
Fax. 001 604 681 2503,
E. Congress@venuewest.com

7th European Congress of Neuropathology, Neuropathology 2002
14-17 July, 2002; Helskinki, Finland
Tel. + 3 58 9 56 07-5 00, Fax. + 3 58 9 56 07-50 20, E. Neuropathology2002:congrex.fi, www.congrex.fi/neuropathology2002

8th International Conference on Alzheimer's Disease and Related Disorders
20-25 July, 2002; Stockholm, Sweden
Tel. 001 312 335 5813, Fax. 001 312 335 5781, www.alx.org/international-conference

August

WFNRS Symposium Neuroradiologicum XVII
18-24 August, 2002; Paris, France
Tel. 0033 3 83851456, Fax. 0033 3 838 51391, E. l.picard:chu-nancy.fr

5th International Congress of Neuroendocrinology
31 August-4 September, 2002; Bristol, UK
Tel. 01454 619347,
E. Icn2002@endocrinology.org

September

9th International Child Neurology Congress & 7th Asian and Oceanian Congress of Child Neurology
20-25 September, 2002; Beijing, China
Fax. 0086 10 66176450,
E. icnc@public3.bta.net.cn

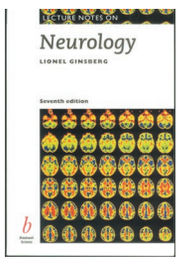
October

ABN Autumn meeting/British Neuropsychiatry Association
2-4 October, 2002; London, UK
Susan Tann, ABN, Tel. 020 7405 4060,
Fax. 020 7405 4070,
E. abn@abnoffice.demon.co.uk

7th International Congress of the World Muscle Society
2-5 October, 2002
Mr Jacob Muller, Tel. 0031 71 527 52 97, Fax. 0031 71 527 52 62,
E. j.j.l.muller@lumc.nl

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

Lecture Notes on Neurology 7th Edition



Author: Lionel Ginsburg
Published by: Blackwell Science
Pages: 199
ISBN No: 0632048271
Price: £14.95

The dual meaning of the word "concission" neatly encapsulates the dilemma faced by the author of a textbook for undergraduates: the need to balance brevity with the risk of mutilating the subject in the process of being brief. The measured authorship of Dr Lionel Ginsburg assures the success of this text in achieving the former, without being guilty of too much of the latter.

Lecture Notes on Neurology has been a staple of the undergraduate neurology diet for many years; six editions appeared between 1965 and 1985, written by Dr Ivan Draper. However, as an undergraduate in the mid 1980s, I recollect a feeling that the book had become rather long in the tooth, reflective of an era before the revolutions in neuroimaging and neurogenetics. Newer texts (e.g. Marsden & Fowler, Wilkinson, Donaghy) posed serious competition in a circumscribed market. Had the Lecture Notes format run its course?

The secret of longevity, seemingly as applicable to textbooks as to popstars, is reinvention. This is an entirely new text, clearly written, and divided into two parts, devoted to the "neurological approach" (history, examination, investigation) and "neurological disorders." The figures and tables are clear, and the illustrations generally of a good quality. Hence the book scores highly on the accessibility factor, with the possible exception of the index where no explanation is advanced for entries which are italicised, bold, or both (it seems that these refer, respectively, to entries in tables, in diagrams, and in tables and diagrams on the same page).

One may quibble about certain points. It is no more true that "a score below 24/30 on the Mini-Mental State Examination is indicative of dementia" (p19) than that a score of 30/30 excludes it, nor that Lhermitte's phenomenon is "near pathognomonic" (whatever one makes of the grammar) of multiple sclerosis (p139). However, these points simply reflect attempts to portray in black-and white the vista of grey so often encountered in neurological practice. It may have been advisable to say something of the shortcomings of the swinging torch test in bilateral optic nerve disease (p24), and some would regard it a mistake to use the term migrainous neuralgia in favour of cluster headache (p77).

Often the first question which undergraduates ask when beginning an attachment at the neurological centre is "What can I read?" Of course, no book can substitute for the experience of clerking patients, and observing a practitioner skilled in the art, but nonetheless I will feel confident in recommending this book to students as a supplement to those activities.

AJ Larner,
Walton Centre for Neurology and Neurosurgery

EDITOR'S CHOICE

The risk of Alzheimer's disease reduced by long term NSAID usage

As the growing body of animal and in vitro evidence suggests an inflammatory component to the pathology of Alzheimer's Disease (AD), a large prospective population based cohort study helps in strengthening this belief by demonstrating protection against the development of AD by nonsteroidal antiinflammatory drugs (NSAIDs). Previous retrospective observational studies have produced an overall equivocal association between the benefits of NSAIDs and the risk of developing AD. But this study from Rotterdam assessed the use of NSAIDs in 6989 subjects free of dementia and older than 54 years of age at baseline. Four categories of use were defined: short term use (< 1 month), intermediate use (between 1 month and 24 months of use), long-term use (greater than 24 months) and non-use. The commonest reasons for use of NSAIDs were joint symptoms (50%), osteoarthritis (24%) and rheumatoid arthritis (3%), with Diclofenac used most frequently (43%), followed by Ibuprofen (22%) and Naproxen (18%). Because data of usage was determined from computer based pharmacy records over an eight-year period when NSAIDs were only available on prescription these figures are probably accurate for NSAID use. However, because oral salicylates did not require a prescription definitive records on its use were not available. Development of dementia was assessed by screening using the Mini-Mental State Examination (<25) and Geriatric Mental State Schedule (D1) with confirmation by the Cambridge Mental Disorders of the Elderly Examination. Sub diagnosis of vascular dementia or AD was then made. 394 subjects developed dementia with 293 developing AD, 56 vascular dementia and 45 other types of dementia.

