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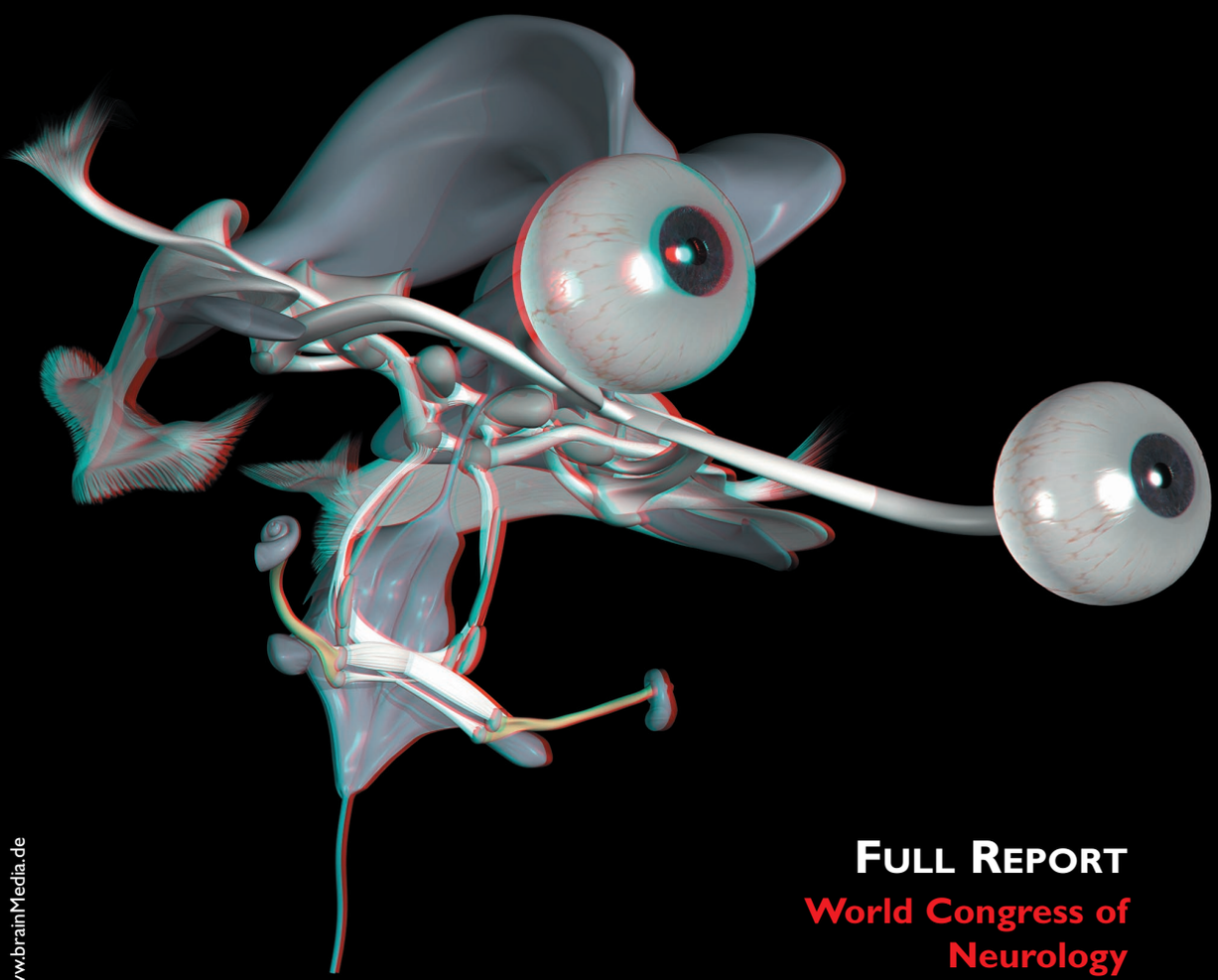
ACNR

Advances in Clinical Neuroscience & Rehabilitation



Full Report
World Congress of Neurology

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Review Articles: New advances in Alzheimer's disease
Stem cells as an alternative cell source for neural transplantation
Rehabilitation Article: Rehabilitation in Motor Neurone disease
Management Topic: Epilepsy in women

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† Benamer H *et al*. Accurate differentiation of Parkinsonism and Essential Tremor using visual assessment of ^{123}I-FP-CIT SPECT imaging: the ^{123}I-FP-CIT Study Group. Movement Disorders 2000;15:503-510

contents

july/august 2001

This issue of ACNR again attempts to combine articles on clinical neurology with ones covering aspects of basic neurobiology. Therefore we have a review article by Peter Nestor and John Hodges that explores some of the new developments in Alzheimer's Disease - a disorder that is slowly yielding to a combined approach involving molecular genetics, detailed longitudinal clinical assessment coupled to functional imaging and ultimately pathology. Such an approach provides a wealth of information which will allow for the pathogenesis of this disorder to be better understood, and with this, more specific therapies can be developed. Indeed recently there has been great excitement following reports of effective immunisation against amyloid in animal models (e.g. Janus C *et al* (2000) Nature 408:979 et seq; Schenk D et al Nature (1999) 400:173-177). Such concepts a few years ago would have seemed like science fiction, as might the idea that the adult brain contains dividing stem cells that can give rise to new neurons. Dr Anne Rosser in this issue of ACNR discusses this and the whole field of neural stem cell research, which is already starting to impact on the field of clinical neurology. Understanding the developmental and reparative capacity of these neural stem cells holds much potential for the future in repairing the brain as well as in our understanding of how the CNS develops and may go awry in some diseases. Furthermore this whole area of research is a very topical one given the political, media and public interest in these cells, but results have to be viewed critically as many of these cells are the sole product of a number of biotech. companies.

We also feature a number of conference reports. David Burn reviews the field of movement disorders as seen at the recent American Academy of Neurology meeting and a number of reports from the recent World Congress of Neurology in London are to be found summarising the major developments in a variety of clinical fields. We have our usual regular features with the anatomy primer and journal review as well as a new article in our series on Epilepsy by Mark Manford.

We also have an excellent article by Dr Nigel Sykes on the multidisciplinary approach to motor neuron disease - a difficult and much neglected area. Finally we have a new book editor, Dr Andrew Larner, who has kindly agreed to also provide a regular historical slot on neurology and neuroscience for future issues. So there we have it, another cracking issue - but do let us know your comments and ideas. We are always on the look-out for innovative changes!

Happy reading.

Roger Barker
Editor
AdvancesinCNR@aol.com

Features

Regulars

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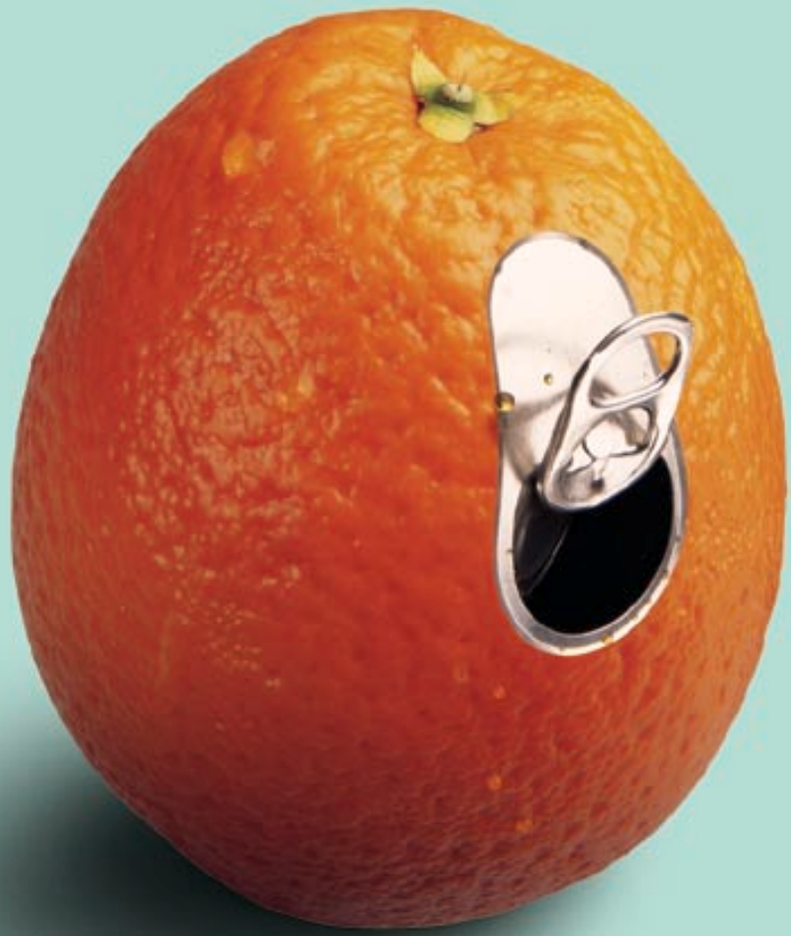
The Treatment Of Epilepsy

Has Evolved



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Editorial Board and regular contributors

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.

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

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

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

.

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

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

Anne Rosser is a member of the editorial board and has contributed this issue's review article on Stem Cells. She is a Lister Institute Clinical Research Fellow at Cardiff University, and an Honorary Consultant in Neurology at the University of Wales College of Medicine. She trained in medicine at Cambridge University, and in neurology at Addenbrookes hospital, Cambridge, and Queen Square, London. Before moving to Cardiff in January of this year, she had been an MRC Clinician Scientist at the Brain Repair Centre, Cambridge since 1994. Her main laboratory research interest is in stem cell biology, in particular with a view to their therapeutic use in neurodegenerative diseases, and she is join co-ordinator of a UK multicentre clinical trial of neural transplantation in Huntington's disease.

Stem cells as an alternative cell source for neural transplantation in CNS disease

Anne Rosser

Although the ultimate aim of repairing neural damage must be to invoke intrinsic repair, the ability to do this may be many decades away. Neural transplantation, in which developing neural cells are used to replace cells that have degenerated, is emerging as a feasible and effective intermediary therapy, and moreover, is likely to impart many important lessons as to the means by which the CNS may be reconstructed. To date most efforts in this direction have concentrated on CNS diseases in which the burden of pathology is focal, such as Parkinson's and Huntington's diseases, many other conditions may eventually be considered for cell implantation therapy. Indeed, there has been considerable interest in neural transplantation strategies for multiple sclerosis and stroke in which the pathology in most patients is widespread.

So far the only cell source demonstrated to be of functional benefit in clinical studies of neural transplantation is primary human fetal CNS tissue, and in order to be effective it is crucial that certain biological principles are observed. In brief these relate to parameters of tissue collection, the most important being the gestational age of the tissue, the precise CNS area taken for transplantation, and the tissue handling and preparation procedures. If these principles are adhered to, transplantation can be effective[1-4], but a problem that has dogged this field is the use, in some quarters, of techniques that have not been adequately verified before being employed in human studies[5] (see also ACNR volume 1 issue 2).

However, despite the demonstration of efficacy, the use of human fetal tissue carries with it ethical issues, and also significant practical obstacles in terms of the amount and timing of tissue collections, making it likely that neural transplantation will not be widely applicable until an alternative source of cells is identified. A number of alternatives are being actively explored, and as yet it is not clear which of these options will eventually be clinically applicable (table 1). The theoretical attraction of stem cells is that they can be expanded in number in the laboratory, and in addition, a defined cell source of this nature raises the possibility of improved safety based on better characterisation, improved standardisation, and more extensive pathological screening than can be achieved for primary fetal tissue in the limited time frame before it must be transplanted.

Stem cells can be defined in a number of ways, but in general they can be considered to be cells that are capable of self renewal as well as producing more lineage-restricted progenitors that will eventually differentiate into the mature differentiated cell types (shown in Fig. 1 for neural stem cells). Clearly, the major role of stem cells is in embryogenesis, although cells with stem cell like properties also persist into adult life in numerous tissue types, and such cells have now been identified in the adult mammalian CNS[6]. Stem cells from different origins have different properties and currently it is possible to identify a number of sources from which they may be isolated for eventual use in neural transplantation (fig. 2). ES cells are grown from blastocysts on a feeder layer and although their propagation is banned in some parts of the world, notably the US, it is currently legal to grow such cells in the UK, albeit under tight regulation. These cells are truly totipotent and seemingly can be propagated indefinitely. However, their totipotency raises concerns about their tumourgenic potential, and so the first challenge for ES cells is to restrict their differentiation to a neural phenotype (fig 2). It also has yet to be proven that strategies for achieving this are sufficient to allow for safe transplantation of these cells into the CNS.

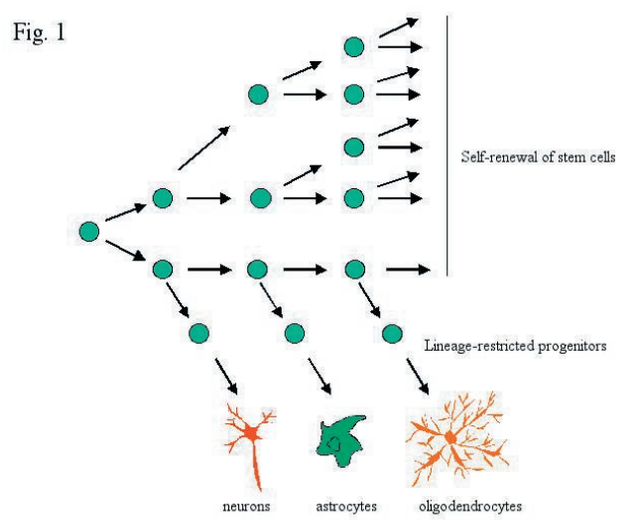


Fig 1. illustrates the principal properties of stem cells, using as an example neural stem cells which differentiate into the major cell types of the CNS. This is a greatly simplified schema demonstrating the capacity of a stem cell to either self renew or produce lineages that will eventually differentiate into the fully differentiated cell type.

