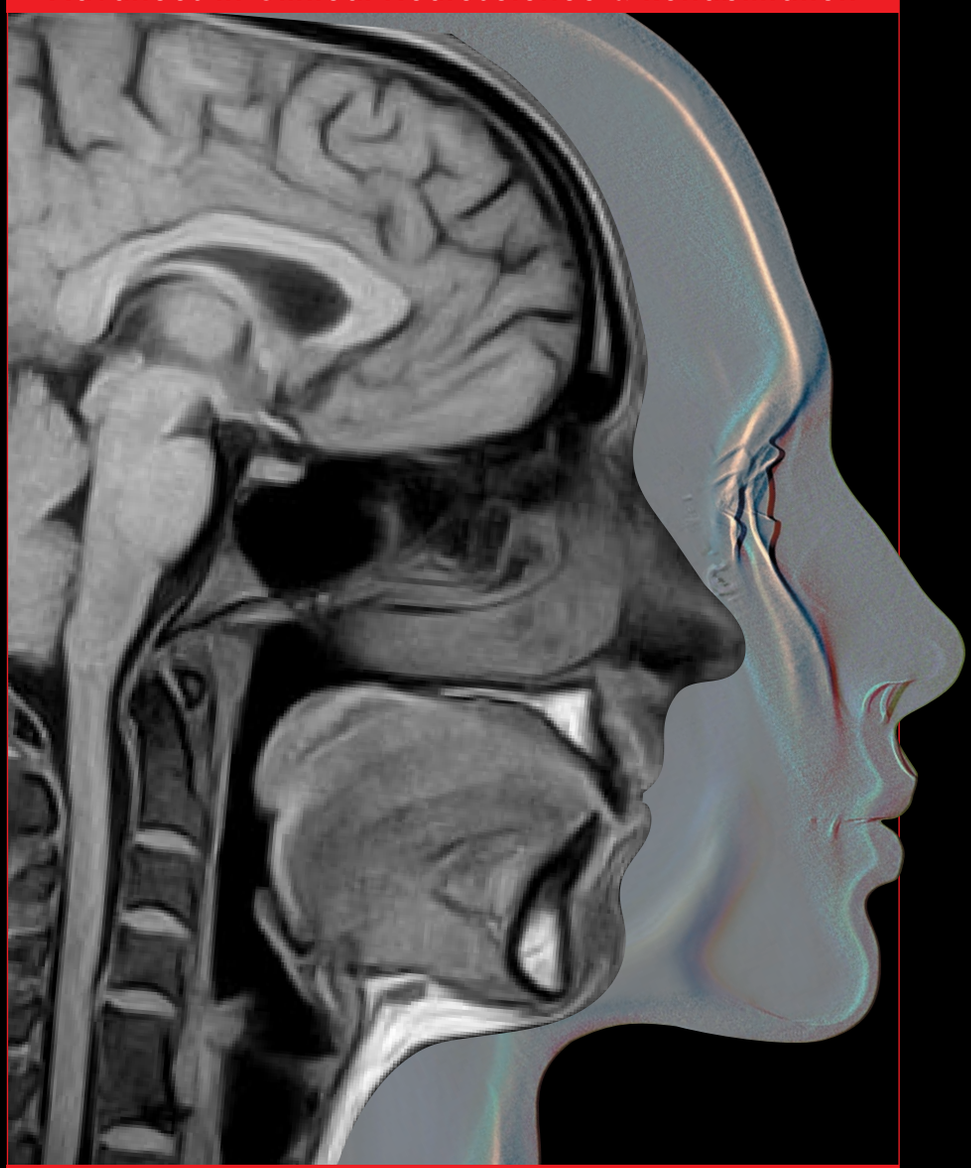
ISSN 1473-9348 Volume 1 Issue 1 March/April 2001

ACNR

Advances in Clinical Neuroscience & Rehabilitation



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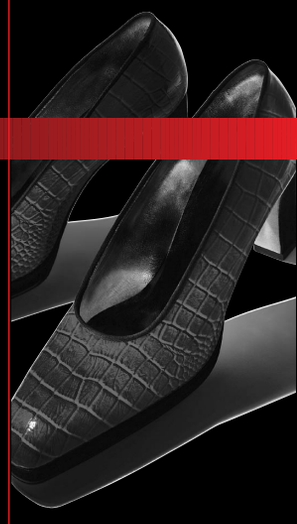

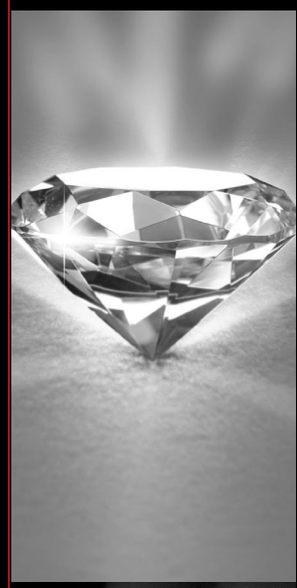

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Neuroimaging has proved to be both sensitive and highly effective in detecting dopaminergic dysfunction in Parkinsonian Syndromes. It can help establish the truth of the disorder when clinical features are incomplete or contradictory.

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Abbreviated Prescribing Information

Presentation: Vials containing 185 MBq ioflupane (^{123}I) at reference time.

Uses: Detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian Syndromes in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease (PD), Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP). DaTSCAN is unable to discriminate between PD, MSA and PSP.

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.

Contraindications: Pregnancy and in patients with hypersensitivity to iodide or any of the excipients.

Precautions: Radiopharmaceuticals should only be used by qualified personnel with appropriate government authorisation and should be prepared using aseptic and radiological precautions. DaTSCAN is not recommended in moderate to severe renal or hepatic impairment.

Interactions: Consider current medication. Medicines that bind to the dopamine transporter may interfere with diagnosis; these include amphetamine, benzotropine, buproprion, cocaine, mazindol, methylphenidate, phentermine and sertraline. Drugs shown during clinical trials not to interfere with DaTSCAN imaging include amantadine, benzhexol, budipine, levodopa, metoprolol, primidone, propranolol and selegiline. Dopamine agonists and antagonists acting on the postsynaptic dopamine receptors are not expected to interfere with DaTSCAN imaging and can therefore be continued if desired.

Pregnancy and Lactation: Contraindicated in pregnancy. Information should be sought about pregnancy from women of child bearing potential. A woman who has missed her period should be assumed to be pregnant. If administration to a breast feeding woman is necessary, substitute formula feeding for breast feeding.

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Marketing Authorisation number: EU/1/00/135/001

Basic NHS price: £420

Date of Preparation: July 2000

Nycomed Amersham plc., Amersham Place, Little Chalfont, Buckinghamshire, England HP7 9NA. www.na-imaging.com

† 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

DaTSCAN differentiates Essential Tremor from Parkinsonian Syndromes

DaTSCAN, Ioflupane is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian Syndromes, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.

Efficacy of DaTSCAN in the diagnosis of Parkinsonian Syndromes was established in a multicentre Phase III trial. In this study images of patients clinically diagnosed with Parkinsonian Syndromes were compared with those patients diagnosed with Essential Tremor. The images were evaluated by visual assessment. Semi-quantitative image evaluation of the images in a Phase II study had indicated a suitable time window post injection for imaging, as well as visually different striatal uptake in images for patients at all stages of Parkinson's Disease when compared to those for healthy volunteers. The results of the Phase III trial and their extrapolation to wider patient populations are discussed in subsequent sections.

Multicentre Phase III trial

Differentiation between Parkinsonian Syndromes and Essential Tremor

This study was designed to compare the striatal uptake of DaTSCAN in patients with PS to that in patients with benign ET. The DaTSCAN SPECT images were evaluated by visual assessment after definition of normal and abnormal images from previous experience in healthy volunteers and PD patients in a Phase II study. PS was defined as either Parkinson's Disease, Multiple System Atrophy or Progressive Supranuclear Palsy. Both the PS and ET patient groups had similar symptoms, however PS is associated with degeneration of nigrostriatal dopaminergic neurons. In ET, this dopaminergic neuronal system remains intact. These two conditions are often confused, especially in elderly patients. It was expected that DaTSCAN images would be abnormal in patients with PD and related syndromes and normal in those with ET.

Study Population and Imaging Conditions

A total of 224 male and female subjects were enrolled in the study, comprising 160 PS, 29 ET and 35 healthy volunteers (HV) across six centres in Europe (UK, Germany, Netherlands and Belgium). Images of 6 healthy volunteers were produced in each centre with the local SPECT equipment to define normal images for the institutional read and normal values of uptake ratios. Administered activity was in the range of 111-185 MBq allowing an acceptably short acquisition time while remaining within the normal radiation absorbed dose for diagnostic radiopharmaceuticals.

Accepted clinical criteria for PD (UKPOS), MSA, PSP and ET were strictly applied for patient inclusion (Gibb and Lees, 1988; Findley and Koller 1995; Fahn and Elton 1987; Hughes, Lees and Stern, 1990; D'Costa et all 1991; Gasser et al 1992; The Consensus Committee 1996).

After thyroid blocking, all subjects were administered DaTSCAN intravenously and imaged between 3-6 hours post injection using the local SPECT equipment available in each of the centres.

Image evaluation: efficacy variables

At each of the six centres the investigator assessed the acquired DaTSCAN SPECT images for their own subjects, blinded to the subject's clinical diagnosis. This process was termed the 'Institution read'. Centrally standardised scans were further assessed by a panel of five investigators who were also blinded to the subject's clinical diagnosis, and who separately and independently judged the scans to be visually normal or abnormal by comparison with reference images: this process was termed the 'blinded panel read'. The primary efficacy variable was defined as 'Ioflupane striatal uptake assessed by visual inspection during the institutional read'. Secondary efficacy variables included 'Ioflupane striatal uptake as assessed by visual inspection the (blinded) panel read', and the 'semi-quantitative assessment of regions of interest ratios'.

Results of the visual assessment: Response rate (Sensitivity) and Specificity

Of the 220 'intend to treat' (ITT) subjects images, 35 were healthy volunteers, 185 patients were either diagnosed with PS or ET (158 diagnosed with PS and 27 diagnosed with ET).

Positive response rates for the institutional reads and the panel read as primary and secondary evaluations are given in the table below. PS and ET groups were taken as indicators of sensitivity and specificity, respectively. The definition of sensitivity being the number of abnormal images found within the PS population: specificity is defined as the number of normal images within the ET population. Normality of images was to be judged by comparison with images obtained from healthy volunteers (see table below, images of a healthy volunteer, an early stage PD patient with Hoehn and Yahr stage 1, and advanced stage PD patient, and ET patient, a patient with MSA and a patient with PSP).

Sensitivity = abnormal/(normal + abnormal) in PS population
Specificity = normal/(normal + abnormal) in ET population

Table: Results of the Institutional read

Patients	PS	ET	Total
Abnormal Scan	154	0	154
Normal Scan	4	27	31
Total	158	27	185

Sensitivity	154/158	97.5%
Specificity	27/27	100%
Positive Predictive Value	154/154	100%
Negative Predictive Value	27/31	87.1%

The results demonstrate the effectiveness of DaTSCAN SPECT in differentiating between the two patient groups.

Mismatches

In this Phase III study, there were ten mismatches (ie approximately 5% of the study population) where the DaTSCAN SPECT seen did not confirm the diagnosis. This led to are-diagnosis in five cases eg from Parkinson's Disease to Essential Tremor, to non-parkinsonism, and to neuroleptic-induced parkinsonism respectively, and from MSA to Essential Tremor. The other cases are undergoing monitoring and follow up.

This indicates that symptomatology may not be as reliable a predictor of the underlying pathology as imaging by DaTSCAN.

Early and atypical disease

To compare DaTSCAN SPECT with the best available diagnostic standard strict diagnostic criteria were applied when patients were included in the PS or ET groups for the Phase III study described above. However, DaTSCAN will be used clinically where the diagnosis of the patient is doubtful or inconclusive.. DaTSCAN detects PS with equal sensitivity in early stage disease when symptoms have insufficiently developed to meet full diagnostic criteria.

Reference:
Benamer *et al.* Movement Disorders. 2000; 15:503-510

A magazine by experts, for experts

The field of neurology and neuroscience moves forward at an alarming pace and it is difficult to keep up with the advances as they are made. This magazine is designed to help with this problem, through a combination of unique and innovative approaches that will include in each issue:

- Two short reviews of current therapeutic controversies from leading experts in the field
- A primer of neuroanatomy
- A review of the major neurological journals by a panel of experts with short summaries and comments on the most important articles
- Product updates
- A review on an aspect of rehabilitation
- A short account of best management practice in the form of a series of articles around a disease (e.g. epilepsy - diagnosis, first line therapy, driving, pregnancy, therapy in refractory cases, role of surgery)

As the magazine grows and develops we will also be including a short summary of a neuroscientific topic that will impinge on the clinical arena in the near future, conference reports on important/interesting meetings and book reviews, amongst other features.

The magazine has been devised and structured following discussions between myself and a number of my neurological colleagues, which means that it has been devised by experts for experts in the field. The involvement of a large number of young neurologists as part of the editorial and review team will ensure that the articles are accessible and relevant to current clinical practice. Furthermore each of the team has an area of expertise which will ensure that the identification of breakthroughs and advances are accurate and pertinent.

''The magazine has been designed and devised for those in the field''

As with any new venture there are always ways in which the presentation of information can be improved or refined and if there are areas that you the reader wish to see included then do let us know. The magazine has been designed and devised for those in the field and is free from any pharmaceutical drug company bias - none of those contributing are in any way supported or remunerated by any of the companies advertising in this magazine. Thus it remains an independent publication.

I have taken on the editorship of this magazine as I feel it offers a unique opportunity to bring neuroscience to neurology and take advances in neurology out into the community of neurologists and associated specialties. It is this exciting prospect that represents the challenge for neurology as it moves into the 21st century.

Roger Barker
Editor

Roger Barker is editor 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.

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Manjit S Matharu is a clinical research registrar at the Institute of Neurology and the National Hospital for Neurology and Neurosurgery, Queen Square, London. His research interests include cluster headache, and the neuroimaging of the primary headache disorders.

Peter J Goadsby is Professor of Clinical Neurology at the Institute of Neurology, and an Honorary Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, Queen Square, London, as well as the Hospital for Sick Children at Great Ormond Street in London. In addition, he is a Wellcome senior research fellow in clinical science. His chief research interest is in the neurophysiology and neuropharmacology of headache.

Mark Manford 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.

Alasdair Coles 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.

Angela Vincent studied medicine but soon turned to research. While working on acetylcholine receptors with Ricardo Miledi FRS, at UCL, they begun to study myasthenia with John Newsom-Davis, and in 1977 she joined Newsom-Davis at the Royal Free to help establish a myasthenia research group. The group moved to Oxford in 1988 when Newsom-Davis was made Professor of Neurology. Since his retirement, she runs the Neurosciences Group. She is a University Lecturer in Neuroimmunology, and Professor of Neuroimmunology since 1998.

Nigel Leigh is Professor of Clinical Neurology and Head of Department at the joint IoP and GKT Department of Neurology, King's College. He is also Director of King's MND Care and Research Centre, and leads a programme of research in neurodegeneration, especially motor neuron disease, in association with the Institute of Psychiatry Neurodegeneration Research Group. His research interests include clinical neuroscience, neurodegenerative disorders (motor neuron disease and Parkinson's disease) and cellular pathology.

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march/april 2001

Advances in Clinical Neuroscience & Rehabilitation

Advances in Clinical Neuroscience & Rehabilitation (ACNR) is a bi-monthly magazine addressing the problems of information overload and lack of time. In it, a team of doctors provide personal reviews of original papers from major journals allowing you to quickly keep up to date, feature articles address current issues, News Review highlights latest developments, and Events gives news of meetings.

A complimentary subscription is yours thanks to the hard work of all the specialists involved and to support from industry. We would like to thank Aventis Pharmaceuticals, UCB Pharma, Nycomed Amersham and Glaxo Wellcome for their involvement in this first edition.

We hope you enjoy it!

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Features

Regulars

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

Christopher J. Boes, Manjit S. Matharu, Peter J. Goadsby

Management of difficult migraine

Migraine is a common disorder. A study of over 20,000 people in the USA showed that 17.6% of women and 5.7% of men experience severe migraine headaches[1]. The first step in managing difficult migraine is accurate diagnosis. Separating migraine the disorder from migraine the attack can alleviate mistakes made in diagnosis. Migraine, the attack, is well defined by the criteria of the International Headache Society (Table 1). Migraine the disorder is certainly manifest by these episodic attacks of pain with associated features. However, migraine the disorder is probably a more complex neurobiological problem that includes the patient's predisposition to headache, the triggering of attacks from menses, skipping meals or altered sleep patterns, as well as the frequent, daily or near-daily headache that develops in many migraineurs, with or without analgesic overuse. In 1922, James Collier noted that patients could develop chronic frequent migraine[3]. He observed that over time, some patients with episodic migraine developed intervening headaches between their migrainous attacks leading to chronic daily headache. He also noted that both the clearly migrainous attacks and the intervening headaches responded to migraine medications, predicting the results of the Spectrum Study that was to be performed approximately 80 years later[4]. It is often not clinically rewarding to diagnose both episodic migraine and chronic tension type headache if a patient presents with a chronic, persistent, fluctuating headache with migrainous features, since many of these patients, and certainly the most disabled group, can be usefully described as having migraine the disorder or, in other words, chronic migraine[5] (Table 2).

