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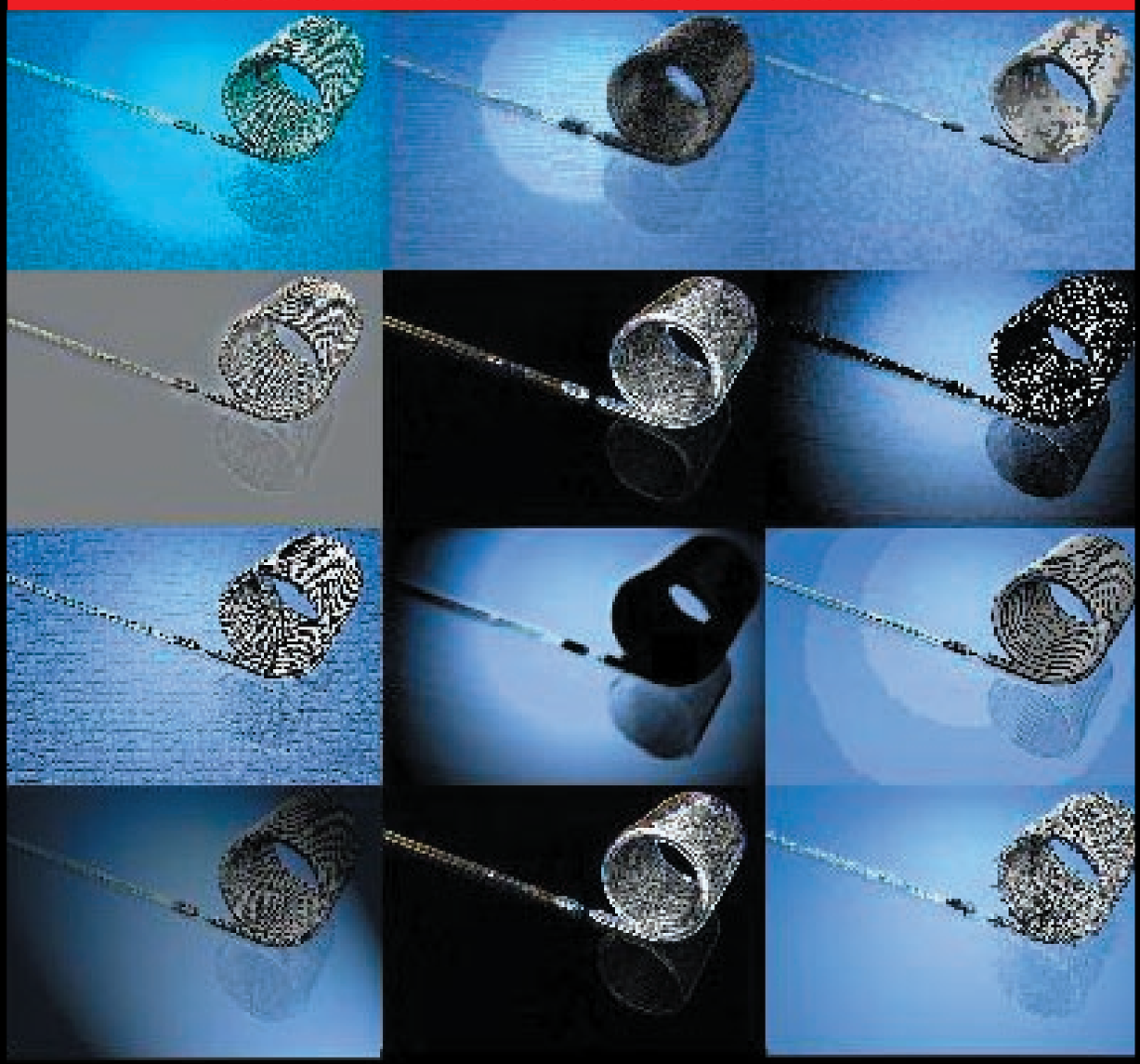
ACNR

Advances in Clinical Neuroscience & Rehabilitation



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

Review Articles: New advances in the management of late stage Parkinson's Disease
Cognition in Huntington's Disease

Rehabilitation Article: Developments in the rehabilitation of unilateral neglect

Management Topic: Social effects of epilepsy

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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

september/october 2001

This fourth issue of ACNR continues to bring new members to the team whilst maintaining the excellent high quality of articles that has characterised the first three issues. We are delighted to welcome Dr David Burn on board as the conference news editor along with our new book editor, Dr Andrew Larner. We hope that in future issues these items will gain greater prominence.

In this issue we have an excellent review article by Professor Andrew Lees on the management of advanced Parkinson's Disease (PD). These patients present a very taxing clinical problem and its is often difficult to know what is the best approach given the range of options that are available and championed by their various proponents. However Professor Lees gives a beautifully clear and sensible account on the approach to such patients, highlighting the relative merits and indications for both medical and surgical approaches. This article comes at an opportune time, given the recent announcement (July 27th 2001) by the Medical Research Council and Parkinson's Disease Society to support a multi-centre study on surgery in Parkinson's Disease, organised and co-ordinated by Professor Adrian Williams. The second review article by Niall Pender discusses another disabling neurodegenerative disorder, Huntington's Disease and explores behavioural and cognitive aspects of this disorder and how best to manage it. This article discusses issues that continue to challenge even the most experienced of clinicians, especially given the complexity of the situation that exists with these patients and their families and spouses.

We continue with our regular features on epilepsy by Mark Manford and anatomy with Alasdair Coles. Finally this month's rehabilitation article concentrates on patients with unilateral neglect, a highly topical issue as our review of the latest issues of the neuroscience and rehabilitation journals shows (see the "Editors Choice"!).

So that's about it. Obviously we are always keen to know what we can do to improve the magazine and what topics we should be including.... so if you have any thoughts or ideas then do let us know.

Roger Barker
Editor
AdvancesinCNR@aol.com

Features

Regulars

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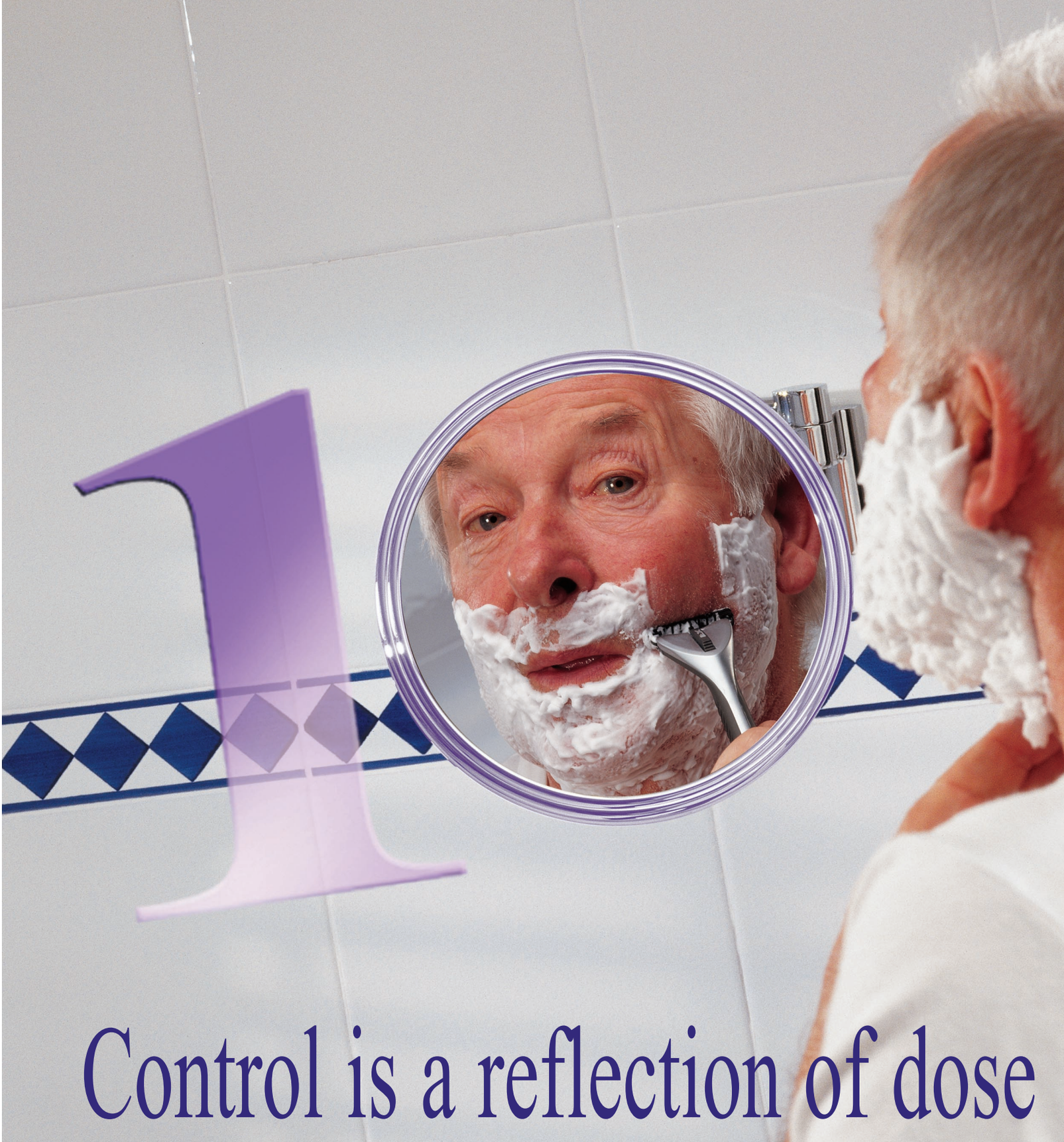

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Editorial Board and regular contributors

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

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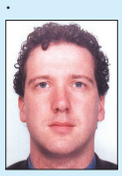

Niall Pender is a new recruit to the editorial board. He is a Neuropsychologist and Clinical Leader of the Neuro-behavioural Rehabilitation Unit at the Royal Hospital for Neuro-disability, London. He is also Neuropsychologist to the Huntington's Disease Unit at the Royal Hospital. In addition he is an 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 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.