The relative risk of AD was 0.95 in the short-term group, 0.83 in the intermediate group and impressively **0.2** in the long-term use. There was no difference across the groups for the development of vascular dementia. There was no association between the use of oral salicylates, age, and APO E genotype (where the presence of APO E e4 allowed) and risk of AD. In addition to the striking relative risk ratio in the long-term use group the data from the other usage groups (ie. <24 months) demonstrates a lag before the onset of effect of the NSAIDs. This lag may explain some of the conflicting reports showing no protection by NSAIDs, as these studies were not geared to detect an effect beyond this critical time period. ***-TH***

Bas A. in 'T Veld, Annemieke Ruitenberg, Albert Hofman, Lenore Launer *et al.*
Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease.
NEW ENGLAND JOURNAL OF MEDICINE
2001; 345:1515-21

EPILEPSY

★★★ RECOMMENDED

Fit or faint?

It is sometimes hard to tell fits and faints apart. These papers are designed to make it harder. Tinuper *et al* describe 3 cases and review the literature of ictal bradycardia, which may be implicated in some cases of sudden death in epilepsy. They found that bradycardic patients were on average older than other epilepsy patients. The epilepsy arose more commonly in the left hemisphere (3:2). Experimental data shows that stimulating the left cingulate cortex may cause bradycardia but on the right tachycardias. Conversely left sided amylobarbital injection tends to cause tachycardia. They suggest avoiding treatment with carbamazepine, which may have some effects on cardiac conduction.

In an adjacent paper, Druschky *et al* evaluate cardiac autonomic function in patients with temporal lobe epilepsy, using MIBG-SPECT. This technique allows evaluation of sympathetic innervation of the heart. They also measured heart rate variability in their patients. They excluded ischaemia as a cause with scans of myocardial perfusion, which was normal in all patients. They found reduced MIBG uptake in TLE patients compared to controls suggesting reduced sympathetic innervation and increased heart rate variability with a pattern suggesting parasympathetic dominance. These changes in autonomic control could predispose to the bradycardias described

by Tinuper *et al*, but the authors could not rule out that this was a drug-related effect, rather than an epilepsy effect.

On the other side of the coin, faints can mimic fits. Reflex anoxic seizures are familiar. Venkataraman *et al* describe 3 patients with seizure-like episodes due to primary cardiac disturbances. One 29 year-old woman developed episodes with an epigastric sensation then a smell of burning followed by collapse with asystole for 24 seconds. An ictal EEG showed no signs of epilepsy. If I saw her tomorrow I suspect I would still confidently diagnose epilepsy on the basis of the clinical history. The lesson seems to be that if the response to treatment is unsatisfactory, go down the alternative avenue of investigation, almost irrespective of the clinical pattern of the attack.
-MM

Tinuper P, Bisulli F, Cerullo A, Carangui R, Marinin C, Pierangeli G, Cortelli P.
Ictal Bradycardia in partial epileptic seizures. Autonomic investigation in three cases an literature review.
BRAIN 2001;124:2361-71

Druschky A, Hilz MJ, Hopp P, Platsch G, Radespiel-Troger M, Druschky K, Kuwert T, Stefan H, Neudorfer B.
Interictal cardiac autonomic dysfunction in temporal lobe epilepsy demonstrated by [123I]metaiodobenzylguanidine SPECT.
BRAIN 2001;124:2372-82

Venkataraman V, Wheless JW, Willmore LJ, Motookal H.
Idiopathic cardiac asystole presenting as intractable adult onset partial seizure disorder.
SEIZURE 2001;10:359-64

DEMENTIA & LEARNING

Decline in dementia - Use it or lose it even more rapidly

Reality Orientation Therapy is an intervention that is commonly used by Occupational Therapists working with people with dementia. Its aim is to reorient the patient by continual reference to time, place and person. This process can be done informally during the course of contact with carers or care staff or may be carried out more formally and in more depth in especially arranged classes.

In an attempt to see if formal classes of this kind are an effective treatment, Metitieri *et al* carried out a large retrospective study of 74 patients who attended a day hospital in Italy. They looked at four important outcomes: cognitive decline measured using the Folstein Mini Mental State Examination, functional decline defined as the appearance of urinary incontinence, institutionalisation and death.

They found that day hospital patients who underwent a number of intensive courses (2-10) over a period of months (8-40 weeks) had significantly less cognitive decline and institutionalisation than patients who attended only one four week course of treatment. There was also less decline into urinary incontinence in the intensively treated group though this did not reach significance. No difference in the number of deaths was found.