Table 1

Modified International Headache Society migraine without aura criteria[2]

A. At least five attacks fulfilling B-D.
B. Headache lasting 4-72 hours (untreated or unsuccessfully treated).
C. Headache has at least two of the following characteristics:
   1. Unilateral location.
   2. Pulsating quality.
   3. Moderate or severe intensity (inhibits or prohibits daily activities).
   4. Aggravation by walking stairs or similar routine physical activity.
D. During headache at least one of the following:
   1. Nausea or vomiting, or both.
   2. Photophobia and phonophobia.

Table 2

Proposed criteria for transformed migraine (chronic migraine)[6]

A. Daily or almost-daily (>15 days/month) head pain for >1 month.
B. Average headache duration of >4 hours/day (if untreated).
C. At least one of the following:
   1. A previous history of IHS migraine.
   2. History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months.
   3. Current superimposed attacks of headaches that meet all the IHS criteria for migraine except duration.

Photophobia can help further clarify the difference between migraine the disorder and migraine the attack. Part of the migraine attack includes the associated symptom of light-induced pain greater on the side of a unilateral headache[7]. Migraine the disorder would encompass the general sensitivity to glare that persists between migraine attacks in some patients, leading them to wear sunglasses indoors and oftentimes identifying them as a difficult to treat migraine patient.

This review will focus on several different aspects of difficult migraine: analgesic overuse, treatment of frequent refractory headache, and migraine in specific populations or situations including the elderly, pregnancy, and menstrually-triggered migraine.

Analgesic overuse

Analgesic overuse is a common problem in the community and particularly in refractory migraine patients. In one population-based study, 31.1% of transformed migraine (chronic migraine) patients overused symptomatic medications[8]. Effective management starts with limiting symptomatic medication use. Although the actual dose limits needed to develop rebound headaches have not been rigorously defined, it seems prudent to limit acute medication use to two days a week at most. A recent European consensus statement recommended (with some exceptions) that the maximum usage of ergotamine should be 4-6 times a month[9]. If symptomatic medication overuse is present, it is generally agreed that the drugs must be withdrawn before prophylactic medications can be effective[10]. The key is to start an effective prophylactic once the acute medication is reduced in order to decrease headache frequency, and thus the need for symptomatic medication, rather than to keep adding more symptomatic medication. While it is true that some patients simply improve when the acute medication is reduced, which is a good reason to make this the first step, many do not and will need preventative management.

"Effective management starts with limiting symptomatic medication use. Although the actual dose limits needed to develop rebound headaches have not been rigorously defined, it seems prudent to limit acute medication use to two days a week at most."

Table 3

Prophylactic medications to consider in difficult migraine

Drug	Reasonable Dose
Readily available:	
• Valproate	800-1200 mg/day
• Methysergide	1-6 mg/day
Named patient basis:	
• Flunarizine	5-10 mg/day
Useful but limited by side effects:	
• Phenelzine	45 mg/day
Promising new treatments:	
• Gabapentin	900-2400 mg/day
• Topiramate	50-200 mg/day
• Lisinopril	20 mg/day
Drug combinations:	
• Tricyclic antidepressant plus beta-blocker	
• Valproate plus tricyclic antidepressant	

Treatment of refractory migraine

In this paper, refractory migraine will be defined as those patients who fail to respond to typical prophylactic medications, including beta-blockers, tricyclic antidepressants, and pizotifen, given at adequate doses for adequate periods of time (generally at least three months). Table 3 lists medications to consider when the typical preventatives have failed. Again it is crucial to ensure that a prophylaxis trial is undertaken while the patient is not overusing symptomatic medications. Clinical experience has shown that a patient may fail a preventative while overusing symptomatic medication but later find it effective when the overused drug is withdrawn[11].

Table 4
Difficulties in using acute and prophylactic migraine medications in the elderly (after 12)*

Drug	Comments
Acute medication:	
• Ergots, triptans	Avoid in elderly patients with hypertension, coronary artery disease, peripheral vascular disease, cerebrovascular disease.
• NSAIDs	Avoid in elderly with peptic ulcer disease. May have cognitive side effects. Elderly vulnerable to renal failure.
Prophylactic medication:	
• Beta-blockers	Avoid in elderly patients with cardiac conduction abnormalities, asthma, COPD, uncontrolled congestive heart failure and possibly diabetes.
• Tricyclic antidepressants	May produce sedation, confusion, or aggravate arrhythmias in the elderly. May exacerbate prostatism and glaucoma.
• Methysergide	Similar contraindications as the ergots and triptans.

*These contraindications and cautions apply to patients of all ages with the named diseases. However, one must use extra care in the elderly as most of these diseases increase in frequency with age.

Migraine in the elderly

Although migraine prevalence peaks around 40 years of age, it continues to occur in older patients. Migraine prevalence is 5% in women and 2% in men over age 70, and approximately 2% of migraine cases begin after age sixty-five[12]. Giant cell arteritis presenting as migraine must always be ruled out before proceeding with migraine treatment, and it is worth remembering that approximately 5% of giant cell arteritis patients experience visual scintillations[13]. Nitroglycerine and oestrogen, both commonly used in the elderly, can exacerbate underlying migraine or cause migraine-like headaches. In these circumstances, either lowering the dose of nitroglycerine (if possible)[12], or assuring that hormone replacement is continuous rather than cyclic can be helpful[14]. Table 4 outlines the difficulties in treating the older migraineur. Because of their side effect profiles, some migraine prophylactics may be better tolerated than others in the elderly (Table 5).

Table 5
Prophylactic medications to consider earlier in migraine management in the elderly because of their good benefit-to-side-effect profiles

Drug	Comments
• Nortriptyline	Generally has less pronounced side effects than amitriptyline.
• Pizotifen	Drowsiness common side effect.
• Gabapentin	Only one controlled study.
• Valproate	
• Lisinopril	Only one study published thus far.

Migraine in pregnancy

Studies suggest that 60-70% of migraine patients experience an improvement in their headache during pregnancy, especially in the second and third trimesters[15]. However, some patients experience their first migraine attack during pregnancy[16]. There is no evidence that migraine has any effect on the outcome of the pregnancy[17]. As stated by Dr. John Edmeads, the ramifications for the treatment of the pregnant woman are profound, if only because the neurologist is treating two patients[18]. Nonpharmacological therapies should be used first. Obviously, avoiding any medication during pregnancy is optimal, and this is certainly the manufacturers' usual advice. At times, drug treatment may be necessary. Tables 6 and 7 list acute treatment options when the potential benefit of treatment is felt to outweigh the risks. Ergotamine is contraindicated in pregnancy, and the use of triptans or dihydroergotamine cannot be routinely recommended. Pregnant patients may rarely require prophylactic medications because of severe frequent headaches. This option should be a last resort and only used after a thorough discussion of the risks for foetus and mother. Propranolol has not been established to be safe in pregnancy, but has been widely used, and is felt by some to be the only prophylactic that can be recommended in this difficult situation[17].

Menstrually-triggered migraine

There is a clinical impression that migraines are more common and severe around the time of menses. Recent studies support the notion that migraine without aura is more likely to occur 2 days before the onset of menses and on the first 2 days of menses[19,20]. Stewart *et al*'s study did not support the notion that headaches are more severe during the perimenstrual period compared to other

Table 6
Symptomatic treatment options in the pregnant migraneur (after 15)

Drug	Comments
For headache:	
• Paracetamol	Mild analgesic of choice in pregnancy.
• Ibuprofen, Naproxen	Neither has been shown to have a teratogenic effect. Avoid in third trimester as may cause premature closure of foetal ductus arteriosus, inhibition of labour, decreasing amniotic fluid volume.
• Codeine	Indiscriminate use may present a risk to foetus during first or second trimester. Cleft lip and palate, inguinal hernia, hip dislocation, cardiac and respiratory system defects reported.
• Other narcotics	
For nausea:	
• Metoclopramide	No congenital malformations have been reported.
• Chlorpromazine	Most studies indicate safe for mother and foetus if used in occasional low doses.
• Prochlorperazine	Most evidence indicates that both this drug and promethazine are safe for mother and foetus if used occasionally in low doses.
• Promethazine	

Table 7
Treatment regime for severe acute attacks in the pregnant migraineur (after 15):

- Hydration
- Prochloperazine 10 mg IV
- IV narcotics can supplement

Table 8
Prophylactic treatment of menstrually-triggered migraine

Drug	Dose
Nonhormonal prophylaxis:	
• NSAIDs	Mefenamic acid 500 mg 3-4 times per day or Naproxen 500 bd starting 1-2 days before expected onset of headache and continued for duration of vulnerability (typically days -2 to +3 of menstrual cycle).
• Ergotamine	1 mg od or bd (or 1/2 suppository nocte) for 3-5 days when vulnerable.
Hormonal prophylaxis:	
• Transdermal oestrogen	100 micrograms begun 3 days before menstruation, continued for 7 days.
• Oestradiol gel	1.5 mg in 2.5 g gel begun 3 days before expected menstruation, continued for 7 days.
• Other hormonal manipulations can be undertaken in consultation with gynaecologist or endocrinologist.	

times in the cycle[19]. The study did not address whether perimenstrual migraine headaches are more difficult to treat, but this does not appear to be the case as sumatriptan, zolmitriptan, and rizatriptan are as effective for menstrually-associated migraine as for nonmenstrually-associated migraine[21, 22, 23]. Thus, menses appears to be a robust trigger for migraine[19]. The acute treatments for menstrually-triggered migraine are the same as those used for migraine

" It is important to remember when managing the refractory migraine patient that it is the disorder, not the patient, that is difficult"

unassociated with menses. The periodicity and predictability of menstruation allows the physician to employ short-duration prophylaxis. The primary trigger for migraine occurring during menses may be oestrogen withdrawal[19], thus increasing the prophylactic medication options. Table 8 reviews prophylactic treatment regimens that have been successfully employed in menstrually-triggered migraine.

Conclusion

It is an exciting time to be involved in migraine therapeutics. Researchers have started to identify the genes involved in causing the problem[24], and functional neuroimaging has pointed to the brainstem as being the seat of the basic pathophysiologic process[25]. The ultimate goal of this research is improved treatment of the migraine sufferer, and it is important to remember when managing the refractory migraine patient that it is the disorder, not the patient, that is difficult.

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Acknowledgements: MSM is a Migraine Trust Research Fellow. PJG is a Wellcome Trust Senior Research Fellow.

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NICE recommends riluzole for the treatment of ALS

Introduction

The decision by NICE to recommend the use of riluzole for the treatment of patients with amyotrophic lateral sclerosis (ALS; Motor Neurone Disease, MND) will be welcomed by most people affected by the disease, and by many (probably most) neurologists. The search for drugs to slow the progression of neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and ALS has been wearisome - witness the disappointing outcome of the DATATOPS study in Parkinson's disease, and of trials of branched chain amino acids and several neurotrophic agents in ALS. It is not surprising therefore that the advent of riluzole was met by some scepticism in neurological circles.

The effectiveness of riluzole

Riluzole, a drug with complex effects on glutamate neurotransmission including inhibition of presynaptic glutamate release (Doble, 1996), was first selected for study in ALS by Professor Vincent Meininger, Dr Gilbert Bensimon and colleagues at the Hopital Pitie-Salpetriere in Paris on the basis of evidence that glutamate homeostasis might be impaired in ALS, resulting in excitotoxic cell death (Shaw; 1999; Al-Chalabi and Leigh, 2000). With a team from the French pharmaceutical company Rhone-Poulenc Rorer (now Aventis) they designed and carried out the first trial in which 155 ALS patients were randomised to take either riluzole (100 mg) or placebo over periods of up to 21 months. Patients were stratified according to bulbar or limb onset. The primary outcome measure was survival. At 12 and 21 months there was a significant difference in survival in favour of riluzole in the whole patient group (Bensimon *et al*., 1994). There was a suggestion that the effect of riluzole was more evident in patients with bulbar onset disease, although in retrospect, this was a bias resulting from the small sample size. Deterioration in muscle strength was significantly slower in patients receiving riluzole compared to placebo.

If this study was under-powered, it was nevertheless a landmark in trial design in ALS and, arguably, in the field of neurodegenerative disease. The primary endpoint chosen is robust, easy to ascertain, and clearly relevant to the disease. The statistical analysis of survival is relatively straightforward. Functional endpoints suffer from missing values, especially in long trials, and statistical methods to deal with this problem are not entirely satisfactory.

A larger trial was clearly necessary, both to establish the efficacy of the 100mg dose, and to investigate a dose effect. This study was started in 1992, completed in 1995, and published in 1996 (Lacomblez *et al*., 1996). 959 ALS patients from seven countries were randomised to placebo, or to riluzole 50 mg, 100 mg or 200 mg daily. The primary outcome measure was tracheostomy-free survival. Patients were stratified according to bulbar or limb onset. A variety of functional measures were studied including muscle strength and vital capacity. Regrettably no attempt was made to assess quality of life (QL). In retrospect, that was a significant weakness, and since then several generic QL instruments have been used in trials (e.g., Borasio *et al*., 1998) and a new disease specific instrument has been developed (Jenkinson *et al*., 2000).

The outcome of this study was a trend towards increased survival with riluzole at 18 months, the end of the double-blind phase of the study. There was a significant improvement in survival at one year. The difference in survival and/or tracheostomy between placebo and riluzole 100mg was 6.4% at 18 months. The gain in survival with riluzole was about three months, but as the Kaplan-Meier survival plot did not reach the median at 18 months, this is only a rough estimate. There was a clear dose effect, but the side-effect profile suggested that 100mg would be the best dose for clinical use.

The purist would argue that as the primary, unadjusted log-rank analyses of the data at 18 months were negative, showing only a trend towards improved survival with riluzole, the trial should have been regarded as negative. That would risk abandoning an active treatment in a fatal disease for which no other drug treatment exists. The trial was powered to detect a hazard ratio of 0.67 for the 100mg dose compared to placebo at 18 months, assuming a survival of 35% in the placebo group. In the event, the survival in this group was about 50% at 18 months, so the number of events was lower than expected. This cohort of ALS patients was thus somewhat less severely affected than the sample on which these power calculations were based. It was thus important (and specified in the trial protocol) to carry out an adjusted analysis using the Cox proportional hazards model. The Cox model allows slight differences in known prognostic factors to be balanced between the treatment groups. This revealed a relative risk of death for riluzole versus placebo of 0.65 (CI 0.50-0.85) at 18 months. Differences in survival at 18 months between placebo and riluzole 100mg and 200mg daily were highly significant after adjustment for prognostic factors. For some commentators (Guiloff *et al*.,1996) this was inadmissable evidence. We (Lacomblez *et al*., 1996) felt that this approach was appropriate (indeed necessary) since it is well known that such factors profoundly influence prognosis in ALS.

These two trials form the core of the evidence in support of riluzole, but four randomised trials were taken into account by NICE. Two have been outlined above. Another trial considered was a Japanese study which showed no benefit with riluzole (Yanagisawa *et al*., 1997). The fourth study (Meininger *et al*., 1995; still unpublished in a peer review journal, but presented in the Comprehensive Medical Report of the company) was a double blind randomised placebo controlled trial carried out in France including 168 patients who were not suitable for inclusion in the dose-ranging study - in essence, those patients who were not eligible for the Lacomblez *et al*. (1996) trial. These patients were more severely affected than patients recruited for the latter trial. There was no significant difference between riluzole treated and placebo groups. Nevertheless, a meta-analysis of the three trials with similar design (Bensimon *et al*., 1994; Lacomblez *et al*., 1996; Meininger *et al*.,1995) revealed a significant effect of riluzole on survival (CMP report,1995).