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

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New advances in the management of late stage Parkinson's Disease

The mean duration of disease at death of pathologically confirmed cases of Parkinson's Disease is around 17 years, with a mortality ratio of around 2:1. In the earliest phase of the malady, symptomatic treatment may not be needed but within five years of diagnosis virtually all patients will be receiving a combination of anti-Parkinsonian medication including L-dopa.

This is the easiest period of medical management and after the initial confirmation of diagnosis by a movement disorder hospital specialist many people can be effectively cared for and treated by their general practitioner. After ten years of disease, however, most patients are running into difficulties either as a result of increasing gait, balance, speech and mobility problems, neuropsychiatric symptoms including visual hallucinations, confusion, psychosis and dementia or the emergence of the long-term L-dopa syndrome with unpredictable and disabling motor fluctuations and dyskinesias.

Management of these late phase disabilities are a major therapeutic challenge and unfortunately the newer adjuvant drugs including the latest commercially available dopamine agonists, COMT inhibitors and selective MAOIs have had a relatively modest impact on improving overall quality of life.

Author

Professor Andrew Lees holds a personal chair in neurology at University College London. He is director of the Reta Lila Weston Institute of Neurological Studies, UCL and also directs the Brain Research Centre, Institute of Neurology, Queen Square, London. Professor Lees is co-editor of Movement Disorders Journal and President of the European Section of the Movement Disorder Society.

Management of Refractory Off periods and Dyskinesias

(a) Amantidine

It is remarkable that the anti-dyskinetic effects of amantidine were completely missed until basic scientific studies related to the potential therapeutic role of glutamate antagonists led to the demonstration of its anti-dyskinetic potential in L-dopa primed MPTP-lesioned primates. In 1998 its clinical potential was highlighted, and sustained reduction in dyskinesias for up to a year reported. Doses as high as 600mg/day have been recommended but many patients derive benefit at doses of only 300mg a day. The beneficial effects seem to occur without any substantial aggravation of the Parkinsonian syndrome and there is a wealth of literature demonstrating modest anti-Parkinsonian effects at 200mg/day. All patients with disabling dyskinesias should therefore be given a therapeutic trial with amantidine before proceeding to consideration of apomorphine or neurosurgery, although it should be stressed that amantidine should be built up and withdrawn slowly to avoid toxic confusional states.

(b) Subcutaneous apomorphine infusions

Continuous subcutaneous apomorphine infusions markedly improve off period disability when optimum oral therapy has failed and benefit can be maintained for up to 5 years. Despite its undoubted efficacy this therapeutic approach has been relatively slow to gain acceptance by physicians in much the same way as insulin infusions has in Type 1 diabetes. For a successful apomorphine programme, proper facilities for pump training and medical supervision must be in place and there must be a commitment and belief in the concept of continuous dopaminergic stimulation as a pharmacological goal in treating these complications. This effectively limits its use to regional neuroscience centres and funding issues have also led to delays in its application in some regions. Furthermore there are a number of patients who do not warm to the idea of daily injections and a pump, some of who are much keener on exploring neurosurgical avenues. Nevertheless all patients with refractory motor fluctuations and disabling dyskinesias should be enthusiastically offered a trial of subcutaneous continuous apomorphine. The procedure should be fully explained in the out patient clinic and for those who are keen to proceed it is generally advisable to admit the patient to hospital for a 5 day period of instruction and treatment initiation. During the wait to be admitted, adjuvant therapy can start to be reduced. Once admitted and with domperidone cover, a subcutaneous challenge with apomorphine is administered to guide the initial pump starting dose, following which the infusion is started and the dose built up with the aim of minimising off periods. During the in-patient admission the patient and their family need to be familiarised with the technique by the neurologist and skilled nurse practitioner, and the remainder of the adjuvant anti-Parkinsonian medication can be tailed off (Dopamine agonists, COMT inhibitors, amantidine, anti-cholinergics and selegiline). The patient must then be seen at weekly intervals for the first fortnight in out patients and then at slowly increasing time intervals but no less frequently than three monthly when blood should be taken to check for any haemolysis - a very rare complication of this therapy. During the first six months of pump treatment patients must be strongly encouraged to slowly reduce their L-dopa at a rate of about 50mg/day/week until they are only receiving a single nocturnal dose of L-dopa, after the pump is removed for the day and possibly also a kick-start dose while the pump is being set up in the morning. With encouragement about 75% of patients can discontinue all oral anti-Parkinsonian medication while the pump is running. This strategy results in immediate marked reduction in off periods (3-4 hours a day on average or 60% reduction in total off time) and over the ensuing months a marked and sustained diminution in dyskinesia duration and severity. Subcutaneous abdominal wall panniculitis with itchy nodules which may scab and ulcerate are the commonest complication. These seem to be in part idiosyncratic and can be helped by aseptic technique of needle insertion, abdominal wall ultrasound, and silicone gel patches. When severe they may lead to erratic absorption of apomorphine and a return of off period disability and dyskinesias. In addition some patients become unacceptably drowsy on treatment and a few develop a dopamine dysregulation syndrome with behavioural disorders and neuropsychiatric complications. However generally the treatment is well tolerated and the beneficial effects continue for over five years. These results cannot be reproduced by oral dopamine agonist monotherapy as the clinical potency of the available medications is less than both L-dopa and apomorphine.

(c) Functional neurosurgery

New insights into basal ganglia circuitry scientifically underpinned the resurgence of interest in ventrolateral pallidotomy. A decade later the value of this procedure in the long-term appears somewhat clearer in that it appears to be an extremely effective procedure for abolishing contralateral L-dopa induced dyskinesias and rest tremor. However, its long-term beneficial effects on bradykinesia are uncertain. Furthermore there is a significant morbidity, even in the most proficient hands, with some fatalities. Speech problems and neuropsychological sequelae are the commonest unwanted effects and balance and posture are not improved. Most functional neurosurgeons now seemed to have abandoned lesioning, including subthalomotomy which showed considerable early promise, in favour of bilateral deep brain stimulation. Although expensive and labour intensive (because of the

need for frequent post-operative adjustments of the stimulation frequency), extremely impressive results with up to 2 years follow-up have been reported with subthalamic and pallidal stimulation. At least half the patients who have received subthalamic stimulation are able to withdraw anti-Parkinsonian medication completely and the rest markedly reduce it. Tremor, rigidity and bradykinesia are all helped and the marked reduction of L-dopa abolishes dyskinesias. Marked improvements in alertness and drive are reported but a few patients have experienced unwanted neuropsychiatric complications such as suicidal depression, and incontinent laughter or crying. It is unclear whether postural instability can be helped in the long-term. Fewer pallidal procedures have so far been reported but comparable results can be seen.

Management of Neuropsychiatric Complications

Visual hallucinations occur in at least 40% of patients and increasing age, duration of disease, and deteriorating cognition and vision are predisposing factors although some patients develop them early in the course of the illness in the absence of dementia. Anticholinergics and dopaminergic agents may cause, or aggravate, them but there is increasing evidence to suggest that the pathological substrate of Parkinson's Disease is primarily responsible. Daytime somnolence may be another marker for visual hallucinations and a REM sleep behaviour disorder akin to narcolepsy has been also suggested as a pathophysiological component. In many instances the visual hallucinations are minor, non-frightening and are evaluated by the patient as being fictitious. However, the presence of shadey strangers, beasts and insects and Capgras phenomena may cause great distress and require therapy.

Dopaminometic psychoses resembling those seen in amphetamine and cocaine addicts can occur with paranoid delusions and hypomania and a few patients develop dopamine dysregulation syndromes with excessive and destructive overuse of medication leading to hyperlibidinous behaviour, compulsive gambling, hoarding behaviour and errors of judgement. Toxic confusional states are also common and intercurrent causes such as infections, metabolic disturbances, drug interactions or falls with subdural haematomata need to be excluded.

Psychotic behaviour and dysregulation may be helped by dopamine blocking drugs. Most of these unfortunately aggravate motor disability and may induce severe akinetic crises which may take many weeks to reverse even after discontinuation of the offending neuroleptic. Clozapine is an exception but the need for regular white cell monitoring limits its routine practicability. However, quetiapine another novel neuroleptic in doses from 25-400mg/day holds out promise as a second selective anti-psychotic agent. Like clozapine it has marked effects on 5HT2A receptors. Occasionally unilateral electroshock therapy can be useful for confusional states especially on a background of severe drug refractory major depressive episodes. There is also now great interest in the use of the central cholinesterase inhibitors, donepezil, rivastigmine and galantamine to help confusion, visual hallucinations and attention in Parkinsons disease with dementia. Many of these patients have severe central cholinergic deficits and cerebral Lewy bodies.

Management of Freezing, Falls, Speech and Swallowing difficulties

These symptoms which become increasingly common and disabling as the disease progresses often defy all available medical and surgical approaches. However intensive physical, speech and swallowing therapy programmes conducted by skilled and specialised therapists can be of great help. Gastrostomies are still probably underused and silent aspiration, a common cause of death in Parkinson's Disease underdiagnosed.