When neural stem cells differentiate, they appear to default to neural lineages, although there is some evidence that, given the right signals, they are capable of differentiating along alternative pathways[7]. They are isolated from the embryonic CNS and can be grown as free-floating aggregates (see Figs 2 and 3). It now appears that similar cells may be isolated from the adult

Table 1. Potential alternative sources of cells for neural transplantation

Cell type	Examples	Major advantages	Major disadvantages
Stem cells	• ES cells • Neural stem cells • Other origins eg bone marrow	• Can be produced in large numbers from small amount of starting material • Amenable to genetic manipulation	• Currently problems producing specific neuronal phenotypes for transplantation
Xenogeneic tissue	• Usually embryonic porcine tissue	• Already committed to required phenotype	• Immune rejection of xenograft yet to be overcome
Genetically engineered cells and cell lines	• Neural • Non-neural eg. fibroblasts	• Prospect of designing cells for specific requirements • Prospect of homogeneous cell populations	• Safety issues (e.g. tumour production) • Production of specific neuronal phenotypes still an issue

Fig. 2

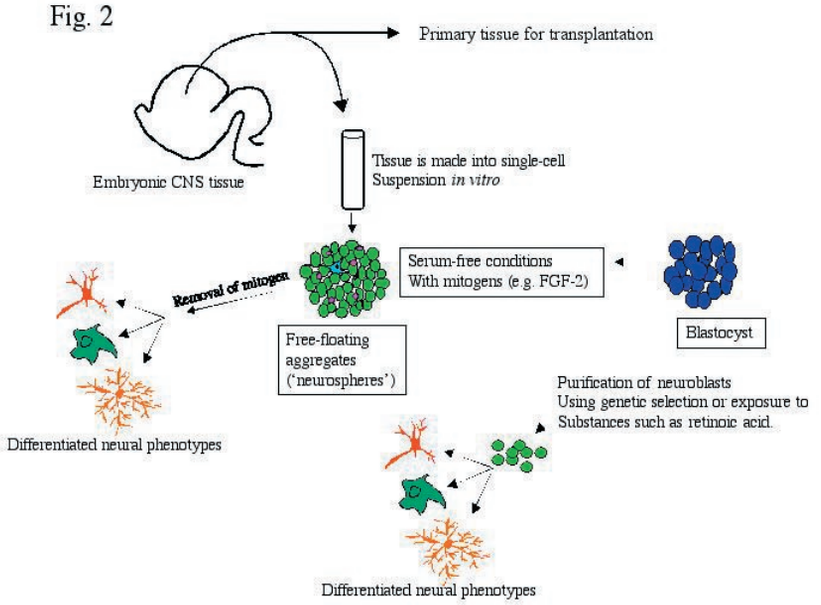
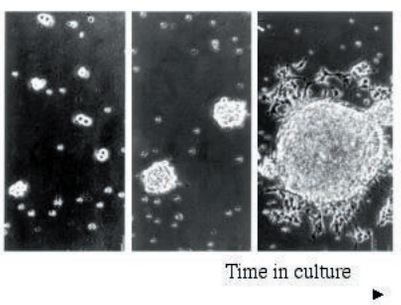


Fig. 2 illustrates the use of neural and embryonic (ES) cells to produce differentiated neural cells. Neural stem cells are isolated from areas of the developing brain and are encouraged to divide in vitro by the addition of mitogens such as fibroblast growth factor-2 (FGF-2). Treated in this way they grow as free-floating cell aggregates as shown in 3, so called 'neurospheres'. After withdrawal of the mitogen and exposure to a suitable substrate in vitro, the stem cells differentiate into the major cell types of the CNS. ES cells are derived from blastocyst embryos and are totipotent. Methods for achieving neural commitment include producing 'neurospheres' by growing them in serum-free conditions with FGF-2, for example, performing a genetic selection according to SOX expression), and exposure to substances such as retinoic acid.

CNS raising the possibility of autologous grafts. Grown in this way it is likely that neural stem cells are actually a heterogeneous population containing some true stem cells as described above and also large numbers of progenitor cells that are more fate-restricted and have a lesser division potential (Fig 3), although the term 'stem cell' is retained here for ease of presentation. Indeed, ideas about the origins of neural stem cell populations are currently evolving and recent work (reviewed by Alvarez-Buylla *et al*[8], has suggested that conventional ideas of a didactic progression of differentiation may be misleading in that neural stem cells appear to have many characteristics in common with glia. These issues are of fundamental importance if we are to fully understand and manipulate these cells, a goal which is frustrated currently by the dearth of cellular markers for the various stages of differentiation. The development of such markers is likely to impact dramatically on our ability to understand, and thereby control the differentiation of such cell populations.

Fig. 3a



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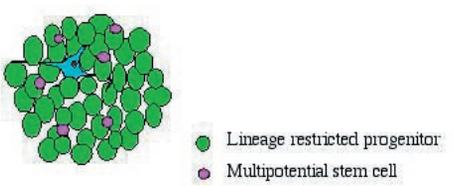

Fig 3 a) shows free-floating 'neurospheres' in culture from small aggregates after immediate plating in culture to large aggregates containing many thousands of cells (after more than a week in vitro). b) is a schematic to illustrate the heterogenous nature of these aggregates which probably contain small numbers of true stem cells, larger numbers of more lineage-restricted progenitors, and occasional differentiating cells (the latter shown in blue).

Clearly the holy grail of stem cell neurobiology is to persuade pluripotent cells from various sources to produce neurons useful for transplantation. A good example of the problem is to generate dopaminergic projection neurons for cell therapy in Parkinson's disease, and this challenge is the same whatever the starting source. To date a number of groups have demonstrated dopaminergic cell differentiation from stem cells (for example [9,10]), although long term survival of such cells in the adult CNS has yet to be demonstrated. Moreover, the numbers of surviving neurons is low following transplantation into the adult CNS, and it is not clear as yet whether this is due to death of differentiating neurons or preferential glial differentiation. So, although stem cell technology is a promising and rapidly advancing area of research, understanding the biology of such cells still has some way to go, and thus it is difficult to predict how long it will be before it will be possible to use such cells to achieve long-term survival of specific neuronal phenotypes in the adult damaged CNS.

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New concepts in Alzheimer's disease research

Authors

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Peter Nestor graduated in medicine from the University of Melbourne, Australia. After a residency in internal medicine at the Royal Melbourne Hospital, he trained in neurology at the Alfred Hospital, Melbourne and then the National Hospital for Neurology and Neurosurgery, London. He is presently a research associate in behavioural neurology at the University of Cambridge Neurology Unit.

John Hodges MD FRCP
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The advent of the first therapies has forced a reappraisal of the clinical approach to Alzheimer's disease (AD). Standard diagnostic criteria (e.g. DSM-IV) are of greatest use in avoiding false positive diagnoses of dementia, but are insensitive to the earliest stages of disease; if therapeutic interventions are to be optimally utilised then sensitive measures to the earliest stages of AD are also necessary.

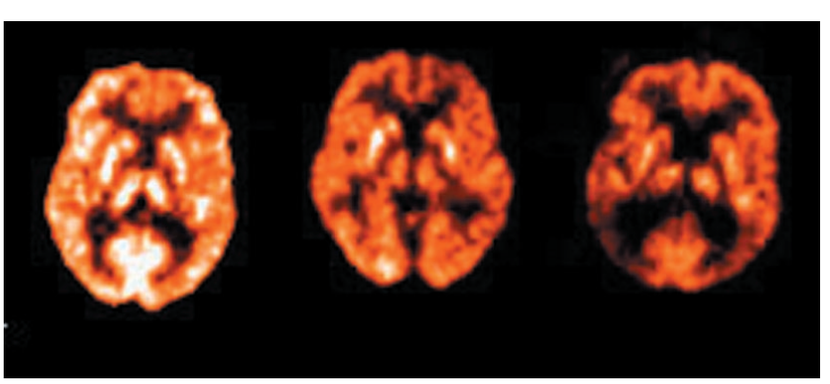
In typical cases of AD, it is increasingly apparent that there is a prodromal period in which patients have a focal amnesic syndrome without evidence of global cognitive decline[1] and that this state may persist for several years before progressing to clinically probable Alzheimer's disease. Non-problem oriented, general cognitive screening batteries (such as the Mini-Mental State Examination) may miss this stage, whereas tests focusing on the recall of recently studied information after a few minutes of an intervening distracting task (delayed recall) are highly sensitive. Delayed recall is routinely evaluated as part of formal neuropsychological assessments, however, it is usually impractical to use such tests in the neurology clinic. At the bedside, delayed recall of a name and address, as included in the Addenbrooke's Cognitive Examination[2], offers increased sensitivity to this early stage of AD.

In addition to this 'typical' natural history of AD, it is also clear that Alzheimer type pathology can be found in patients presenting with focal cortical syndromes where memory symptoms are not the most prominent feature[3]. The best characterised of the 'variants' affect higher order visual processing or language. The former (figure), usually referred to as 'posterior cortical atrophy' or 'biparietal AD', present with features of a Balint's syndrome (simultanagnosia, optic ataxia, ocular apraxia). The aphasic presentations may be of either progressive fluent or non-fluent types. Progressive aphasic syndromes are more usually associated with frontotemporal dementia; this latter condition can usually be discriminated by its early onset (<65 years), prominent behavioural symptoms (e.g. rituals, repetitiveness, disinhibition, apathy, change of dietary preference) and preservation of visuospatial skills[4].

Other than in the rare, dominantly inherited young-onset, form of the disease, no laboratory test is diagnostic for AD. Mutations of three genes have been associated with dominantly inherited young-onset AD, these being: to the amyloid precursor protein gene on chromosome 21; the presenilin 1 gene on chromosome 14; and the presenilin 2 gene on chromosome 1. Although these genes have been identified, it is worth noting that in the majority of young-onset AD cases, no mutation is identified[5]. A fourth genetic factor, the presence of the apolipoprotein E4 allele, has been shown to be a risk factor for late-onset sporadic AD; however, as its presence only increases the risk, while its absence does not rule out the diagnosis, of AD, it is not in use, clinically, at this time (for review of genetics of AD see[6]).

Considerable research effort has recently been invested in imaging techniques aimed at increasing diagnostic sensitivity and specificity as well as in monitoring disease progression. These have focused, particularly, on quantitative measurements of the medial temporal lobe structures such as the hippocampus and entorhinal cortex - these areas being known to have both an important role in new memory formation (deficits of which are the hallmark of the amnesic prodrome) as well as being early sites of AD pathology. Group studies have demonstrated a consistent statistical difference in such measures between early AD and controls (for example[7]), but overlap between groups limits the utility of such techniques in diagnosing individual patients. Serial measurements, however, have been effective in demonstrating progressive brain atrophy and may be applicable to single cases. For instance, Fox et al [8] have demonstrated that serial co-registration of volumetric MRI can be used to show accelerated loss of whole brain volume in patients at risk of Alzheimer's disease (1.5%/year versus 0.2%/year in controls).

Three specific therapies are now available in the UK for the treatment of AD: donepezil, rivastigmine and galantamine. Each has anti-acetylcholinesterase activity and aims to improve cognitive function by reducing the cholinergic deficit of AD; galantamine is also thought to modulate nicotinic acetylcholine receptors in a way that potentiates their response to acetylcholine. In double-blind, placebo-controlled trials of six months duration, each showed mild, but statistically significant, superiority over placebo on tests of cognition and global impression of function [9-11]. They are reasonably well tolerated with principle side-effects being gastrointestinal. Of the two agents with which we have first hand experience, donepezil and rivastigmine, we have found that such side-effects are usually self limiting, may be dose-dependent and can be minimised by taking drug with food. Finally, looking to the future, considerable interest has recently been given to an anti-Alzheimer vaccine in which subjects are immunised with amyloid ßpeptide. Vaccinating a transgenic mouse model of AD, mice showed both better performance on a memory task and a lesser amyloid burden than placebo-vaccinated animals[12]. Results of trials in human subjects are awaited with interest.



The figure shows 18-flourodeoxyglucose PET scans of (from left to right) a healthy, aged matched, control; a subject with 'typical' Alzheimer's disease (MMSE=24/30); and a subject with the biparietal variant of Alzheimer's disease with characteristically striking hypometabolism in the parieto-occipital regions.

Key points:

- The 'traditional' diagnostic criteria of Alzheimer's disease are insensitive to the earliest, clinically detectable, stages of the disease.
- The typical prodrome to the development of impairment in multiple cognitive domains is that of isolated anterograde memory failure.
- Rarely patients may present with relatively focal impairments in other cognitive domains, particularly Balint's syndrome or aphasia.
- Volumetric MRI measurements of medial temporal structures are reduced in group studies of AD when compared to controls, but have limited utility in diagnosis of individual cases.
- Drugs designed to enhance function of central cholinergic pathways have been shown to offer modest symptomatic benefits in Alzheimer's disease.

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Epilepsy in women

Mark Manford

Introduction

Managing epilepsy in women requires an understanding of the effects of epilepsy and its treatment on sexuality, the menstrual cycle, fertility and pregnancy. These issues need to be discussed with women in advance of treatment and before conception.

The effect of the menstrual cycle on epilepsy

- A few women suffer seizures predominantly or exclusively at specific times of their menstrual cycle "catamenial epilepsy". Many more have a weaker tendency to more seizures at particular phases of the cycle.
- Seizures are more likely when epileptogenic oestradiol concentrations are higher and anti-epileptic progesterone concentrations are lower. In ovulatory cycles there may be premenstrual or ovulatory exacerbation. In anovulatory cycles seizures increase during the entire second half of the cycle.

- **Treatment**
  - Intermittent clobazam 10mg daily over the risk period.
  - Acetazolamide 250-1000mg daily over the risk period.
  - Endocrine manipulations been evaluated in very small numbers of patients: Medroxyprogesterone in doses sufficient to produce amenorrhoea Progesterone supplementation over the at-risk period

Fertility

- **Fertility** may be reduced by one third in women with epilepsy from psychosocial effects, reduced marriage rates, reduced sexual arousal or antiepileptic drug (AED) effects.
- **Menstrual disorders** may be commoner in women with epilepsy. Polycystic ovaries (PCO) may affect up to 20% of women with epilepsy although the incidence of full polycystic ovary syndrome is much less clear. This may partly be due to epilepsy itself but AED, especially valproate have also been implicated.

Contraception

- Contraception is an issue for women with epilepsy because of the teratogenicity of AED and genetic implications of some epilepsy syndromes. Women with epilepsy are best advised to plan their pregnancies.
- **Hormonal contraception** is advisable for most women with epilepsy, alternatives are a contraceptive coil or surgical sterilisation, if a woman has completed her family.
- **Enzyme-inducing AED** increase the rate of metabolism of hormonal contraceptives (table 1). The dose of the hormonal contraceptive may need to be doubled or tripled with these medications. However, even with good cycle control, effective contraception is not ensured.

Table 1: Hormonal contraception requirements with different AED

Drugs requiring high dose contraception	Drugs requiring regular dose contraception
Carbamazepine	Benzodiazepines
Oxcarbazepine (slight effect)	Ethosuximide
Phenobarbitone	Gabapentin
Phenytoin	Lamotrigine
Primidone	Levetiracetam
Topiramate	Tiagabine
	Valproate
	Vigabatrin

Epilepsy and pregnancy

- **Epilepsy severity** remains unchanged on average during pregnancy. Some women withdraw AED from fear of teratogenic effects. Early counselling increases compliance and improves epilepsy control.
- For most AED no specific action is required in pregnancy unless there is a deterioration of seizure control.
- **Obstetric complications** such as placental abruption, antepartum haemorrhage, pre-eclampsia, low birth weight and premature labour are all increased in some studies of women with epilepsy.
- **Convulsive status epilepticus** carries a high risk of ischaemic damage for the foetus but other seizures generally carry a low risk for the pregnancy.

Effects of antiepileptic drugs on the foetus

- **AED** are the major determinant of foetal abnormality in children of women with epilepsy. All long-established AED's appear to be teratogenic in humans. Some newer drugs, appear safe in animal studies, but no AED can reliably be considered safe in humans.
- **Severe abnormalities** may occur in 6% of patients taking AED. Valproate is emerging as a particular culprit, increasing the risk of neural tube defects ten fold to 2.5%, the highest risk is at doses above 1000mg daily. Folic acid supplements (5mg daily) may help.
- **Mild malformations** may be increased to 7% of monotherapy patients and 10% on dual or triple therapy.
- **Subtle cognitive deficits** may affect the offspring of women with epilepsy. They may not be apparent early on and require testing into adolescence. Suggested risk factors are maternal polytherapy and valproate or primidone.
- **Drug-specific syndromes** occur such as foetal valproate syndrome or foetal hydantoin syndrome combine a specific facial appearance with low IQ and other abnormalities. (table 2, see next page)
- **Enzyme-inducing AED** reduce vitamin K levels in the foetus and may predispose to haemorrhagic disease of the newborn. Vitamin K supplementation (10mg/day for the last month of pregnancy) and vitamin K injection for the newborn baby may help prevent this complication.

Factors in the choice of anti-epileptic drug in pregnancy

- **epilepsy** such as absences or mild partial seizures may not require treatment.
- **Epilepsy syndrome** determines the AED most likely to be effective.
- **Minimising foetal risk** by minimising the number of AED and their doses. Preconceptual folic acid.
- **New AED**. If a woman's epilepsy is well treated with an older drug, there is currently insufficient evidence to change her to a newer drug during pregnancy and risk loss of seizure control.