Furthermore, a meta-analysis of two published trials (Bensimon *et al*., 1994; Lacomblez *et al*., 1996) by the Cochrane collaboration (Miller *et al*., 2000) came to similar conclusions. The odds ratio for the primary outcome measure selected (% mortality at 12 months) for the combined studies was 0.57 (95% confidence interval[CI] 0.41-0.80; Z= -3.29, p=0.001). NICE commissioned its own meta-analysis, and the Summary of Evidence document is a mine of information about the disease as well as the efficacy and cost effectiveness of the drug. This analysis concluded that riluzole is associated with a hazard ratio of 0.83 (95% CI 0.75-1.02) for the

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Presentation: Rilutek® 50mg film-coated tablets contain riluzole 50mg. **Indications:** Riluzole is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS). Clinical trials have demonstrated that Rilutek® extends survival for patients with ALS. There is no evidence that riluzole exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength or motor symptoms. Riluzole has not been shown to be effective in the late stages of ALS. The safety and efficacy of riluzole has only been studied in ALS. **Dosage and administration:** Treatment should only be initiated by specialist physicians with experience in the management of motor neurone disease. *Adults and Elderly:* One 50mg tablet bd; *Children:* Not recommended; *Renal impairment:* Not recommended; *Hepatic impairment:* See warnings and precautions. **Contraindications:** Severe hypersensitivity to riluzole. Patients with hepatic disease where baseline transaminases are greater than 3 times ULN. Pregnancy, breast feeding. **Warnings and Precautions:** Prescribe with care in patients with history of abnormal liver function or patients with increased transaminases, bilirubin and/or GGT levels. Measure serum transaminases before and regularly during treatment with riluzole and more frequently in patients who develop elevated ALT levels during treatment. Treatment should be discontinued if ALT level increases to 5 times ULN. Discontinue riluzole in the presence of neutropenia. Any febrile illness must be reported to the physician. Do not drive or use machines if vertigo or dizziness are experienced. **Interactions:** *In vitro* data suggests CYP 1A2 as the primary isozyme in the oxidative metabolism of riluzole; inhibitors or inducers of CYP 1A2 may affect the elimination of riluzole. **Pregnancy and lactation:** Contraindicated. **Side effects:** Asthenia, nausea and elevations in LFTs are the most frequent events seen. Less frequent events include pain, vomiting, dizziness, tachycardia, somnolence and circumoral paraesthesia. Very rarely anaphylactoid reaction, angioedema, pancreatitis and neutropenia may occur. **Legal Category:** POM. **Package Quantities and Basic NHS Price:** Each box of Rilutek® Tablets contains 4 blisters of 14 tablets; £286.00. **Marketing Authorisation Number:** Rilutek® tablets 50mg EU/1/96/010/001. Full Prescribing Information and further information is available on request from Aventis Pharma Limited, 50 Kings Hill Avenue, Kings Hill, West Malling, Kent. ME19 4AH. **Date of preparation:** November 2000.

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Aventis

Date of Preparation: January 2001 RIL0121200AD

three trials for which full data was available. In addition, there was a small reduction in the rate of deterioration of the functional measures.

We can conclude, as NICE has done, that riluzole treatment at 100mg daily is associated with a modest increase in survival. The increase in life expectancy lies between 2 and 4 months (at 18 months), but it is uncertain whether there is any further gain across the whole duration of the disease, since there is no long-term evaluation of survival with placebo versus riluzole. Long-term projections of gain in life expectancy rely on modelling using Weibull or Gompertian extrapolation. Nevertheless, analysis of new evidence submitted to the NICE assessors by Aventis on 48 month follow-up of patients receiving riluzole 100mg daily in the Lacomblez *et al.* (1996) trial indicated about six months difference in survival compared to placebo (Bryan *et al*., 2001: NICE Report and Summary of Evidence).

Is riluzole cost-effective? The analysis performed for NICE concluded that the base-case incremental cost-effectiveness ratio (ICER) gave a cost per life year of £39,000 and a cost per quality adjusted life year (QALY) of £58,000. The Technology Appraisal Document quotes a discounted cost per QALY estimate for riluzole of between £34,000 and £43,000. The most optimistic ICER (cost per QALY) was £20,000. However, estimates of cost per QALY based on the new long-term data referred to above (Bryan *et al*., 2001) suggested a range of £16,500 to £20,000 depending on the model used - a more attractive cost-effectiveness profile. NICE estimates that the additional cost of making riluzole available to all individuals with ALS in England and Wales would be about £5M per annum.

The impact of the NICE guidance

The NICE Guidance makes recommendations on the place of riluzole in the management of ALS. Recommendations for the safety of riluzole are well known. Other recommendations are not controversial. The guidance suggests that riluzole therapy should begin as early as possible in the course of the disease. Although there is no conclusive evidence for this statement, it makes good sense to use a drug which is supposedly neuroprotective when there are surviving neurones to protect. Reasonably, NICE recommends that riluzole therapy should be initiated by neurologists with expertise in the management of MND - one hopes that this would apply to all neurologists in the UK. Supervision and monitoring "should be managed by locally agreed shared care protocols undertaken by general practitioners". NICE recommends that we should take a flexible approach to continuation of therapy in the late stages of the disease, as compassion dictates.

No doubt there will still be wrangles about who bears the cost of prescribing - clarification on this would have been helpful, since such arguments can be very distressing for patients. The NICE recommendation alone will not force health authorities to fund riluzole, although they will find it difficult not to do so.

Who should receive riluzole? NICE has got into a predictable tangle over the terms ALS and MND, mainly because the committee was required to abide by the terminology used in the product licence. ALS refers to the classical form of the disease with upper and lower motor neurone signs (as in Charcot's original description of the disease). The term MND incorporates ALS and the progressive lower motor neurone syndrome known as progressive muscular atrophy (PMA). Since pathological studies clearly show that the majority of patients with PMA have ALS (i.e., they have both upper and lower neurone damage), it is to be hoped that neurologists will interpret the term ALS somewhat liberally. It would be invidious to exclude patients who have only lower motor neurone signs if they have progressive disease suggesting MND, and if other conditions such as multifocal motor neuropathy or Kennedy's disease have been excluded. We should dissuade health authorities from taking a restrictive view that will disadvantage a minority of patients with 'ALS'.

Conclusions

Having weighed the evidence, the NICE Appraisal Committee, like individual clinicans, had to decide whether or not to recommend riluzole for the treatment of ALS. Interestingly, they do not state precisely why they concluded in favour of the drug - after all, the evidence presented could be interpreted as equivocal. The cynic might think that riluzole passed muster because the overall cost was modest - after all, ALS is a rare disease compared to multiple sclerosis, and riluzole is relatively cheap compared to ß-interferon. Clinicians who wish to make rational, but humane, decisions, are not much wiser for NICE - although those who like to prescribe riluzole may feel more comfortable, and those who do not will feel less comfortable. The evidence has not changed.

I believe, however, that NICE has given the right advice. Riluzole has been granted the benefit of the doubt. This is vitally important for people affected by ALS. It could be said to give people 'rational hope'. If we cannot show an effect on quality of life, that is our fault - we did not ask the right questions during the trials. The criticism that riluzole prolongs the end-stage of the disease is not supported by evidence. We know that other treatments that extend survival can improve quality of life. Non-invasive ventilation, for example, is associated with improved quality of life in key domains, even though patients are severely disabled physically (Pinto *et al*., 1995; Lyall *et al*., 2001).

The approval of riluzole is also crucial for further progress in developing new treatments for neurodegenerative disorders. The investment necessary for such studies is large, the rewards for industry at present uncertain. The experience with riluzole in ALS shows that it is possible to influence the outcome of a progressive neurodegenerative disorder using drugs. Although the ultimate goal is to arrest disease progression, at this stage we can only expect drugs to yield modest gains in survival, hopefully associated with tangible impact on function and quality of life. A pressing need is for understanding of the basic mechanisms leading to neuronal death, and although much progress has been made we are some way from unravelling the molecular cascade that could reveal new targets for rational drug design (Al-Chalabi and Leigh, 2000).

Important questions remain open. The NICE document recommends further trials to examine the relative effectiveness of different dose regimes. This does not address the question of whether it is now ethical to carry out placebo-controlled trials on riluzole. Whatever neurologists might think about this, people with ALS are unlikely to join such trials. Comparative studies of different doses are certainly possible, but who will fund these? Industry has little incentive to do so, and ALS does not figure high in the list of NHS priorities. If one were to use a 'real life' randomised design, patients choosing or being allocated to take placebo would comprise a biased sample. Our own database shows that patients who take riluzole are significantly younger than those who do not, and age is a potent prognostic factor (unpublished data). Studies with biased samples are not likely to answer the questions posed.

Perhaps, like Meininger *et al.*(2000), we should consider using large clinical databases to compare 'historical controls' from the pre-riluzole era with cohorts of patients diagnosed from 1996

onwards. Meininger *et al.*(2000) analysed survival in a group of 161 patients studied between 1989 and 1991 before riluzole was available, and a second group of 356 patients who had been treated with riluzole between 1995 and 1997. The median survival in the treated group was 18.4 months, compared to 12.4 months in the untreated group. Unfortunately such comparisons are difficult to interpret since it is possible (indeed likely) that patterns of care, particularly interventions such as gastrostomy and non-invasive ventilation that are known to influence survival, changed over this period. Such studies are not easy - complete data on important prognostic factors, quality of care, interventions (gastrostomy, non-invasive ventilation) drug exposure, and survival is a prerequisite if the effect of riluzole is to be separated from other variables. I believe that this approach deserves attention, in parallel with new prospective studies.

At present we must make do with the evidence as it stands. Most patients with ALS (MND) want an honest discussion about the pro's and con's of riluzole and then to choose whether to take it or not. How we impart the information will influence that choice. Following the NICE guidance, who gets riluzole and who does not will depend less on the judgements of health authorities and more on the attitudes of neurologists to the data, but also on their attitudes to patient choice.

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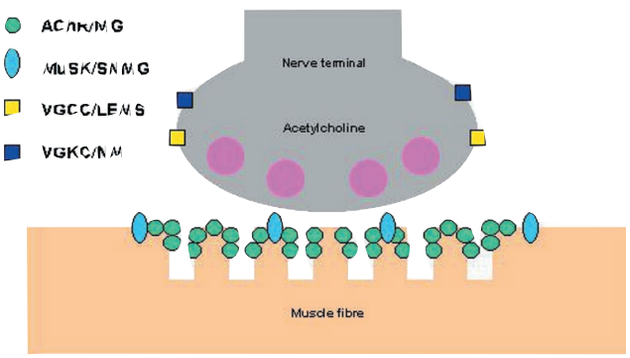
Antibody-mediated diseases of the neuromuscular junction

The neuromuscular junction is, unlike most of the nervous system, easily accessible to circulating factors, making it particularly vulnerable to autoantibodies, and it is also the target for many highly-specific neurotoxins. It is now clear that there are at least four different antibody-mediated disorders directed at specific membrane proteins. The proteins are all important functional molecules and the antibodies bind to extracellular determinants of the proteins and lead to loss of their numbers or function. In three of these conditions, the antibodies can be measured by immunoprecipitation of the relevant protein indirectly labelled by a specific radioactive neurotoxins (Table; for a review see[1] -). The roles of these antibodies in causing the diseases has been confirmed by showing substantial improvement following plasma exchange, and by "passive transfer" to experimental animals of defects in neuromuscular transmission. Although the diseases can be treated symptomatically by drugs that partially compensate for the loss of function, such as acetylcholine esterase inhibitors, the patients may also require immunosuppressive therapies. In addition, thymectomy is performed in the majority of patients with early-onset antibody positive myasthenia gravis (presenting before middle-age) or in the rarer cases of thymoma.



Antigenic targets and autoimmune disorders of the neuromuscular junction

Autoantibodies to acetylcholine receptors in young and old

The role of autoantibodies to acetylcholine receptors in myasthenia gravis (MG) is well recognised; detection of these antibodies is now routine in laboratories throughout the world, and the beneficial effects of immunosuppressive treatments are clear. The AChR antibodies cause loss of functional AChRs by increasing its turnover, targeting the postsynaptic membrane for complement-mediated destruction and, to a lesser extent in most cases, by inhibiting AChR function directly[2].

Measurement of the antibodies has made it possible to diagnose the disease much more easily. This, and the increasing mean survival age of the population, may be major factors in the increasing number of patients who are presenting and being diagnosed in their later years. A recent survey of all the positive AChR antibody results reported over the last three years in the UK and Eire suggests that more than 60% are in individuals over the age of 50 (Vincent et *al* in preparation). MG is a disease that can present at any age up to 100!, and moreover, the age related incidence is much greater in the later decades reaching as high as 7/100,000 per year.

During pregnancy antibodies cross the placenta and "neonatal" MG can result, although it is relatively uncommon for reasons that are not clear. The AChR comes in two forms, adult and fetal and in most cases the antibodies are directed against the alpha subunits that are shared by both forms. However, in a small proportion of female patients who develop MG during or after their first pregnancies, the antibodies seem to be particularly directed towards a functional epitope on the fetal AChR. In a few reported cases these antibodies cause fetal paralysis, leading to a potentially fatal condition called arthrogryposis multiplex congenita in which the baby is born with fixed joint contractures and other deformities. Since these antibodies are so biased towards fetal AChR, the mother herself may be asymptomatic[3] and thus detection of AChR antibodies in women who have had babies with contractures may point to a potentially recurring problem that can be avoided if the woman is treated during pregnancy to reduce the antibodies[4]. Moreover, it raises bigger questions as to the role for maternal antibodies in other developmental conditions.

"Seronegative" MG is a different disease

Up to 20% of patients with typical generalised symptoms of MG will not have detectable antibodies against the AChR, so-called "seronegative" MG. A recent report shows that many of these patients have antibodies to the muscle-specific kinase (MuSK), which is a receptor tyrosine kinase that is present at the neuromuscular junction where it plays a crucial role during development. Its role in adult life is not clear, but IgG antibodies binding to extracellular domains of MuSK have been detected in 70%, using an ELISA assay[5], of so-called seronegative MG patients. It is hoped that this test will soon be available for routine diagnostic use. Although the clinical presentation of these patients is similar to that of AChR antibody-mediated MG, "seronegative" or "MuSK antibody positive" MG appears to be relatively more common in children. the relationship of this condition to thymic pathology and the response of these patients to thymectomy is currently unresolved.

Targets shared by the central nervous system

The Lambert Eaton myasthenic syndrome (LEMS) is caused by antibodies to the P/Q-type voltage-gated calcium channel (VGCC) that is present on the motor nerve terminal (Table) and also expressed in the central nervous system (CNS), particularly on the cerebellar Purkinje cells. The VGCC antibodies reduce the action-potential-induced influx of calcium into the motor nerve terminal leading to a drastic reduction in ACh release. During prolonged voluntary contraction, calcium accumulates within the nerve terminal and ACh release increases which leads to the characteristic "increment" in the compound muscle action potential that can be observed in electromyographic studies. Confirmation of the diagnosis of LEMS, and distinguishing it from MG, is important, not least because up to 60% of LEMS patients have a small cell lung cancer[6]. Thus LEMS can be a "paraneoplastic" disorder, and detection of the antibody is an important indication to look for a lung tumour - particularly if the patient is or has been a smoker. In addition some

Antibody targets and associated conditions

Target	Antigen used for immunoassay	Condition
AChR	^{125}I-bungarotoxin-AChR (fetal and adult)	Myasthenia gravis Arthrogryposis multiplex congenita
MuSK	Recombinant extracellular domains of MuSK on ELISA	"Seronegative" (or "MuSK antibody positive") myathenia gravis
VGCC	^{125}I-conotoxin MVIIC-VGCC	Lambert Eaton myasthenic syndrome with or without small cell lung cancer Cerebellar syndromes with or without small cell lung cancer
VGKC	^{125}I-dendrotoxin-VGKC	Acquired neuromyotonia Limbic and hypothalamic syndromes, with or without neuromyotonia

tumour patients with cerebellar ataxia have both antibodies to VGCC and to Hu, the antibody most typically associated with small cell lung cancer[7]. In addition, a few patients with predominant ataxia and VGCC antibodies only, with or without tumours, have also been identified[8].

Acquired Neuromyotonia is a heterogeneous condition associated with spontaneous muscle activity including fasiculations, undulating myokymia, pseudomyotonia and cramps, and can be detected by electromyography as bursts of spontaneous motor unit potentials. About 40% of patients with neuromyotonia have antibodies to voltage-gated potassium channels (VGKC) and, although the data are less complete than for MG and LEMS, it is very likely that these antibodies are responsible for the neuronal hyperexcitability which arises mainly in the distal motor nerve and motor nerve terminal. Interestingly, patients with neuromyotonia sometimes have a thymoma and MG, or a thymoma without evident MG. Thus a proportion have AChR antibodies as well as VGKC antibodies. Although documented cases are rare, a surprising number of patients with neuromyotonia, with or without thymomas, have evidence of central nervous system disease with limbic or hypothalamic involvement, and two patients with reversible limbic syndromes apparently caused by VGKC antibodies have been identified in a recent study[8].

Conclusions

Detection of antibodies to neuronal and muscle ion channels has shed light on the pathophysiology of neuromuscular junction disorders. We may now be starting a new era, when similar techniques and approaches begin to demonstrate a role for autoantibodies in central nervous system disease and in neurodevelopmental disorders.