Management of Disabling L-Dopa Provoked Peak Dose Dyskinesias

- Reduce L-dopa dose to minimum required to control mobility
- Partially replace L-dopa with a dopamine agonist
- Add amantidine
- Trial of continuous waking day subcutaneous apomorphine therapy
- Consider functional neurosurgery

Management of off period Dystonia

- Introduce a dopamine agonist (at night if early morning disability main problem)
- Trials of baclofen and lithium
- Consideration of botulinus toxin therapy
- Apomorphine pump
- Functional neurosurgery

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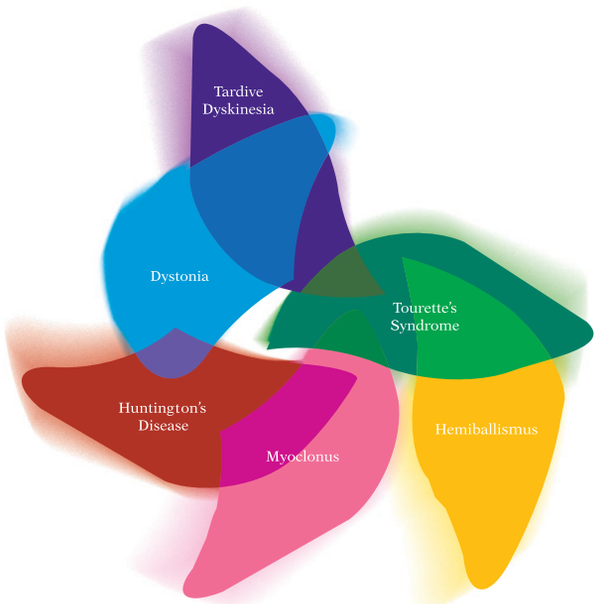

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XENAZINE™ 25 ABBREVIATED PRESCRIBING INFORMATION: Please refer to Summary of Product Characteristics before prescribing Xenazine™ 25. Each tablet contains 25mg tetrabenazine. **USES**: Movement disorders associated with organic central nervous system conditions, e.g. Huntington's chorea, hemiballismus, and senile chorea. Moderate to severe tardive dyskinesia, which is disabling and/or socially embarrassing, and persistent despite withdrawal, switching or reduction of the dose of antipsychotic medication, or where withdrawal of the medication is not a realistic option. **DOSAGE**: Organic Movement disorders: Dosage and administration are variable and only a guide is given. An initial starting dose of 25mg three times a day is recommended. This can be increased by 25mg a day every three or four days until 200mg a day is being given or the limit of tolerance, as dictated by unwanted effects, is reached, whichever is the lower dose. If there is no improvement at the maximum dose in seven days, it is unlikely that Xenazine™ 25 will be of benefit to the patient. Tardive Dyskinesia: An initial starting dose of 12.5mg a day is recommended, subsequently titrated to response. Again medication should be discontinued if there is no clear benefit or side effects cannot be tolerated. Children & Elderly: No specific dosage recommendations are made for the administration of Xenazine™ 25 to children or the elderly. **CONTRAINDICATIONS, WARNINGS, ETC.** Contra-indications: Xenazine™ 25 blocks the action of reserpine. Precautions: Xenazine™ 25 may cause drowsiness and could interfere with activities requiring mental alertness. Patients should be advised not to drive or operate machinery until their individual susceptibility is known. For use in tardive dyskinesia the condition should be persistent despite withdrawal, reduction in dose or alteration of antipsychotic medication, or where withdrawal of the medication is not a realistic option. Pregnancy and Lactation: There is inadequate evidence of safety of the drug in human pregnancy and no evidence from animal work. Xenazine™ 25 should be avoided in breast-feeding mothers. Interactions: Levodopa should be administered with caution in the presence of Xenazine™ 25. **Side effects:** Side effects are usually mild with little hypotensive action and few digestive disorders. The main unwanted effect reported to date has been drowsiness, which occurs with higher doses. If depression occurs, it can be controlled by reducing the dose or by giving antidepressant treatments. Xenazine™ 25 should not be given immediately after a course of any of the monoamine oxidase inhibitors as such treatment may lead to a state of restlessness, disorientation and confusion. A parkinsonian-like syndrome has been reported on rare occasions, usually in doses above 200mg per day, but this disappears on reducing the dose. Neuroleptic malignant syndrome (NMS) has been reported rarely. This may occur soon after initiation of therapy, following an increase in dosage or after prolonged treatment. The clinical features usually include hyperthermia and severe extrapyramidal symptoms. Skeletal muscle damage may occur. If NMS is suspected Xenazine™ 25 should be withdrawn and appropriate supportive therapy instituted, treatment with dantrolene and bromocriptine may be effective. **Overdosage**: Signs and symptoms of overdosage may include drowsiness, sweating, hypotension and hypothermia. Treatment is symptomatic. **PHARMACEUTICAL PRECAUTIONS**: Store below 30ºC **LEGAL CATEGORY POM PRESENTATION, PACK SIZE, PRODUCT LICENCE NUMBER & BASIC NHS COST:** Round yellowish buff tablets, printed with CL25 containing 25mg of tetrabenazine in packs of 112. PL 14576/0005 £100.00 **FURTHER INFORMATION IS AVAILABLE FROM THE PRODUCT LICENCE HOLDER**: Lifehealth Limited, 23 Winkfield Rd, Windsor, Berkshire, SL4 4BA. Date of preparation: July 2000. © Cambridge Laboratories.

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Cognition in Huntington's Disease

Introduction

Huntington's Disease (HD) is a rare, complex and challenging condition to manage. It occurs at a rate of 5-10 per 100, 000 but this rate varies within and between countries. It is estimated that there are approximately 5000 people with the condition in the UK. The core genetic anomaly in HD is the expansion of the trinucleotide repeat CAG[1] .

The central triad of deficits in HD has changed little since Huntington's description (see Table 1) but the nature, speed and specificity of presentation of these symptoms is variable and inconsistent. The inconsistency of cognitive impairments remains problematic.

Author

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Frequent symptoms of HD

There are many clear descriptions of the neurobiology and genetics of HD[2]. The principal structures involved include the substantia nigra, internal and external portions of the globus pallidus, sub-thalamic nucleus, amygdala, thalamus and hypothalamus. Extensive cortical damage has also been noted. Studies using procedures such as Proton Magnetic Resonance Spectroscopy (pMRS) have found increased lactate levels and decreased N-Acetyl Aspartate (NAA) in the frontal and occipital lobes[3]. Moreover, PET studies have shown reduced glucose and oxygen metabolism in the basal ganglia and cortex in HD before structural scanning changes or clinical signs become apparent.

It is clear that HD produces damage that, although markedly apparent in the basal ganglia, can be widespread and may involve many cortical regions particularly as the disease progresses. This has considerable impact on the nature and presentation of cognitive impairments. However, it is only recently that detailed descriptions of cognitive dysfunction are emerging.

Cognitive impairments in HD

With the advent and increasing use of diagnostic technology for HD there has been a growth in studies of cognitive functioning. We are still far from being clear about the nature of such impairments in HD and this is particularly important given the need to evaluate outcome following treatment trials for HD[4,5].

Early cognitive impairments

In the early stages of the condition patients with HD are consistently impaired on general intellectual and cognitive measures relative to other neurodegenerative groups such as multiple sclerosis, Parkinson's Disease and AIDS dementia[6]. Several tests have been noted to successfully discriminate HD from healthy participants (See Table 2).

Table 1. Frequent symptoms of HD

Neurological/Psychiatric	Cognitive
Chorea	Executive dysfunction
Athetosis	Episodic memory impairments
Paranoia	Relatively better recognition
Self-neglect	Flat temporal gradient in autobiographical memory
30% experience major depressive episode	Impairments in emotional perception
Higher than base rate suicide	Impairments with focused, sustained and divided attention
Personality changes	
Dysarthria	

Executive functions in HD

Recently there has been increased interest in the executive deficits experienced by patients with HD. This not only results from the earlier application of more sophisticated diagnostic testing but also reflects the improved resolution of current neuroimaging techniques. Lesions are seen to extend beyond the territory of the basal ganglia and encompass the frontal lobes. Moreover, the nature of the reciprocal connections between the basal ganglia and the oculomotor region, dorsolateral prefrontal cortex and lateral orbitofrontal area would suggest that an exploration of executive deficits in HD would be prudent. This is supported by behavioural evidence and clinical reports of patients at various stages of the disease.

HD patients appear to be impaired on tests of planning, organising, initiating, executing and sustaining behaviour[7]. Impairments of verbal fluency and behavioural features of perseveration have also been reported.

Marked perseveration can be observed and HD patients are impaired at learning new stimulus-response associations relative to healthy subjects and more importantly patients with Dementia of the Alzheimer Type (DAT)[8]. Double dissociations within the class of executive functions have also been noted between HD and DAT patients[9].

HD patients are particularly impaired on tests of planning and this translates directly into their daily functioning where they often appear to lead chaotic and disorganised lives. HD patients are impaired, in particular at shifting set, again an obvious feature of the condition where patients become fixed on particular ideas and issues.

Attentional function in HD

In terms of attentional functioning, alertness, divided attention and response flexibility are markedly impaired in patients with HD patients[10]. These fundamental impairments are exacerbated by their extensive executive impairments and contribute to significant difficulties in activities of daily living and occupation.

Emotional Perception in HD

Few studies have addressed perceptual skills directly. By far the most frequent are the intriguing studies of emotional and facial perception in this group.

HD patients have been shown to be impaired at recognising facial and vocal expressions of emotion, especially fear and disgust[11]. Furthermore, patients are impaired at comprehending emotional prosody in speech, matching facial affect, facial recog-

Table 2. Cognitive abilities discriminating HD patients from healthy controls

Cognitive ability
Mental arithmetic
Spatial perception
Auditory verbal short-term memory
Social knowledge
Verbal and visual long-term memory
Verbal fluency
Response inhibition

nition and discriminating faces[12]. These impairments have direct relationships to patients' ability to cope in their daily lives and interpret and use facial expression accurately.

Memory functioning

There has been a great deal of debate concerning the nature of the memory impairment in HD and the pattern of impaired and preserved skills in this patient group.

However, some clear details have consistently been reported. Global memory deficits are common in HD[13]. Implicit motor tasks are more impaired than lexical tasks[14]. It has been suggested that recognition memory is preferentially preserved until later stages and therefore a retrieval deficit is favoured by many authors[7]. However, some controversy remains as to whether the principal deficit is in fact an executive dysfunction mediating a retrieval or even an encoding deficit.

Interestingly a flat temporal gradient is seen in retrograde memory functions with equal impairments observed across decades. Cueing, in particular phonemic cues, seem to improve performance for recently diagnosed patients but not for the later stage patients.