Delivery and the puerperium

- **Peripartum seizure** risk is 2-4%. AED must be continued throughout.
- **Benzodiazepines** may prevent further seizures. This may cause maternal sedation, increase the likelihood of requiring an instrumental delivery and sedate the neonate.
- **Pharmacokinetics change** rapidly to the non-pregnant state. If medication has been increased, then it should be changed back, usually over 6-8 weeks, during the puerperium to avoid drug toxicity.

Antiepileptic drugs and lactation

- **Breast-feeding** confers significant health advantages for most infants. No currently available AED is contraindicated during lactation but the risks vary between drugs.
- The effect of AED on the newborn baby depends on the kinetics of transfer to the baby (table 3).
- **Bottle-feeding** causes rapid withdrawal from AED's to which the baby has been exposed for an extended period in utero, which may confer health risks.
- **Bottle-feeding** allows partners to share the burden reducing maternal sleep deprivation and potentially helping maternal epilepsy.

Care of children

- **Fear** of dropping, drowning or smothering their baby in a seizure is common. Such events are rare and mothers can be reassured.
- **Simple precautions**
  - Changing the baby on the floor, rather than on a raised surface
  - Washing the baby with someone else or else wiping them down rather than bathing them
  - Pushing rather than carrying the baby
  - Avoiding hot drinks that may scald the baby

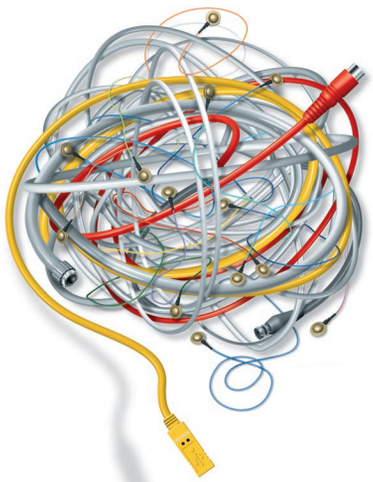
Table 2. Effects of in utero exposure to different AED

Drug	Abnormality	Possible mechanism
Barbiturates	Craniofacial abnormalities and congenital heart defects.	Unknown
Benzodiazepines	Probably little effect themselves but may worsen valproate-associated defects.	Unknown
Carbamazepine	Spina bifida (0.5-1%) Also noted are congenital heart disease, congenital dislocation of the hip, hypospadias.	Unknown
Ethosuximide	Rarely used in monotherapy but an association with facial clefts suggested.	Possible effect on endogenous retinoids
Hydantoins	Major deficits include facial clefts, congenital heart defects and urogenital abnormalities. Distal phalangeal hypoplasia in up to 11%. Foetal hydantoin syndrome comprises hypertelorism digital hypoplasia, growth delay, microcephaly and developmental delay.	Possibly due to hypoxia caused by suppression of the foetal heart during a sensitive phase of cardiac development. Folate antagonism may contribute.
Valproate	Neural tube defects in 1-3%. Other abnormalities are radial ray aplasia, rib and vertebral abnormalities. Foetal valproate syndrome includes brachycephaly, microstomy, microcephaly thin lips, rotated ears and development delay, which may be severe. Subtle cognitive effects may occur.	Possible effect on folate metabolism or on endogenous retinoids important in foetal development. Dose-related with highest risk over 1000mg daily.

Table 3. Different AED in breast milk

Drug	Breast milk : Plasma concentration ratio	Comments
Carbamazepine	0.4-0.6	Usually safe and at low levels in the baby. Rare hepatic toxic effects in the baby
Clonazepam	0.3-0.4	May cause sedation or respiratory depression.
Ethosuximide	>0.8	May accumulate and cause sedation. May cause irritability on withdrawal
Lamotrigine	0.61	Nursed infants blood levels 25-50% of maternal levels.
Oxcarbazepine	0.5	Presumed safe
Phenobarbitone	0.4-0.6	Slow accumulation in the baby may cause sedation. Rapid withdrawal may cause jitteriness and seizures.
Phenytoin	0.1-0.5	Safe
Primidone	0.7-0.9	Similar effects to phenobarbitone but milder
Valproate	0.01-0.1	Generally safe but very rare idiosyncratic reactions to valproate in infants

NEW ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS



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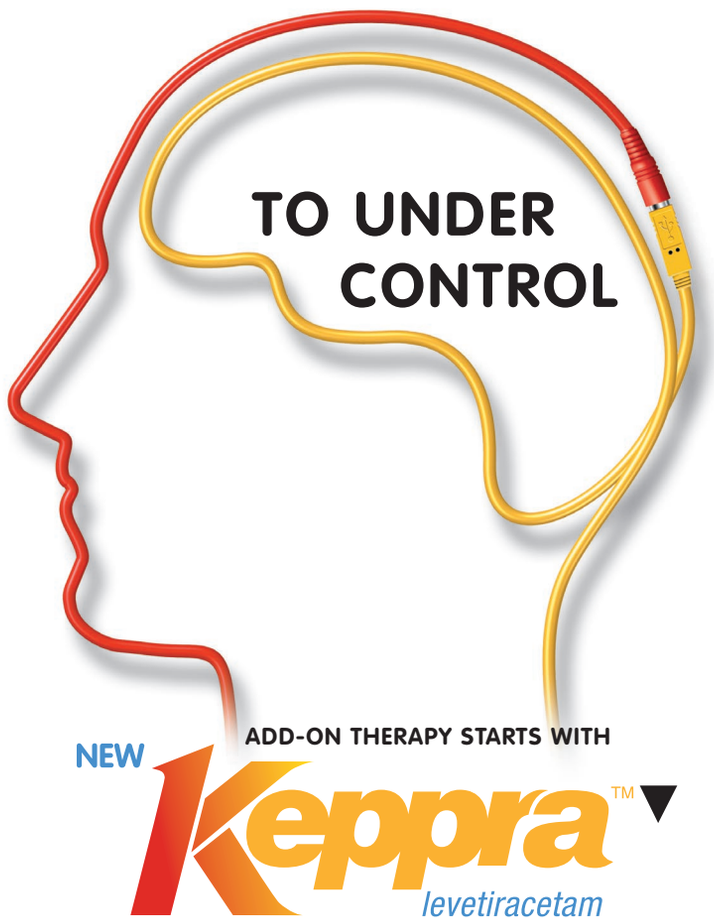

- Highly effective: up to 4 out of 10 refractory patients had ≥50% partial seizure reduction[1,2,3]
- Excellent tolerability, discontinuation rates not significantly different from placebo[4,5]
- No known drug/drug interactions[6]
- Therapeutic starting dose (500mg bd)

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Presentation: Keppra 250 mg, 500 mg and 1,000 mg film-coated tablets containing 250 mg, 500 mg and 1,000 mg levetiracetam respectively. **Uses**: Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy. **Dosage and administration:** Adults and adolescents older than 16 years: The initial therapeutic dose is 500 mg twice daily which can be started on the first day of treatment. Depending upon clinical response and tolerance the dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. Elderly: Adjustment of the dose is recommended in elderly patients with compromised renal function. Children (under 16 years): Not recommended. Patients with renal impairment: Adjust dose according to creatinine clearance as advised in SPC. Patients with hepatic impairment: No dose adjustment with mild to moderate hepatic impairment. In patients with severe hepatic impairment and creatinine clearance <70 ml/min a 50% reduction of the daily maintenance dose is recommended. **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Warnings and special precautions for use:** If discontinuing treatment reduce dose gradually as advised in SPC. **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel) or levels of luteinizing hormone or progesterone. Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Undesirable effects:** The most commonly reported undesirable effects are somnolence, asthenia and dizziness. In the pooled safety analysis there was no clear dose-response relationship but incidence and severity of the central nervous system related undesirable effects decreased over time. Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: Very common (>10%): asthenia and somnolence. Common (between 1%–10%): accidental injury, headache, anorexia, diarrhoea, dyspepsia, nausea, amnesia, ataxia, convulsion, depression, dizziness, emotional lability, hostility, insomnia, nervousness, tremor, vertigo, rash and diplopia. **Legal category:** POM. **Marketing Authorisation numbers:** 250 mg x 60 tablets: EU/1/00/146/004. 500 mg x 60 tablets: EU/1/00/146/010. 1,000 mg x 60 tablets: EU/1/00/146/024. **Basic NHS cost:** 250 mg x 60 tablets: £27.00. 500 mg x 60 tablets: £49.50. 1,000 mg x 60 tablets: £94.50.
Further information is available from: UCB Pharma Ltd., 3 George Street, Watford, Herts WD18 0UH. Tel: 01923 – 211811.
Date of Preparation: October 2000.
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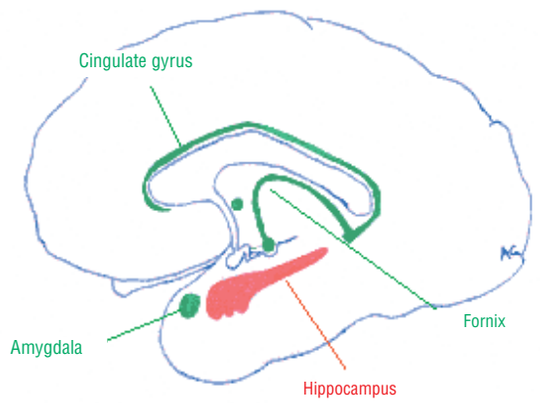
SIMPLIFYING SEIZURE CONTROL

The Hippocampus

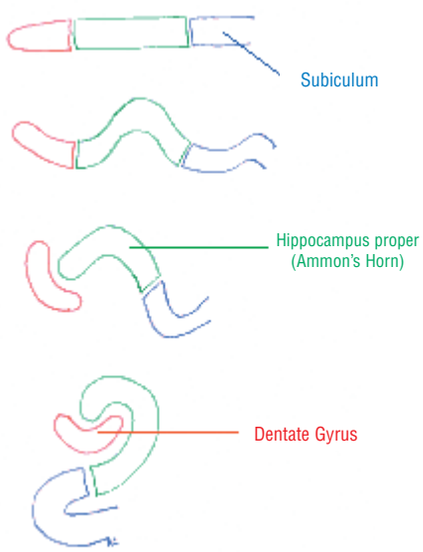
Alasdair Coles

The Basics. The hippocampus is a folded layer of cortex that is tucked under the inferior horn of the lateral ventricle, on the medial side of the temporal lobe. It was thought to resemble a sea-horse (hence the name) in that it has a head anteriorly (that abuts the amygdala), body and tail (that disappears beneath the splenium). Hippocampal sclerosis is a long-term sequela of prolonged febrile seizures and causes temporal lobe epilepsy. Some of the earliest pathological changes of Alzheimer's occur in the hippocampus.

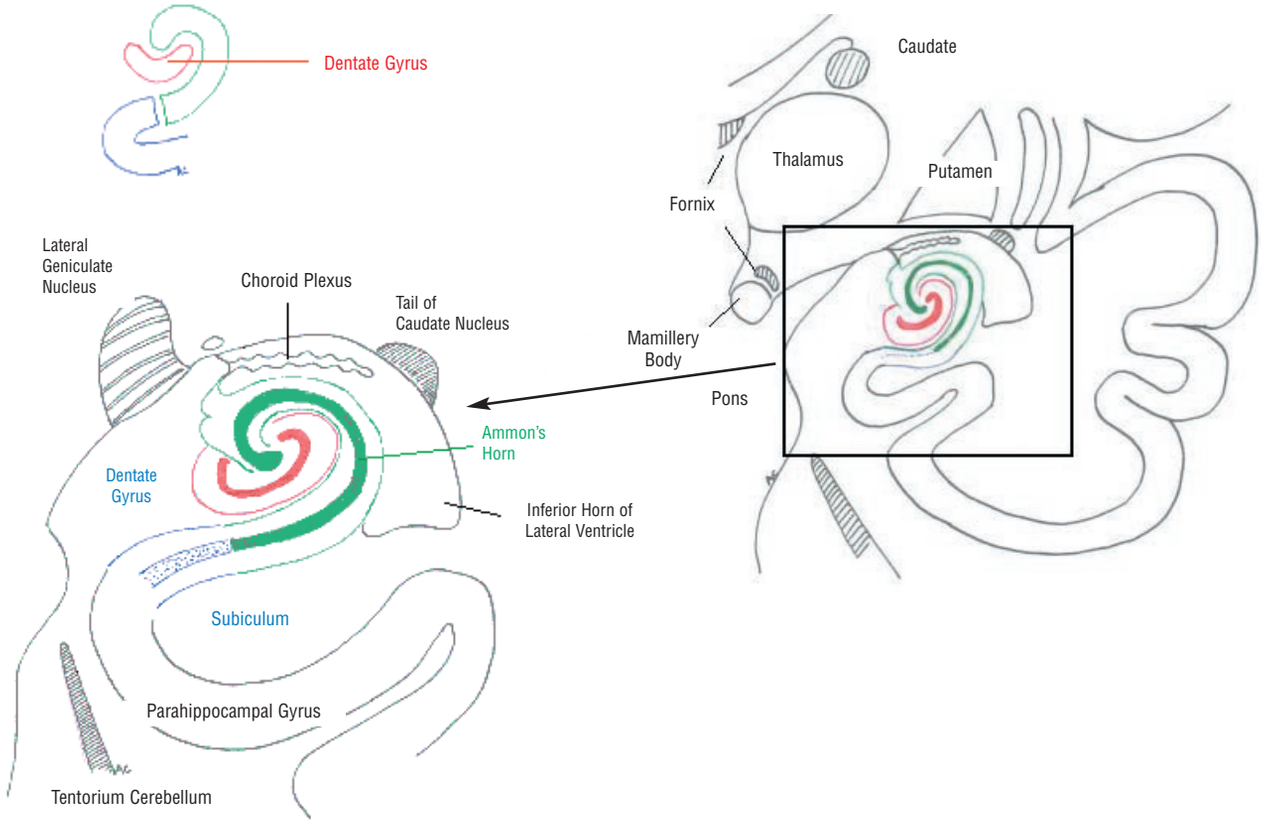


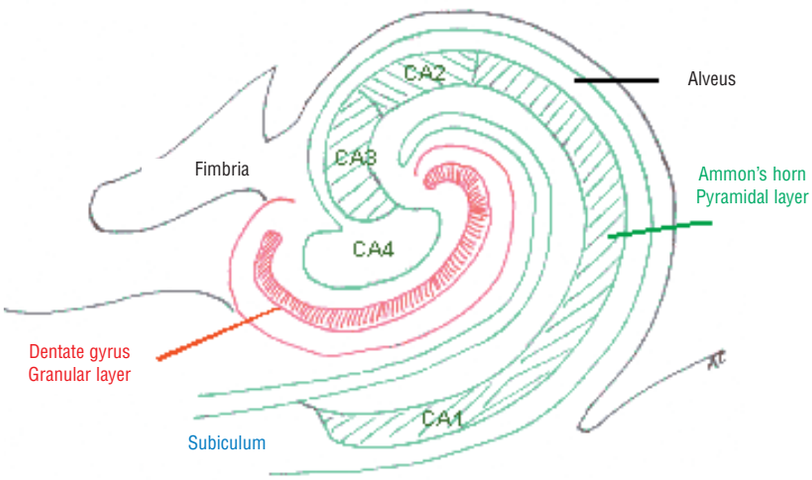
The histology of the hippocampal formation. The hippocampus proper (sometimes called "Ammon's Horn") and dentate gyrus are made up of three-layered cortex called **archicortex**. The dentate gyrus is distinguished by having a dense granular layer. The subiculum is **paleocortex,** in transition from the six-layered cortex of the **entorhinal** cortex of the parahippocampal gyrus. The dentate gyrus, Ammon's horn and subiculum are referred to as the "Hippocampal Formation".