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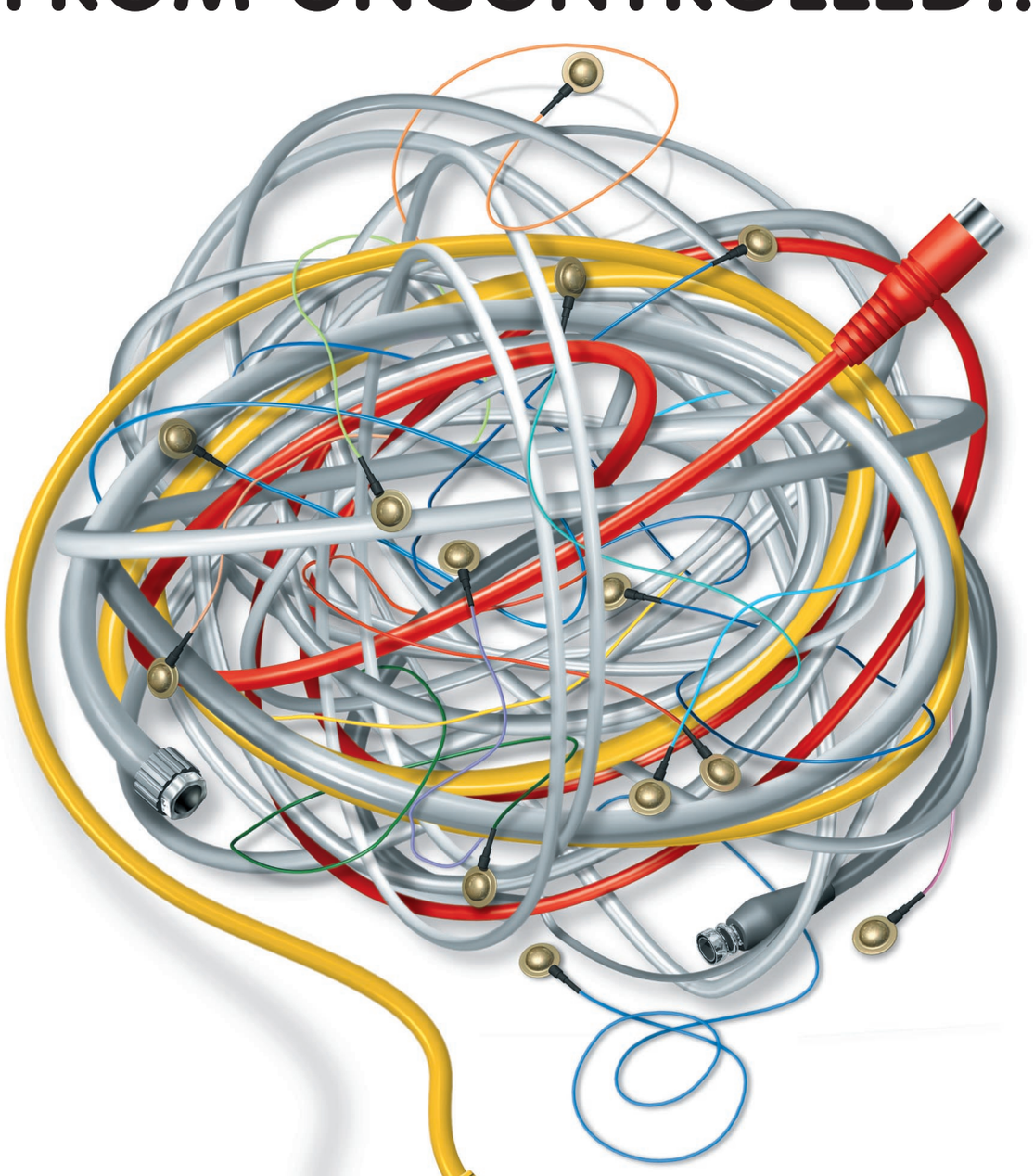

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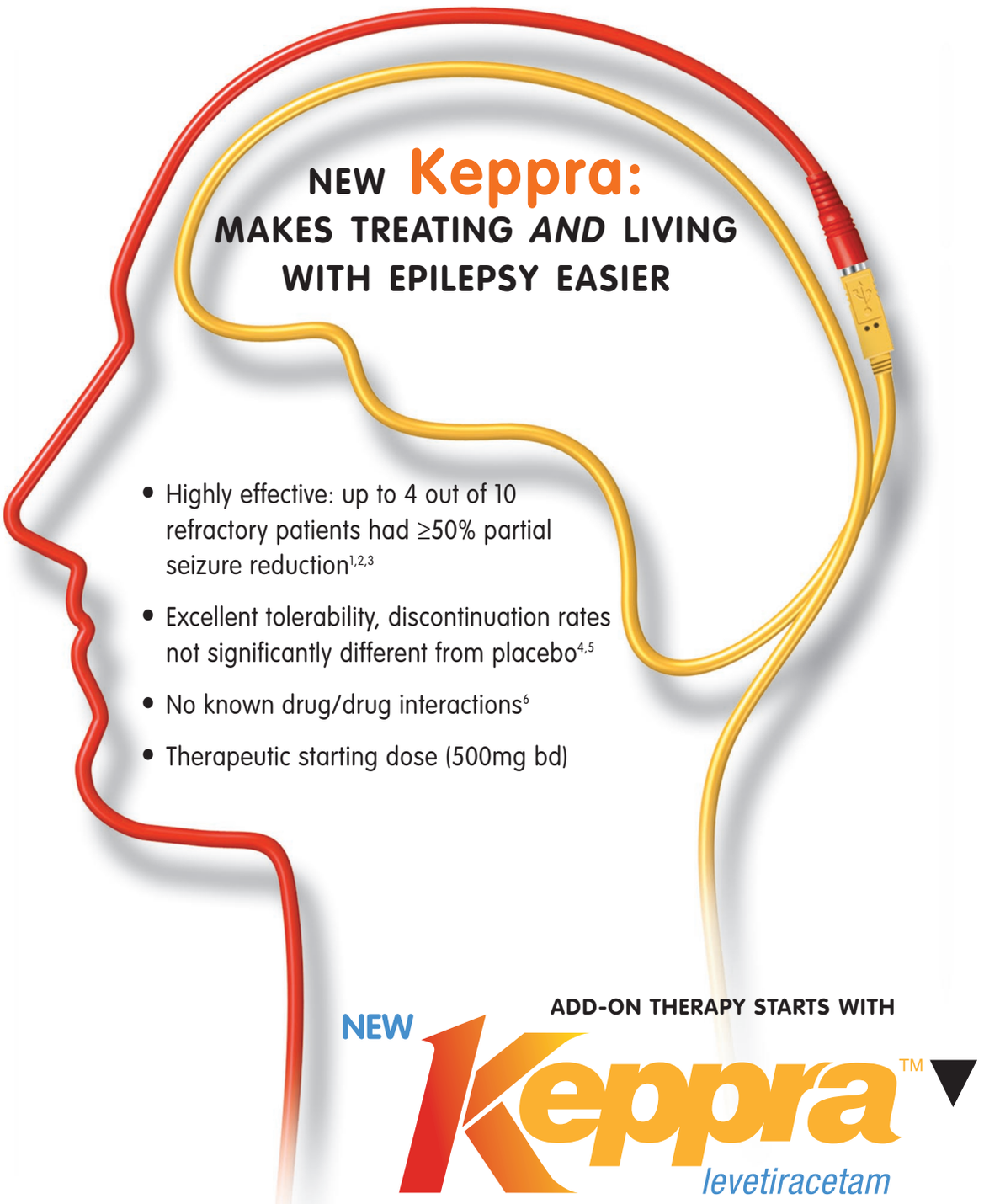

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Further information is available from: UCB Pharma Ltd., 3 George Street, Watford, Herts WD18 0UH. Tel: 01923 – 211811.
Date of Preparation: October 2000.

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EIZURE CONTROL

Mark Manford

Diagnosis of Epilepsy

Introduction

Epilepsy enters the differential diagnosis of virtually any paroxysmal disorder of CNS function. The first step is to differentiate epilepsy from other common paroxysmal disorders. The next step is to diagnose the seizure syndrome in order to estimate prognosis and optimise treatment.

The great majority of seizures cause an ictal scalp EEG abnormality and the gold-standard diagnosis is made by ictal electroclinical correlation.

If the diagnosis is uncertain, it is often better to wait and see rather than impose an incorrect diagnosis of epilepsy with all its psychosocial consequences.

Key clinical features in diagnosing attack disorders

- Organic attacks tend to be more stereotyped than psychogenic attacks.
- Attacks may occur under stereotyped circumstances. For example morning myoclonus, micturition syncope or acute emotional distress causing psychogenic non-epileptic seizures (PNES). Sleep deprivation, fever and alcohol are common triggers of epileptic seizures in susceptible individuals.
- Convulsive movements are common in syncope but are usually brief and asynchronous. The precipitating situation and rapid recovery are the best clues to diagnosis. Reflex anoxic seizures may complicate syncope.
- Attacks arising from sleep are organic (though not always epileptic) but it may take an EEG to prove that the patient is asleep at the onset.
- Focal deficits point to focal epilepsy and may signify a significant structural lesion.

The so-called classical symptoms of convulsive seizures

No single symptom is diagnostic of epilepsy but some are helpful (table 1).

Differential diagnosis of paroxysmal focal neurological symptoms

Paroxysmal focal neurological symptoms are most commonly due to epilepsy, migraine, cerebral ischaemia or psychological causes, including hyperventilation. Some important characteristics are:

- The timing; especially the speed of onset and the duration of the symptoms (figure 2)
- Positive symptoms (extra symptoms such as jerking of a limb)

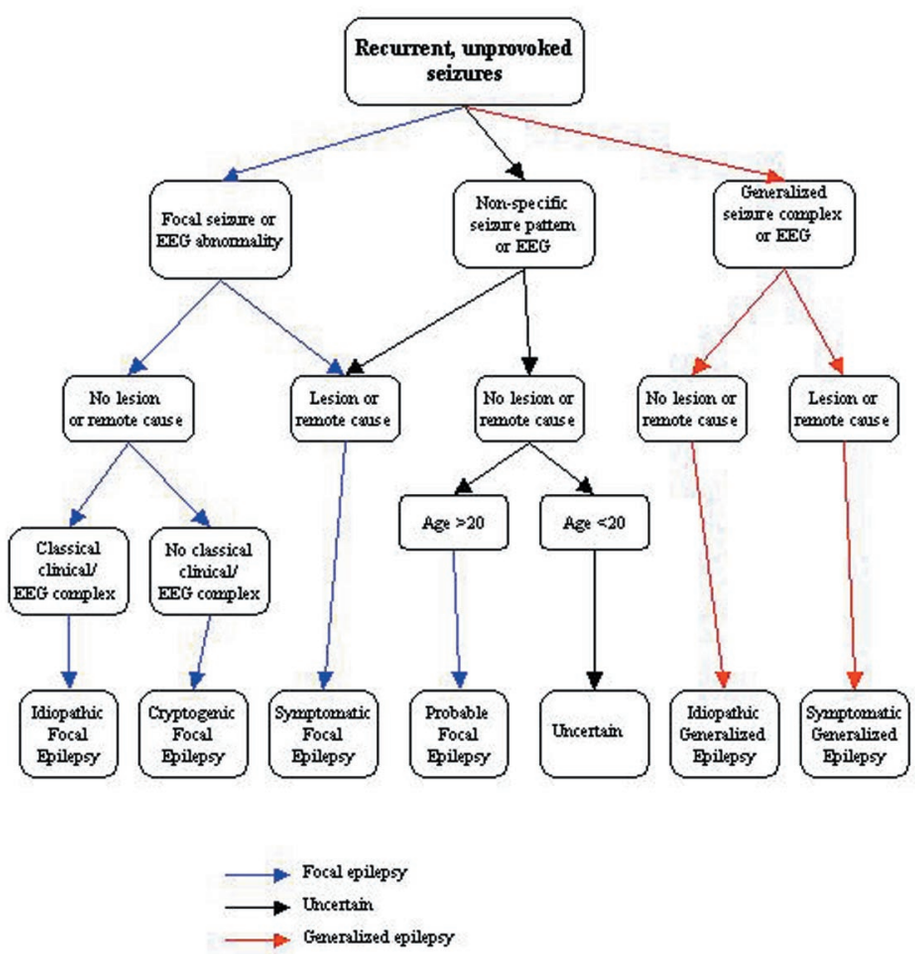

Figure 1
Focal epileptic symptoms are usually positive. They start suddenly and stop quickly but may leave a transient postictal deficit. Focal symptoms of ischaemia are almost always negative and start and finish quite abruptly. Migrainous symptoms are more gradual and have both negative and positive qualities. For example a limb that tingles and feels heavy or a slowly enlarging bright spot that obscures central vision.

Table 1.

Symptom	Comment
Incontinence of urine	May occur in any black out if the patient's bladder is full
Cyanosis	May be mimicked by a Valsalva manoeuvre in PNES
Tongue-biting	Usually epilepsy, especially if severely bitten
Injuries	Depend on the circumstances, rather than the seizure-type
Burns	Severe burns usually mean epilepsy
Carpet burns	These usually mean psychogenic non-epileptic seizures

usually signify epilepsy. Negative symptoms (a loss of a function such as paresis) are usually due to transient focal ischaemia. Migraine often causes a mixture of symptoms such as a tingling, heavy limb or flashing lights and blurred vision.

- Some specific symptoms are helpful, for example déjà vu is not a feature of migraine or vascular disease, whereas diplopia is very rare in epilepsy.
- Altered awareness is much commoner in epilepsy and psychogenic episodes.
- Multiple and stereotyped episodes are rare in TIA, except amaurosis fugax.
- The evolution of neurological symptoms in focal epilepsy and migraine suggest a pattern of spread that does not reflect vascular territories of the cerebral cortex, contrasting with TIA.

Less common seizure manifestations

Negative symptoms: dysphasia, amnesia, loss of vision or transient paresis. Confusional states may be due to non-convulsive status epilepticus. Major fluctuations in clinical state and subtle motor activity e.g. twitching of the face are clues. It may occur *de novo* or in the context of known epilepsy.

Drop attacks are unlikely to be epileptic unless there are other associated seizure types. They may be due to severe epilepsies of childhood or refractory adult epilepsy.

The EEG diagnosis of epilepsy

- Epilepsy cannot be diagnosed from an EEG alone. There must be a clinical description of episodes that are compatible with epilepsy.
- False negative interictal results occur in 50% of routine recordings and 20% of sleep-deprived recordings.
- False positive interictal EEGs occur in up to 0.5-2% of healthy young adults.
- Ictal video-EEG-telemetry is the most sensitive and specific test for epilepsy. The EEG is abnormal during most but not all kinds of seizure. Auras, focal motor and frontal lobe seizures may not manifest on ictal scalp EEG recordings. A video recording is needed to diagnose these types.

Neuroimaging in epilepsy

- Neuroimaging is undertaken to identify a cause of the patient's epilepsy that needs treatment in its own right, such as a tumour and to investigate refractory epilepsy with a view to surgery.
- Some lesions may be coincidental findings such as most arachnoid cysts.

Classification of epilepsy

The epilepsies are syndromes classified according to a combination of characteristics including clinical seizure type, EEG and aetiology.

- **Generalised epilepsies** are characterised by EEG discharges with generalised onset. **Focal epilepsies** are characterised by EEG discharges with focal onset.
- In **symptomatic epilepsies** the aetiology of the epilepsy is known. In **cryptogenic epilepsies** an aetiology is presumed but not established for example an adult with focal epilepsy and normal neuroimaging. In **idiopathic epilepsies** there is assumed not to be a major pathological cause, a polygenic trait is often considered important.
- Each of the main diagnostic clues (aetiology, neuroimaging, clinical seizure pattern and EEG) needs to be taken into account in differentiating focal and generalised epilepsy. The clinical and EEG manifestations of focal and generalised epilepsies may overlap (figure 2a). It may only be the presence of an epileptogenic frontal lesion on MRI that enables one to make a diagnosis of a focal epilepsy. Equally some generalised epilepsies such as juvenile myoclonic epilepsy may include some elements of focal motor activity such as head turning and focal features in the EEG.

Table 2. Common idiopathic epilepsies

Idiopathic focal epilepsies of childhood	Idiopathic generalised epilepsies of childhood
Benign epilepsy with centrotemporal spikes	Childhood absence epilepsy
Benign occipital epilepsy	Juvenile absence epilepsy
Benign focal epilepsy with variable foci	Juvenile myoclonic epilepsy
	Epilepsy with eyelid myoclonias

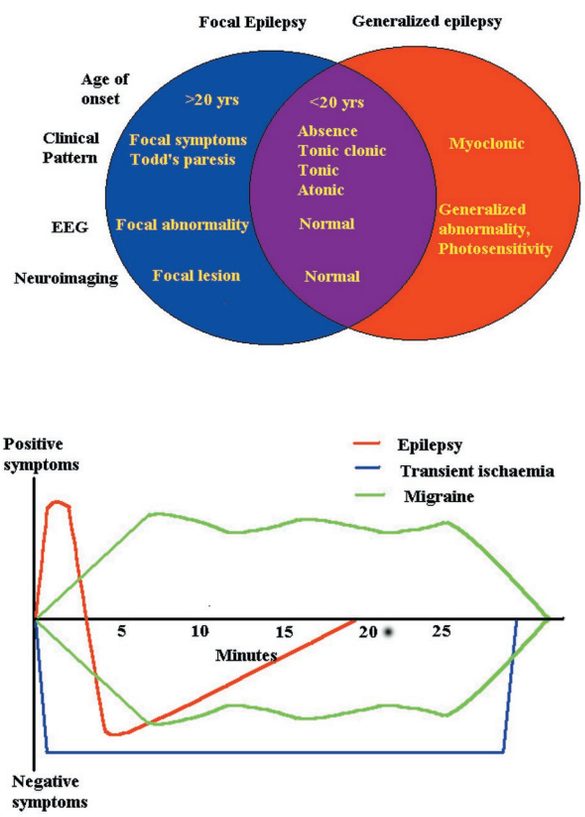

Figure 2a and 2b
There is significant overlap between the features of focal and generalized epilepsies (figure 2a). Combining the clinical features and results of investigations is essential to make an accurate syndromic diagnosis. Figure 2b shows a simplified scheme, excluding acute symptomatic seizures.