Longitudinal changes in cognition

Long-term evaluations of patients with HD are currently underway and in the most recent and best-conducted studies there appear to be some particular consistencies among the data.

In a recent three-year follow-up study of HD patients[15] significant impairments were noted at the end of the first year on executive and memory tasks, particularly verbal fluency, the Stroop test and object recall. At the final follow-up, a similar pattern of scores was obtained. Speed based tasks and memory changed significantly over time. The authors suggested that the observed impairments in memory relate to a primary deficit in executive functioning which impacts on encoding and retrieval.

A further recent study[16] reported that performance on tests of attention, executive functioning, language comprehension and visual-spatial memory deteriorated over a four-year period. Early episodic memory impairments remained stable over the course of the study.

Thus studies of cognitive functioning in HD report decline on a range of measures over the course of the condition. More recent longitudinal studies appear to be finding consistent changes in executive functioning and a less dramatic deterioration in memory functioning over time. However, there still appears to be marked variability in the experimental designs with different studies employing different measures of cognitive functioning. More importantly, many studies use insufficient patient numbers to achieve adequate power.

Summary

HD is a complex and challenging condition. The care of such patients generally requires the expertise of multi-disciplinary teams. Complicating this picture is the patient's fluctuating yet deteriorating level of cognition, which subsequently leads to a reduction of the patient's mental capacity. Clear and obvious deficits in executive functioning and memory are noted early in the course of the disease but impairments in other areas of ability are apparent as the disease progresses. Such deficits compound the existing impairments in motor functioning, communication, nutrition and psychiatry and can exacerbate any behavioural difficulties. A detailed neuropsychological assessment in the context of an MDT evaluation can provide much useful information for the care of such patients.

Acknowledgement

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Social effects of epilepsy

Mark Manford

Introduction

Epilepsy creates some real risks for patients that need to be anticipated and some imagined risks, for which the clinician must try to allay the fears of patients and relatives. Many social spheres need to be addressed, including, education, work, hobbies, relationships, sexuality, marriage, parenting and driving. Stigmatization may spread beyond the patient to other family members, employers and schools.

Social effects of epilepsy

Predictors of psychosocial underfunctioning

- Biological aspects of the epilepsy partly determine the quality of life measures in some but not all studies.
- Social aspects, especially supportive family dynamics are important in enabling patients to cope with their epilepsy (table 1). Some patients with severe epilepsy lead remarkably normal lives, whilst others with relatively mild epilepsy may become over-protected and socially isolated.

Education

- School failure may affect one third of intellectually normal children with epilepsy, and one third may require special educational support.
- Education may be impaired by organic factors, by the social consequences of the epilepsy or by the attitudes of teachers.
- Psychiatric support may be needed by nearly a quarter during the education years.

Employment

- The number of patients who are unemployed or on permanent sick pay in the UK (table 2) correlates with epilepsy severity but differs substantially between countries and cultures. Reduced educational achievement contributes to unemployment.

Leisure activities

- Individuals with epilepsy are less likely to pursue leisure activities than the unaffected population. Reasons include low self-esteem and fear of seizures in company. Epilepsy sufferers are less physically fit than the rest of the population.

Stigma of epilepsy

- Cross-cultural differences are marked. Around 30% of patients feel stigmatized in Spain or Poland and 52% in the UK.
- Factors associated with stigma include worry, negative feelings, long-term health problems, injuries and adverse effects of AED.
- Prejudice against epilepsy also varies greatly. In China 57% of parents object to their children playing with a child with epilepsy, compared with 7% in Denmark.

Marriage and fertility

- Marriage rates are inversely correlated and divorce rates are positively correlated with epilepsy severity in the UK.
- Fertility is 60-80% of normal in women with epilepsy and is also reduced in men with epilepsy. Reasons include reduced marriage rates, reduced sexual arousal or satisfaction, altered gonadal function, effects of AED and fear of the effects of epilepsy on the ability to care for children.

Epilepsy and driving

- The responsibility of reporting the onset of epilepsy to the driving authorities (DVLA in the UK) rests with the patient in the UK. However, if a clinician knows that a patient is putting others at risk by continuing to drive, their duty to the community usually takes precedence over their duty of confidentiality.
- UK regulations are summarised in table 3. These are regularly updated and are available from DVLA http://www.dvla.gov.uk/drivers/drivers.htm
- Group 2 licences (heavy goods or passenger-carrying vehicles) generally require the patient to be free of attacks for at least ten years without medication.
- The aetiology of the seizures may modify the ruling. Malignant tumours carry more stringent regulations.
- All seizures are the same to the DVLA, no matter how mild.
- Insurance companies should be informed as well as the DVLA.

Situations of risk - advice to patients and carers

Each seizure carries a small risk. A balance needs to be struck between alarmist over-protection and sensible precautions. This will depend on the frequency of seizures, whether they are nocturnal or diurnal and whether there is an aura, which allows the patient to take evasive action.

Reducing the risk from seizures

In the kitchen

1. Cooker guards reduce the risk of falling onto a cooker.

Table 1: Some factors in determining social outcome in epilepsy

Factor	Effect
Learning disability	Affects employment and reduces the chance of having a partner in adult life
Seizure-frequency	Correlates inversely with QOL measures*, physical and social functioning and positively with perceived stigmatization
Multiple seizure types	More than one seizure type is associated with worse QOL measures*, worse physical and social functioning and perceived stigmatization
Young onset and long duration of epilepsy	These are generally correlated with poorer social development, higher unemployment and less chance of marriage.
Cultural background	Patients from different backgrounds may suffer different levels of under-functioning. Europeans may fare best.
Family support	Good family support confers a higher chance of successful psychosocial outcome and improves self-esteem
Coping strategies	Favourable, active coping strategies are correlated with lower perceived epilepsy severity ad less psychological complaints than more passive approaches.

*QOL (quality of life) measures include family relationships, friendships, employment, feelings about self, plans and ambitions, standard of living, mental health, energy/vitality and pain

2. Microwave cooking is much safer.
3 Hot water taps can have temperature control devices.
4. Electric tea- or coffee makers are safer than kettles.

In the bathroom
1. Showering is safer than bathing.
2. If there is only a bath, only fill to 3-5cm depth.
3. Only wash when someone else is in the house.
4. Don't lock the door when washing.
5. It is better if the door of the bathroom opens outwards so can be opened easily from outside.

In the bedroom
1. Sleep with a firm pillow to avoid suffocation.
2. Sleep on a mattress on the floor if seizures are very violent.

Elsewhere
1. Avoid sharp furniture.
2. Avoid glass or other dangerous ornaments.
3. Avoid unguarded fires or heating appliances.
4. Use reinforced glass for windows and door panels.

Sports
- Some sports pose unacceptable risks such as motor sports or aerial sports and many are completely safe
- Some sports are intermediate. For example individuals with epilepsy should not swim alone and probably should not swim in open waters where first aid is more difficult.
- Someone in a position of responsibility, such as a lifeguard, should be made aware of the problem.
- Many sports have regulatory authorities that can give advice.

Social activities
- There is no reason why patients with epilepsy should not engage fully in social activities.
- Sleep deprivation and alcohol withdrawal may trigger seizures in susceptible individuals. It is reasonable to advise patients to avoid binge drinking.
- Photosensitivity affects only about 3% of patients with epilepsy and can be excluded by an EEG with photic stimulation.

Employment
- Few jobs are closed to epilepsy sufferers. Examples involve flying, driving or working at heights or close to dangerous machinery. An employer in the UK has a duty to try and accommodate an employee with a disability, where possible.

Table 2. Unemployment among patients with epilepsy

Seizure severity	Percentage unemployment
Seizure-free	19%
<1 seizure per month	35%
>1 seizure per month	52%

- Fear of seizures may make some jobs particularly stressful, for example where the individual is on show as a musician.
- Misunderstanding of epilepsy in the workplace may be helped by education of colleagues.

Travel
- There is no restriction on travel for patients with epilepsy but it is advisable that they are accompanied.
- Medication should be to hand at all times, a back-up set may be needed. Check whether medication is available at the destination, especially if travelling for a long period.
- A doctor's letter may help clarify the problems for clinicians abroad.
- Long-haul flights and jet lag may cause sleep deprivation and trigger seizures. A benzodiazepine may ensure good sleep and act as an AED for the journey but should first be tried at home on a "dummy run" to make sure there are no untoward effects.

Table 4. Useful organisations

National Society for Epilepsy, Chalfont St Peter, Gerrards Cross, Bucks, SL9 ORJ A source of information for patients, relatives, health care professionals and other interested parties. UK Epilepsy Helpline tel 01494 601 400.
http://www.epilepsynse.org.uk/
British Epilepsy Association. A source of information for patients, relatives, health care professionals and other interested parties. Freephone UK Helpline on 0808 800 5050
http://www.epilepsy.org.uk/index.html
American Epilepsy Society. Mostly a source of information for clinicians
http://www.aesnet.org/
Epilepsy bereaved? PO Box 1777, Bournemouth BH5 1YR Patient support group for relatives of those bereaved through epilepsy
http://www.bodley.ox.ac.uk/external/epilepsy/

Table 3. Summary of DVLA guidelines for epilepsy

Situation	Regulation for an ordinary driving licence
Newly diagnosed epilepsy	Driving ban until one year after seizures have ceased
Recurrent blackouts of uncertain cause	Driving ban until one year after blackouts have ceased
Single blackout of uncertain cause with epileptic features eg. tongue-biting.	Driving ban for one year
Blackout of uncertain cause with no epileptic features	Driving ban for 6 months
Single provoked seizure or bout of status epilepticus	Driving ban is discretionary, sometimes until 6 months after the seizure providing the cause has been removed unless alcohol or illicit drugs were implicated.
Single provoked seizure related to alcohol or illicit drugs	Driving ban until one year after seizures have ceased. A medical report and urine toxicology may be required to confirm current drug status before a licence is issued
Recurring seizures whilst awake	Driving ban until one year after seizures have ceased
Recurring seizures whilst asleep	Even if seizures continue to occur, a patient may resume driving where it has been established for at least three years that they only occur in sleep
Withdrawal of all medication in a seizure-free patient	The clinician should advise the patient not to drive until 6 months after completion of drug withdrawal