Development of the hippocampal formation.



History of ideas on the function of the hippocampus. In 1878 Broca defined the **Limbic Lobe** as those structures that lay on the margin (Latin limbus) of the brain: the hippocampal formation, anterior hippocampal gyrus and cingulate gyrus. In 1937, Papez postulated a network of structures that controlled emotion and behaviour. This **Papez circuit** included the cingulum, the hippocampus, the mammillary bodies and the anterior nucleus of the thalamus, but not the amygdala. In 1949 McLean expanded this circuit to include cortical structures and subcortical forebrain nuclei, including the amygdala, naming the arrangement the **Visceral Brain**. These descriptions, and Kluver and Bucy's findings in monkeys, suggested that the main role of the hippocampus was in emotion. It was not until patient HM that its role in memory was fully appreciated.

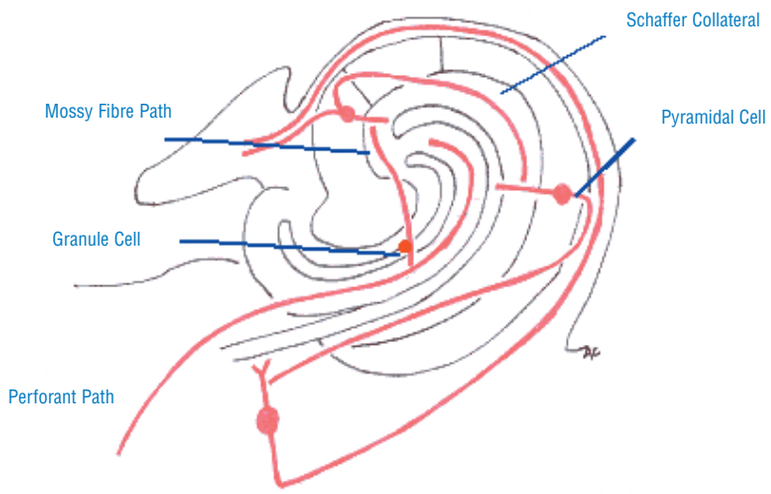




Internal Connections of the hippocampus. Sensory cortical afferents converge on the entorhinal cortex, which then project, via the perforant path, to the granule cells of the dentate gyrus. Their mossy fibres contact pyramidal cells of the CA3 subfield, which project both to the fimbria and (via Schaffer Collaterals) to CA1 pyramidal cells. These in turn contact cells in the subiculum which have a minor efferent tract back to the entorhinal cortex and a major tract,via the alveus, to the fimbria which leads into the fornix.

Long term potentiation is a feature of the NMDA-mediated synapse between the Schaffer collaterals connecting the CA3 and CA1 pyramidal cells. Long term depression is mediated by glutamate in CA3 region.

Hippocampal Sclerosis classically affects Sommer's Sector (between the subiculum and parahippocampal gyrus) although may give total destruction of all hippocampal subzones.



Alzheimer's Disease first affects the entorhinal cortex, subiculum and CA1.

Efferents of the hippocampal complex:
Fimbria fibres form the fornix which go to the anterior thalamus (some via the mamillary bodies), there to the cingulate gyrus and from their back to the entorhinal cortex. This is the Papez circuit.
However, anterior thalamus also projects widely to association motor cortex and midline thalamic nuclei.

Kluver-Bucy Syndrome

In 1939, Kluver and Bucy described the behavioural effects of bilateral temporal lobectomy in rhesus monkeys. Similar effects are seen in man with bilateral temporal lobe destruction (that is, more than just hippocampal lesions) due to:

- herpes encephalitis,
- Pick's disease,
- Alzheimer's disease,
- trauma,
- cerebrovascular accidents

The syndrome in man consists of:

- visual (or even tactile or auditory) agnosia
- compulsion to orally examine objects (including inedible objects)
- emotional blunting
- increased sexual activity

Hippocampus & Memory

In 1957 Scoville and Milner reported on the case of HM, who had both medial temporal lobes removed to control his epilepsy. Afterwards he was unable to store and retrieve new information about events. Recently magnetic resonance imaging has shown that HM's resection included the amygdala, perirhinal and entorhinal cortex, and the anterior hippocampus.
Recent studies of patients with selective hippocampal damage has shown that the human hippocampus is important for episodic memory (memory for events in the person's life) and less necessary for semantic memory (general knowledge of the world).

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Date of Preparation: January 2001 RIL0121200AD

Rehabilitation in Motor Neurone Disease: A palliative care perspective

Author

Dr Nigel Sykes is Consultant in Palliative Medicine at St Christopher's Hospice, London, where he and his colleagues work closely with the MND Centre, Department of Neurology, in the Institute of Psychiatry at King's College Hospital. His interest extends beyond the clinical to the ethical dimensions of MND care, and he has been a member of the Ethics Committee of the Association for Palliative Medicine. The Hospice has cared for people with MND for over 25 years, and has an active multiprofessional approach to achieving symptom control and maximising function. Having founded the first team for palliative care at home in 1969, it continues to work closely with community services to enable people with advanced disease to remain in their own surroundings.

Rehabilitation is defined by the World Health Organisation as "all means aimed at reducing the impact of disabling and handicapping conditions and at enabling disabled people to achieve optimal social integration"[1]. The essence of providing such a service for people with MND is the co-ordinated harnessing of the skills of a multiprofessional team to provide relevant help at an appropriate time. The composition of such a team will alter according to the needs of the individual, as MND is very variable in the pattern of its progression. Its leadership is likely to change over the course of the disease.

In practice the co-ordinating function is often lacking unless there is a dedicated MND team locally. However, this is a role which a palliative care service can be well-placed to fulfil, because the essential style of working in cancer and the other disease settings with which the speciality is associated is that of the creative bringing together of different disciplines to the advantage of the patient and their family. Although the contribution of palliative care will increase as the disease progresses, an earlier involvement is valuable. This is partly because function is aided by good symptom control (over 50% of people with MND have pain) and partly because it then becomes a familiar part of the caring team rather than being seen as the harbinger of death.

The range of professionals whose efforts are relevant to rehabilitation in MND is very wide.

They include:
Neurologists; Physiotherapists; Occupational therapists; Speech and language therapists; Rehabilitation physicians; Nutritionists; Social workers; Chaplains; Psychologists; Respiratory physicians; Wheelchair specialists; Interventional radiologists

Physical function

Physical function suffers through discomfort and loss of limb muscle power. Even if muscles cannot be made stronger again, much can be done with the help of physiotherapy to prevent painful stiffness and the development of deformities resulting from reduced joint movement range. This is complemented by analgesia using paracetamol, NSAIDs, muscle relaxants (employed with care in order to avoid exacerbating weakness) and opioids.

Tuition in safe transfers, say from bed to wheelchair, is needed, aided by the provision of aids such as turntable discs or banana boards. Provision of wheelchairs needs careful planning to ensure the arrival of the right chair (manual or electric) at the right time. The rate of progression of the individual's condition has to be taken into account together with factors such as the extent of neck weakness, which may require the supply of a tilting chair.

Patient rehabilitation in the day centre.

The need for aids and appliances is said to mark the half-way point in the course of MND, and is guided by an occupational therapy assessment. Thick-handled, angled cutlery may assist a person's ability to feed themselves. Raised toilet or shower seats, provision of lever taps and easy access showers help to satisfy hygiene needs. A variety of arm and wrist supports is available to assist in writing, typing and eating, but matching them to the individual needs especially expert advice.

Nutrition

Ability to eat an adequate diet is compromised by loss of mobility and manual dexterity through limb weakness, but will also suffer if dysphagia is present. Insufficient nutrition worsens muscle weakness, and specialist advice can help formulate an appropriate, manageable diet.

As swallowing deteriorates, a gastrostomy tube should be considered before eating has become too arduous and before forced vital capacity (a measure of respiratory function) has declined to under 70% of normal. Enteral feeding via a gastrostomy allows eating to be for pleasure and companionship rather than a struggle to sustain life. A tube can be placed, either endoscopically or radiologically, before it is strictly needed, as it is unobtrusive and can form an insurance against eating becoming too difficult.

Communication

Loss of speech is one of the most disabling aspects of bulbar MND. A speech and language therapist (who, incidentally, may also advise on techniques to aid safe swallowing) can assist maintenance of speech and the provision of communication aids. These range from simple letter boards, through Lightwriters, to scanning and text-to-speech computer devices.

Respiratory compromise

The application of palliative medicine to MND has shown that, as in cancer, breathlessness can be alleviated by use of modest doses of morphine and benzodiazepines. Poor sleep pattern and malaise or headache on waking can indicate nocturnal carbon dioxide retention. These symptoms can be relieved by non-invasive positive pressure ventilation (NIPPV) at night.

With progression of chest muscle involvement, use of NIPPV tends to extend into daytime and frequently becomes virtually 24 hour, as it offers highly effective relief of breathlessness. It is helpful if there is palliative care team support for patient and family in the use of NIPPV at home, to reinforce chest physiotherapy techniques such as assisted cough, and to adjust medication as respiratory function deteriorates further.

Psychological support

MND is a devastating series of losses, with the knowledge that it will culminate in the loss of life itself. The increasing dependence is emotionally (as well as physically) taxing for both patients and carers. It is important to ensure that they have all the financial

and practical help that is available, including respite admissions to a nursing home or a hospice.

In addition, some will benefit from psychological support from the palliative care team social worker or psychologist. Through such counselling carers may be enabled to continue to care and patients enabled to accept more readily the adjustments that living with MND requires. Psychological assessment has become yet more important with the recent realisation that cognitive impairment is not a rarity but occurs in 20 - 30% of people with MND, particularly those with bulbar involvement. Participation in hospice day centre programmes has been found to benefit morale and hope in people with MND[2].

Conclusion

The palliative care team is not only concerned with managing dying, but with maximising the quality of the life that goes before it for the person with MND.

St Christopher's Hospice

References

1. World Health Organisation. Disability prevention and rehabilitation. *Report of the WHO expert committee on disability prevention and rehabilitation.* Geneva,WHO, 1981.
2. Kennett CE. *Participation in a creative arts project can foster hope in a hospice day centre.* Palliative Medicine, 2000; 14: 419-425.

Also see relevant chapters in:

Oliver D, Borasio GD, Walsh D. Palliative Care in Amyotrophic Lateral Sclerosis. Oxford: Oxford University Press, 2000.

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SE26 6DZ
www.hospiceinformation.co.uk

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by August 6th, 2001.

2001

July

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

ISNIP 2001 - A Brain Space Odyssey. VIth World Congress/International Society for Neuroimaging in Psychiatry
29 August - 2 September, 2001; Bern, Switzerland
ISNIP 2001, University Hospital of Clinical Psychiatry, Bolligenstrasse 111, CH-3000 Bern 60.
Tel. 0041 31 930 9798,
Fax. 0041 31 930 9977,
E-Mail. Badertscher@puk.unibe.ch,
www.unibe.ch/isnip2001

1st Congress of the EU Geriatric Medicine Society
30 August-1 September, 2001; Paris, France
M Bia, E-Mail mbia@wanadoo.fr

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
Anne Warner, University of Nottingham, Tel. 01332 625680,
E-Mail. Anne.warner@nottingham.ac.uk

BSRM/University of Nottingham Advanced Rehabilitation Course
4-7 September, 2001; Nottingham, UK
Sandy Weatherhead, BSRM,
Tel/Fax. 01992 638865,
E-Mail admin@bsrm.co.uk

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

Foundation Studies in Neuro-disability nursing
10 September-30 November, 2001; London, UK Lisa Reis, Tel. 020 8780 4500 ext 5236, E-Mail. Conferences@neuro-disability.org.uk

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

ECTRIMS 2001
12-15 September, 2001; Dublin, Ireland
International Conference Consultants, 3 Kingram Place, Fitzwilliam Place, Dublin 2, Ireland.
Fax. 00353 1 676 9088,
E-Mail. Info@ectrims2001.ie

XXVII Congress of the European Society of Neuroradiology, 11th Advanced Course & ESHNR 14th Annual Meeting
13-16 September, 2001; Ancona, Italy
Ms Mara Carletti, c/o MGR - Congress Division, Via Ripamonti, 129, I - 20141 Milan, Italy.
Tel. 0039 02 56601212,
Fax. 0039 02 56609045,
E-Mail. ecnr2001@mgr.it,
esnr2001@mgr.it

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.

World Congress of Neurosurgery
16-20 September, 2001; Sydney, Australia
Tel. 0061 2 9241 1478,
Fax. 0061 2 9251 3552,
E-Mail. reply@icmsaust.com.au

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

International Multiple Sclerosis Conference
30 September - 4 October, 2001; Melbourne, Australia
Nadia Agostinelli, 34 Jackson Street, Toorak, Vic. 3142, Australia.
Tel. 0061 3 9828 7222,
Fax. 0061 3 9828 9054,
E-Mail.
Msconference@mssociety.com.au,
www.msaustralia.org.au

October

2nd International Congress on Vascular Dementia
4-7 October, 2001; Cyprus, Greece
Vascular Dementia, PO Box 50006, Tel Aviv 61500, Israel.
Tel. 00972 3 514 0014,
Fax. 00972 3 514 0077,
E-Mail. vascular@kenes.com,
www.kenes.com/vascular

Epilepsy Research Foundation 10th Anniversary Meeting
17 October, 2001; London, UK
Epilepsy Research Foundation, PO Box 3004, London W4 1XT.
Tel/Fax. 020 8995 4781,
E-Mail. Info@erf.org.uk

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

European Federation of Neurological Sciences Congress
26-30 October, 2002; Vienna, Austria
EFNS.
Tel. 0043 1 880 00270,
Fax. 0043 1 888 925581,
E-Mail efns-head@magnet.at

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

Rehab & Care
14-15 November, 2001; Birmingham, UK
Tel. 020 7874 0200

12th International Symposium on ALS/MND
18-20 November, 2001; Oakland, USA
Karen Walker, MND Assocation, PO Box 246, Northampton NN1 2PR.
Tel. 01604 250505,
Fax. 01604 638289,
E-Mail. Symposium
@mndassociation.org

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

BSRM Autumn 2001 Meeting
26-27 November, 2001; Manchester, UK
Sandy Weatherhead, BSRM,
Tel/Fax. 01992 638865,
E-Mail admin@bsrm.co.uk

55th Annual Meeting of the American Epilepsy Society
30 November - 5 December, 2001; Philadelphia, USA
Maria Rivera,
Tel. 001 860 586 7505,
Fax. 001 860 586 7550

December

12th Course in Otology & Otoneurosurgery
4-7 December, 2001; Toulouse, France
Secretariat ORL, Hopital Purpan, Toulouse.
Tel. 0033 5 61772401,
Fax. 0033 5 61493644,
E-Mail. Fraysse.b@chu-toulouse.fr

2002

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

3rd World Congress in Neurological Rehabilitation
3-6 April, 2002; Venice, Italy
Aristea, Tel. 0039 06 844 98364,
Fax. 0039 06 844 98332,
E-Mail. Neurorehab2002@aristea.com

13th European Congress of Physical Medicine & Rehabilitation
28-31 May, 2002
Melanie Ramsdell, Concorde Services, 42 Canham Road, London W3 7SR.
Tel. 020 8743 3106,
www.bsrm.co.uk/ec2002

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

6th European Headache Congress
17-22 June, 2002; Istanbul, Turkey
Flap Tourism & Organisation, Cinnah Cad. No: 42, 06690 cankaya, Ankara-Turkey.
Tel. 0090 312 4420700,
E-Mail. Flaptour@flaptour.com.tr

10th International Congress of Neuromuscular Diseases
7-12 July, 2002; Vancouver, Canada
#645-375 Water Street, Vancouver, BC, Canada.
Tel. 001 604 681 5226,
Fax. 001 604 681 2503,
E-Mail. Congress@venuewest.com

5th European Congress on Epileptology
6-10 October, 2002; Madrid, Spain
5th European Congress on Epileptology, 253 Crumlin Road, Dublin 12, Ireland.
E-Mail: epicongress@eircom.net.