The main problem with the study, acknowledged by the authors, was the composition of the control group. These were patients who having attended one course were unable to attend for any more; usually because the caregiver was unwilling or unable to transport the patient every day to the day hospital. At baseline there were no differences in clinical and sociodemographic variables between the two groups and there was no difference in cognitive and functional status after the first four weeks of classes. However it is possible that the nature and amount of support given by the patients' families could have affected outcome. With the ethical dilemma that arises from withholding therapies that are already established (though not well supported by research evidence) it is very difficult to find comparable controls for evaluation. Metitieri *et al* have provided a good retrospective study upon which to base further investigation of the factors that determine the progression of dementia and the effectiveness of therapies that are designed to slow down decline. ***-AJT***

Metitieri T, Zanetti O, Geroldi C, *et al.*
Reality orientation therapy to delay outcomes of progression in patients with dementia. A retrospective study.
CLINICAL REHABILITATION
2001: 15: 471-78

Surprising events in the human frontal cortex

The basis of associative learning theory, we are told in this paper from Cambridge, is that humans learn from surprising, rather than predictable, events. So 11 subjects were given a series of connected drugs and syndromes (a positive relationship) to learn, as well as negative associations (drug-no syndrome). Then the rules were broken and the subjects were presented with surprising relationships to learn. In line with previous experience, the subjects were more likely to learn a new positive relationship where there had been none before, rather than learn a negative relationship when there had previously been a positive one. The novel aspect to his study was that the subjects underwent functional MRI imaging. During the initial learning period, both frontal lobes were active, but they attenuated quickly. Then, when surprising events occurred, the right dorsolateral prefrontal cortex became active, with positive events eliciting more activation than negative events. It seems then that the right dorsolateral prefrontal cortex may be a key area for surprise-dependent learning in humans, guiding attention to unexpected events and attenuating as predictability is established. ***-AJC***

Fletcher PC, Anderson JM, Shanks DR, Honey R, Carpenter TA, Donovan T, Papadakis N, Bullmore ET.
Responses of human frontal cortex to surprising events are predicted by formal associative learning theory.
NATURE NEUROSCIENCE
2001 Oct; 4(10):1043-8.

CEREBROVASCULAR

★★★ RECOMMENDED

Arteriovenous malformations of the brain

Ever been confused by the vascular malformations of the brain? If so, this paper shows why such confusion is entirely justifiable. Sifting over 9000 publications, approximately 2500 of which were judged relevant to a review of arteriovenous malformations (AVMs), the authors show that it is difficult to reach meaningful conclusions on many aspects of their natural history from the available data. The problem begins with definition, shrouded by a variable nomenclature. Here a classification based on morphology and the location of the nidus or fistula is adopted (arteriovenous shunting of blood is the key feature for definition of an AVM), so that other intracranial vascular malformations, such as dural AVMs, are excluded.

Since most published series are small, retrospective, hospital-based, and lack adequate radiological investigation, conclusions about the frequency, clinical presentation, and prognosis of AVMs are subject to many biases. However, selecting the most methodologically sound studies, the authors' suggest the incidence of AVMs is ~ 1/100000 per year in an unselected population, with a point prevalence of ~ 18/100000 in adults. AVMs may account for: 1-2% of all strokes, and perhaps 4% in young adults; 9% of subarachnoid haemorrhages

(SAH); and ~ 4% of all primary intracerebral haemorrhages (PICH), but possibly one-third of PICH in young adults. AVMs are a far less common cause of first presentations with unprovoked seizures (1%). Only 0.3% of patients with headache without focal neurological signs harbour an AVM; for migraineurs the figure is 0.07%.

Perhaps 15% of AVMs are asymptomatic at the time of detection; around 20% present with seizures, but the majority (two-thirds) present with haemorrhage, half with PICH (> SAH > intraventricular haemorrhage). The annual risk of first-ever haemorrhage is ~ 2% but the recurrence rate is possibly as high as 18% in the first year. The annual risk of developing *de novo* seizures is ~ 1%, with good prospects for control with anti-epileptic medications.

The long-term crude annual fatality rate is ~ 1-1.5%. 50-70% of deaths are due to haemorrhage. There are no randomised controlled trials of the various treatment modalities (stereotactic radiotherapy, endovascular embolization, surgical excision).

For a condition that is increasingly diagnosed due to increased access to brain imaging, much remains uncertain. How to resolve these outstanding issues? A large prospective study in a well-defined, stable population: Scotland seems a good candidate! ***-AJL***

Al-Shahi R, Warlow CP.
A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults.
BRAIN
2001;124(10):1900-1926

★★★ RECOMMENDED

Progress in secondary prevention of stroke by lowering blood pressure

The publication of the Progress (perindopril protection against recurrent stroke study) trial, which aimed to determine the effects of blood pressure lowering by ACE inhibitors, should alter the way we manage secondary prevention of stroke in normotensive as well as hypertensive patients. This large multi-centre randomised placebo controlled trial involved 6105 patients with a follow up of over 4 years after a minor stroke or a history of a TIA. Patients received placebo or a flexible perindopril regimen where indapamide could be added to the treatment regimen at the discretion of the treating physician. Active treatment reduced systolic BP by 9 mm Hg and diastolic BP by 4 mm Hg. 28% fewer patients in the active treatment group suffered a stroke whilst 26% fewer patients in the active treatment group suffered major vascular events (vascular death, non fatal MI and non fatal stroke). Intensified lowering of BP by 12/5 mmHg by combination of therapy with indapamide reduced the risk of a stroke by 43%. These risk reductions were similar in non-hypertensive and hypertensive patients. Although the results are clearly in favour of lowering BP, it is unclear the level to which BP should be lowered and which agents should be used as perindopril alone did not significantly lower the risk of stroke or major vascular events. None the less it would seem pragmatic to institute slow but intensive lowering of BP to <130/85 in patients without occlusive or severe stenosis of carotid vessels assuming there are no contraindications to BP lowering treatment and that they are are in a stable condition after a TIA or minor stroke. ***-TH***