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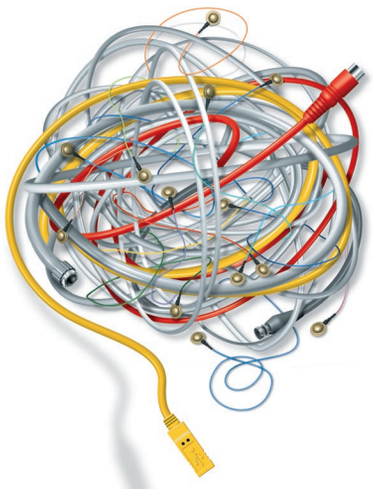

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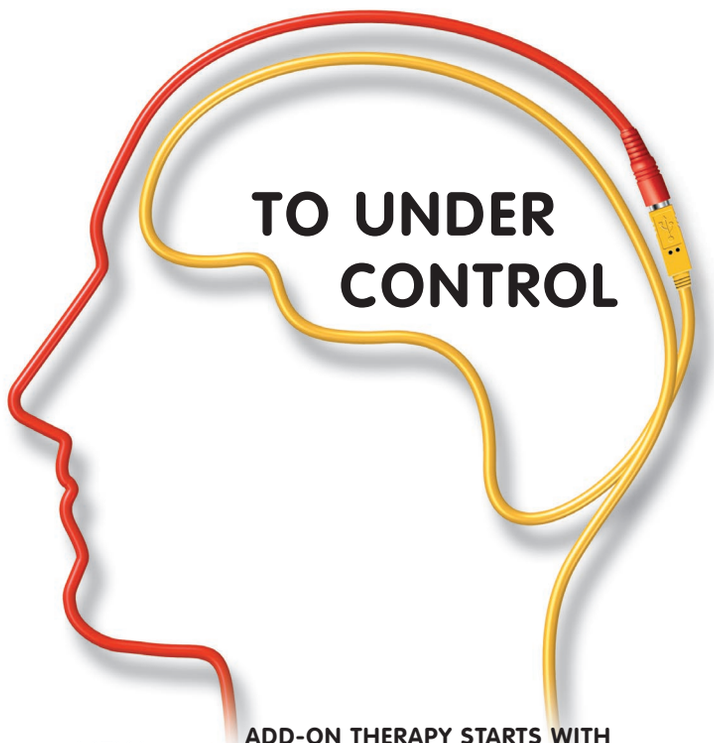

- Highly effective: up to 4 out of 10 refractory patients had ≥50% partial seizure reduction[1,2,3]
- Excellent tolerability, discontinuation rates not significantly different from placebo[4,5]
- No known drug/drug interactions[6]
- Therapeutic starting dose (500mg bd)

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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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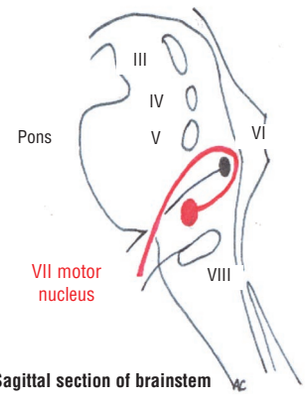
SIMPLIFYING SEIZURE CONTROL

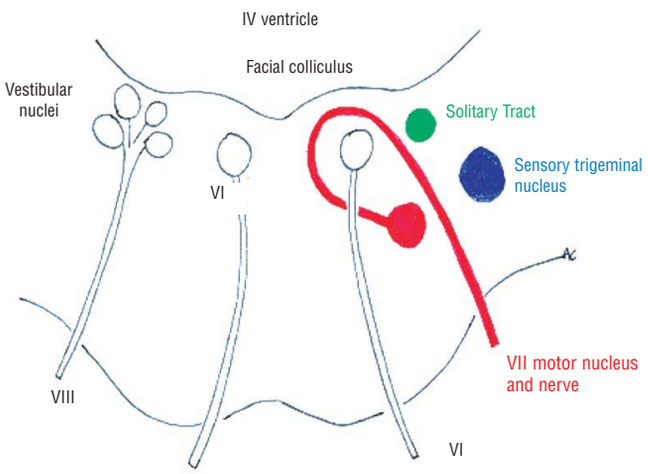
The Seventh Cranial Nerve

Alasdair Coles

The Basics. The facial nerve consists of two "roots", the motor root and the intermediate nerve (that is sometimes called the sensory root, a poor name as it contains motor fibres as well as sensory). The motor root is easy to understand: it supplies the muscles derived from the second branchial arch, which are mainly the muscles of facial expression. The intermediate nerve is complex and consists of taste fibres, parasympathetic efferents to lacrimal and salivary glands as well as a minor cutaneous sensory branch. The anatomical course of the seventh nerve is characterised by four sharp turns, two of which are described as genu (knee). It emerges at the lower end of the pons, passes through the petrous portion of the temporal bone and exits the styolomastoid foramen to bury its fibres in the parotid gland. The commonest lesion of this nerve is a "Bell's Palsy", an idiopathic condition with a lifetime prevalence of 6/1000.



Sagittal section of brainstem



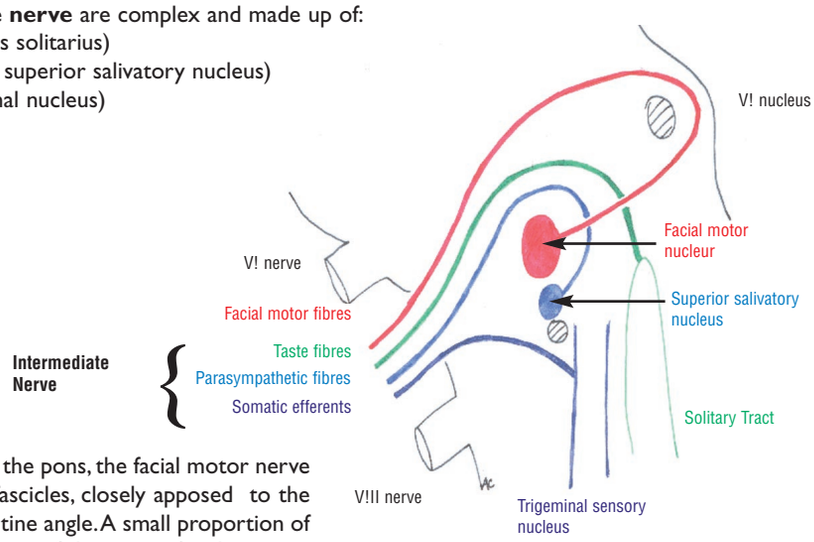
Axial section of lower pons

The fascicle of the motor facial root has two bends in its intrapontine course that take it around the sixth nerve nucleus in both the axial and sagittal planes. This is called the **internal genu** of the facial nerve and its impression on the floor of the fourth ventricle is called the **facial colliculus**. The VIth nerve diverges from the VIIth once they leave the pons and therefore a lesion of the VIth and VIIth nerves, without involvement of the VIIIth nerve, is almost always intrapontine. Likewise a VIIth and VIIIth lesion without a VIth is likely to extra-axial.

The motor nucleus of the facial nerve, situated in the pons, is composed of several subnuclei. The oral muscles are represented by the lateral cell group which receives crossed corticobulbar fibres. However there is bilateral corticobulbar input to the pars intermedia which supplies the frontalis, corrugator supercilii and orbicularis oculi. Hence the classic finding that lower motor neuron facial palsies may be complete, but upper motor neuron palsies always spare the upper part of the face. The facial motor nuclei also receive projections from the superior colliculi, the superior olive and sensory trigeminal tract; these subserve the blink reflexes to light and sound, and the corneal reflex respectively. There is ill-defined input from the globus pallidus, red nucleus, thalamus and mesencephalic reticular formation, that may be responsible both for the preservation of emotional facial expression in the context of an upper motor neuron facial palsy and for the hypomimia of extrapyramidal disease.

Brainstem connections of the intermediate nerve are complex and made up of:

- taste sensation afferents (to the nucleus tractus solitarius)
- preganglionic parasympathetic fibres (from the superior salivatory nucleus)
- somatic afferents from the ear (to the trigeminal nucleus)



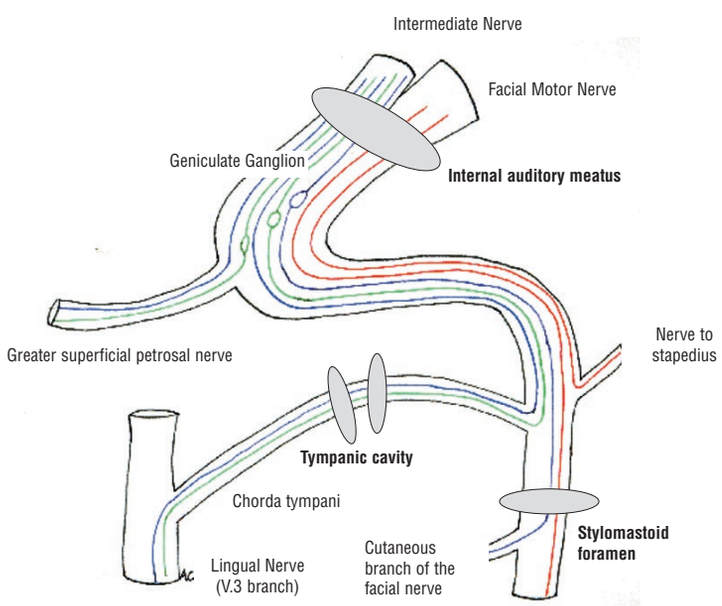
On leaving the brainstem at the caudal end of the pons, the facial motor nerve and intermediate nerve are two separate nerve fascicles, closely apposed to the vestibulocochlear (VIII) nerve, in the cerebellopontine angle. A small proportion of cases of hemifacial spasm may be caused by irritation of the motor facial nerve at this point by an aberrant vascular loop.