2003

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

XV International Congress of Neuropathology
14-18 September, 2003; Turin, Italy
Newtours spa, Via San Donato 20, 50127 Florence, Italy.
Tel. 0039 055 33611,
Fax. 0039 055 336 1250,
E-Mail. newtours@newtours.it

The World Congress of Neurology

London, 17-22 June, 2001

The 2001 World Congress of Neurology was vast. The four main themes of stroke, epilepsy, dementia and multiple sclerosis were accompanied by presentations from a wide array of major and minor neurological specialities.

The congress opened with Ruth Bonita of the World Health Organisation, presenting forecasts of between 7-10 million deaths worldwide from stroke by the year 2020, and emphasising the need for us to focus on primary prevention in order to significantly impact on this figure. The importance of secondary prevention was also reinforced by the results of the PROGRESS trial, which shows a 28% risk reduction of recurrent stroke among patients, treated with combination anti-hypertensive therapies.

Geoffrey Donnan reviewed acute stroke therapies and now recommends rTPA treatment for acute ischaemic stroke if administrable within 3 hours, which is estimated might lead to 140 fewer deaths per 1000 patients treated. Aspirin should also be started within 48 hours of stroke onset, and clinical outcome is further improved following admission to a stroke unit. Jean-Claude Baron gave us hope for more tailored individual stroke treatments with PET, SPECT and MRI evidence that the ischaemic penumbra around infarcted brain tissue may persist for 12-24 hours in some individuals and has considerable individual heterogeneity. Further evidence of phase 4 trials of thrombolytic therapy are awaited.

A new trial is also underway to discover whether intra-ventricular rTPA to promote clot dissolution may benefit patients with intra-ventricular extension of intracerebral or subarachnoid haemorrage.

In the dementia conference, Walter Rocca reviewed the epidemiology estimating that 29 million people are currently affected worldwide and he predicted that this figure will double by the year 2025. Konrad Beyreuther subsequently described the role of amyloid ß in the development of cerebral plaques and discussed the relationship between cholesterol levels and Aß production that might open new possibilities for the use of statins as treatment or preventative therapy. In a separate lecture, Donald Price produced convincing evidence that the enzyme BACE 1, which cleaves APP (amyloid precursor protein), is directly pathogenic and as such provides a conceptually appealing site for therapeutic/prophylactic intervention. Regarding current therapies, Serge Gauthier suggested that there is evidence that cholinesterase inhibitors may slow progression of symptoms, (donepezil being strongly associated with delayed need for nursing home placement), but the use of NSAIDS, antioxidants and estrogens remain of unproven value. Treatment of concomitant disorders such as depression and control of vascular risk factors was re-emphasised.

Within the epilepsy field, Lars Forsgren from Sweden described the elevated mortality ratios from epilepsy in developed and even more so in developing countries, and the possible roles of infection and malnutrition in the aetiology of the disease. The more rapid expansion of the elderly population in developing countries will place an even greater burden on services and resources. Sam Berkovic discussed epilepsies as "channelopathies" with reference to the acetylcholine gated cation channels as well as voltage gated sodium and potassium channels, and mutations in the GABA receptor gene have now being recognised as the cause of phenotypically distinct seizure types. Andre Palmini described the usefulness of MRI imaging in the classification of epilepsies, but pointed out the resource limitations of both imaging and epilepsy surgery especially in the developing world.

The world of Multiple Sclerosis is progressing rapidly with new diagnostic criteria for the disease to be published in the Annals of Neurology (June 2001). The whole concept of MS as purely a white matter disease is now being challenged since there are now measurable changes in both grey matter and "normal appearing white matter" between MS patients and controls. However in general the MS presentations were dominated by three main themes, addressing issues of disease heterogeneity, measurement of disability and progress in drug therapy. Hans Lassmann discussed the heterogeneity of multiple sclerosis pathology, which is reflected in four distinct immunopathological patterns of active lesions. Whilst these patterns show profound inter-individual differences, suggesting differing degrees of autoimmune, vascular or degenerative mechanisms of demyelination, all currently active lesions within one patient seem to share the same immunopathological process. Interestingly, a small study looking at the relation between sex hormones and MRI activity, which was presented by Dr V. Tomassini, suggests that multiple sclerosis in women may have more inflammatory features than in men. Genetic factors are likely to influence disease heterogeneity and advances in genetic technology have given new impetus to the search for relevant susceptibility genes. Alastair Compston described the GAMES experiment, a large international collaboration of 23 centres in Europe, where each centre will use the same 6000 microsatellite markers to perform genome wide linkage disequilibrium screens in affected individuals and controls. The aim is to eventually compare screens and perform a meta-analysis. So far, the UK screen is the only completed survey and several associated markers have been identified. Whilst some of these markers are located in the MHC region, others, such as markers on chromosome 17 or 10, overlap with peaks in recent linkage screens. The difficulties in measuring and defining disease progression and disability dominated several presentations. Conventional imaging methods are valuable for detecting lesions and their change over time. However, they have not proven sensitive for demonstrating changes in the normal appearing white matter and early axonal loss, which are important in determining the accumulation of disability.

Professor M. Filippi pointed out that other MRI techniques such as MR spectroscopy, magnetization transfer imaging, diffusion tensor imaging and functional MRI can overcome these limitations. A composite MRI score can be calculated from the combined utilisation of these techniques and shows much better overall correlation with disability. Dr A. Petzhold presented data on the prognostic value of baseline CSF neurofilament quantification for the development of disability. A presentation by Dr Y. Semra suggested that CSF actin and tubulin levels in chronic MS correlate with disability. Several papers focusing on drug therapies confirmed the beneficial effects of beta-interferons and Glatiramer Acetate on relapse rate and MRI lesion load in relapsing remitting multiple sclerosis.

However, as Professor C. Polman pointed out, the effect of these therapies on disease progression remains uncertain and studies on the use of beta-interferon in secondary progressive multiple sclerosis are inconclusive. Less conventional therapies which were presented included a small survey on T-cell vaccination which promoted anti-clonotypic cytotoxic T-cells against different myelin antigens and scheduled regular courses of IV methylprednisolone resulting in favourable clinical and MRI findings compared with steroid treatment for relapses. Finally future potential therapies were discussed by John Noseworthy and include immunomodulators, neuroprotective agents, remyelination through cell transplantation, and molecules promoting axon regeneration.

In the neurodegeneration symposium, Michael Hayden presented data which suggests that the spontaneous mutation rate

leading to trinucleotide repeats in the Huntingtin gene could be as high as 7.3 %, which contradicts the long held belief that HD is a disease with the lowest spontaneous mutation rate. His data strongly linked the use of the genetic test to significantly positive psychological profile in those testing positive in addition to those who were negative for the extended trinucleotide repeat. Furthermore, his team have produced evidence linking for the first time wild type Huntingtin, to a physiological function. The work suggests that Huntingtin is required to upregulate transcription of Brain Derived Neurotrophic Factor, which is essential for the survival of striatal neurons.

Stanley Fahn delivered the C. David Marsden memorial lecture with an accompanying tribute to a great neurologist. He described the evolution of the classification of dystonia, which is now based on 13 different mutations and closely mirrors the original clinical descriptions of dystonic diseases. A further tribute lecture to Melvin Yahr was delivered by Donald Calne reminding us of the heterogeneity of Parkinson's disease, the debatable relevance of the Lewy body and the likely importance of both environmental and genetic factors in the development of the disease. David Brooks described the use of PET imaging in PD, emphasising the involvement of non basal ganglia structures in the disease and the possible importance of activated microglia in the early stages of PD as well as in Alzheimer's disease and MS.

In the prion disease session, John Collinge and RG Will presented the evolution of the concept of prion diseases historically, the current state of variant CJD (102 confirmed cases), and a sobering warning about the unpredictability of future disease frequency. Pragmatically, the National Prion Clinic was officially launched at St Mary's hospital, London. Clearly defined referral criteria are available which should allow this centrally funded clinic to provide a fully integrated service for diagnosis and support of any unexplained progressive neuropsychiatric, cognitive, ataxic disorder with sensory complaints, with or without a family history of neuropsychiatric disease (Tel 020 7886 6883). Current difficulties with laboratory testing are also being addressed. The finding that the pathological form of the prion protein from different species with prion disorders binds to plasminogen could form the basis of a diagnostic test (Published in the Lancet recently). A second breaking news presentation by members of the Serono group could make diagnostic testing technically much more simple if the technique of cyclic amplification of small amounts of clinically available prion protein can be amplified by repetitive cycling in a manner conceptually similar to PCR. In this, the abnormal prion protein from the sample is sonicated to produce multiple "seeds" of abnormal prion aggregates, which will be easier to work with and produce an earlier result. The technique has produced promising levels of sensitivity and specificity in experimental models. The additional spin off benefits of this technique in the basic research of prion disease is expected to be immense.

The Fulton transplantation symposium featured Ron McKay describing the potential and limitations of stem cell technology. Olle Lindvall, who presented the Soriano lecture, defined the current state of neural transplantation and cautiously predicted that neural transplantation could still provide significant benefits despite recent adverse publicity, as long as sound biological principles precede clinical trials.

The treatment aspects of CIDP (Chronic inflammatory demyelinating polyradiculopathy) were addressed using evidence from a recent randomised cross over study comparing steroids and IVIg. This study presented on behalf of the INCAT group by Richard Hughes showed that both IVIg and Prednisolone were effective but failed to show a significant advantage of one over the other.

The session on Motor Neuron disease was particularly popular. Robert Brown discussed the role of SOD-1 in familial forms of ALS, and the likely role of protein aggregation in subsequent neurotoxicity rather than copper catalysis. The possibility that vascular endothelial growth factor may lead to hypoxia and thus to motor neurone degeneration is also the subject of exciting future research. Professor Ludolph also described the range of experimental therapies for the disease targeting excitotoxic, oxidative stress, and apoptotic mechanisms.

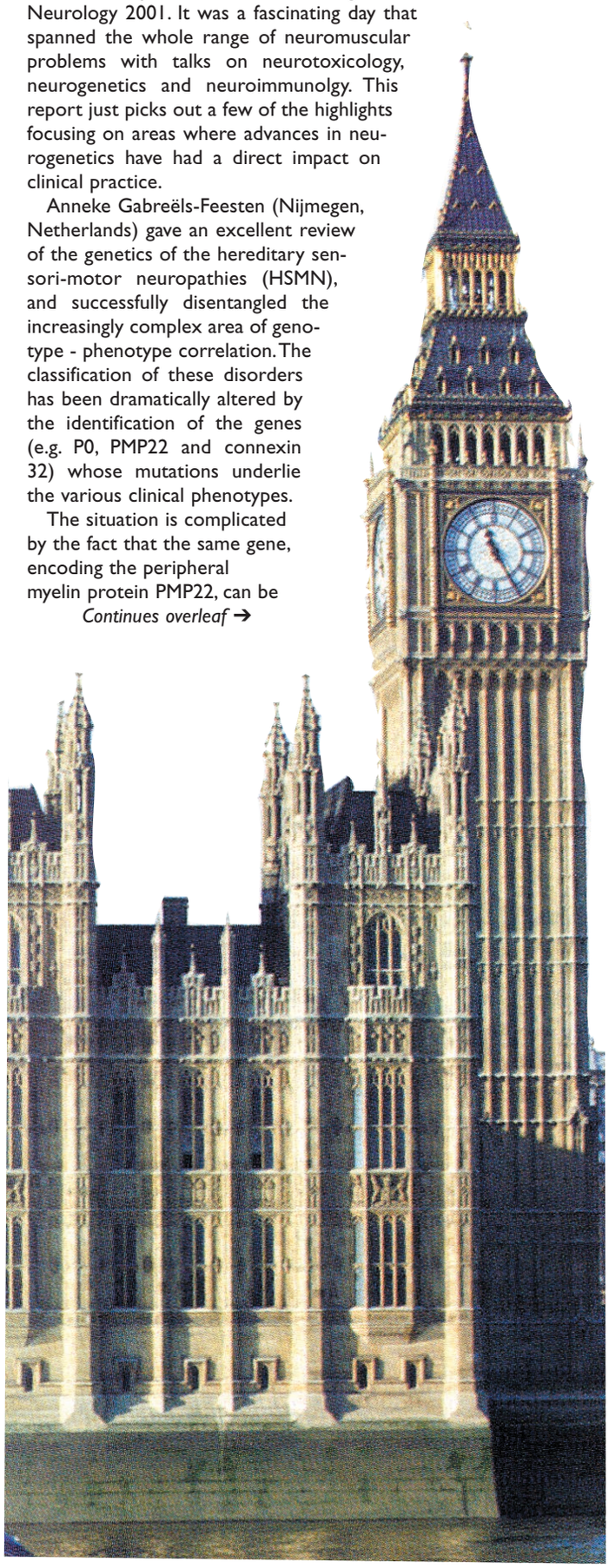
Neuromuscular disease theme day

Neuromuscular disease was the main theme for the final day of the World Congress of Neurology 2001. It was a fascinating day that spanned the whole range of neuromuscular problems with talks on neurotoxicology, neurogenetics and neuroimmunolgy. This report just picks out a few of the highlights focusing on areas where advances in neurogenetics have had a direct impact on clinical practice.

Anneke Gabreëls-Feesten (Nijmegen, Netherlands) gave an excellent review of the genetics of the hereditary sensori-motor neuropathies (HSMN), and successfully disentangled the increasingly complex area of genotype - phenotype correlation. The classification of these disorders has been dramatically altered by the identification of the genes (e.g. P0, PMP22 and connexin 32) whose mutations underlie the various clinical phenotypes.

The situation is complicated by the fact that the same gene, encoding the peripheral myelin protein PMP22, can be

Continues overleaf ➔



mutated in both the axonal and the demyelinating forms of HSMN.

Moreover the phenotype resulting from PMP22 mutations depends not only on the codon involved but also on the nature of the mutation. Thus duplications in the PMP22 gene lead to the classical phenotype of HSMN1, deletions in the same gene produce hereditary neuropathy with a liability to pressure palsies, and missense mutations have a particularly severe demyelinating phenotype, Dejerine-Sottas disease.

The final two talks of the day focused on the muscular dystrophies starting with Michel Fardeau (Paris, France) who summarised the new approach to classification of these disorders which combines phenotype and genotype. In the last decade, not only have several gene mutations underlying different types of muscular dystrophy been discovered, but the proteins they encode have been isolated (hence the dysferlinopathies, calpainopathies and sarcoglycanopathies). However, the functions of many of these proteins, and the mechanisms by which their absence results in degeneration of the muscle fibre, are still not well understood. Moreover as with HSMN, the more we learn about the genetics the more complex the situation becomes. Thus mutations in the dysferlin gene can produce two distinct phenotypes, the predominately proximal limb girdle dystrophy pattern (LGMD 2B) and the more distal pattern known as Miyoshi myopathy.

The day ended with Kay Davies (Oxford, UK) looking to the future and discussing a potential gene therapy for duchenne muscular dystrophy which involves up-regulating the expression of utrophin, a protein that shares 95% homology with dystrophin. Utrophin is naturally expressed in the muscle but only at the neuromuscular junction, and so any therapeutic approach would involve not only up-regulating utrophin expression, but also using an extrinsic promoter to ensure that the protein was expressed throughout the muscle membrane. Using a transgenic mouse model, Professor Davies' group has demonstrated that a therapeutic response only required a three-fold increase in muscle utrophin expression and no toxicity was observed at this level. Moreover, since utrophin, unlike dystrohin, is expressed in patients with duchenne muscular dystrophy, there is no risk of stimulating an immune response against the muscle, and this approach may offer a realistic hope for treatment of this devastating disease.