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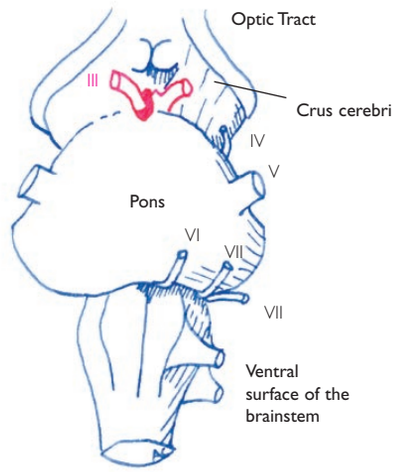
Alasdair Coles

The Third Cranial Nerve

The basics. The third cranial nerve, the oculomotor nerve, provides the parasympathetic supply which causes pupil constriction and innervates four out of the six external ocular muscles; the inferior oblique and the medial, superior and inferior rectii. Its nucleus lies in the dorsal midbrain and the nerve fascicles run ventrally to emerge just above the pons in the midline. From here the nerve moves ventrally and caudally to join the fourth (trochlear) and sixth (abducens) nerves, as well as the first division of the fifth (ophthalmic) nerve, to enter the orbit through the superior orbital fissure.

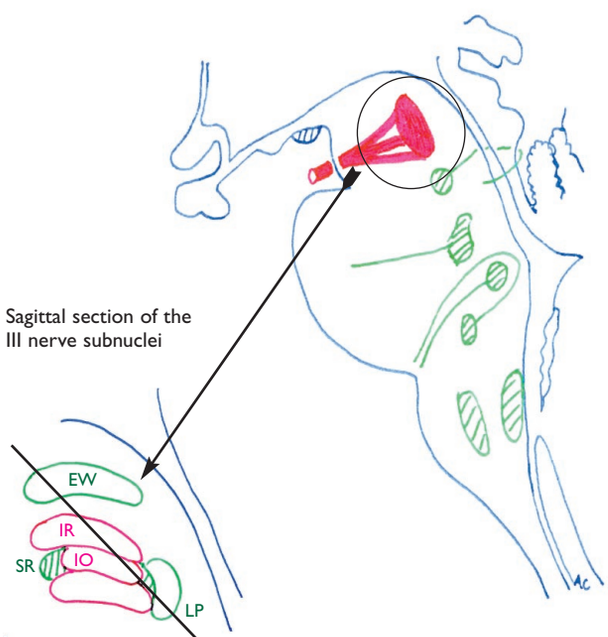


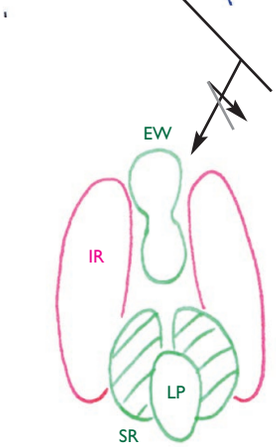
The Classic Third Nerve Palsy

A third nerve palsy gives ipsilateral signs only:

- complete ptosis,
- unreactive dilated pupil
- the affected eye looks "down and out" (due to the unopposed actions of superior oblique and lateral rectus).

Sagittal section of the brainstem





Section of the third nerve subnuclei in the indicated plane (tilted forward from the coronal)

The nucleus of the third nerve is a complex of subnuclei that lie just in front of the aqueduct in the midbrain.

The most rostral subnucleus is that of Edinger-Westphal (**EW**): a single mid-line nucleus that supplies parasympathetic fibres to the sphincter pupillae and ciliaris. Similarly the fibres to levator paplebrae (**LP**) are served by a single midline subnucleus at the caudal end of the complex.

The remaining subnuclei are paired and bilateral. But fibres from both superior rectus subnuclei (SR) cross, so they may be considered a single entity. The paired nuclei to the inferior recti (IR) and inferior oblique (IO) muscles are distinct, but the fibres to the medial recti arise from at least three separate sites within the complex. So a unilateral medial rectus deficit from a nuclear lesion is unlikely. The old concept of a distinct "Perlia nucleus" controlling convergence has been dismissed.

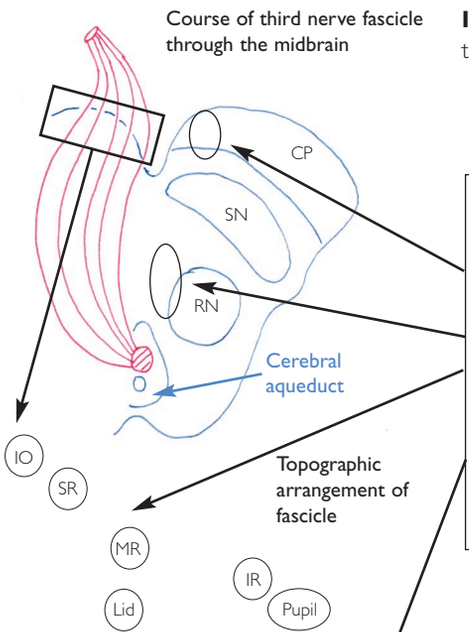
Nuclear Third Nerve Palsies

Because of this arrangement of subnuclei, nuclear lesions of the third nerve usually cause:

- Bilateral incomplete ptosis
- Bilateral weak superior rectii
- Ipsilateral weakness of inferior oblique and inferior rectus

Partial lesions of the nuclei may damage selective subnuclei giving a number of rare syndromes:

- Bilateral oculomotor palsies with sparing of levator
- Isolated bilateral ptosis
- Isolated weakness of Inferior oblique and inferior rectus

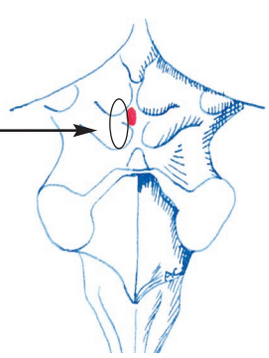


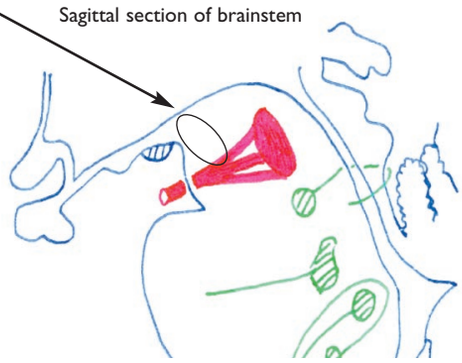
In the brainstem, the third nerve fascicle runs forward, topographically organised, through the red nucleus (RN), substantia nigra (SN) and cerebral peduncle (CP).

Fascicular Third Nerve Palsies

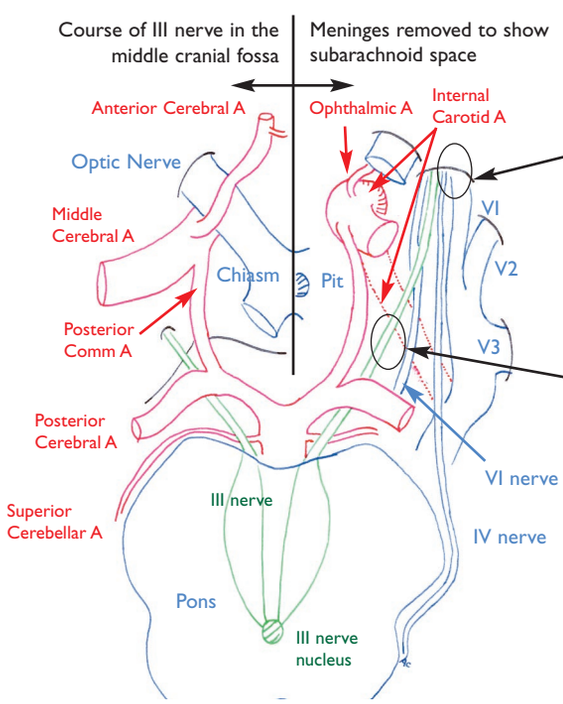
Lesions of the third nerve fascicle in the pons are recognised by the symptoms caused by damage to neighbouring tracts:

- **Weber's Syndrome**: contralateral hemiparesis (*involvement of the cerebral peduncle*)
- **Claude's Syndrome**: contralateral ataxia and rubral tremor (*red nucleus*)
- **Isolated fascicular lesions**: are rare, such as palsies of superior & medial rectil with levator weakness. However, some believe this is the site of the lesion causing the pupil-sparing third nerve palsy of diabetes.
- **Nothnagels's Syndrome**: ipsilateral cerebellar signs (*superior cerebellar peduncle*)
- **Benedikt's Syndrome**: contralateral chorea (*subthalamus*)





After leaving the brainstem, the third nerve goes over the superior cerebellar artery, under the posterior cerebral artery, runs lateral to the posterior communicating artery, then dips down into the subarachnoid space of the basal cistern. Before entering the cavernous sinus, the nerve crosses the sphenopetrossal ligament; it is here that pressure from above, by uncal herniation, may damage the nerve.



Superior Orbital Fissure/Cavernous Sinus Syndromes

The combination of a third nerve palsy with palsies of IV, VI and first division of V localises the lesion to the cavernous sinus or superior orbital fissure. If there is also proptosis, a mass lesion at the superior orbital fissure is most likely, whereas an associated Horner's syndrome suggests a cavernous sinus lesion.

Subarachnoid Third Nerve Palsies

The third nerve may be compressed in the subarachnoid space by uncal herniation (due to raised intracranial pressure) or aneurysms of the internal carotid, or posterior communicating, arteries. There may be no other focal signs.

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I hope the rehabilitation section of this new magazine will be of interest to doctors, therapists and nurses managing people with neurological disability. It will concentrate on practical physical, cognitive, surgical and (almost exclusively unlicensed!) pharmacological treatment options. I would appreciate any comments or suggestion for future topics. *Stephen Kirker, Editor, Rehabilitation Section.*

Contact Dr Stephen Kirker c/o ACNR Magazine, 7 Alderbank Terrace, Edinburgh EH11 1SX.
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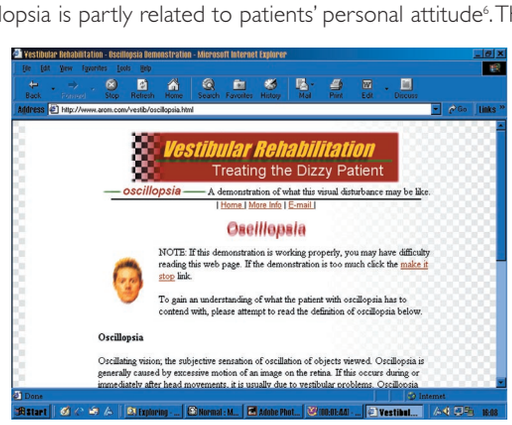
Oscillopsia

Oscillopsia is unpleasant jumping or blurring of the external world, due to poor stabilisation of the retinal image (see *www.arom.com/vestib/oscillopsia.html* for demonstration). While oscillopsia due to nystagmus and opsoclonus occurs even when the head is still, oscillopsia due to an impaired vestibulo-ocular reflex, or weakness of an extraocular muscle, occurs during active or passive head movements. Loss of the vestibulo-ocular reflex is usually due to bilateral vestibular failure, often following aminoglycoside toxicity.

As well as causing oscillopsia, nystagmus reduces visual acuity when the retinal images have high slip velocities[1]. The relationship between retinal image velocity and visual acuity is a fairly direct one, but there is little correlation between image velocity and oscillopsia. In acquired nystagmus, oscillopsia can be abolished and vision is improved if retinal image drift can be reduced below 5°/sec[2].

Early onset nystagmus, e.g. congenital idiopathic nystagmus or latent/manifest nystagmus is not associated with oscillopsia. These patients acquire images during foveation periods and ignore retinal signals at other time i.e. they see in a series of discrete snap shots, taken when the object of interest is on the fovea and the eye is still (sampling theory). In acquired nystagmus, there are no foveation periods, and it is not clear how the brain suppresses visual smear. The remapping theory suggests that the brain monitors an efferent copy of neural signals for eye movements, and interprets retinal signals accordingly[2].

In acquired nystagmus, oscillopsia tends to be initially severe but improves, despite persistent abnormal eye movements, suggesting patients develop some perceptual adaptation to retinal slippage[3]. Reduced velocity discrimination may contribute to this adaptation[3]. Oscillopsia may also improve if vestibular function improves. Fewer patients with ataxia or bilateral vestibular failure[4] have oscillopsia than one might expect. Among a mixed population with ataxia, 28% had diplopia, 16% had reduced acuity but only 5% had oscillopsia[5]. Self rated measures of handicap due to oscillopsia are correlated with external locus of control (i.e. powerlessness), and inversely related to retinal slip speed, suggesting that adaptation to oscillopsia is partly related to patients' personal attitude[6]. The high frequency vestibulo-ocular reflex was abnormal in 81% of geriatric day hospital patients with mean age of 82 years , i.e. retinal images are not stabilised during faster head movements. This may contribute to the high prevalence of dizziness and falls in the elderly, although as this was, by definition, a diseased sample, this conclusion may not apply to the healthy elderly[7].



Demonstration available on this website: *www.arom.com/vestib/oscillopsia.html*

Table 1

Disorder	Drugs reported to be effective
Downbeat or upbeat nystagmus	Clonazepam Baclofen Scopalamine
Acquired pendular nystagmus	Scopalamine Trihexyphenidyl Isoniazid Valproate Barbiturates
Periodic alternating nystagmus	Baclofen
See-saw nystagmus	Ethanol Baclofen
Superior oblique myokymia	Carbamazepine Propranolol
Saccadic oscillations	Clonazepam Phenobarbital Amphetamines Propranolol

The underlying cause can rarely be treated directly, and most therapy is symptomatic, but carbamazepine and phenytoin levels can be reduced[8]. Vestibular rehabilitation for bilateral vestibular failure focuses on facilitating maximal use of any remaining function, improving gaze and postural stability through use of visual and somatosensory cues and improving home and workplace safety[9].

Leigh *et al* have written a comprehensive, well referenced review of ocular motor requirements for clear stable vision and treatment options[2]. They point out that most treatment reports describe a few cases and are not controlled: these are summarised in table 1 taken from their review.

More recent controlled studies have reported visual acuity improved in acquired pendular nystagmus, largely due to MS, with gabapentin[10] and memantine[11], a glutamate agonist, but not baclofen or scopalamine. Retrobulbar or intramuscular botulinum toxin effectively abolishes nystagmus and may improve visual function but usually also causes misalignment, ptosis or diplopia[12,13]. Most pharmacological treatments are limited by side effects and most patients don't persevere or have a second botulinum toxin injection[2].

Patients whose nystagmus is greatly reduced in one direction of gaze may benefit from wearing prisms to place their eyes in the null position: base out prisms may help patients whose nystagmus reduces with convergence. Another approach is to use a high plus

spectacle lens and high minus contact lens: this greatly stabilises the image on the retina, but it also disables the vestibulo-ocular reflex and negates voluntary eye movements, so it is only useful when the patient is stationary[14]. This may partially be overcome by wearing the contact lens in the better eye only. For best acuity e.g. when reading or watching television, the spectacles are worn, but when moving about and balance is more important they are removed[15]. Technique is also limited by the small visual field, discomfort from the contact lens and the difficulty patients have inserting them independently.

Surgery has largely been done for congenital nystagmus, when the horizontal rectus muscles are recessed. The long term effects of this are uncertain. Modest improvements have been reported in acquired supranuclear and internuclear disorders, but with follow up of less than 12 months[16]. Suboccipital decompression of Arnold-Chiari malformation has been reported to help downbeat nystagmus and to arrest progression of other neurological conditions[2]. Surgery in other cases and pharmacology in general, is symptomatic treatment.