At the **internal auditory meatus,** the facial motor nerve lies in a groove on the VIII nerve separated by the smaller intermediate nerve. The facial and intermediate nerves then enter the facial canal which, at the geniculate ganglion, turns sharply in a dorsolateral direction where it soon lies close to the tympanic cavity (separated only by thin bone). This is the second genu of the facial nerve (sometimes called the external genu). One more caudal turn takes it away from middle ear to exit through the stylomastoid foramen. Immediately it gives off branches to supply the stylohyoid, the posterior belly of digastric and platysma. The remaining fibres enter the parotid gland and then fan out to supply the muscles of facial expression (orbicularis oculi and oris, buccinator, zygomaticus, frontalis, occipitalis and so on).

Pertrous temporal VII lesions

The commonest lesion of the VIIth nerve in the petrous temporal bone is a Bell's palsy. Petrous fractures may also affect the nerve facial as may cholesteatomas: Antral cholesteatomas may extend into the facial canal as far as the geniculate ganglion and antro-adito-attical cholesteatomas may involve the chorda tympani. Such lesions may be localised by their different effects on taste, ear sensation, hearing and lacrimation.

Course of the facial nerve in the petrous temporal bone, seen from the side

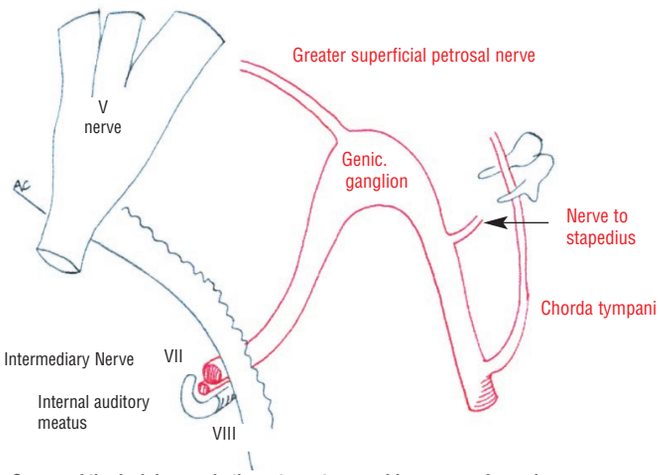


Bell's palsy

A lesion of the facial nerve in the petrous temporal bone of unknown cause.

- Lower motor neuron type facial weakness that progresses over 3-72 hours
- Pain in or behind the ear in half of cases
- Deficits in tearing seen in 33%
- Bell's phenomenon (upwards rotation of the globe in the orbit on eyelid closure)
- Symptom of loss or alteration of taste (rarely demonstrable clinically)
- Hyperacusis (noises sound louder and harsher)

30% of patients will have permanent facial weakness, often with facial contractures. Aberrant regeneration of motor fibres explains the phenomenon of synkinesis (seen in up to 50% patients) where eyelid closure is accompanied by contraction of other facial muscles. A similar process in the parasympathetic fibres causes crocodile tears (5% of cases) when eating (which should produce salivation) causes lacrimation.



Course of the facial nerve in the petrous temporal bone, seen from above

Taste (visceral afferent fibres) from the anterior two thirds of the tongue is subserved by fibres that travel in the lingual nerve (mandibular branch of the trigeminal) and form the chorda tympani. Taste from the soft palate is carried by the greater superficial petrosal nerve. These two nerves join the intermediate nerve in the petrous bone and project to the nucleus of the solitary tract along with taste fibres from the glossopharyngeal nerve (posterior third of the tongue) and vagus (epiglottis). If a facial palsy is accompanied by loss of taste from the anterior two-thirds of the tongue, then the lesion must be between the pons and the branch of the chorda tympani.

The nerve to stapedius (somatic efferent) controls the gain of oscillation of the ossicles. If stapedius is weak, the patient experiences hyperacussis. Occasionally this symptom is present, but taste from the tongue is intact, which can be explained by an anatomical variation of tongue taste fibres travelling in the greater superficial petrosal nerve.

Cutaneous branch of the facial nerve (somatic afferent fibres). Some 15% of the sensory fibres in the intermediate nerve (in the cat) are somatic afferents and supply a variable area of cutaneous sensation in the external auditory meatus and just behind the ear (an area also supplied by the auricular ramus of the Xth and the IXth nerves). These fibres probably originate in the trigeminal sensory nuclei. Their existence was predicted by Ramsay Hunt in 1907 following his observation of vesicles in the ear of a patient with herpes zoster oticus. They explain the ear and retroauricular pain often felt with Bell's palsy and occasionally in facial nerve tumours.

Autonomic functions of the intermediate nerve (parasympathetic preganglionic efferents). Efferents from the superior salivatory nucleus (just below the motor facial nucleus) travel in the intermediate nerve to either:

- the sphenopalatine ganglion via the greater superficial petrosal nerve to innervate the lacrimal glands and the nasal mucosa, or
- The submandibular ganglion (via the chorda tympani and lingual nerve) to the sublingual and submandibular glands).

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Developments in the rehabilitation of unilateral neglect

Unilateral neglect, a deficit in noticing, acting on, or even thinking about information from one part of space is among the most striking and surprisingly frequent consequences of vascular brain damage. Classically linked with lesions to the posterior parietal cortex, neglect has been observed following damage to a wide variety of cortical and subcortical structures, including the frontal cortex, thalamus and brain stem[1]. It can affect visual, auditory and tactile modalities, which, taken together with a dissociation from basic perceptual loss, has led to it being primarily viewed as a disorder of attention. Although transient forms of the condition are seen following damage to either hemisphere, chronic forms are almost always observed following right-sided lesions[2].

Neglect has come under intensive academic scrutiny. To date, however, little from this extensive effort has percolated through into the care or rehabilitation of patients. In the majority of cases, such special efforts may be rather redundant as apparently spontaneous remission of the more salient symptoms may take place within days or weeks. For chronic cases, however, the manifestations of the disorder represent major threats to functional independence and, therefore, important targets for rehabilitation.

Author

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Tom Manly trained in clinical psychology at University College London, including specialist placements at the National Hospital for Neurology and Neurosurgery Rehabilitation Unit. He is a scientist at the Medical Research Council Cognition and Brain Sciences Unit in Cambridge with a particular interest in the rehabilitation of childhood and adult attention disorders.

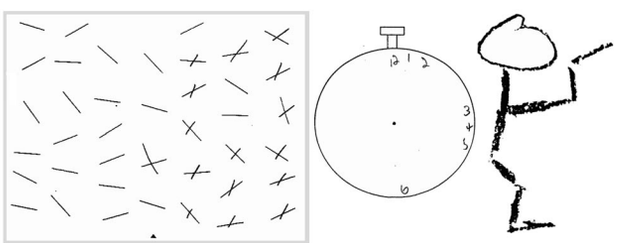

Figure 1: Evidence of neglect on bedside tests: A 56 year old man is asked to cross out all of the lines on the page, to complete a clock and to draw a man.

The most straightforward approach to rehabilitation is to target the key symptoms of the condition. Early attempts at training compensatory leftward visual scanning (e.g. asking patients to first find the left side of a line of text before attempting to read it) indeed reported significant improvements (e.g. [3, 4]). A major drawback was the difficulty in generalising changes from one context to another. At times the specificity was remarkable. Lawson, for example, reported that a nun who had successfully been trained in reading her own Bible reverted to a large number of left-sided word omissions when reading a different edition[5]. Although lack of generalisation does not necessarily preclude a useful rehabilitation effect, it means that training must be highly relevant to a patient's functional goals and ideally conducted in the home setting. This, of course, has resource implications.

Learning any new skill, such as driving or playing an instrument, takes many hours of practice before even modest competence is achieved. More recent evidence suggests that the duration of early scanning training studies may simply have been insufficient to produce generalised changes. Antonucci and colleagues offered patients over 40 hours of training using a progressive programme incorporating a variety of scanning tasks. Improvements that generalised to untrained and naturalistic contexts were reported[6].

There has been considerable debate about why chronic forms of neglect are seen following right rather than left hemisphere lesions. One persuasive argument is that other deficits associated with right hemisphere (RH) damage may in some way form the setting conditions that perpetuate the condition. It is a notable that neglect patients often appear drowsy and have difficulty remaining engaged in any task, regardless of its spatial content. This clinical observation is supported by neuropsychological evidence showing general alertness is disproportionately compromised by RH lesions and, within RH damaged groups, disproportionately associated with unilateral neglect[7]. Most compellingly, non-spatial interventions designed to modulate alertness have significantly reduced or even reversed the spatial biases of the disorder[7]. One slightly paradoxical approach to rehabilitation, therefore, may be to target these non-spatial RH functions. Following this logic, Robertson et al. trained neglect patients in consciously self-maintaining an alert, 'ready-to-respond' state over the course of one week. This led to improvements in the performance of sustained attention tasks and, most importantly, to a reduction in neglect on untrained tasks[8].