Progress Collaborative Group.
Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack.
THE LANCET
2001; 358: 1033-41

Aspirin and warfarin equal benefit for secondary prevention of stroke

In view of the superior protection of warfarin in cardiogenic embolic stroke, and the 3-7% annual recurrence rate of strokes even with aspirin treatment, there is a rationale for trying warfarin in the secondary protection of stroke. Thus a comparison of warfarin versus aspirin was undertaken using a multi-centre, double-blind randomised trial. 2206 patients who had had an ischaemic stroke (patients with evidence of cardioembolic stroke or patients on the waiting list for carotid surgery were excluded) within the previous 30 days were randomised. 1103 patients being assigned to receive warfarin where an INR of 1.4 - 2.8 was targeted and 1103 patients received aspirin 325 mg daily. There was no significant difference in the primary end point of death or recurrent ischaemic stroke between the groups after a follow up period of just over 2 years. Furthermore no difference in the frequency or time to the primary end point between the groups was detected. No difference in the rate of major haemorrhage (defined as intracranial, intraspinal, intracerebral, subarachnoid, subdural, epidural haemorrhage or any other bleeding event requiring transfusion) was demonstrated. Given the lower targeted INR the risk of haemorrhage was lower than in the SPIRIT study (INR target 3-4.5) that had to be stopped because of excessive bleeding in the warfarin group. So because aspirin treatment requires little monitoring, has less potential of excessive bleeding events and appears now to have equivalent efficacy in secondary prevention of stroke, it should remain the agent of choice. ***-TH***

J.P.Mohr, J.L.P.Thompso, R.M.Lazar, B.Levin, R.L. Sacco, K.L. Furie, J.P. Kistler, G.W. Albers, L.C.Pettigrew, H.P. Adams, C.M. Jackson and P Pullicino.
A comparison of warfarin and aspirin for the prevention of recurrent ischaemic stroke.
NEJM
2001;345:144-51

Simple screening for depression after stroke

It is clearly recognised that stroke is a devastating and common condition that often relies heavily on extensive rehabilitation for favourable long-term outcomes. This rehabilitation process is complicated by the presence of depression and this is manifest by prolonged hospital recovery periods and poorer survival rates in this cohort.

Sadly depression in stroke patients is often not diagnosed and this may reflect deficits in communication and cognitive impairment that accompany the pathology. Many multiple item inventories for assessing this aspect of well-being do exist but their implementation may be difficult in certain cases. In this study Watkins *et al* sought to determine the accuracy of a single item tool, comparing the results obtained against the well validated Montgomery Asberg depression rating scale (MADRS). The single item tool took one question from the Yale-Brown obsessive-compulsive scale for screening depression. Patients merely had to indicate 'yes' or 'no' to the Yale-Brown question "Do you often feel sad or depressed?"

During their second week of hospital stay following stroke, seventy-nine patients who had no communication or cognitive difficulties participated in the study and their results on the MADRS were compared with response to the Yale-Brown question. Patients answering, "yes" to the single item were found to have significantly higher scores on the MADRS compared to those answering "no" ($p < 0.05$).

The Yale-Brown results revealed sensitivity 86% (75% to 95%), specificity 78% (65% to 91%), positive predictive value 82% (71% to 93%) and negative predictive value 82% (69% to 95%). Furthermore, the paper shows the single question to have an incremental gain in diagnostic capability across a range of assumed prevalence rates for depression.

This paper highlights a very common problem in clinical practice and illustrates that addressing this issue is far from difficult. ***-SL***

Watkins C, Daniels L, Jack C, Dickinson H, van den Broek M.
Accuracy of a single question in screening for depression in a cohort of patients after stroke: comparative study.
BRITISH MEDICAL JOURNAL
2001; 323: 1159

MULTIPLE SCLEROSIS

Extraordinary use of the beta-interferons

There can be few academic medical series as blue chip as the Case Records of the Massachusetts General Hospital, recorded in the New England Journal, in which the sophisticated ruminations of the Bostonian medical hierarchy are painstakingly reproduced. However, by any assessment, this recent case in the series is an embarrassment. A 54-year-old woman is described, who is "confined to a bed because of multiple sclerosis of 20 years' duration". The point of the case is that she develops a T cell lymphoma. In passing it is mentioned that her "customary therapy" is both interferon beta-1b and interferon beta-1a. (Presumably Betaseron and Avonex). It is hard to justify the simultaneous use of these two forms of beta-interferon.