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abn@abnoffice.demon.co.uk

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"First Floor, 32 Market Place"
Burgess Hill
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RH15 9NP
Tel: 01444 258377
Fax: 01444 239123
birt@disabilities-trust.org.uk

British Association for the Study of Headache
The Princess Margaret Migraine Clinic, Charing Cross Hospital
Fulham Palace Road,
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British Brain & Spine Foundation
7 Winchester House, Kennington Park, Cranmer Road
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New Anstey House, Gate Way Drive, Yeadon
Beds LS19 7XY
www.epilepsy.org.uk

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Human Communication & Deafness Group
Faculty of Education, University of Manchester, Oxford Road,
Manchester M13 9PL
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Fax: 0161 275 3373
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c/o Royal College of Physicians
11 St Andrews Place,
London NW1 4LE
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sandy.weatherhead@bsrm.co.uk
www.bsrm.co.uk/

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PO Box 3004, London W4 1XT
Tel: 020 8995 4781
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www.erf.org.uk

European Federation of Neurological Societies
KH Rosenhugel
Riedelgasse 5, A-1130
Vienna, Austria
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Fax: 0043 1 8892 581
headoffice@efns.org

Headway National Head Injuries Association
7 King Edward Court
King Edward Street
Nottingham NG1 1EW
Tel: 01159 240800
Fax: 01159 121011
www.headway.org.uk

Joint Epilepsy Council
71 Craighouse Gardens
Edinburgh EH10
Tel: 0131 466 7155

Migraine Trust
45 Great Ormond Street
London WC1N 3HZ
Tel: 0207 831 4818
Fax: 0207 831 5174
migrainetrust@compuserve.com
www.migrainetrust.org

Motor Neurone Disease Association
PO Box 246
Northampton NN1 2PR
Tel: 01604 250505
Fax: 01604 638289
research@mndassociation.org
www.mndassociation.org

MS Society of Great Britain & Northern Ireland
25 Effie Road, London SW6 1EE
Tel: 0207 610 7171
Fax: 0207 736 9861
www.mssociety.org.uk

National Society for Epilepsy
Chalfont Centre, Chalfont St Peter, Gerrards Cross
Buckinghamshire SL9 0RJ
Tel: 01494 601300
Fax: 01494 871927
www.erg.ion.uci.ac.uk/NSE.home/

Neuro-Disability Research Trust
Royal Hospital for Neuro-disability, West Hill Putney
London SW15 3SW
Tel: 020 8780 6052
Fax: 020 8780 4555

Parkinsons Disease Society
United Scientific House
215 Vauxhall Bridge Road
London SW1V 1EJ
Tel: 020 7931 8080
Fax: 020 723 39908
enquiries@parkinsons.org.uk
http://glaxocentre.merseyside.org/pds.html

Royal Association for Disability & Rehabilitation (RADAR)
12 City Forum, 250 City Road
London EC1V 8AF
Tel: 0207 250 3222
www..radar.org.uk

Society for Research in Rehabilitation
c/o Ann Hughes
Division of Stroke Medicine
Clinical Science Building
Nottingham City Hospital,
Hucknall Road
Nottingham NG5 1PB
Tel: 0115 840 4798
Fax: 0115 840 4790
ann.hughes@srr.org.uk
www.srr.org.uk/

The Stroke Association
CHSA House
White Cross Street
London EC1Y 8JJ
Tel: 0207 490 7999
Fax: 0207 490 2686

2001

March

Heart & Brain - 5th International Conference on Stroke and 2nd Mediterranean Stroke Society
21-24 March, 2001; Istanbul, Turkey
Prof. Bornstein.
Tel 00972 3 5140018/9, Fax: 00972 3 5175674 or 00972 3 5172484,
E-Mail stroke5@kenes.com

5th International Conference on Progress in Alzheimers and Parkinsons Disease
31 March - 5 April, 2001; Kyoto, Japan
Ms Machiko Sako. Tel: 0081 75 341 1618, Fax: 0081 75 341 1917,
E.Mail: Adpd@jtbcom.co.jp

April

7th European Congress of Research Rehabilitation
1-5 April, 2001; Madrid, Spain
INYECCC- Congress Avda.
Tel: 00 3 41 357 1938, Fax: 00 3 41 357 1997, E-Mail inyecc@arsys.es

British Geriatric Society
5-7 April, 2001; Cardiff, UK
BHM Ltd, 1 Arun House, River Way, Uckfield, East Sussex, TN22 1SL. Tel: 01825 768902, Fax: 01825 768902,
E-Mail: contact@bhm.co.uk

The Future of Epilepsy - The Geriatric Problem, BGS Satellite Symposium
6 April, 2001; Cardiff, UK
Scope Medical, Tel: 01474 871111,
Fax: 01474 871122,
E.Mail: SatSymp@scopemedical.com

British Neuroscience Association
8-11 April, 2001; Harrogate, UK
BNA Conference Office, New Medical School, Liverpool L69 3GE.
Tel: 0151 794 5449, Fax: 0151 794 5517, E.Mail: bna@liv.ac.uk,
http://bna.umds.ac.uk

National Society of Epilepsy Advanced Lecture Series
12 April, 2001; London, UK
NSE. Tel: 01494 601300,
Fax: 01494 871977.

International League Against Epilepsy - British Branch
18-21 April, 2001; Liverpool, UK
Denise Hickman, Conference 2000, 81-83 Willow Street, Oswestry, Shropshire SY11 1AJ. Tel: 01691 650290,
Fax: 01691 670302,
E.Mail: denise@conference2000.co.uk

ILAE Satellite Symposium - Practical Usage of Oxcarbazepine: A UK Consensus View
20 April, 2001; Liverpool, UK
Sam Barnes, Novartis Pharmaceuticals, Tel: 01276 692255.

European Neurological Society
21-25 April, 2001; Nice, France
ENS Administrative Secretariat, c/o AKM Congress Service, Clarastrasse 57, PO Box CH 4005, Basel, Switzerland.
Tel: 0041 61 686 7711,
Fax: 0041 61 686 7788,
E.Mail: Info@akm.ch

American Association of Neurological Surgeons (AANS)
21-26 April, 2001; Toronto, Canada
American Association of Neurological Surgeons, 5550 Meadowbrook Drive, Rolling Meadows, IL 60088. Tel: 001 847 0500, Fax: 001 847 378 0600, E.Mail: Info@aans.org

European Neurological Society, Nycomed Amersham Symposium
23 April, 2001; Nice, France
Sam Widdicombe, Nycomed Amersham, Tel: 01494 798600.

Society of British Neurosurgeons
25-28 April, 2001; Newcastle, UK
m.s.eljamel@dundee.ac.uk

2nd European Meeting on Brain Stem Reflexes, & Related Movement Disorders
25-28 April, 2001; Amsterdam, NL
Ms M Verweij. Tel: 0031 20 5668585,
Fax: 0031 20 6963228,
E.Mail: m.verweij@amc.uva.nl

Joint Meeting of the British Neuropsychological Society and Societa Italiana di Neuropsicologia
25-27 April, 2001; London, UK
Human Communication and Deafness Group, Faculty of Education, University of Manchester, Oxford Road, Manchester M13 9PL. Tel 0161 275 3401,
Fax (0161) 275 3373,
E.Mail: audrey.bowen@man.ac.uk

May

4th World Congress of Brain Injury
5-9 May, 2001; Turin, Italy
Stilema, Via Cavour 8, 10123 Torino, Italy.
Tel: 0039 011 53 00 66,
Fax: 0039 011 53 44 09,
E.Mail: ibia2001.stilema@fileita.it,
Email:denise@conference2000.co.uk

American Academy of Neurology (AAN) 53rd Annual Meeting
5-11 May, 2001; Philadelphia, US
AAN, 1080 Montreal Avenue, St Paul, MN 55116-2325. Tel: 001 651 695 1940, Fax: 001 651 695 2791.

24th International Epilepsy Congress
13-18 May, 2001; Buenos Aires, Argentina. Fax: 0054 11 4382 6703,
E.Mail: Anajuan@anajuan.com

10th European Stroke Conference
16-19 May, 2001; Lisbon, Portugal
Lisbon Convention Bureau, Apartado 3326, 1300 Lisbon, Portugal.
Fax: 00351 361 03 59,
E.Mail: atl@atl-turismolisboa.pt

15th European Congress of Clinical Neurophysiology
16-20 May, 2001; Buenos Aires, Argentina. Ana Juan Congresos, Sarmiento 1562 4º F, 1042 - Buenos Aires, Argentina. Tel: 0054 11 4381 1777, Fax: 54 11 4382 6703,
E.Mail: anajuan@anajuan.com

UK Radiological Congress 2001
21-23 May, 2001; London, UK
UKRC Secretariat, PO Box 2895, London W1A 5RS. Tel: 020 7307 1410/1420,
Fax: 020 7307 1414,
E.Mail: ukrc@dial.pipex.com

International Paediatric Radiology
28 May-1 June, 2001; Paris, France
Europa Organisation. Tel: 0033 5 34 45 26 45, Fax: 0033 5 34 45 26 46 (or 47),
E.Mail: europa@europa-organisation.com

June

ECNR Seventh Cycle: First Course Brain
1-5 June, 2001; Cambridge, UK
Dr Wendy J. Taylor and Dr H. Rolf Jäger. Tel: 0207 837 7660, Fax: 0207 278 5122,
E-Mail w.taylor@ion.ucl.ac.uk,
r.jager@ion.ucl.ac.uk

5th International Congress on Cerebral Palsy
7-10 June, 2001; Bled, Slovenia
Prof. Dr. Milivoj Velickovic Perat. Tel: 00386 61 2324297,
Fax: 00386 61 2324293,
E.Mail: milivoj.velickovic@mf.uni-lj.si,
http://www2.mf.uni-lj.si/~velickovic/

RCN & JEC 4th Joint Epilepsy Congress
8 June, 2001; Newcastle, UK
Info: Joint Epilepsy Council,
Tel: 0131 466 7155.

Organisation for Human Brain Mapping 7th Annual Meeting
10-14 June; 2001; Brighton, UK
Terry Morris, HBM Wellcome Department of Cognitive Neurology, 12 Queen's Square, London WC1N 3BG.

Joint Congress of the European Federation of Neurological Societies & the World Federation of Neurology
16-23 June, 2001; London, UK
European Federation of Neurological Societies, KH Rosenhugel, Riedelgasse 65, A-1130 Vienna, Austria. Tel: 0043 1 8800 0270, Fax: 0043 1 8892 581, E.Mail: Headoffice@efns.org

17th World Congress of Neurology
17-22 June, 2001; London, UK
Concorde Services Ltd, 42 Canham Road, London W3 7SR. Tel: 020 8743 3106, Fax: 020 8743 1010.

Association of British Neurologists
17-22 June, 2001; London, UK
ABN, Ormond House, 27 Boswell Street, London. Tel: 020 7405 4060, Fax: 020 7405 4070, E.Mail:
abn@abnoffice.demon.co.uk

International Society for the Study of the Lumbar Spine (ISSLS)
19-23 June, 2001; Edinburgh, UK
Medicongress, Waalpoel 28-34, B-9960, Assenede, Belgium. Tel: 0032 9 344 39 59, Fax: 0032 9 344 40 10, E.Mail:
Congresses@medicongress.com

July

National Society of Epilepsy Advanced Lecture Series
5 July, 2001; London, UK
NSE. Tel: 01494 601300,
Fax: 01494 871977.

1st World Congress of the International Society of Physical & Rehabilitation Medicine
7-13 July, 2001; Amsterdam, NL
Eurocongres Conference Management, Jan van Goyenkade 11, 1075 HP Amsterdam, The Netherlands. Tel: 0031 20 679 34 11, Fax: 0031 20 673 73 06,
E.Mail: Eurocongres@rai.nl

International Congress on Parkinsons Disease
28-31 July, 2001; Helsinki, Finland
Congress Secretariat, CongCreator CC Ltd, PO Box 762, FIN-00101, Helsinki, Finland. Tel: 001 358 9 4542 190, Fax: 00358 9 4542 1930, E.Mail:
Secretariat@congcreator.com

August

11th Nordic Meeting on Cerebrovascular Diseases & Second Biennial Symposium on Ischaemic Stroke
11-14 August, 2001; Kuopio, Finland
Jukka Jolkkonen, Dept of Neuroscience & Neurology, University of Kuopio, PO Box 1627, FIN 70211, Kuopio, Finland.
Tel: +358-17-162519,
Fax: 358-17-162048,
E.Mail: Jukka.Jolkkonen@uku.fi

World Federation of Neuroradiological Societies
18-23 August, 2001; Paris, France
T Moses, 2210 Midwest Road, Suite 207, Oak Brook, IL 60523-8205, US. Tel 001 630 574 0220, Fax: 001 630 574 1740,
E.Mail: meetings@asnr.org

September

EHF Summer School on Headache & Related Disorders
1-5 September, 2001; Cambridge, UK
British Association for the Study of Headache, The Princess Margaret Migraine Clinic, Charing Cross Hospital, Fulham Palace Road, London W6 8RF.
Tel: 0208 846 1191, Fax: 0208 741 7808,
E.Mail: M.kyriacou@ic.ac.uk

6th International Congress of Neuroimmunology, & Introductory Course
3-7 September, 2001; Edinburgh, UK
Congress Secretariat, Triangle 3 Ltd, Triangle House, Broomhill Road, London SW18 4HX. Tel: 020 8875 2440,
Fax: 020 8875 2421,
E.Mail: 2001@neuroimmunology-Congress.org

4th Advanced Rehabilitation Course
4-7 September, 2001; Nottingham, UK
Ann Warner, University of Nottingham, Tel: 01332 625680.

International Psychogeriatric Association
9-14 September, 2001; Nice, France
Nice Acropolis, 1 Esplanade Kennedy, BP 4803, Nice Cedex 4, FRANCE. Tel: 0033 4 93 92 83 00, Fax: 0033 4 93 92 82 55,
E.Mail: nskandul@nice-acropolis.com

Association of British Neurologists
12-14 September, 2001; Durham, UK
ABN, Ormond House, 27 Boswell Street, London. Tel: 020 7405 4060, Fax: 020 7405 4070, E.Mail:
abn@abnoffice.demon.co.uk

International Brain Injury Association
12-15 September, 2001; Edinburgh, UK
1150 South Washington Street, Suite 210, Alexandria, VA 22314, USA. Tel: 001 703 683 8400, Fax: 001 703 683 8996, E.Mail:
Info@internationalbrain.org

XXVII Congress of the European Society of Neuroradiology, 11th Advanced Course & ESHNR 14th Annual Meeting
13-16 September, 2001; Ancona, Italy
Ms Mara Carletti. Tel: 0039 02 56601212, Fax: 0039 02 56609045, E.Mail:
ecnr2001@mgr.it, esnr2001@mgr.it

European Congress of Paediatric Neurology
13-16 September, 2001; Baden-Baden, Germany
Prof. F Hanefeld, Georg-August-Universitat Gottingen, Kinderklinik, Robert-Koch-Strasse 40, D-37075, Gottingen, Germany. Tel: 0049 551 398035, Fax: 0049 551 296252, E.Mail:
Hanefeld@med.uni-goettingen.de

XII International Congress of the World Federation of Neurosurgical Societies
15-21 September, 2001; Sydney, Australia
ICMS Australasia Pty Ltd, GPO Box 2609, Sydney 2001, Australia. Tel: 0061 2 9241 1478, Fax:. 0061 2 9251 3552.

126th Annual Meeting of the American Neurological Association
30 September-3 October, 2001; Chicago, US
ANA, 5841 Cedar Lake Road, Suite #204, Minneapolis, MN 55416, US.
Tel: 001 612 545 6284,
Fax: 001 612 545 6073,
E.Mail: Lwilkerson@compuserve.com

October

British Geriatric Society
18-19 October, 2001; London, UK
BHM Ltd, 1 Arun House, River Way, Uckfield, East Sussex, TN22 1SL. Tel: 01825 768902, Fax: 01825 768902, E-Mail: contact@bhm.co.uk

November

Alzheimer's Society (UK)
5-8 November, 2001; London, UK
Tel: 020 7306 0606, Fax: 020 7306 0808,
E.Mail: Info@alzheimers.org.uk

National Society of Epilepsy Advanced Lecture Series
22 November, 2001; London, UK
NSE. Tel: 01494 601300, Fax: 01494 871977.

2002

3rd World Congress in Neurological Rehabilitation
3-6 April, 2002; Venice, Italy
Dr Paolo Tonin, Instituto de Crua San Camillo, 30011 Alberoni, Venezia-Lido, Venice, Italy

13th European Congress of Physical Medicine & Rehabilitation
28-31 May, 2002, Medicongress, Waalpoel 28/34 - B9960 Assenede, Belgium.
Tel: 0032 9 344 3959, Fax: 0032 9 344 40 10, E.Mail: werner@medicongress.com

Tenth Congress of the
International Psychogeriatric Association
Cosponsored with the
French Society of Psychogeriatrics,
Psychiatry and Medical Psychology Clinic,
and the Memory Center at
the University of Nice-Sophia Antipolis

9-14 September 2001 in Nice, France

Bridging the Gap Between Brain and Mind

Topics Include:

Cognitive approach to consciousness
Consciousness in persons with dementia
A neuropsychological approach to the relationship between emotion and cognition
Psychopathology and neuroscience: gap or bridge?
Frontal dysfunction in elderly subjects with or without dementia
Sleep disturbances in older persons
Behavioral and psychological symptoms of dementia (BPSD)
Special care units: Do they work?

For more information contact Nicole by email to nicole@ipa-online.org, by phone to 001 847.784.1701, by fax to 001 847.784.1705 or bookmark our website for the most recent information at http://www.ipa-online.org.

INTERNATIONAL LEAGUE AGAINST EPILEPSY - BRITISH BRANCH
Annual Scientific Meeting
"WESTERN APPROACHES"
Adelphi Hotel, Liverpool
18th - 21st April 2001

Wednesday 18th April
Adelphi Hotel - Early Evening
- Pre-Conference Meeting: Rites Of Passage - From Children's To Adult Care In Epilepsy - Models Or Muddle?