A strong theme in contemporary attention theory is that its primary function lies in supporting action. Following an observation that the hand used by a patient to perform a task influenced the degree of neglect[9], Robertson and colleagues systematically investigated this issue. The results are summarised in Figure 2. Although unable to see their movements, when patients moved their left hand within left space significant reductions in neglect were observed. The reduction when either the left hand was moved in right space, or when the right hand was moved in left space were much less striking and simultaneous use of both hands completely abolished any benefit[10, 11]. The results suggest that the interaction of movement of the left hand within left space is sufficient to activate improved attentional representations of left-sided locations. Although clearly not appropriate for densely hemiplegic patients, it is likely that many neglect patients under use their left arm for primarily attentional reasons. Two recent investigations show that 'limb-activa-

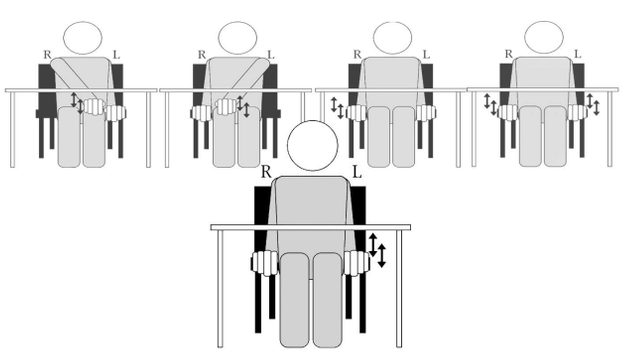

Figure 2: Summary of hand movement conditions examined by Robertson and colleagues. Only the movement of the left hand within left space is reliably associated with reduction in visual neglect.

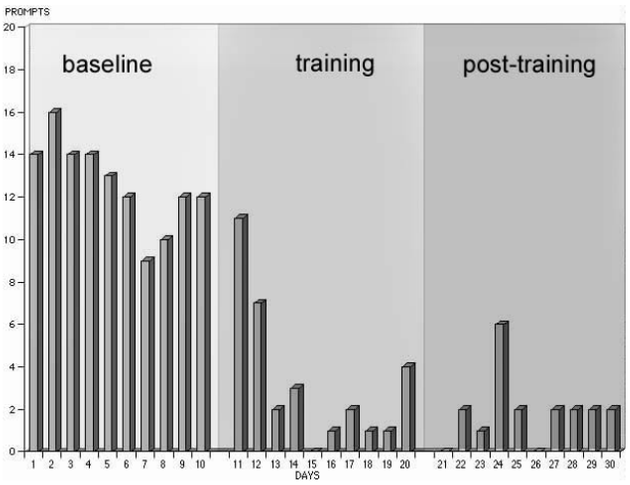

Figure 3: Improvements in everyday activities: Reduction in the prompts needed by a 62 year old neglect patient in completing his morning wash before, during and after training in making left-sided hand movements.

tion' training can produce lasting and generalised benefits including improvements in essential activities of daily living[12,13].

Neglect is not a unitary disorder but a highly fractionated set of syndromes that can result from damage to a widespread network of brain regions. Further work is required in examining which rehabilitation techniques are best suited to particular patients and on the extent to which useful generalisation is observed. The progress made to date, however, has both assisted patients in regaining a degree of functional independence and in further illuminating the nature of these complex disorders.

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XIV International Congress on Parkinson's Disease

28 July-1 August 2001, Helsinki, Finland

Pharmacologic perspectives revisited

The XIV International Congress on Parkinson's Disease provided delegates with a comprehensive overview of new research and clinical developments in Parkinson's disease (PD) and movement disorders, including epidemiology, genetics and advances in surgical intervention. In addition, a series of informative morning seminars and plenary lectures focused on current clinical perspectives in the medical management of PD.

Treatment considerations

Professor Olivier Rascol, University Hospital of Toulouse, France, discussed the management of patients with early PD as part of a series of plenary lectures on the medical treatment of patients with different stages of disability. Treatment considerations include symptomatic efficacy, prevention of motor complications and safety.

While levodopa (L-dopa) therapy is inexpensive and highly effective, he noted, it is becoming less frequently considered as a first line therapy because it primes the parkinsonian brain for poorly reversible long-term motor complications. This propensity to induce motor complications may be due to the abnormal pulsatile dopamine stimulation induced by L-dopa, which is quite different from the theoretically more desirable and smoother endogenous 'dopamine stimulation'. Alternative options to L-dopa are therefore usually considered.

The early use of a dopaminergic agonist, supplemented as a second line therapy by low doses of L-dopa, adequately controls parkinsonian symptoms and reduces the risk of long-term complications. The benefit of the early use of COMT inhibitors remains to be assessed, as well as that of other drugs such as amantadine or anticholinergics.

Are there clinically significant differences between dopamine agonists?

In a morning seminar on Monday July 30, Fabrizio Stocchi, Professor of Neurology at the University of Rome, discussed the issue of whether there are clinically significant differences between dopamine agonists. He outlined the historical development of dopamine agonists in the treatment of PD, dominated initially by pharmacologic strategies centred on their use as add-on therapy to L-dopa, then shifting to dopamine agonist monotherapy prior to L-dopa treatment and now as starting therapy for long-term benefits in treating PD patients.

Professor Stocchi argued that the pharmacokinetic properties of the various dopamine agonists commercially available, in particular their respective elimination half-life, was an important determinant of clinical efficacy.

"Experimental data indicate that L-dopa and short-half-life dopamine agonists are more likely to induce dyskinesias than long-acting dopamine agonists such as cabergoline, ropinirole, pramipexole and pergolide," explained Professor Stocchi. "Long-half-life dopamine agonists appear safer in terms of rescuing patients from developing dyskinesias and fluctuations. Pulsatile stimulation also is more likely to induce dyskinesia."

He noted that poor response to one dopamine agonist does not necessarily predict continuing failure to respond to another dopamine agonist. "Switching to another dopamine agonist should be considered in cases of initial treatment failure on first-choice dopamine agonist therapy," Professor Stocchi advised. "Also, clinical experience in combining dopamine agonist therapies is encouraging. Physicians are encouraged to pay attention to the elimination half-life of the various agents available and to use the best possible dose - too low a dose will disappoint."

"Dopamine agonists are the preferred initial treatment choice in all de novo PD patients," continued Professor Stocchi. "There is also emerging evidence that in fluctuators, you can actually deprime these patients using long-acting dopamine agonists to achieve sustained dopaminergic stimulation."

Evaluating sleep disorders

Addressing a morning seminar on Tuesday July 31, Jan Petter Larsen, from Central Hospital of Rogaland, Stavanger, Norway, discussed sleep disorders in Parkinson's disease, a common non-motor problem accompanying the motor manifestations of parkinsonism.

Excessive daytime sleepiness (EDS) is common in PD while sleep attacks seem be rare manifestations of the disease or its treatment. Significant EDS is found in approximately 15% of PD patients, compared to 1% among healthy elderly populations. While sleep attacks are observed in patients treated with all dopaminergic medications, epidemiological evidence indicates that the disease process of PD causes somnolence observed among these patients.

An interesting poster presentation by Bliwise et al outlined results of an observational study evaluating PD patients reporting excessive daytime sleepiness while being treated with dopaminergic agents. Twenty-two PD patients using the dopaminergic agents pergolide, pramipexole or ropinirole alone or combined with L-dopa and with a Significant Other Epworth Sleepiness Scale (SOESS) score $\geq$10 were enrolled.

Results demonstrated a high prevalence of pathological sleepiness among PD patients whose significant others report sleepiness by means of the SOESS. In this study cohort, unintended sleep episodes (USE) were observed with a variety of dopamine agents. Importantly, patients who experienced USE have a background of EDS similar to no-USE patients, and both groups were sleepier than the general population. Study authors concluded that the occurrence of 'sleep attack' or USE typically occurs on a background of severe daytime sleepiness.

Rod McNeil, Medical Journalist

Scientific and Clinical Basis for the use of Dopamine Agonists in the Treatment of Parkinson's Disease

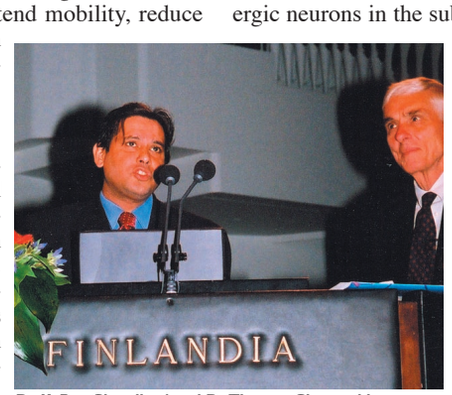
Current clinical and research issues regarding the use of dopamine agonists in the management of Parkinson's Disease (PD) - discussed by leading experts during two satellite symposiums - highlight the need for a reappraisal of treatment strategies.

Symposia faculty explored the aetiology and pathogenesis of PD, the role of dopamine agonists in the prevention and treatment of motor complications, the treatment of troubling early PD symptoms such as akinesia, rigidity and rest tremor and the rationale for continuous dopaminergic stimulation with long-acting dopamine agonists in preventing and alleviating disabling motor complications. Several lectures also addressed preliminary scientific studies that have now paved the way for testing dopamine agonists as putative neuroprotective agents in PD.

Securing 24-hour symptom control in Parkinson's Disease

Although the exact pathogenesis of motor fluctuation and dsykinesias is not known, experiments in animals indicate that repeated dosing of levodopa (L-dopa) results in a pulsatile stimulation of striatal dopamine receptors, leading to events downstream from the dopamine system that contribute to these motor alterations.

Dr Thomas Chase, Chief, Experimental Therapeutics Branch at the National Institute of Neurological Disorders and Stroke, Bethesda, explained the expected benefits of continuous dopaminergic stimulation compared to intermittent pulsatile stimulation: extend mobility, reduce 'off' periods and perhaps minimise dyskinesia in advanced PD, and reduce the risk of motor fluctuations and dyskinesia in early PD patients.



Dr K. Ray Chaudhuri and Dr Thomas Chase address congress delegates in Helsinki

Continuous stimulation recommended

Study data using the MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated primate model of PD demonstrate that long-acting dopamine agonists alone or in agonist-dominant combination with L-dopa are far less likely to induce dyskinesia. "Continuous dopaminergic stimulation with long-acting dopamine agonists significantly reduces dyskinesia induction, providing valuable options in both the early avoidance of dyskinesia and the control of involuntary movements in late-stage disease," argued Professor Peter Jenner, Professor of Pharmacology at Guy's, King's & St Thomas' School of Biomedical Sciences at King's College, London. "Dopamine agonists may also reverse the priming induced by L-dopa that leads to dyskinesia, suggesting that switching strategies in later-stage disease need to be explored."