They are essentially the same compound, differing by only one amino acid and their pattern of glycosylation. Certainly there is no clinical trial data to promote their use together. Furthermore very few multiple sclerosis therapists would support any immunological treatment of a bed-bound patient, who is almost certainly in the secondary progressive phase of the disease. It is perhaps a measure of the commercial penetration of the beta-interferons in the US market that not only was such a patient receiving two beta-interferons, but their unorthodox use in this case excited no comments from the discussants. For instance, might it not be a potential cause of her T cell lymphoma? ***-AJC***

Jacobson J, de Leval L.
Case 34-2001— A 54-Year-Old Woman with Multiple Sclerosis, Prolonged Fever, and Skin Nodules.
NEW ENGLAND JOURNAL OF MEDICINE
345: 1409-1415

★★★ RECOMMENDED

Regular corticosteroids may reduce brain atrophy in relapsing-remitting MS

It is axiomatic that IV methylprednisolone reduces the duration of a multiple sclerosis relapse but not the acquired disability nor the long-term outcome. Similarly, it is generally understood that repeated regular doses of IV corticosteroids do not have a disease-modifying effect. However, as with so much other dogma, the data supporting it is surprisingly flimsy. So this group from Trieste randomised 90 people with relapsing-remitting multiples sclerosis to receive either steroids only during relapses, as conventionally given, or regular pulsed steroids: 5g methylprednisolone over 5 days every four months for three years, followed by every six months for the next two years. The annual relapse rate, at 0.6, was the same

for both groups. But the regular pulsed group had significantly less disability, lower probability of sustained disability accumulation, lower T1 lesion volume and less brain atrophy at the end of five years. The only parameter that did not reach significance was less accumulation of T2 lesion load in the regular steroid group. Eight patients entered the secondary progressive phase of the illness during the study: one in the regular steroids group and 7 in the controls. The adverse effects of regular pulsed steroids were: acute glomerulonephritis, osteoporosis (3 patients), hypertension (one) and recurrent herpetic infections (one).

The implication is that regular pulsed corticosteroids do not alter the underlying mechanisms that initiate relapses in multiple sclerosis, but they do reduce both brain atrophy and the accumulation of disability clinically. Perhaps they should be considered neuroprotective rather than truly disease-modifying. Perhaps they might best be used in combination with a drug that reduces relapses? ***-AJC***

Zivadinov R, Rudick RA, De Masi R, Nasuelli D, Ukmar M, Pozzi-Mucelli RS, Grop A, Cazzato G, Zorzon M.
Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS.
NEUROLOGY
2001 Oct 9; 57 (7):1239-47

MOTOR NEURON DISEASE

Non-invasive ventilatory support improves quality of life in motor neuron disease

Non-invasive ventilatory support is available in many centres caring for individuals with motor neuron disease (amyotrophic lateral sclerosis, ALS). While the wide regional variations in the uptake of this service partly reflect resource availability, they can also be the result of doubts on the part of patients or caregivers about the appropriateness of the intervention. Since evidence-based guidelines on the subject are a long way off, we rely heavily on our own and others' observations.

The authors present their experience of 27 ALS patients with symptoms of alveolar hypoventilation who tolerated non-invasive positive pressure ventilation (NIPPV) for more than 4 hours per 24-hour period for over 2 weeks. While information about forced vital capacity and resting arterial blood gases was also available, they found they placed a lot of weight on a careful history to detect deteriorating respiratory function. Symptoms of orthopnoea, disturbed sleep and dyspnoea were prominent at the time of institution of NIPPV and all responded well to the intervention.

Of particular interest was their observation that NIPPV did not prevent unexpected and acute respiratory decompensation. The authors reasonably caution against a false sense of security in patients on NIPPV, particularly if they remain ambulatory. But the same findings also suggest that active ventilatory support does not condemn a person to an unnecessarily drawn out period of respiratory decline. ***-WR***

The use of non-invasive positive pressure ventilation (NIPPV) in ALS patients. A need for improved determination of intervention timing.
Sivak E, Shefner J, Mitsumoto H, Taft J.
AMYOTROPHIC LATERAL SCLEROSIS
2001: 2: 139-145

PARANEOPLASIA

PET scanning for paraneoplastic disease

Paraneoplastic disorders (PND) are rare non-metatstatic manifestations of cancer, the symptoms of which usually precede those of the underlying malignancy. Tumour detection may be difficult with conventional imaging techniques. This retrospective study suggests that [18F] fluoro-2-deoxyglucose positron emission tomography (FDG-PET) might be helpful in these circumstances, due to its excellent spatial resolution (of the order of 6-8 mm). An unselected series (n = 43) of patients with suspected PND underwent FDG-PET scanning. The group was clinically heterogeneous, neurological features including cerebellar +/- brainstem syndrome, sensory neuropathy/neuronopathy, motor neuropathy, and Lambert-Eaton myasthenic syndrome. Discrete areas of hypermetabolism, consistent with malignancy, were seen on FDG-PET in 16 patients (37%); 27 (63%) had normal scans. Of the PET +ve patients, 7/16 subsequently had malignancy confirmed histologically (2 at postmortem). Of the PET –ve patients, 26/27 remained free of malignancy over a mean follow up of 18 months (range 2-44 months); in the one exception the tumour discovered was thought incidental to the neurological syndrome. In the PET +ve group, 43% were positive for antineuronal antibodies and 46% had CSF oligoclonal bands; in the PET –ve group the respective figures were 16% and 26%, differences that did not reach statistical significance.

The authors suggest that FDG-PET may be useful in the detection of small tumours in patients with suspected PND. As this was a preliminary study, the specificity and sensitivity of the test could not be given. The period of follow up was relatively short, and longer periods of follow up may alter the results. Although early tumour detection may help to establish the diagnosis of PND, whether this will influence management or outcome remains to be determined. ***-AJL***

Rees JH, Hain SF, Johnson MR *et al.*
The role of [18F] fluoro-2-deoxyglucose-PET scanning in the diagnosis of paraneoplastic neurological disorders.
BRAIN 2001;124(11):2223-2231

Complimentary Journals Reviewed

We would like to thank the following publishers who have provided us with complimentary review subscriptions to their journals. For subscription details please contact the relevant publisher direct.