In addition to the theme day poster and oral presentations throughout the week focused on many important areas in the field, and during the parallel session on Myasthenia Gravis (MG) the pathogenesis and clinical features of both the congenital and acquired forms were discussed.

John McConville presented data which would make the seronegative Myasthenia Gravis (SNMG) group smaller (currently about 10-20% of all cases). His novel work demonstrating that SNMG without ocular involvement are positive for the antibody directed against the MuSK (muscle specific kinase). This protein is found in the neuromuscular junction and is involved in binding agrin and aggregating the ACh receptors in the formation of the neuromuscular junction.

In addition to the oral presentations, over 1500 poster presentations were submitted, some of which were undoubted highlights. The congress also included 30 educational sessions, 23 satellite symposia and a highly entertaining neurological tournament which featured Australia beating Thailand in the final.

We look forward to the next congress in Sydney in four years time.

Tom Foltynie, Tim Harrower, Anke Hensiek, Clare Galton and Camilla Buckley

The American Academy of Neurology: 53rd Annual Meeting

Philadephia, May 5-11, 2001

A Movement Disorder Perspective

The Academy meeting in Philadelphia promised much, yet I have to say that at the end of the conference the highlight for me was undoubtedly the lecture given by the former U.S. Attorney General Janet Reno. Ms Reno spoke about her Parkinson's disease, mixing anecdote and fact, light and shade, to amazing effect, all without the use of audiovisual aids. Noteworthy academics were heard to mutter afterwards: "Now that's how to give a talk"!

Moving on to the usual exotic collection of posters and platform presentations, what else caught the eye? Restless legs is a "growth industry": prevalence studies, validated scales and trials of dopamine agonists all featured prominently. Functional imaging with ?CIT-SPECT indicates that Parkinson's disease (PD) patients treated with pramipexole have lower annual changes in striatal CIT uptake than those treated with levodopa, although the trend was not statistically significant. Similar results have previously been reported for ropinirole and pergolide, although the explanation remains open to conjecture. An increase in 18F-dopa uptake in early PD in the internal globus pallidus was reported, perhaps representing upregulation of function in the dopaminergic nigropallidal projection as a compensatory response.

More reports of cholinesterase inhibitors in the management of cognitive impairment in PD are starting to emerge. Both rivastigmine and donepezil trial data were presented and the results from small series were encouraging. The sensitivity and specificity of the McKeith diagnostic criteria for dementia with Lewy bodies continues to excite debate.

A plethora of reports indicated the benefits of deep brain stimulation of the subthalamic nucleus (STN), in particular, for PD. "Device related events" (including lead revisions and replacements) seem to be common. Lower "on drug" motor disability, axial and gait scores and higher Mattis and Frontal scores preoperatively may predict better outcomes from STN stimulation.

Intraventricular administration of recombinant human glial cell line-derived neurotrophic factor (GDNF) does not improve parkinsonism as assessed using the UPDRS over an 8 month period. The adverse events observed indicated some biological activity but it may be that this route of administration does not permit the GDNF to adequately reach target tissues.

Of 350 twins examined through the Veterans Twin Cohort Study, four (2 MZ, 2DZ) met clinical diagnostic criteria for progressive supranuclear palsy (PSP) and information was available in three for both twins. All three twin pairs were discordant for PSP. One MZ twin was found at post-mortem to have multiple system atrophy (MSA), while the surviving twin brother had newly-diagnosed mild parkinsonism, possibly PD. These data support a prominent role for environmental factors in the aetiology of PSP and MSA.

David Burn, Consultant Neurologist, Newcastle General Hospital

NeuroBloc®
botulinum toxin type B solution for injection

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élan

WCN Satellite Symposium Report

London, 21 June, 2001

New developments in the use of NeuroBloc® (botulinum toxin type B)

Introduction

A number of studies suggest a clear potential for the use of NeuroBloc® - a new type B botulinum toxin - in the treatment of spasticity caused by dystonia, stroke and traumatic brain injury[1,2] and multiple sclerosis (MS)[3].

During the WCN presentations, several speakers covered the new research, the practicalities of NeuroBloc and new safety data on repeat doses in cervical dystonia.

Practical considerations in the use of NeuroBloc/Myobloc™

Professor Michael Barnes, Hunter's Moor Rehabilitation Centre, Newcastle-upon-Tyne

Commenting that NeuroBloc is a welcome addition to the armoury of treatments, Professor Barnes' presentation covered a number of practical advantages that NeuroBloc exhibit over the existing type-A toxins:

- NeuroBloc's main advantage is that it appears to be as efficacious in type A resistant patients as in type A responsive patients[4,5] and is clearly indicated in those with primary and secondary non-responsiveness to type-A toxins.
- It is ready-to-use, and appears to be more stable at room temperature (Setler) – an advantage for peripheral clinics.
- It is also a highly purified complex and has high batch-to-batch consistency, suggesting that it has less antigenic potential and a good consistency of response[6].
- Initial studies suggest that NeuroBloc may have a slightly longer duration of action - around 16 weeks - as opposed to an average of 11 weeks in most type-A studies[4,5].
- It does not seem to have many significant side effects. Only dry mouth, headache and dysphagia occurred with more frequency than placebo[4,5].

Professor Barnes observed that NeuroBloc will also have significant advantages if the longer duration of action is borne out in clinical practice.

Initial NeuroBloc dosing data in the treatment of spasticity:

1 Multiple Sclerosis

Dr Peter Moore, The Walton Centre for Neurology and Neurosurgery, Liverpool

Dr Moore explained that patients with adductor spasticity of the lower limbs present scissoring thighs which may interfere with hygiene, dressing, sexual intimacy, siting, transfers, standing and gait. He reported that a study of multiple sclerosis patients with adductor spasticity of the lower limbs is being undertaken. Two studies have already indicated that botulinum toxin type A may reduce the effort associated with perineal hygiene in these patients[7,8]. The aim of the NeuroBloc study is primarily to evaluate the safety and tolerability of NeuroBloc in the treatment of MS patients.

2 Upper limb stroke and traumatic brain injury

Dr Allison Brashear, Indiana University School of Medicine, Indiana

Dr Brashear performed a 12 week study with 10 patients (9 post-stroke and 1 traumatic brain injury) with a modified Ashworth scale (MAS) score of ≥2 at the elbow, wrist and finger joints.

She reported that results from this study suggest that NeuroBloc may be a useful treatment in the spasticity which can follow a stroke. 10,000 U intramuscular injection of NeuroBloc resulted in statistically significant improvements from baseline in the MAS seen at the elbow, wrist and finger flexors at all post injection visits (weeks 4, 8 and 12).

3 Lower limb stroke

Dr Christopher O'Brien, Vice President Medical Affairs North America, Elan Pharmaceuticals

Dr O'Brien reported on a similar 12-week prospective, open-label study, involving 10 subjects with an initial arm or leg spasticity of MAS>2. All patients received an intramuscular injection of NeuroBloc either 10,000 U or 5,000 U.

The key findings include a reduction in MAS (1-2 points) that was most prominent in the wrist and finger flexors at weeks 4 and 8. There was only slight reduction in mean MRC (measure of power) of approximately 0.5 points in the injected muscle at week 4, with no unwanted weakness observed in non-targeted muscles. Improvements were seen in global assessments, goal attainments and pain scales; any side effects were transient and self-limiting.

Dr O'Brien concluded that NeuroBloc was well tolerated and efficacious, showing a reduction in MAS with minimal reduction in MRC.

Based upon the results of the two studies above, both Dr Brashear and Dr O'Brien stated that their data point to both the need for, and safety of, further investigation of NeuroBloc, at higher doses, in the treatment of spasticity.

Efficacy and safety profile of repeated doses of NeuroBloc/Myobloc

Dr Paul Cullis, Wayne State University of Medicine, Detroit

Dr Paul Cullis presented results from another key study[9] with CD patients who were type-A responsive or type-A resistant. Patients were treated with 10,000 U of NeuroBloc, and were put on repeat doses of 12,500 U and then 15,000 U.

Results showed that the majority of patients, 86% (125/145), participated at all three dose levels. Dry mouth and dysphagia were the adverse events most commonly reported and were generally mild to moderate, self limiting and tended to decrease following repeat injections. TWSTRS-total movement scores improved from baseline to week 4 at all doses, and improvements were slightly higher at 12,500 and 15,000 U compared with 10,000 U. For the majority of patients, the duration of effectiveness was 12–16 weeks.

Concluding, Dr Cullis reported that NeuroBloc is well-tolerated and effective at doses up to 15,000 U, providing clinicians with a wide dosing range to individualise patient treatment.

References:

1. Data on file
2. Data on file
3. Data on file
4. Brashear A, Lew MF, Dykstra AA, Comella CL, Factor SA, Rodnitzky RL, Trosch R, *et al. Safety and efficacy of Neurobloc (botulinum toxin type-B) in type-A responsive cervical dystonia*. Neurology 1999; 53: 1439-1446.
5. Brin MF, Lew MF, Adler CH, Comella CL, Factor SA, Jankovic J, O'Brien CF, *et al. Safety and efficacy of Neurobloc (botulinum toxin type-B) in type-A resistant cervical dystonia*. Neurology 1999; 53: 1431-1438.
6. Settler P. *The biochemistry of botulinum toxin type B*. Neurology 2000; 55(Suppl 5): S22-S28.
7. Snow BJ, *et al. Treatment of spasticity with botulinum toxin: a double-blind study*. Annals of Neurology 1990; 28: 512-515.
8. Hyman *et al. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective randomised, double blind, placebo controlled, dose ranging study*. Journal Neurology Neurosurgery Psychiatry 2000; 68: 707-712.
9. Data on file

Footnote:

The views expressed in the presentations were those of the presenters.

Useful Website: Further information related to NeuroBloc and this satellite meeting can be access at Elan's website at www.elan-neurology.com.

For further information contact:

Marianne Lambertson, Senior Product Manager, Elan Pharma, Abel Smith House, Gunnels Wood Road, Stevenage, Herts SG1 2FG.

EDITOR'S CHOICE

Anticonvulsant drugs in pregnancy

Controversy still remains as to whether birth defects in babies born to mothers with epilepsy are due to anti-epileptic drugs (AED) or genetic abnormalities in the mother, which give rise to both the mother's epilepsy and the babies birth defects. In this study three groups of pregnancies were defined ie. firstly pregnancies in women on AED for epilepsy or other conditions (n=223), secondly pregnant women not exposed to AED but with a history of seizures (febrile seizures excluded) confirmed by EEG or review of case notes (n=96), and thirdly pregnant women with no exposure to AEDs and no history of seizures (n=508). The aetiology of the seizures and seizure types in both seizure groups was roughly similar. The frequency of embryopathy (major malformations, hypoplasia of the midface and fingers, microcephaly, and small body size) was determined by systematically examining the infants by using predefined criteria in each of the three groups. The odds ratio of embryopathy for an infant exposed to a single AED was 2.8, whilst the odds ratio for two or more AEDs was 4.2. Pregnancies in women with a history of seizures but no usage of AEDs had the same risk as the control group. Interestingly mothers who took AEDs for indications other than the treatment of epilepsy also had an increased risk of embryopathy with growth retardation or microcephaly occurring in 25.3 % and major malformations in 9.3% of cases. First trimester convulsive seizures occurred in 27 women resulting in 2 cases of major malformations (7.4%), which compared favourably to 22 major malformations out of 281 (7.8%) cases of reported seizures of all other types. Although this study goes a long way to point the blame of embryopathy on AEDs it has two major shortcomings, which weaken the link. Firstly there is no account of pregnancies terminated because of fetal abnormalities and secondly it would seem that mothers with a history of seizures but no exposure to AED had less severe epilepsy compared to the mothers on AEDs, which may have influenced the outcome of this study. **-TH**

The teratogencity of anticonvulsant drugs.
Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, Ryan LM.
NEW ENGL J MED
2001;344,1132-8.

BASIC NEUROSCIENCE

★★★ RECOMMENDED

Growing cells from the dead

There has been a lot of recent interest in trying to repair the brain in a number of conditions using neural stem cells. These cells are found in the developing embryo and give rise to the CNS, but are also known to exist in the adult brain where their role is unknown. To date, however, there have been problems in isolating such cells in sufficient numbers from ethically acceptable sources. This recent paper from the Gage group now reports that they are able to isolate neural stem cells from cadaveric human brains. These researchers have managed to isolate neural stem cells from 23 tissue samples from people of different age, with the longest period from death to harvesting being 20 hours. They report in detail on 2 cases, the first being an 11 week old postnatal male that died from myofibromatosis and the other a resected temporal lobe from a 27 year old male. In all cases neural stem cells were isolated and propagated in culture with the aid of various growth factors but critically with conditioned medium from genetically modified rat stem cells that overproduce a secreted form of FGF-2 and a glycosylated form of cystatin C. The cells isolated in either case expanded in culture, this being greater in the younger tissue, and could differentiate into neurons and glia.

This study is significant because it is the first to isolate such cells from the human brain after death, although others have isolated such cells from surgically resected temporal lobe specimens. This study therefore raises the possibility that neural stem cells could be harvested from a more ethically acceptable and practical source. At the present time such cells can only be isolated from human embryonic brain tissue obtained through therapeutic abortions or possibly from the adult human brain, although to date there are major problems in doing this. Whatever the mode of isolation however, the major problem still facing the field is getting these neural stem cells to do what you want them to do, and the failure to get such cells to differentiate in a regulated fashion means that at the present time their therapeutic potential is still limited **- RAB**

Progenitor cells from human brain after death.
Palmer TD, Schwartz PH, Taupin P, Kaspar B, Stein SA, Gage FH .
NATURE
(2001) 411: 42-43.

CEREBELLAR DISEASE

Gluten sensitivity in sporadic cerebellar ataxia

Coeliac disease (gluten-sensitive enteropathy) has been associated with various neurological features, including cerebellar ataxia with or without dorsal column demyelination (spinocerebellar syndrome) and myoclonus (myoclonic ataxia), dementia, peripheral (symmetrical sensory) neu-

ropathy, and seizures. Cerebellar ataxia of late-onset for which no cause can be identified is not an unfamiliar problem in the neurology outpatient clinic. This study from Germany looked for evidence of gluten sensitivity in patients with previously diagnosed idiopathic cerebellar ataxia (ICA).

Of 104 patients, 12 were found to have gluten-sensitivity (11.4%); 11/12 were positive for anti-gliadin antibodies (AGA), but of those undergoing duodenal biopsy (10/12) only 2 showed villous atrophy (one with normal antibodies). Hence, mucosal pathology is not obligatory for the diagnosis. No patient had evidence of malabsorption or hypovitaminosis E.

All those identified with gluten-sensitivity had clinical evidence of cerebellar ataxia of stance and gait though all were still ambulatory; most also had limb ataxia. Other clinical features included dysarthria, cerebellar oculomotor abnormalities (e.g. gaze-evoked nystagmus), loss of proprioception, and dysphagia. MRI showed atrophy of cerebellar vermis and hemispheres. CSF was normal (AGA not found). Electrophysiological studies showed evidence of dorsal column degeneration and axonal sensorimotor neuropathy. Neuropsychological testing showed deficits in verbal memory and executive function.