Thursday 19th April
Plenary Session
- What We All Need To Know About Children's Epilepsy

Parallel Session
- Outcome Of Pregnancy In Women With Epilepsy
- Counselling On Sexual Function In People With Epilepsy
- Epilepsy: The Diagnosis Of Funny Turns
- Non Epileptic Seizures - Diagnosis And Management

Friday 20th April
Adelphi Hotel
- Nursing Symposium

Walton Centre
- Scientific Presentations
- The Mersey Beat: Epilepsy Research & Audit In Liverpool

Evening : Reception and Gala dinner

Saturday 21st April
Adelphi Hotel
- Current Management Of Adult Epilepsy - A Review

For more information contact:
Denise Hickman, Conference 2000
81-83 Willow Street, Oswestry
Shropshire SY11 1AJ
Tel: 01691 650290 Fax: 01691 670302
E-Mail: denise@conference2000.co.uk
www.conference2000.co.uk

4th World Congress on Brain Injury
May 5-9, 2001 - Torino, Italy

Research, innovations and quality of life for the new millennium

CONGRESS SCOPE AND FORMAT

The fourth World Congress on Brain Injury organised by the International Brain Injury Association, is a professional education conference whose goal is to provide a comprehensive overview of state-of-art information about brain injury issues and research.
The format for the Congress will include Pre-Congress Seminars and Workshops, Plenary Sessions, Posters and selected Peer Review Papers presentations.

PROGRAMME OVERVIEW

Saturday May 5, 2001

PRE-CONGRESS SEMINARS AND WORKSHOPS

1. Safety issues and injury prevention in Olympic winter sports
2. Update on evidence-based guidelines
3. Recent advances in memory rehabilitation
4. Advanced life support in brain injury
5. New advances in spasticity treatment
6. Focus on visual disturbances after TBI
7. Updates on post-traumatic epilepsy
8. Enteral nutrition after severe brain damage
9. Medico-legal aspects of TBI

Sunday May 6, 2001
- Research, innovations and new technologies

Monday May 7, 2001
- Brain injury in children and adolescents
- Cognitive deficits
- Emotional and behavioural difficulties
- TBI in developmental age: new trends

Tuesday May 8, 2001
- Focus on pharmacology
- Rehabilitation: team work and practical issues
- Practical problems in motor dysfunction and movement disorders
- Rehabilitation of language and executive functions
- Neuromedical issues

Wednesday May 9, 2001
- Long-term outcome and quality of life
- Special open forum on mild traumatic brain injury

Monday May 7, 2001
Family Day Forum: Current tools and future perspectives to implement the Quality of Life

Updated Programme is available at
www.internationalbrain.org/programs/4wc

Additional information may be obtained from:
Stilema (Torino - Italy): Tel. 0039 011 530066, Fax. 0039 011 534409
E-Mail. ibia2001.stilema@fileita.it

The Pearson Group (Alexandria, Va - USA):
Tel. 001 703 683 6334,Fax. 001 703 683 6407
E-Mail. ibia2001@pearsonplanners.com

CEREBRAL CORTEX

The functional division of neural circuitry performing attentional control within the prefrontal cortex

Attentional control has been a much investigated aspect of neuropsychology. Impairment has been demonstrated in patients with frontal lobe lesions and in those conditions where there is disruption of neural connections with this region (e.g. Huntington's chorea and Idiopathic Parkinson's disease).

Set shifting, the ability to change response from one perceptual attribute of a complex visual stimulus to another (such as from shape to colour) and reversal of stimulus-response association within a perceptual dimension (such as from one colour to another) represent two likely levels of processing required in attentional control. Nagahama *et al* have performed a behavioural study in 10 healthy male subjects (mean age 27.4y, SD 8.1y) of whom six went on to undergo an event related fMRI paradigm to investigate these separate elements. The behavioural data demonstrated that in those trials requiring an active switch in set shifting, reaction time was significantly prolonged however, where the switch required only the reversal of stimulus-response associations no significant delay was found compared to non-switch trials. The results of the fMRI showed significant activation in the postero-ventral prefrontal cortex during both set shifting and reversing the stimulus-response association. However, activation of the antero-dorsal prefrontal cortex only occurred during set shifting.

The authors conclude that there may be distinct areas within the prefrontal cortex providing different levels of attention control in response selection. They also acknowledge that slightly different functional divisions in neural circuitry have been proposed before based on the results of lesion experiments in lower order primates. They accept the need for future work to confirm the circuits identified here and to investigate whether they operate in a hierarchical manner or as independent parallel pathways.-SJGL

Dissociable mechanisms of attentional control within the human prefrontal cortex.
Nagahama Y, Okada T, Katsumi Y, Hayashi T, Yamauchi H, Oyanagi C, Konishi J, Fukuyama H, Shibasaki H.
CEREBRAL CORTEX
2001:11:1:85-92

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Mark Manford, Consultant at Addenbrooke's Hospital, Cambridge and at Bedford Hospital.

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Tom Foltynie, Neurology Research Registrar in Cambridge.

Dr Ailie Turton, Research Fellow at Burden Neurological Institute, Bristol.

Tim Harrower, Addenbrook's Hospital, Cambridge

Brian McNamara, SpR in Clinical Neurophysiology, Addenbrookes Hospital, Cambridge.

For more information on joining our panel of reviewers, E-Mail AdvancesinCNR@aol.com, or Tel. Rachael Hansford on 0131 477 2335.

CLINICAL NEUROPHYSIOLOGY

EEG based communication

Methods of communication based on alterations in the EEG signal were once the stuff of science fiction. However in the last 10 years or so several laboratories have developed EEG communication systems and it is hoped that these systems could eventually provide a means of communication for patients with severe motor impairment. In one such system the Wadsworth Brain Computer Interface, subjects learn to control the amplitude of mu or beta rhythms detected over the sensorimotor cortex and use that control to move a cursor to a target on a video screen. Although initial findings have been encouraging, this system like others is dogged by high error rates.

Schalk *et al*. report some initial findings with this system, they found accuracies ranging from 85% to 94%. Interestingly the occurrence of error was followed by a positive potential centred at the vertex. This positive 'error potential' can be used to improve accuracy rates although this slows the rate of communication.

The subjects used for this study all had received at least 10 training sessions before entering the study. Even in these well trained subjects and incorporating the error potential there was still a significant error rate (up to 12%), so these systems have a long way to go before they become effective methods of communication. ***-BM***

Schalk G, Wolpaw JR, McFarland DJ and Pfurstscheller G.
CLINICAL NEUROPHYSIOLOGY
2000;111:2138-2144

CLINICAL REHABILITATION

Does self-propulsion in a wheelchair help or hinder recovery from stroke?

There is a debate in stroke rehabilitation about the use of wheelchairs in patients early after stroke. The majority of physiotherapists in Britain follow the Bobath treatment regime in which early self-propulsion using the unaffected foot and arm to propel and steer is discouraged for fear that it will cause increased muscle tone on the affected side, poor posture and ultimately a poorer motor recovery. On the other hand many patients are frustrated by their inability to get about while in hospital and some therapists believe that allowing self propulsion in a wheelchair gives the patient early independence and some locus of control. A two centre pilot study by COSTAR, a collaborative stroke research and audit group, was run to assess the feasibility of a trial to answer the question 'Does early self-propulsion in a wheelchair affect the outcome for patients in stroke rehabilitation?'

Forty patients were randomly allocated either to an 'encouraged to self-propel' or a 'discouraged to self-propel' group for the duration of their in patient stay in the rehabilitation units. Measures of functional and psychological outcome were made at 3 and 12 months post stroke and assessments of muscle tone were taken at 3 months and at the time of discharge from the rehabilitation units.

The groups were fairly well balanced on entry to the study and no major differences in outcome were found. Compliance with the study instructions were relatively low for the patients who were encouraged to self-propel compared with the good compliance scores in those who were discouraged. The authors of the report highlight the considerable time investment needed to obtain the full co-operation and commitment of all the members of the multidisciplinary team in carrying a trial that tests long and strongly held beliefs. With some additions to the outcome measures they are preparing to proceed to a full multicentre trial. Many people will look forward to the result which it is hoped will inform policy on wheelchair use early post stroke.***-AJT***

The COSTAR wheelchair study: a two-centre pilot study of self-propulsion in a wheelchair in early stroke rehabilitation.

Barrett JA, Watkins C, Plant R *et al.* COSTAR wheelchair study group.
CLINICAL REHABILITATION
2001:15:32-41

EPILEPSIA

Adherence to treatment in children with epilepsy: who follows doctors orders?

It is said that if all the insulin prescribed in the UK were actually taken by patients then 90% of diabetics would be permanently hypoglycaemic. Similarly all the research into developing new antiepileptic drugs is rendered futile if pill never meets mouth. This study obtained a variety of clinical and psychosocial measures prospectively in 119 children. The children were followed up for up to 30 months. The measures of adherence to therapy were attendance rate for appointments, serum anticonvulsant levels and parental reports of medication adherence.

Attendance was not influenced by seizure severity, race, class, first language or other social factors. The strongest association with non-attendance was behavioural problems superimposed on epilepsy. This factor was also important in medication adherence. Interestingly if there were major life stresses the likelihood of attending was increased. A less supportive family environment was the strongest determinant of poor parental reports of medication adherence. Non-attendance did not correlate directly with poor medication adherence: different children experienced these problems.

There are always methodological problems with such studies. Some patients probably flush most of their pills down the lavatory, only taking a couple just before their appointment, to please the doctor. However, this study dispels some prejudicial myths about the kind of people who do not adhere to therapy. It provides some insight into the kind of children who may need the most targeted support from epilepsy nurses and community-based clinical staff.***-MM***

Mitchell WG, Scheier LM, Baker SA.
EPILEPSIA
2000;41:1616-1625

JOURNAL OF EPIDEMIOLOGY AND BIOSTATISTICS

Recent infection as a risk for acute cerebrovascular ischaemia

Previous studies have reported higher incidence of stroke during winter, and it has been proposed that an increase in infections may be responsible, mediated by the presence of a hyper-coagulable state.

A matched case control study, published in 1995 by Grau *et al.* compared the number of infections that occurred in the week before admission, among 197 patients with clinical and CT evidence of acute cerebrovascular ischaemia between 1991 and 1992, and an equal number of matched controls. Patients with acute cerebrovascular ischaemia were 4.3 times as likely (odds ratio) to have suffered from an infection in the week before admission, but only 1.8 times as likely to suffer from hypertension. From a public health perspective, although the elevated odds ratio is significant, it does not necessarily reflect the importance of infection as a risk factor for the population.

In this paper, Becher *et al.* re-analysed the study data in order to estimate the risk of cerebro-vascular ischaemia that is attributable to recent infection - the population attributable risk percentage (AR). In other words, this is the proportion of the disease that could be prevented by eliminating infections. Adjustment was made for the effects of other risk factors. They showed that 15% (AR) of all their cases of cerebro-vascular ischaemia were attributable to recent infection. For comparison, the number of cases attributable to hypertension was 26%.

In order to derive absolute numbers of cases occurring due to infection, the authors took published incidence figures of cerebro-vascular ischaemia in Germany and multiplied them by the AR calculated in this study, equal to 18,000 cases per year. The authors conclude that vaccination, and early treatment of infection with antibiotics, may be important in reducing stroke incidence especially in high risk patients, although prospective interventional studies will be necessary to confirm this.***-TF***

Previous infection and other risk factors for acute cerebrovascular ischaemia: attributable risks and the characterization of high risk groups.

Becher H, Grau A, Steindorf K, Buggle F, Hacke W.
JOURNAL OF EPIDEMIOLOGY AND BIOSTATISTICS
2000:5:5:277-283

JOURNAL OF NEUROIMMUNOLOGY

Herpes simplex virus infections may trigger multiple sclerosis

The most consistent immunological abnormality in patients with multiple sclerosis is the presence of oligoclonal immunoglobulin bands in their cerebrospinal fluid. Despite decades of research, no one knows why these antibodies are produced. Recently several researchers have used phage-displayed random peptide libraries to investigate this question. Using this technique, Nicosia's group in Italy had found previously that some oligoclonal bands bind to a

family of peptides with the common amino acid motif, KPPNP. In this study, they took this finding further. First they showed that the CSF that bound to this peptide also bound to measles and herpes simplex I (HSVI), but no other viruses. Then they demonstrated that the peptide blocked CSF binding to HSVI, but not to measles, implying that the immunoglobulin was recognising part of HSVI. Sure enough, the peptide showed sequence homology to part of the HSVI envelope glycoprotein B and immunoprecipitation of HSVI fragments with the CSF showed a pattern that mimicked HSVI gB binding. The hypothesis then would be that HSVI infection causes antibodies to be raised against HSVI gB that cross-react with an epitope in the brain and cause demyelination. Nicosia and colleagues did not demonstrate this completely, but they did show that antibodies against the peptide identified an 84kD protein in mouse, monkey and human brain. They need now to find out what this protein is. Exciting certainly, but based on CSF from only two patients, so the results may not be widely applicable. ***-AJC***

Cross-reactive phage-displayed mimotopes lead to the discovery of mimicry between HSV-1 and a brain-specific protein.

Cortese I, Capone S, Luchetti S, Cortese R, Nicosia A.
J NEUROIMMUNOL
2001:113:1:119-128

JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY

Cerebral haemorrhage and coma are bad news in cerebral venous thrombosis

The treatment of cerebral venous thrombosis has always been controversial, perhaps because it has always been difficult to assemble a large enough cohort of patients to undertake a reasonable clinical trial. The Dutch European Cerebral Venous Sinus Thrombosis Trial was a randomised trial of heparin in 59 patients. This study, which showed a statistically insignificant benefit for heparin, was reported two years ago in Stroke. Now the authors present data on the outcome of the patients in their study and an analysis of prognostic factors. At the outset, the patients were fairly typical: 50 were women (35 on oral contraceptives and 7 in the puerperium) and 19 patients had a coagulation disorder. Six patients died and four were dependent at 12 weeks after the event. A poor prognosis was heralded by: papilloedema, altered consciousness, age greater than 33, a delay in diagnosis over 10 days and involvement of the straight sinus. However, the most powerful predictors of death or dependency were coma (odds ratio 8) and cerebral haemorrhage (odds ratio 21). -AJC

Clinical features and prognostic factors of cerebral venous sinus thrombosis in a prospective series of 59 patients.

de Bruijn SF, de Haan RJ, Stam J, for the Cerebral Venous Sinus Thrombosis Study Group.
JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY
2001:70:1:105-108

Everyone over the age of 80 has MRI white matter lesions but what do they mean?

A standard discussion point at X-ray conferences is the extent to which MRI white matter abnormalities in the elderly are normal or pathological. Often there is little consensus. A Dutch collaboration, organised around the epidemiology department at Erasmus Medical Centre in Rotterdam, has reported some work that helps, to a certain extent. They contacted subjects, aged 60-90, who were participants in two on-going prospective population studies in Zoetermeer and Rotterdam. From the responders, they excluded people with dementia, blindness or standard MRI contraindications and were left with 1077 subjects whom they scanned with a 1.5 Tesla MR machine. Not surprisingly, they found that the older patients had a greater frequency of white matter MRI abnormalities. Two interesting points emerged though. First, subcortical white matter MRI "abnormalities" are really very prevalent, being found in 86% of subjects aged 60-70 and 100% of those aged 80-90. Secondly, at all age cohorts women had more severe white matter lesions than men, especially in the frontal region (despite the fact that vascular risk factors were equally distributed between the sexes). Frustratingly though, the authors did not systematically examine the subjects to see if subtle subclinical deficits (for instance neuropsychological) were associated with a greater volume of white matter lesions. So we still do not know the extent to which white matter MRI lesions contribute to the symptoms of ageing. ***-AJC***

Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study.

de Leeuw FE, de Groot JC, Achten E, Oudkerk M, Ramos LM, Heijboer R, Hofman A,Jolles J, van Gijn J, Breteler MM.
JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY 2001:70:1:9-14

LANCET

Hope for dementia with Lewy Bodies

Although dementia with Lewy Bodies (DLB) is being recognised more frequently (15-25% of presentations of Dementia) treatment has been fraught with difficulties. Neuroleptics can precipitate neuroleptic sensitivity reactions and worsen Parkinsonism. Antiparkinsonian treatment can worsen the confusion and the hallucinations. However the observations that the neocortical cholinergic function is deficient and postsynaptic muscarinic receptor function is reasonably conserved compared to Alzheimer's disease, makes the use of anticholinergic therapy an obvious choice in this disease. Therefore in a randomised double-blind placebo controlled trial of rivastigmine (a carbamate type cholinesterase inhibitor) significant benefits have been observed. This multi-centre European trial of 120 patients over a 20 week treatment period produced significant improvement in apathy, anxiety, hallucinations and delusions in the treatment group. These primary efficacy outcome measures were based on carer interviews. Further primary efficacy measures were obtained from computerised cognitive assessment tests, which showed signifi-

cant improvement in these tests as well as in the speed of the responses in the treatment group. Side effect profile was as would be expected from this class of drug i.e; nausea, vomiting and anorexia and were mild. These side effects may be reduced by slower titration to an effective dose, which is suggested to be in the range of 6-12mg daily. No worsening in parkinsonism symptoms, haematological test, biochemical tests and cardiovascular vital signs occurred. The effect was only evident whilst on treatment indicating a symptomatic effect rather than a disease modifying effect. This study goes a long way to define a group of patients who would clearly benefit from rivastigmine and possibly other drugs in this class. ***-TH***

Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study.

McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R.

LANCET 2000:356:2031

NEUROLOGY

Anti-MAG antibodies do not influence the prognosis of paraproteinaemic neuropathy

Serum antibodies to MAG, myelin-associated glycoprotein, are detected in about half of patients with a neuropathy and IgM paraprotein. They are believed to be pathogenic as they are found deposited between the myelin lamellae of peripheral nerves at biopsy and passive transfer of patients' serum into chickens causes a demyelinating neuropathy. But does their detection help the clinician? Does their presence alter the phenotype or prognosis of the neuropathy? These questions were addressed in this study, from Groningen and Leiden, of 65 patients with an IgM polyneuropathy. The cohort was fairly typical: 35 had a slowly progressive sensorimotor demyelinating neuropathy, 2 patients had a motor demyelinating neuropathy only, 9 had a sensory axonal neuropathy and 5 a sensorimotor axonal neuropathy. 28 patients had the sensory ataxia that is so characteristic of these paraproteinaemic neuropathies. 36 had been treated with various immunosuppressants (cyclophosphamide, steroids, plasma exchange and IVIG) and 24 had responded. 45/65 patients had anti-MAG antibodies that often cross-reacted with other peripheral myelin components such as sulfoglucuronyl paragloboside and sulfatide. But their presence did not correlate with any particular prognostic feature. Indeed, on a univariate analysis, only two variables were significant. First, initial sensory symptoms in the feet were associated with a slowly progressive disease course. Secondly, electrophysiological evidence for demyelination was associated with weakness and hand symptoms within 4 years. No factor was predictive of disability at 4 years. It seems then that, however interesting they are, the detection of anti-MAG antibodies is not useful clinically. ***-AJC***

Neuropathy and IgM M-proteins: Prognostic value of antibodies to MAG, SGPG, and sulfatide.

Eurelings M, Moons KGM, Notermans NC, Sasker LD, De Jager AEJ, Wintzen AR, Wokke JHJ, and Van den Berg LH.

NEUROLOGY 2001:56:228-233

MUSCLE AND NERVE

Provocative clinical tests and carpal tunnel syndrome

Two new tests have been proposed for the clinical diagnosis of carpal tunnel syndrome, the carpal tunnel compression test (CCT) and the pressure provocative test (PPT). To perform the CCT the patient's wrist is placed in the neutral position with the forearm supinated and the examiner applies moderate pressure over the transverse carpal ligament. The test is considered positive when median nerve paraesthesias are induced within 30s. For the PPT the patient's wrist is again placed in a neutral position with the forearm supinated, a pressure cuff is then applied and inflated to 50mmHg, pressure is then increased to 150mmHg by application of direct pressure over the median nerve.

Kaul *et al.* compared the outcome of these tests with rigorous nerve conduction studies in a group of veterans with symptoms suggestive of carpal tunnel syndrome. 135 veterans had the CCT and nerve conduction studies, 134 veterans had the PPT and nerve conduction studies. Using the nerve conduction studies as a gold standard they found that the CCT had a sensitivity of 52.5% and a specificity of 61.8%, the PPT had a sensitivity of 54.5% and a sensitivity of 68.4%. Using a clinical gold standard did not appear to significantly alter the outcomes for the CCT.

There is great potential benefit in clinical tests for carpal tunnel syndrome, accurate bed-side tests would reduce the number of referrals for nerve conduction studies and lead to more rapid referral for surgical or other treatments. Unfortunately the results of this well performed study suggest that these two tests are of marginal benefit and are unlikely to replace nerve conduction studies for the diagnosis of carpal tunnel syndrome. ***-BM***

Kaul MP, Pagel KJ, Wheatley MJ and Dryden JD.

MUSCLE AND NERVE 2001:24:107-111

NEJM

No risk of developing multiple sclerosis (MS) after Hepatitis B vaccination

Using the two Nurses' Health studies a nested case control study was used to define the risk of developing MS after Hepatitis B vaccination. 192 women with MS were matched to 534 healthy controls and 111 with breast cancer. Vaccination certificates confirmed details of vaccination and cases were defined by criteria established by Poser *et al*. The relative risk as determined by multivariate analysis of developing MS at any time after hepatitis B vaccination was 0.9 and was 0.7 within two years of the vaccination. This lack of association between hepatitis B vaccination and development of MS was maintained when data was restricted to women who received vaccination with the formulation. The number of doses of vaccine had no significant effect on relative risk calculations. This negative association study should allow vaccination against hepatitis B to go ahead with a reasonable amount of reassurance in terms of safety with respect to MS. ***-TH***

Hepatitis B vaccination and the risk of multiple sclerosis

Ascherio A, Zhang SM, Hernan MA, Olek MJ, Coplan PM, Brodovicz K and Walker AM.

NEJM 2001:344:53:27-32

Reader Enquiry

March/April 2001

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Report calls for investment in employment rehabilitation

A report published by The British Society of Rehabilitation Medicine calls for investment to minimise the disruption caused by sickness absence from work, estimated to cost British businesses over £10 billion annually. The BSRM expresses concern at the growing separation of employment and health services and says that more resources must be put into ensuring that people can move from illness back to employment - proposing that one professional in every health care district is appointed to liaise between the employment and occupational health services.

'Vocational Rehabilitation: the way forward' was launched at a national conference on vocational rehabilitation at the SECC in Glasgow. The conference of the BSRM, the Society of Occupational Medicine and the Scottish Seating and Wheelchair Group, in association with Rehab Scotland, heard how loss of work affects not only patients but also their families, employers and the State through the benefits system and loss of taxation, as well as services such as the NHS. The report calls for the establishment of a new Institute for Vocational Rehabilitation. The new Institute would promote multi-professional research on how to help people return to work more quickly, be able to accredit training programmes to update health workers in vocational rehabilitation, and work to increase awareness of the importance of employment to good health.

A summary of the report is posted at www.bsrm.co.uk

Rilutek® gets NICE approval for Motor Neurone Disease

The National Institute for Clinical Excellence (NICE) has issued Guidance to recommend the use of Rilutek® (riluzole) for the treatment of amyotrophic lateral sclerosis (ALS), the most common form of Motor Neurone Disease (MND).

"This is good news for people with MND," said Professor Nigel Leigh, Professor of Clinical Neurology and Director of MND Care and Research Centre at King's College Hospital. "This Guidance means that all suitable individuals with MND (ALS) should now be treated with riluzole. The inequities of postcode prescribing of riluzole should now cease."

The NICE Guidance clearly endorses Rilutek as a clinically effective treatment that prolongs life expectancy in ALS by delaying progression of the disease. The major benefit of Rilutek is that it enables individuals to remain longer in the earlier stages of the disease, when their functional ability and quality of life are less impaired.

Independent economic analyses have demonstrated that Rilutek is cost effective. NICE also concluded that "the net increase in cost for the NHS of the use of riluzole in this indication was reasonable when set against the benefit, assessed as extended months of an acceptable (to patients) quality of life."

The costs associated with MND depend on the severity of the disease, with milder stages having a smaller economic impact than the later terminal stage. A recent economic evaluation of Rilutek in the UK confirmed that the drug extends the time that people with MND spend in these milder, less costly phases of the disease thereby prolonging the overall health-related quality of life. NICE identified the need for developing earlier methods of diagnosis in order to enable earlier treatment and enhanced clinical outcomes using Rilutek.

NICE Chief Executive Andrew Dillon said, "The added month of life which this medicine offers to people with the ALS form of MND makes it an important and worthwhile treatment. It is both a clinically and cost effective intervention when used in accordance with its licensed indications and the Institute is very pleased to be able to recommend its use."

For further information contact Aventis Pharma on Tel. 01732 584000, Fax. 01732 584080. For an overview of the guidelines and how they might impact on clinical practice, see Professor Leigh's article on page 11.

New Disposable Neuro-Surgical Micro-blades

Feather neurosurgical blades were developed as special disposable blades for microsurgery in the field of neurology. According to Meddis Ltd, the high blade quality guarantees excellent ease of use and working efficiency, unsurpassed by conventional blades. Feather neurosurgical blades are made from hardened stainless steel and are individually packed sterile and housed in a sterilisable plastic case.

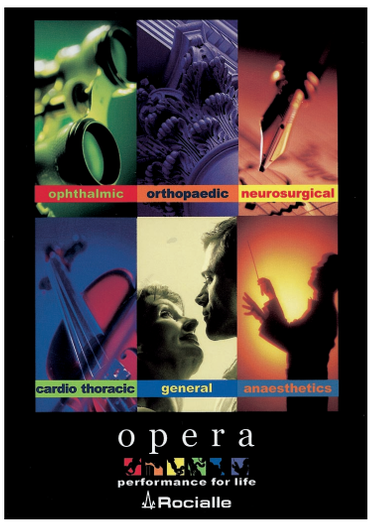
A range of 14 blade designs allows a choice of cutting angles and depths eg for arachnoid membrane or dura mater.

The special blade handle made of titanium-nickel alloy is lightweight and easy to use and is said to have excellent durability.

For further information please contact Customer Services at Meddis Limited, Tel: 01491 825500, Fax: 01491 826600 or E-Mail: info@meddis.co.uk

Rocialle launch new OPERA brand

Rocialle Medical believes that their new Opera branding concept, reflected throughout their range of procedure packs and supporting literature, will transform and unify the theatre pack supplies area. Individual Opera 'themes' will be used to clearly illustrate the six distinct and colour-coded product areas of neurosurgical, ophthalmics, orthopaedics, cardiothoracic, general surgery and anaesthetics. Strong imagery and colour-coding will be extended to packaging and ordering systems for ease of handling and storage.



Rocialle Medical are confident that over the years their customers have benefited from the one-stop-shop philosophy of You Specify, We Comply, giving cost effectiveness, efficiency, consistency and the reliability that comes from long-term relationships. The company today has a strong and recognisable corporate image, brand and message. Now Rocialle is positioning its product offerings in a similar mode, creating awareness and high status for its theatre pack range.

Arash Farboud, Marketing Manager at Rocialle believes the new branding will increase customer satisfaction. "Whilst we're already incredibly proud of our product range and its cost saving benefits, we're convinced that the striking new Opera branding with its clever, illustrative visuals will breath new life into the industry," he says.

For further information contact Arash Farboud at Rocialle Medical on Tel. 01223 495700, or see www.rociallemedical.com

Keppra (levetiracetam) add-on for epilepsy

A new drug for epilepsy, Keppra (levetiracetam), has been launched. Keppra is indicated as add-on therapy for partial seizures in adults and adolescents older than 16 years.

Keppra is said to be a highly effective antiepileptic drug. 6.3% of patients with refractory partial seizures became entirely seizure free in pivotal trials. In long term follow-up studies of 1422 patients, 17% of patients exposed to Keppra for more than six months were seizure free for at least six months, indicating that efficacy is sustained over time.

Keppra is generally well tolerated and has straightforward pharmacokinetics. The most common side effects are somnolence, asthenia and dizziness. This profile may facilitate the clinical management of patients with epilepsy by providing a less-complicated therapeutic strategy.

The initial dose of Keppra is 500mg twice daily, which can be increased to up to 1500mg twice daily depending on clinical response and tolerability.

For further information contact UCB Pharma Ltd on Tel: 01923 211811, or E-Mail. medicaluk@ucb-group.com

Aspirin put in its place

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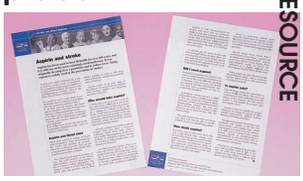

A free patient information sheet, 'Aspirin & Stroke' explains the role of aspirin in preventing ischaemic strokes in people who have already suffered one, or had a transient ischaemic attack (TIA). Aspirin is well known to health professionals for a range of beneficial effects, but for many members of the general public it is simply regarded as a pain killer.

The A4 fact sheet provides information on how aspirin works and how it is used in particular in the prevention of strokes. There is a section on aspirin and blood clots, explaining the action of the drug on platelets, and describing the role of aspirin in prevention of stroke. The differences between ischaemic and haemorrhagic stroke are clearly described.

'How do I know if I need aspirin?' explains the hospitalisation and diagnostic processes which a patient may undergo following stroke or TIA. Aspects of aspirin dosage in prevention, together with the benefits of combination with modified release dipyridamole are discussed, as well as safety issues.

The production of 'Aspirin & Stroke' is supported by an educational grant from Boehringer Ingelheim Ltd.

Copies of the fact sheet are available from The Stroke Association, Northampton Resource Centre, 61-69 Derngate, Northampton NN1 1HD. Up to 10 copies are free; for more than 10 copies please ring 01604 623 934 for postage and packing costs.

Southampton takes quantum leap

The official opening of the new MR Scanner by Mr Nigel Mcnair Scott has taken place in the Wessex Neurological Centre at Southampton General Hospital.

The high specification 1.5 Tesla Siemens Magnetom Symphony, which was primarily funded through charitable donations, is the centre's second MR unit. It has the benefit of Siemens 30mT/sec 'Quantum Gradient system'. This enables the use of specialist software packages such as advanced neurological, cardiac, peripheral angiography and spectroscopy. All these packages will allow the imaging department to offer a world class service to patients in the region and will encompass all specialities within the hospital.

Siemens is pleased to be involved in a long-term partnership with this site, where technical developments can be very quickly brought into clinical practice to validate techniques and bring added value for clinicians and patients alike.

For further information contact Siemens Medical Engineering on Tel. 01344 396317, Fax. 01344 396337.

(l to R) Paul Hunter, General Manager, Siemens Medical Engineering, Nick Eastcott, General Manager, Radiology, WNC, Dr Jo Fairhurst, Consultant Radiologist, WNC, Vince Golledge, SW Regional Sales Manager, Siemens Medical Engineering and Sue King, Senior radiographer, WNC.

Prescribing information

Lamictal (lamotrigine)

Brief Prescribing Information. Presentation: Pale yellow tablets containing 25mg, 50mg, 100mg and 200mg lamotrigine, and white dispersible/chewable tablets containing 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. 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. The 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. 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. The usual maintenance dose is 5-15mg/kg/day given in two divided doses. The weight of the child should be monitored and the dose adjusted as appropriate. If the calculated dose is 2.5-5mg/day then 5mg may be taken on alternate days for the first two weeks. With the currently available 5mg tablet strength it is not possible to accurately initiate Lamictal therapy in paediatric patients weighing less than 17kg. *Elderly patients:* Treat cautiously. *Dose Escalation:* Starter packs covering the first four weeks treatment are available. When the pharmacokinetic interaction of any AED with Lamictal is unknown the dose escalation for Lamictal and concurrent sodium valproate should be used.

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 lamotrigine withdrawn unless the rash is clearly not drug related. High initial dose, exceeding the initial recommended dose, 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. Dose reductions recommended in hepatic impairment. *Concomitant AED therapy:* Avoid abrupt withdrawal except for safety reasons. ***Pregnancy and Lactation.*** **Lamictal was not carcinogenic, mutagenic or shown to impair fertility in animal studies. There are insufficient data available on the use of lamotrigine in human pregnancy to evaluate its safety. Lamotrigine 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:* The individual response to AEDs 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. In addition with add-on therapy: diplopia, blurred vision, conjunctivitis, unsteadiness, GI disturbances, irritability/aggression, tremor, ataxia, agitation, confusion, halucinations and haematological abnormalities. Severe skin reactions including angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely, with or without signs of hypersensitivity syndrome (including hepatic failure – see Precautions).

Legal category: POM.

Basic NHS costs: £14.97 for Monotherapy Starter Pack of 42 x 25mg tablets (PL0003/0272); £25.46 for Non-Valproate Starter Pack of 42 x 50mg tablets (PL0003/0273); £7.49 for Valproate Starter Pack of 21 x 25mg tablets (PL0003/0272). £58.57 for pack of 56 x 100mg tablets (PL0003/0274); £99.56 for Calendar Pack of 56 x 200mg tablets (PL0003/0297). £7.96 for pack of 28 x 5mg dispersible tablets (PL0003/0346). £19.97 for pack of 56 x 25mg dispersible tablets (PL0003/0347). £58.57 for pack of 56 x 100mg dispersible tablets (PL0003/0348).

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 **Glaxo Wellcome 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

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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.
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5. Messenheimer J *et al.* Drug Safety 1998; **18** (4): 281-296.
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GlaxoWellcome

GEN 26713-ALP/September 2000

Before you treat her epilepsy, put yourself in these.

Imagine you're a teenage girl diagnosed with epilepsy. There are certain things you need to be assured of before starting monotherapy. Will I get spots? Will I put on weight? Will it affect my periods? Unlike some other therapies, Lamictal can offer the reassurance a girl seeks. Lamictal is not associated with cosmetic side effects or menstrual disorders.[1-3] It does not interact with the contraceptive pill.[4,5] Lamictal causes significantly less sedation than carbamazepine[6,7] and phenytoin.[8] In addition to these benefits – vital to a girl's future – it still provides the effective seizure control you expect.[6-8]

What other AED can offer a girl so much?

Lamictal™
lamotrigine

Epilepsy treatment with women in mind