Cerebrovascular Diseases, Neuroepidemiology
S. Karger AG - Medical and Scientific Publishers,Allschwilerstrasse 10, CH - 4009 Basel, SWITZERLAND.
Tel. 0041 61 306 11 11, Fax. 0041 61 306 12 34, E-Mail. t.nold@karger.ch www.karger.com

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

Clinical Rehabilitation, Multiple Sclerosis
Arnold, 338 Euston Road, London NW1 3BH. Tel. 020 7873 6339, Fax. 020 7873 6325,
E-Mail.arnoldjournals@hodder.co.uk,www.arnoldpublishers.com/journals

New Magstim 200² range of monophasic magnetic stimulators

Magstim develop, manufacture and market state-of-the-art equipment for neurologists, neurophysiologists, neurosurgeons and psychiatrists, enabling them to assess, protect and improve the functioning of the nervous system in various applications.

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The new range replaces the established Magstim 200 and has been developed as a result of extensive consultation with existing users throughout the world both in clinical and research arenas.

For further information on system specification, demonstration and pricing please contact John Scandone - International Sales Manager (john.scandone@magstim.com), Andrew Thomas - Marketing Executive (andrew.thomas@magstim.com), Magstim, Spring Gardens, Whitland, Carmarthenshire, Wales SA34 0HR, Tel. 01994 240798, Fax. 01994 240061, www.magstim.com

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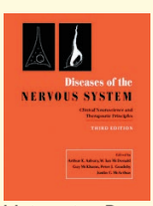


Diseases of the Nervous System (2-VOL Set), Clinical Neuroscience and Therapeutic Principles, Third Edition

The third edition of a neurology classic, this two-volume text is said by Cambridge University Press to be the most comprehensive neurology reference available. It encompasses the basic neuroscience and clinical features of the full range of neurological disorders, written by leading international experts in the field.

Disease mechanisms are reviewed comprehensively, with particular relevance to the principles of therapy. Sections cover the general principles of neurological disease, disorders of higher function, motor control, special senses, spine and spinal cord, bodily function, headache and pain, neuromuscular disorders, epilepsy, cerebrovascular disorders, neoplastic disorders, autoimmune disorders, disorders of myelin, infections, trauma and toxic disorders, degenerative disorders, and neurological manifestations of systemic conditions. Each section, under the direction of one of the distinguished editors, is a text-within-a-text offering what is, according to the publisher, the most reliable account of its topic currently available.

Current, comprehensive and authoritative, this is the definitive reference for neurologists, neurosurgeons, neuropsychiatrists, indeed everyone with a professional or research interest in the neurosciences. The title is due for publication in June 2002.

For further information Tel. 01223 312393, Fax. 01223 326079, www.cambridge.org

Bio-Cut from Kimal

UK & International medical device manufacturer Kimal plc will celebrate the start of the New Year with the UK launch of the Bio-Cut - their new and innovative Biopsy Needle range.

The new range offers improved compatibility with other devices, improved design and more extensive uses. Enhancements that Kimal are confident will be welcomed enthusiastically in the medical market place.

The company is embarking on a co-ordinated campaign throughout the early months of 2002 involving medical journal advertising, a focused direct marketing campaign, a pro-active sales operation and incorporating the international launch at Arab Health at the end of January.

Commenting on the launch, Kimal Managing Director, Mr Alan Press said, "Yet again we find ourselves at the forefront of the medical device industry with our new Bio-Cut range. These needles are of excellent quality and are specifically designed for today's professional. We look forward to the range being welcomed and used by healthcare professionals in the Radiology, Urology and Nephrology fields."

For further details and product information, contact Errord Jarrett on Tel. 01895 270951, E-Mail errord_Jarrett@kimal.co.uk

FREE RESOURCE Health Improvement Programme Template for Stroke

A new, outline Health Improvement Programme (HImP) is now available. The "Template for a Health Improvement Programme for Stroke" and the supporting material, "Developing a Health Improvement Programme for stroke care: an evidence-based approach" is available as a booklet and CD-ROM free of charge to health professionals.

HImPs are now required as part of the Government's health plan and will assist in meeting the requirements of the NSF for Older People.

The materials call on the health authority and primary care organisations to collate information on local health needs, inequalities and make comparisons with national targets in stroke. The development of a 'Stroke Register' is fundamental, and integral to this will be organised systems for reviewing secondary stroke prevention.

Secondary prevention

Patients who have already had a stroke or TIA are 13-15 times more likely to suffer a further episode than the general population. Secondary prevention can reduce this risk considerably and is vital for these patients.

The HImP for Stroke template uses recent RCP recommendations as a guide to secondary preventative treatment. This includes guidance that all patients not on anticoagulation should be taking aspirin (50-300mg) daily or a combination of low-dose aspirin and dipyridamole modified release (MR) (available as Asasantin Retard). Where patients are aspirin intolerant an alternative anti-platelet agent (dipyridamole MR 200mg twice daily or clopidogrel 75mg) should be used. In the presence of atrial fibrillation, anticoagulation (with warfarin) should be considered in ischaemic stroke, whilst therapy with a statin should be considered for all patients with a history of myocardial infarction and a cholesterol >5.0mmol/L following stroke.