This study showed a much lower prevalence of gluten sensitivity in patients with ICA than a previous study, most probably because of different inclusion criteria for patients. Nonetheless, although the association is uncommon, the diagnosis is worth looking for because it is potentially treatable with gluten-free diet, which also reduces the subsequent risk of developing intestinal lymphoma.**-AJL**

Sporadic cerebellar ataxia associated with gluten sensitivity
Bürk K, Bösch S, Müller CA, *et al.*
BRAIN
2001:124(5);1013-1019

COGNITIVE NEUROLOGY

Volumetric MRI in the diagnosis of dementia syndromes

Semantic dementia (SD) is one of the variants of focal lobar degeneration of the brain. Clinically it is characterised by impaired naming, loss of word meaning, semantic memory impairment (cf episodic memory disturbance in Alzheimer's disease [AD]), with or without surface dyslexia and dysgraphia, but with fluent speech and preserved syntax. Despite this typical profile, it may be difficult to differentiate SD from AD clinically. This paper suggests that volumetric magnetic resonance imaging may assist in differential diagnosis, since AD and SD have different patterns of temporal lobe atrophy.

Comparing AD, SD, and normal controls (n =10 in each group, the first two groups matched for comparable full scale IQ), Chan and colleagues observed asymmetric atrophy (L>R) in SD, affecting all anterior temporal lobe structures but particularly entorhinal cortex, amygdala, anterior medial and inferior temporal gyri, and anterior fusiform gyrus. There was an anteroposterior gradient of atrophy in the anterior temporal lobe in SD. In contrast, in AD atrophy was symmetrical, showed no anteroposterior gradient, and

affected particularly medial temporal lobe structures especially hippocampus with lesser involvement of amygdala and entorhinal cortex.
These findings raise questions about the anatomical substrate of semantic memory. The authors suggest that the left anterior medial and inferior temporal gyri may be of particular importance, either alone or as part of a functional network. From the clinical standpoint, the different patterns of temporal lobe atrophy in SD and AD may complement clinical assessment in establishing the correct diagnosis.
-AJL

Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease.
Chan D, Fox NC, Scahill RI.
ANNALS OF NEUROLOGY
2001:49(4):433-442

EPILEPSY

Epilepsy: a dangerous condition

★★★ RECOMMENDED

In recent years evidence has accumulated demonstrating a significant mortality of epilepsy. This is one of a small number of well-conducted, population-based studies of epilepsy that show that the problem is not just one of affecting severe epilepsy as most neurologists see it in the clinic. The original cohort is well-known to many neurologists and has yielded a decade of publications and work for research registrars, myself included. Over 1000 patients with a new onset of definite, possible or probable epilepsy were recruited direct from general practice over 3 years from 1984 to 1987. In this cohort mortality was mostly related to the cause of the epilepsy with increased rates in patients with epilepsy due to congenital causes (SMR 25) cerebrovascular disease, CNS tumours and alcohol-related seizures. Only 5 of 214 deaths were directly attributable to epilepsy, one each from drowning, status epilepticus, burns, cervical fracture and sudden unexplained death (SUDEP). The low incidence of SUDEP is reassuring and perhaps relates to the seizure remission rate of 70% in this cohort. There is a strong relationship between seizure frequency and risk of SUDEP in other studies. The study re-emphasises that epilepsy in the community is different from epilepsy in the clinic. **-MM**

Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term prospective, population-based cohort.
Lahtoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JWAS, Shorvon SD.
ANNALS OF NEUROLOGY 2001;49:336-3444

MOVEMENT DISORDERS

Risk Factors for Parkinson's Disease: The Leisure World Cohort Study

★★★ RECOMMENDED

No single exposure has been implicated in all cases of Parkinson's disease (PD). The epidemiological evidence suggests that certain individuals may have an increased risk of PD following exposure to pesticides or high lipid diets. Cigarette smoking, increasing caffeine intake and possibly vitamin use all seem to lower the risk of PD in otherwise comparable groups of people. Most of this evidence is based on reports of retrospective case control studies, which are at risk of recall bias.
This latest study was a case control study "nested" within a prospective cohort study, which removes the possibility of recall bias. 395 cases of PD were identified from a cohort of 13 979 retired people, from whom prospective risk factor information had been collected over 17 years. After matching to 6 controls per case, odds ratios were calculated for several putative PD risk factors.
After adjustment for the effects of other exposures, current smokers had nearly a 60% reduced risk relative to never smokers, and greater than 2 cups of coffee per day was associated with a 30% reduced risk. Higher intake of vitamins A or C was not associated with a reduced risk, and information on pesticide exposure and lipid intake was not available.
A significant protective association for PD and both hypertension and the use of anti-hypertensive medication was also noted. This association must be checked in other studies including information on drugs used and adequacy of blood pressure control, before accepting hypotheses of elevated cerebral perfusion protecting patients from PD.
It is likely that a range of exposures can increase the risk of different types of PD in subgroups of patients dependent on specific susceptibility genes. Future epidemiological studies should include both genetic and environmental exposure data in order to contribute further to possible models of the mechanisms of neuro-degeneration. **-TF**

Risk Factors for Parkinson's Disease: The Leisure World Cohort Study.
Paganini-Hill A.
NEUROEPIDEMIOLOGY
2001:20:2:118-124

The phenotype of yet another spinocerebellar ataxia: SCA 12

There are now 16 spinocerebelar ataxias: SCA 1-8 and 10-16 (SCA 9 is unaccountably missing) and dentato-rubro-pallido-luysian atrophy (which has resisted aquiring a number but is a SCA all the same). SCA 3 is the commonest and SCAs 5,10,11,12,13,14,15,16 have been found in just one family each. SCA 12 is the most recently identifed gene: affected subjects have 66 to 78 CAG repeats. Two papers in Neurology investigate SCA 12. Margolis' team, from Johns Hopkins were the first to identify it in an American pedigree of German descent. They now present the clinical phenotype. It is often not possible to predict the genotype of the SCAs from their phenotype, but SCA12 may be distinct in that patients present in their mid 30s with action tremor of the arms and progress to a dementia, with spinal cord and akinetic signs as well as ataxia. Worth and Wood, at Queen Square in London, have screened 392 UK cases of undiagnosed ataxia for the SCA 12 expansion and found none, suggesting SCA12 is indeed rare. So there we go: interesting but not exactly an advance in public health.
- AJC

SCA-12: Tremor with cerebellar and cortical atrophy is associated with a CAG repeat expansion.
O'Hearn E, Holmes SE, Calvert PC, Ross CA, Margolis RL.
NEUROLOGY
2001:56:299-303.

Spinocerebellar ataxia type 12 is rare in the United Kingdom
Worth P. F. and Wood N. W.
NEUROLOGY
2001; 56: 419-420

MULTIPLE SCLEROSIS

How does ß-interferon work in multiple sclerosis?

It is clear that the ß-interferons have an impact on disease activity in multiple sclerosis, although the extent of the effect is debated. Yet no one really knows their mechanism of action. Their use in multiple sclerosis was based originally upon their anti-viral properties; but patients on ß -interferon have no fewer viral infections than untreated patients. There is not shortage of research on the immunomodulatory effects of interferon-ß -1a, but no clear consensus, perhaps because cytokines have such widespread effects and it is difficult to know which are relevant. These three papers in the Journal of Neuroimmunology are typical.

Jingwu Zhang's group in Houston (who are partly supported by Biogen) extracted T cells from the blood of 24 patients with multiple sclerosis, of whom 12 were on interferon- ß -1a. They showed, by flow cytometry, that T cells from patients on interferon- ß -1a expressed less of the cell surface chemokine receptor, CCR5. This is the receptor for RANTES (regulated upon activation, normal T cell expressed) and MIP (macrophage inflammatory proteins). The hypothesis would be that a reduction of CCR5 on lymphocytes in the cerebral vessels results in less T cell movement across the blood-brain-barrier. In support of this, Zhang showed that T cells from patients treated with interferon- ß -1a migrated less vigorously across a 5µm pore size membrane, down a gradient of RANTES and MIP-1 alpha, than T cells from untreated patients. So perhaps interferon- ß -1a works by reducing T cell entry into the CNS from blood vessels.

The next two papers examine the role of IL-10 in multiple sclerosis. This is a very trendy cytokine, as it is prominent among the Th2 repertoire. It is believed that MS is driven by Th1 cytokines, therefore if interferon- ß -1a were to upregulate Th2 cytokines, MS disease activity would be reduced.

Sadly, it is not that simple. Richard Rudick's laboratory at the Cleveland Clinic examined, using flow cytometry, the IL-10 expression of peripheral blood cells from multiple sclerosis patients (number not clear). After just one injection of interferon- ß -1a, IL-10 expression by monocytes and CD4+ T cells was increased. Interferon- ß -1a treatment also upregulated the co-stimulatory molecules B7.2 and CD40 on monocytes and CD40ligand on CD4+ T cells. These changes should also boost the Th2 axis. So far, so good. However, the only other cytokine Rudick's group examined was IFN-, the archetypal Th1 cytokine. If there had been a true shift in the immune response from Th2 to Th1, IFN-y expression should have fallen. But it remained doggedly unchanged. Goodkin's team from San Francisco also studied IL-y 10. They showed that serum IL-10 rose as multiple sclerosis disease activity waned, as measured by the resolution of enhancing MRI lesions. However, after six months of interferon- ß -1a treatment, serum IL-10 levels were significantly reduced, to about half pre-treatment levels. It is hard to square these two studies. Perhaps it is just simplistic to hope that measuring the changes in just one cytokine will reveal the mechanism of ß -interferon's action. **-AJC**

Regulation of chemokine receptor CCR5 and production of RANTES and MIP-1alpha by interferon-beta.
Zang YC, Halder JB, Samanta AK, Hong J, Rivera VM, Zhang JZ
JOURNAL OF NEUROIMMUNOLOGY
2001: 112:1-2:174-80.

Immunomodulatory effects of interferon beta-1a in multiple sclerosis.
Liu Z, Pelfrey CM, Cotleur A, Lee J, Rudick RA.
JOURNAL OF NEUROIMMUNOLOGY
2001: 112:1-2:153-62.

Relationship between serum levels of IL-10, MRI activity and interferon beta-1a therapy in patients with relapsing remitting MS.
Waubant E, Gee L, Bacchetti P, Sloan R, Cotleur A, Rudick R, Goodkin D.
JOURNAL OF NEUROIMMUNOLOGY
2001:112:1-2:139-45

PERIPHERAL NERVE

Two Japanese studies make sense of anti-ganglioside antibodies

Koichi Hirata's group in Tochigi, Japan, receives serum samples from neighbouring district and university hospitals for anti-ganglioside antibody assays. Therefore they are well placed to address two topical issues: first, what is the clinical significance of the finding of an anti-GQ1b antibody, and second, is there a chronic form of Miller Fisher syndrome?

Between 1994 and 1998, 245 samples tested positive in Hirata's laboratory for the anti-GQ1b antibody. Clinical data were available on 194 patients of these patients. It is no surprise to read that 60-86% of patients had experienced an antecedent upper respiratory tract infection (0-27% also had diarrhoea). Also as expected, the majority of patients had the Miller Fisher syndrome; 110/194 had the classic form and 31/194 had a Miller Fisher / Guillain-Barre overlap syndrome in that they also had limb weakness. The phenotypes of the remaining patients were more interesting. 23/194 had a reduced level of consciousness with other signs and hence fell under the rubric of Bickerstaff's brainstem encephalitis. 15/194 presented with an acute ophthalmoparesis and had very little else to show for it, and 8/194 had regular Guillain-Barre without any eye signs. It seems that the presence of anti-GQ1b antibody defines a spectrum of post-infectious syndromes from acute ophthalmoparesis to Bickerstaff's brainstem encephalitis.

Willison in Glasgow has suggested that there is a chronic form of Miller Fisher syndrome that he has dubbed CANOMAD: chronic ataxic neuropathy with ophthalmoplegia, M-protein, agglutination and disialosyl antibodies. Koichi Hirata and colleagues, in a paper in the JNNP, take issue with him. They agree that there is a chronic sensory ataxic neuropathy that is associated with a M-protein and IgM antibodies against the b series of gangliosides, especially GD1b. However they compare 5 such patients with 8 classical Miller Fisher patients and find three important differences. Clinically, patients with the chronic sensory ataxia have impaired proprioception but did not have an ophthalmoplegia (both unlike Miller Fisher). Finally, the anti-GQ1b antibodies found in the chronic sensory ataxia all cross-reacted with b series gangliosides, especially GD1b, unlike any of the anti-GQ1b antibodies from Miller Fisher patients. **-AJC**

Anti-GQ1b IgG antibody syndrome: clinical and immunological range.
Odaka M, Yuki N, Hirata K.
JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY
2001:70:1:50-55

Features of sensory ataxic neuropathy associated with anti-GD1b IgM antibody.
Susuki K, Yuki N, Hirata K.

JOURNAL OF NEUROIMMUNOLOGY
2001: 112:1-2:181-7

REHABILITATION

Mental rehearsal of movement may help recovery of arm function following stroke

Sports psychologists have long recognised that mental imagery when combined with physical practice accelerates learning and enhances performance of motor skills. It is thought that events during imagination of movement aid performance by reinforcing coordination patterns in the development of motor skill, moreover imaging studies have shown that the same regions of motor cortex, basal ganglia and cerebellum are activated when imagery is used as when physical activities are actually performed. Even though movement is compromised after stroke many patients are still able to imagine moving. In a pilot study reported in Clinical Rehabilitation, Page and colleagues sought to determine whether giving stroke patients mental practice will help them to recover arm movement.
After two baseline measurements13 patients who were between four weeks and one year post stroke were randomised to receive a six week course of Occupational Therapy and either mental practice aided by instructions on a tape recording or a tape recording with stroke information on it. The tapes were used at home between visits to the therapy department as well as at therapy appointments. Compliance with using the tapes was good. Arm recovery measured by the Fugl Meyer Assessment of Motor Recovery and the Action Research Arm Test was improved in the imagery group but not in the control group.
Clearly this is a small study, but the encouraging result makes a larger study feasible. If clinically significant recovery is enabled through mental imagery as an adjunct to treatment, patients will be able to do more towards their recovery between visits to the therapy department where time and resources are limited.**-AJT**

A randomised efficacy and feasibility study of imagery in acute stroke.
Page SJ, Levine P, Sisto SA, Johnston MV.
CLINICAL REHABILITATION
2001: 15 (3): 233-240

VASCULAR DISEASE

Filling defects in the transverse sinus - Is venous thrombosis always the cause?

In the magnetic resonance era the usual mode by which cerebral venous thrombosis is diagnosed is MR venography supplemented by axial coronal or sagittal magnetic resonance imaging. Variability in anatomy of the cerebral venous sinuses is normal, particularly with regard to the transverse sinuses. The superior sagittal sinus drains predominantly into the right transverse sinus (in about 60% of individuals) and the left transverse sinus is often smaller or hypoplastic. On MR venography it is common to see such asymmetry, and it is also common to see tapering or narrowing of the transverse sinus at its junction with the sigmoid sinus. Possible causes for such tapering or narrowing include hypoplasia, thrombosis, and now a new cause - hypertrophic Paccioni granulations.
In this case report the authors describe a patient with a long history of migraine without aura. She was admitted because of a new type of headache. The headaches were worse at night. There were no associated neurological symptoms or signs.
Magnetic Resonance imaging and venography showed filling defects in both transverse sinuses, worse on the left. It was thought that this was due to transverse sinus thrombosis and she was anticoagulated. However, the CSF pressure was normal. The MR images were reviewed further and it was felt that the filling defects seen were in fact well defined and typical of hypertrophic Paccioni granulations.
The authors go on to discuss the importance of distinguishing thrombosis from hypertrophic Paccioni granulations. Not least of these is exposing patients to inappropriate anticoagulation with its attendant risks. Hypertrophic Paccioni granulations are regular rounded masses causing a filling defect in the transverse sinus, they are often found in the lateral portion of the transverse sinus and are hypodense or isodense relative to the brain. They do not enhance with gadolinium. Their true prevalence is unknown but in a retrospective MRI series they were felt to be present in 13% of 100 brain MR images.
-PM

Intravenous hypertrophic Paccioni granulations: differentiation from venous dural thrombosis.
Giraud P, Thobois S, Hermier M, Broussolle E, Shazot G
JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY
2001: 70: 700-701

★★★ RECOMMENDED

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

Clinical Rehabilitation, Multiple Sclerosis
Arnold, 338 Euston Road, London NW1 3BH. Tel. 020 7873 6339, Fax. 020 7873 6325,
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Pharmacologist becomes peer

Susan Greenfield has been named as one of 15 "peoples' peers" to sit in the House of Lords. According to an interview in the Times, she was fed up with "waving my arms about in lectures and newspaper columns about science funding and nothing ever happening", and so she applied. A little ungraciously the same newspaper only gave her 1/10 marks for how closely she fulfilled the aim of being a peoples' peer. Her background is certainly not privileged: her mother was a chorus girl and her father an electrician. She was the first member of her family to go to university. She went up to Oxford initially to read classics, but switched to science early on, doing her Dphil in the pharmacology department at Oxford, then taking postdoctoral positions at Paris and New York, before returning to Oxford where she has remained ever since. Her work encompasses basal ganglia pharmacology, theorising on the nature of consciousness and popular expositions on the brain. She has a flare for popularising neuroscience, enthusiastically presenting radio and television programmes.

In 1994 she was the first woman to give the Royal Institution Christmas lectures and she became director of the Royal Institution in 1998. In January 2000 she was awarded the CBE. She was declared one of the 50 most powerful women in Britain by the Guardian and ranked number 14 in the "50 Most Inspirational Women in the World" by Harpers and Queen. Her scientific colleagues have not been universally delighted with this media interest but she insists she is a serious scientist and her publication record seems to bear that out. Her most cited paper (as either the first or last author) is a Nature paper on facilitation of a dendritic calcium conductance by 5-hydroxytryptamine in the substantia nigra. Not all of the other professorial researchers in the Pharmacology Department can claim a more highly cited paper. No doubt it is better to have a neuroscientist in the House of Lords than not, and she certainly will be listened to.

Health Select Committee exposes serious brain injury

Recommending that the government, 'spells out clearly what steps it will take to improve the situation in the provision of rehabilitation services for head-injured people, The Health Select Committee's, (HSC's) report to the Department of Health into Head Injury in England has acknowledged a critical lack of services existing for brain injury survivors, families and carers. It identifies 27 areas of serious concern, and recommends an even wider enquiry. Acknowledging for the first time a distinction between brain injury and other neurological and mental health conditions it states, 'a lack of community support and care networks to provide ongoing rehabilitative care is the problem area that has emerged most strongly'.

It also calls for planning and responsibility to be taken for brain injured people after discharge from hospital and for the introduction of specialist staff to care for individual brain injury survivors. Headway - the brain injury association, warmly welcomes the report. Chief Executive Kevin Curley said, "This is the most important report on head injury ever published in this country. The HSC makes it clear that extra resources are also needed but that there will be long-term savings. A young man aged 20 with a brain injury who gets the rehabilitation and training needed to return to work by the age of 23, will save the nation at least £330,000".

The report acknowledges that when assessing brain-injured people for disability living allowance, (DLA) staff involved in this process should, 'have specialist skills which enable them to understand the complex combination of physical, cognitive and behavioural impairments characteristic of this type of neurological disability'. Headway's Bill Alker added, "Headway believes the HSC has identified, as we have, that brain injury is a separate disability and a growing problem. More people are surviving brain injuries. This is why it is calling on the Department of Health to 'urgently' provide better ways of collecting data relating to the incidence of head injury".

For further information contact Headway on Tel. 01159 240800, Fax. 0115 958 4446, E-Mail enquiries@headway.org.uk

NICE denounced in MS Society campaign

The National Institute for Clinical Excellence has been condemned in an MS Society campaign with the slogan 'Government policy on multiple sclerosis does not stand up under the microscope.' The charity's adverts appeared in national newspapers to promote MS Week, and came just days after the DoH reminded the NHS that existing guidelines on MS prescribing should be followed.

Purchasing authorities and providers in the NHS have been told to "develop and implement local arrangements" to MS drug prescribing, and initiate and continue beta-interferon prescribing in hospitals. This guidance was re-stated after a meeting between the MS Society and the MS Research Trust and Health minister John Denham.

The appraisal of beta-interferon and glatiramer has been pending since August 1999, during which time doctors have become uncertain about writing new prescriptions for the drugs.

However, Peter Cardy, President of the MS Society, said, "The best that we can say is that we are no worse off than we were five years ago." The appraisal has suffered unparalleled delays due to appeals against an initial non-recommendation, and the creation of a new economic model to measure the drugs' cost-effectiveness.

The new economic model is now being constructed, and the drug manufacturers are considering NICE's request for patient data. Peter Cardy maintains, however, that re-modelling will not help. "I thought there was a golden rule in research which said you don't torture data until it delivers up the answer you want. There's a strong risk of that happening - I don't think the data that NICE is looking for exists." He added that one "crumb of comfort" was that NICE had recommended some products despite its uncertainty about the cost-effectiveness of the products.

For further information contact the MS Society on Tel. 0208 438 0700.

Epilepsy Research

A new three-year study funded by Action Research seeks to identify how and why brain damage can occur as a result of epileptic seizures. The award of more than £119,000 was announced to coincide with National Epilepsy Week (May 20-26).

The project, based at Cambridge and London, could open up new possibilities for better targeted treatment. Dr Ruth Empson, School of Biological Sciences, Royal Holloway University of London, says, 'Epilepsy places a heavy demand on the NHS and community. It is estimated that epilepsy places a burden of nearly £2billion on the UK economy each year."

Despite improved awareness and understanding, current medication isn't fully beneficial for many sufferers. Dr Empson explains, "Many people suffer considerable side effects from epilepsy drugs. There is a great need to develop drugs that are more selective towards actions in the brain itself and that are targeted to what happens during a seizure." Up to a third of all sufferers cannot control their condition with existing medication, meaning their condition continues putting them at risk of "a downward spiral of brain damage and increased seizure susceptibility", she adds.

Dr Armando Genazzani, University of Cambridge is leading the project. By using modern genetic techniques, the research team aims to identify which genes are being 'expressed' or stimulated by epileptic seizures. Their work could lead to the development of specially-targeted drugs that not only stop the seizures worsening, but also prevent the cells from dying.

For more information about Action Research see www.actionresearch.co.uk

NeuroBloc® (botulinum toxin type B) in the treatment of spasticity

Early results showing clear potential for the use of NeuroBloc® in the treatment of spasticity were presented at the World Congress of Neurology.

These data suggest potential for the use of this new Type B botulinum toxin for a range of movement disorders and associated conditions.

Commenting on the emerging understanding of the role of NeuroBloc in the treatment of hyperactive muscle spasms associated with spasticity, Professor Mike Barnes, Consultant Rehabilitation Specialist, Hunter's Moor Rehabilitation Centre, stated, "The promise demonstrated by NeuroBloc in patients with spasticity is an important early finding. NeuroBloc, which has already provided clinicians with a number of key practical benefits in cervical dystonia clinics, will hopefully in the future provide similar advantages in spasticity".

Methodology and initial results from three dose-ranging studies evaluating the use of NeuroBloc were presented, relating respectively to use in spasticity caused by: stroke and traumatic brain injury, and multiple sclerosis (MS).

For further information on the satellite meeting see the report on page 23 or visit Elan's website at www.elan-neurology.com

New findings in baby head injuries

Babies do not have to be shaken violently to suffer fatal brain damage, according to new research. A study of head injury in children, funded by medical charity Action Research, has found that severe force may not be necessary.

"We have found a type of damage, not previously reported, which would suggest that in a proportion of cases the brain is stretched where it joins the spinal cord, at the top of the neck", says lead researcher Dr Jennian Geddes.

Dr Geddes, Royal London Hospital, adds, "This, together, with our finding that these children do not usually have any evidence of damage elsewhere in the brain, suggests that, contrary to what is widely thought, violent shaking may not be necessary to cause a fatal injury in a baby."

The researchers originally embarked on a general project to see whether brain damage evolves in the same way in youngsters as in adults. However, the team quickly discovered that very few of the fatal paediatric head injury cases they had identified were accidental. As a result, the project became a detailed post-mortem study of the brains of 53 children who had died of non-accidental injury (NAI).

In a proportion of their cases, the researchers found damage due to stretching of the lower brain stem and spinal cord, and believe that this can happen if a baby's head is allowed to flop backwards and forwards. The researchers emphasise that such an unsupported movement would not occur in everyday parent/child interactions but would be one that an onlooker should recognise as harmful. Dr Geddes adds, "Violence - confessed or witnessed - certainly occurs in some cases, but if in a significant proportion the primary damage is a hyperextension injury, then severe force may well not be necessary in order to inflict injury on a baby. The findings have implications for how we interpret NAI cases and how infants should be handled. They suggest that some of the widespread assumptions about inflicted head injury need to be looked at again." The two-year study will be published in Brain and reported in New Scientist.

For more information about Action Research see www.actionresearch.co.uk

Paradigm for MND launched by the RCN

The care of patients with MND is complex and patients require a huge amount of support in order to maintain quality of life. The needs of patient can be complex to understand for professionals not familiar with the disease. Last year the National Institute of Clinical Excellence (NICE) undertook a Health Technology Appraisal of Riluzole used in the treatment of MND. To inform the submission for this appraisal the Royal College of Nursing formed a working group of MND nurse specialists and nurses working with patients who have MND. In order to raise awareness and aid understanding of the needs of people with MND, these nurses have developed a disease management paradigm (RCN 2001). This has been developed along the lines of a similar paradigm for Parkinson's disease suggested by MacMahon and Thomas (1998). The paradigm identifies key points for the management of people with MND and can act as a 'action' checklist throughout the course of the disease for those who are not familiar with the disease. Used in conjunction with other awareness literature (MNDA 2001) the framework will enable a greater understanding of the management of MND in the diagnostic, palliative and terminal stages of the disease.

References

MacMahon DG, Thomas S. *Practical Approach to quality of life in Parkinson's Disease* J Neurol1998 Suppl 1 S19-22

MND a problem solving approach for GP's and Primary Health Care Team 2nd edition MMNDA 2001

The Paradigm is available from the Royal College of Nursing RCN Direct Tel:0845 772 6100
Quote publication 001544. Details of the MND Nurse Specialist Group can be obtained from Sue Thomas Nursing Policy & Practice Adviser RCN 0207 647 3743 E-Mail sue.thomas@rcn.org.uk

Gowers' Prizes 2001

The Council of the British Branch of the International League Against Epilepsy announce the Gowers' Prize 2001 and invite entries. Entries are welcome from all over the world, but must be in English and not more than 5000 words.

1 Young Physician's Prize (£1000)
A dissertation on any aspect of epilepsy.
Entrants must be no older than 35 years on December 31st 2001.

2 Medical Students Prizes (£500 each)
A dissertation on any aspect of epilepsy, including case histories of a patient personally observed by the student. Entrants must be bona fide medical students.

1 Health Professional Prize (£500)
A dissertation on any aspect of epilepsy, by a member of a recognised health profession related to epilepsy care.

1 Nursing Prize (£500)
A dissertation on any aspect of epilepsy by a member of the nursing profession, working in epilepsy care.

ENTRIES CLOSE DECEMBER 2001. PRIZES WILL BE PRESENTED AT THE BRITISH BRANCH ANNUAL SCIENTIFIC MEETING, EXETER, APRIL 3RD - 6TH 2002.
Entries and enquiries should be addressed to: Dr Tim Betts, Birmingham University Seizure Clinic, Queen Elizabeth Psychiatric Hospital, Birmingham, B15 2QZ. Fax. 0121 678 2370.
E-Mail:T.A.Betts@bham.ac.uk

The Council are grateful to UCB Pharma (UK) for sponsoring the prizes

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info@alzheimers.org.uk

Association of British Neurologists
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Blood Pressure Association
60 Cranmer Terrace, London SW17 0QS
Tel: 020 8772 4994
Fax: 020 8772 4999
www.bpassoc.org.uk

Brain & Spinal Injury Charity
Hope Hospital, Stott Lane, Salford, Manchester M6 8HD
Tel: 0161 439 0551

Brain Injury Rehabilitation Trust (BIRT)
First Floor, 32 Market Place, Burgess Hill, West Sussex RH15 9NP
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Fax: 01444 239123
birt@disabilities-trust.org.uk

Brain Research Trust
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Tel: 020 7636 3440
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Brainwave, The Irish Epilepsy Association
249 Crumlin Road, Dublin
Tel: 00353 1 4557500

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
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www.bbsf.org.uk

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2 Oakfield Drive, Hightown, Merseyside L38 9GQ
Tel: 0151 929 3229

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New Anstey House, Gate Way Drive, Yeadon, Beds LS19 7XY
www.epilepsy.org.uk

British Neurological Research Trust
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www.bna.org.uk

British Society of Rehabilitation Medicine
c/o Royal College of Physicians 11 St Andrews Place, London NW1 4LE
Tel: 01992 638865
sandy.weatherhead@bsrm.co.uk
www.bsrm.co.uk/

Chartered Society of Physiotherapy
14 Bedford Row, London WC1 4ED
Tel: 0207 306 6623

Chest Heart & Stroke Scotland
65 North Castle Street, Edinburgh EH2 3LT
Tel: 0131 225 6963
Fax: 0131 220 6313
www.chss.org.uk

Children's Head Injury Trust (CHIT)
c/o Neurosurgery, The Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE
Tel: 01865 224786
www.glaxocentre.merseyside.org/chit.html

College of Occupational Therapy
6-8 Marshallsea road
London SE1
Tel: 0207 357 6480

Different Strokes
Sir Walter Scott House
2 Broadway Market, London E8 4QJ
Tel: 0207 249 6645
www.strokeforum.com/diff-strokes/

Enlighten, Action for Epilepsy
5 Coates Place, Edinburgh EH3 7AA
Tel: 0131 226 5458

Epilepsy Association of Scotland
48 Govan Road, Glasgow G51 1LJ
Tel: 0141 427 4911

Epilepsy Research Foundation
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info@erf.org.uk www.erf.org.uk

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www.edab.net

European Federation of Neurological Societies
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Fund for Epilepsy
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www.headway.org.uk

Joint Epilepsy Council
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Little Foundation
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Fax: 020 7405 5365

Migraine Trust
45 Great Ormond Street, London WC1N 3HZ
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www.migrainetrust.org

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www.mndassociation.org

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www.mssociety..org.uk

National Meningitis Trust
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Tel: 01453 751 738

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
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Tourette Syndrome (UK) Assocation
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Fax: 01892 663649

Myasthenia Gravis Association
Keynes House Chester Park Alfreton Road Derby DE21 4AS
Tel: 01332 290219
Fax: 01332 293641

Prescribing information

Lamictal (lamotrigine)

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

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

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

Contra-indications: Hypersensitivity to lamotrigine.

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

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

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

Legal category: POM.

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

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

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

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

References:
1. Holdich T *et al.* Epilepsia 1991; **32** (Suppl. 1): 96.
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8. Steiner TJ *et al.* Epilepsia 1999; **40** (5): 601-607.
9. Crawford P *et al.* Seizure 1999; **8**: 201-217.

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