The document and CD-ROM are available free of charge from Dorothy Tuffley Boehringer Ingelheim Ltd, Ellesfield Ave, Bracknell, Berks RG12 4YS. Fax. 01344 741206, E-Mail:tuffleyd@bra.boehringer-ingelheim.com, or use the free reader enquiry service with this magazine.

Congratulations!

Congratulations to the winner of our reader survey competition which we held in the last issue. The lucky winner was Dr A H Hewazy, Consultant Neurologist at Southend Hospital, who will receive a copy of *The Year in Neurology*, courtesy of Clinical Publishing.

Many thanks to everyone who entered - we will use your comments and suggestions to ensure ACNR continues to deliver interesting, relevant editorial.

To buy a copy of the book for just £49.50, call Clinical Publishing on Tel. 01865 811116.

FREE RESOURCE Dendron announces first UK coil implants

Dendron GmbH of Germany recently announced that the first UK implantation of the EDCII coils were completed at the Southern General Hospital in Glasgow.

Dr Jo Battacharya and Dr Evelyn Teasdale carried out the procedure on a patient with a large PCom aneurysm and used multiple Dendron coils.

Dr Battacharya said "It was quite a difficult procedure and we used different types of coils, but once we got down in size we used the EDCII's for a very good end result."

Ian Graney, Managing Director of Neurotechnics, the exclusive UK supplier said, "We are delighted that Dr Battacharya has used these coils so successfully and we believe that it will be the start of a long and mutually beneficial relationship with Glasgow. We plan to launch several unique new coiling products to the UK market in early 2002 and look forward to making Dendron products a major supplier to the UK market".

For more information, or a free CD ROM of all products including video clips, contact Neurotechnics on Tel. 01844 260777, Fax. 01844 260778, www.neuro-technics.com

Research confirms significant contribution made by MS specialist nurses

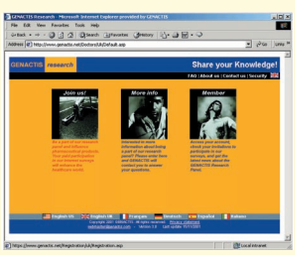
A recent research project provides a clear insight into the contribution MS specialist nurses make towards the care of people with MS, in terms of emotional and practical support, as well as significant cost and resource savings to the NHS. The project, **Evaluation of MS Specialist Nurses: A Review and Development of the Role,** was commissioned by the MS Research Trust.

One of the authors, Jane Johnson, Consultant Nurse, Rehabilitation, Kings College Hospital said, "The impact of nursing is notoriously difficult to evaluate but we urgently need evidence of where nursing makes a difference if senior posts such as Clinical Nurse Specialists are to be justified. This research attempts to provide some of the evidence. By using a variety of perspectives and methods, it tries to capture some of the less explicit effects of specialist MS nurses, as well as exploring some of the employment and support systems necessary for effective working.

For a copy of the full report or an Executive Summary E-Mail. Nicola.Russell@msresearchtrust.org.uk

Internet-based pharmaceutical research

www.genactis.net is a new service for physicians to participate in Internet-based pharmaceutical research, thereby sharing their knowledge and voicing their opinion to aid in drug development. A major innovation is the creation of dedicated specialty boards, such as the Research Board in Neurology, which was successfully launched at the WCN (2001) in London.



By registering with GENACTIS, respondents can participate in surveys but are under no obligation to do so. Subjects include migraine, epilepsy, stroke, neuropathic pain, Parkinson's disease, etc. Not only are the surveys informative and interesting, each participant is remunerated according to the time taken. Communication with the registered members is confidential and achieved through E-Mail and a highly secure web interface. The members will never be contacted for anything but pharmaceutical research.

GENACTIS Ltd. manages global market research for most of the world's leading pharmaceutical companies.

For further information contact GENACTIS on research@genactis.com or visit the web site www.genactis.net.

CJD support network

The CJD Support Network is the only registered charity providing support for people with CJD, their carers and concerned professionals. The aims of the Network include: providing accurate, unbiased and up-to-date information about all forms of CJD through an expanding range of information sheets, leaflets and newsletters; promoting good quality care for people with CJD, by providing training, workshops, conferences, case co-ordination and by encouraging the adoption of good practice guidelines; campaigning through regular contact with ministers and senior government officials and promoting research into CJD.

The Network provides practical and emotional support to individuals affected by CJD and their families; supports families in financial need; links families with similar experiences of CJD and runs a national helpline staffed by professional advisers.

For further information contact Gillian Turner, CJD Case co-ordinator, CJD Support Network, Tel: 01603 673993, CJD Helpline: 01603 673973. ***12 November 2002 will be the first International CJD Day.***

UK human cloning fiasco

In December 2000, the UK parliament voted to legalise cloning for the purposes of providing body parts (so called "therapeutic cloning").

A strong argument at the time was that such therapeutic cloning could alleviate the suffering of patients with neurodegenerative conditions, such as Parkinson's disease, Alzheimer's and Huntington's chorea.

They choose to do this by amending the Human Fertilisation and Embryology Act of 1990. But in November 2001, the High Court ruled that a cell created by nuclear transfer was not an embryo and therefore could not be covered by the HFE Act.

"Now, there are no criminal offences or anything to stop someone cloning a human," says Bruno Quintavalle of the Pro-Life Alliance, which brought the case.

BNA Awards

Lord Brian Rix (pictured left) and Professor Colin Blakemore (right) have received awards from the BNA. Lord Rix received his award for public service, and Professor Blakemore for his outstanding contribution to British Neuroscience.

He specialises in vision and the development of the brain, and is most noted for his research into brain development before birth and the causes of childhood blindness.

For further information, contact the BNA on Tel. 0151 794 4943/5449, Fax. 0151 794 5517.

Brain Awareness Week

Every March hundreds of events to inspire interest in brain research are staged as part of **Brain Awareness Week.** The event is co-ordinated by The European Dana Alliance and will take place from **11-17 March 2002.**

Brain Awareness Week is an opportunity to raise the public profile of brain disorders, brain research, and rehabilitation and to provide information about the brain that everyone can understand.

Any type of event can be relevant. Events from art exhibitions and drama performances to lectures and open days take place.

To find out how you can become involved in this exciting initiative please contact Lisa Cokayne-Naylor on 020 7937 8771 or see their website www.edab.net.

Prescribing information

Lamictal (lamotrigine)

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

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

Dosage and Administration: Initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash. *Monotherapy:* Initial dose is 25mg daily for two weeks, followed by 50mg daily for two weeks. Dose should be increased by a maximum of 50-100mg every 1-2 weeks until optimal response. Usual maintenance dose is 100-200mg/day in one dose, or two divided doses. *Add-on therapy: Adults and Children over 12 years:* To sodium valproate with or without ANY other antiepileptic drug (AED), initial dose 25mg every alternate day for two weeks, followed by 25mg/day for two weeks. Dose should be increased by 25-50mg every 1-2 weeks until optimal response. Usual maintenance dose 100 to 200mg/day in one dose, or two divided doses. To enzyme inducing AEDs with or without other AEDs (but NOT valproate), initial dose is 50mg daily for two weeks, followed by 100mg/day in two divided doses for two weeks. Dose should be increased by 100mg every 1-2 weeks until optimal response. Usual maintenance dose is 200 to 400mg/day given in two divided doses. *Children aged 2-12 years:* To be dosed on a mg/kg basis until the adult recommended titration dose is reached. Add-on to sodium valproate with or without ANY other AED, initial dose is 0.15mg/kg bodyweight/day given once a day for two weeks, followed by 0.3mg/kg/day given once a day for two weeks. Dose should then be increased by a maximum of 0.3mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 1 to 5mg/kg/day given in one dose, or two divided doses. Add-on to enzyme-inducing AEDs with or without other AEDs (but NOT valproate) is 0.6mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2mg/kg/day for two weeks given in two divided doses. Dose should then be increased by a maximum of 1.2mg/kg every 1-2 weeks until optimal response. Usual maintenance dose is 5-15mg/kg/day given in two divided doses. Weight of child should be monitored and dose adjusted as appropriate. If calculated dose is 1-2mg/day then 2mg may be taken on alternate days for the first two weeks. *Dose Escalation:* Starter packs covering the first four weeks treatment are available for adults and children over 12 years. When the pharmacokinetic interaction of any AED with Lamictal is unknown the dose escalation for Lamictal and concurrent sodium valproate should be used. *Elderly patients:* No dose adjustment required.

Contra-indications: Hypersensitivity to lamotrigine.

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

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

Side and Adverse Effects: With monotherapy: headache, tiredness, rash, nausea, dizziness, drowsiness, and insomnia. Other adverse experiences have included diplopia, blurred vision, conjunctivitis, GI disturbances, irritability/aggression, agitation, confusion, hallucinations and haematological abnormalities. Also movement disorders such as tics, unsteadiness, ataxia, nystagmus and tremor. Severe skin reactions including SJS and TEN have occurred rarely, with or without signs of hypersensitivity syndrome. Elevations of liver function tests and rare reports of hepatic dysfunction.

Legal category: POM.

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

Product Licence Holder: The Wellcome Foundation Ltd, Middlesex UB6 0NN. Lamictal is a Trade mark of the Glaxo Wellcome Group of Companies.

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

Note: If changes in AED medication are to be made they should be completed before conception.[9] The UK Pregnancy Register (0800 389 1248) is collecting prospective data on the effects of all AEDs in pregnancy. Please phone for information or to register a patient.

customerservices@glaxowellcome.co.uk
Customer Services Freephone 0800 221441

References:
1. Holdich T *et al.* Epilepsia 1991; **32** (Suppl. 1): 96.
2. Morrell MJ. Neurology 1998; **51** (Suppl. 4): S21-S27.
3. Fitton A, Goa KL. Drugs 1995; **50** (4): 691-713.
4. Patsalos PN, Sander JWAS. Drug Safety 1994; **11** (1): 37-67.
5. Messenheimer J *et al.* Drug Safety 1998; **18** (4): 281-296.
6. Brodie MJ *et al.* The Lancet 1995; **345**: 476-479.
7. Reunanen M *et al.* Epilepsy Research 1996; **23**: 149-155.
8. Steiner TJ *et al.* Epilepsia 1999; **40** (5): 601-607.
9. Crawford P *et al.* Seizure 1999; **8**: 201-217.

GlaxoSmithKline

GEN 26792-ALP/May 2001

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