"Results from clinical investigations support the role of long term, chronic administration of dopamimetics from the onset of treatment," observed Professor Eduardo Tolosa, Director, Movement Disorders Unit, University of Barcelona, Barcelona.

Association between nocturnal disturbance and excessive daytime sleepiness

Dr K. Ray Chaudhuri, Consultant and Co-Director, Movement Disorders Unit, King's College and Lewisham Hospitals, London, discussed the clinical use of the D_2-agonist cabergoline as monotherapy or adjunctive therapy and 24-hour symptom control in elderly and young PD patients.

Dr Chaudhuri explained study results evaluating the use of the novel Parkinson's Disease Sleep Scale (PDSS) to formally quantify aspects of nocturnal sleep disturbance in PD and its impact on excessive daytime sleepiness (EDS). A significant negative correlation was demonstrated between PDSS and ESS (Epworth Sleepiness Scale) scores ($p<0.01$). Patients reporting high levels of nocturnal symptoms (scoring poorly on the PDSS) obtained correspondingly high ESS scores (indicating excessive daytime sleepiness). This association between nocturnal sleep disturbance and excessive daytime sleepiness in PD underscores the need to alleviate nocturnal symptoms by securing 24-hour symptom control in PD. Overnight sustained dopamine agonism may be achieved by using cabergoline, apomorphine or subthalamic nucleus (STN) stimulation.

D_2-agonist cabergoline offers comparable tolerability in the young and elderly

Compelling evidence was presented demonstrating that dopaminergic treatment with dopamine agonists may be used to successfully treat PD in the elderly. Evaluating the hypothesis that sustained dopaminergic agonism using cabergoline may allow good tolerability by avoidance of pulsatile stimulation of dopamine receptors, investigators reported that at two years' follow up, cabergoline therapy was exceptionally well tolerated in both young and elderly PD patients (81.16% of the elderly and 87.07% of young PD patients), with remarkably few neuropsychiatric complications.

"Cabergoline is well tolerated in both young and elderly PD patients and appears to be superior to other oral dopamine agonists particularly in the elderly," noted Dr Chaudhuri. "These results confirm that monotherapy with cabergoline in the elderly can be a useful strategy, and is effective for sleep disability, restless leg syndrome and dyskinesia. Dual agonist therapy with daytime apomorphine infusion and nocturnal cabergoline therapy allows over a 50% reduction in L-dopa therapy and, as such, reduced dyskinesias. This strategy is also a feasible treatment option in cases of treatment-resistant PD unsuitable for surgery."

Putative neuroprotection

The dominant clinical features of PD are caused by the loss of dopaminergic neurons in the substantia nigra pars compacta, explained Professor Anthony Schapira, Chairman of the University Department of Clinical Neurosciences, Royal Free and University College Medical School of University College, London, during a lecture on the pathogenesis of PD and potential neuroprotective-neurorescue strategies in PD. Several identified biochemical abnormalities in the parkinsonian substantia nigra are thought to contribute to the pathogenesis of PD. These include mitochondrial complex I deficiency and free radical-mediated damage. Both processes may affect the mitochondrial membrane potential, a major determinant of mitochondrial mediated apoptosis.

Several dopamine agonists have been shown to have free radical scavenging properties, and to offer some protection to cell lines against certain toxins including MPP+, the active metabolite of the neurotoxin MPTP which causes a parkinsonian-like syndrome in experimental models.

Pramipexole protects against MPP+ - induced cell death

A poster presentation by King et al from Royal Free and University College Medical School detailed results of study evaluations using human neuroblastoma dopaminergic SHSY5Y cells to investigate the potential mechanisms of protection offered by pramipexole. The latter is a nonergot dopamine agonist with high selectivity and specificity for dopamine D_2 subfamily receptors and preferential affinity for dopamine D_3 receptors. Pramipexole is an effective and safe treatment for early PD when administered without L-dopa, providing sustained antiparkinsonian clinical benefit as monotherapy for more than 3 years.

In this investigation, SHSY5Y cells were pretreated for 72 hours with pramipexole at a range of concentrations followed by treatment with MPP+. Results demonstrated that pramipexole protects SHSY5Y cells against MPP+ - induced cell death and inhibits MPP+ - induced loss of mitochondrial membrane potential. Investigators concluded that MPP+ toxicity in SHSY5Y cells can be inhibited by pramipexole and that apoptosis induced by MPP+ in SHSY5Y cells involves loss of mitochondrial membrane potential which can be prevented by addition of pramipexole.

Clinical trials are underway using clinical and imaging markers of nigrostriatal function to test the potential of dopamine agonists to modify the rate of Parkinson's disease progression. If positive, experts suggested that there would be an increased likelihood that dopamine agonists might be initiated at the time of diagnosis and considered in presymptomatic patients at risk to develop Parkinson's disease.

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 October 8th, 2001.

2001

September

Visible Solutions for Invisible Injury - Headway/HIRE
11-12 September, 2001; Grantham, UK
Tel. 0115 947 1913,
E-Mail conferences@headway.org.uk

Association of British Neurologists
12-14 September, 2001; Durham, UK
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
Tel. 001 703 683 8400,
Fax. 001 703 683 8996,
E-Mail. info@internationalbrain.org

ECTRIMS 2001
12-15 September, 2001; Dublin, Ireland
Fax. 00353 1 676 9088,
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XXVII Congress of the European Society of Neuroradiology
13-16 September, 2001; Ancona, Italy
Tel. 0039 02 56601212, Fax. 0039 02 56609045, E-Mail. ecnr2001@mgr.it

European Paediatric Neurology Society
13-16 September, 2001; Germany
Fax. 0049 7621 78 714

XII International Congress of the World Federation of Neurosurgical Societies
15-21 September, 2001; Sydney, 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
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 Tel. 0061 3 9828 7222, Fax. 0061 3 9828 9054,
E-Mail.
msconference@mssociety.com.au

ACTRIMS
30 September, 2001; Chicago, US
Tel. 001 212 476 0452,
E-Mail.Ingrid.shea@nmss.org

October

Epilepsy Research Foundation 10th Anniversary Meeting
17 October, 2001; London, UK
Tel/Fax. 020 8995 4781,
E-Mail. info@erf.org.uk

British Geriatric Society
18-19 October, 2001; London, UK
Tel. 01825 768902,
E-Mail: contact@bhm.co.uk

2001 European Charcot Foundation Symposium
18-20 October, 2001; Venice, Italy
Tel. +31 24 356 1954,
Fax. +31 24 354 0920,
E-Mail. info@charcot-ms.org

✶ Amended Date ✶

Neuro-behavioural Rehabilitation of Severe Brain Injury - Theory & Practise
23 October, 2001; London, UK
Tel. 020 8780 4500 ext 5236,
E-Mail. Conferences@neuro-disability.org.uk

17th Alzheimer's Disease International Conference
25-27 October, 2001; Christchurch, New Zealand Tel. 0064 3 364 2534,
E-Mail. Alz@cont.canterbury.ac.nz

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

British Neuropsychological Society Autumn Meeting
8 November, 2001; London, UK
www.hop.man.ac.uk/bns,
Tel. 0161 275 3401

12th International Symposium on ALS/MND
18-20 November, 2001; Oakland, USA
Tel. 01604 250505, Fax. 01604 638289,
E-Mail. symposium@mndassociation.org

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

Ageing of the Brain - Dementia
23-24 November, 2001; Florence, Italy
Tel. 00390 55 43 68 455,
E-Mail. Oliver@dada.it

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

PDS Conference - Scotland
29 November, 2001; Scotland
Tel. 020 7932 1343,
E-Mail. mcaven@parkinsons.org.uk

The Changing Brain
29 November, 2001; Milan, Italy
www.armenise.meditech-media.com

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

UKABIF Annual Conference
30 November, 2001; London, UK
Tel. 020 8780 4569,
E-Mail secretariat@ukabif.org.uk

2002

March

Brain Awareness Week 2002
12-17 March, 2002; UK
E-Mail. elaine.snell@which.net

April

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

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

5th European Parkinson's Disease Association Conference
21-24 April, 2002; Jerusalem, Israel
Tel. 01273 686889, Fax. 01273 570082,
E-Mail. liz@martlet.co.uk

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

May

XIV International Neuro-Ophthalmology Society Meeting
5-8 May, 2002; Buenos Aires, Argentina
Fax. 0054 11 4331 0223,
E-Mail. inos2002@congresosint.com.ar

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

7th Meeting of the European Society of Neurosonology and Cerebral Hemodynamics
26-28 May, 2002; Bern, Switzerland
Tel. 0041 41 767 34 49,
Fax. 0041 41 767 34 00,
E-Mail. neurosonology2002@jacch.jnj.com

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

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

June

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

6th European Headache Congress
17-22 June, 2002; Istanbul, Turkey
Tel. 0090 312 4420700,
E-Mail. Flaptour@flaptour.com.tr

July

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

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

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

August

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

EDITOR'S CHOICE

Neglect is due to temporal -not parietal- lobe damage!

All neurological teaching and textbooks tell us that hemineglect is a feature of right posterior parietal lobe damage. But that has always been hard to square with the fact that primates get neglect from lesions of either temporal, rather than parietal, lobes. This careful study of stroke patients from Tubingen provides an explanation. Over 5 years the authors collected 49 patients with pure spatial neglect (that is without visual field lesions). Of these, 25 had cortical lesions only. This subgroup was compared, by lesion mapping from magnetic resonance images, with patients with a variety of right-sided lesions; the lesions causing pure spatial neglect were only congruent over the superior temporal gyrus not the parietal lobe. Next they compared lesions causing pure spatial neglect with those responsible for combined spatial neglect and visual field defects. They found that the superior temporal gyrus was always affected, and extension to the posterior horn of the lateral ventricle caused the field defect. It seems then that patients with more widespread deficits, especially visual field defects, have confounded previous studies of neglect. We can also conclude that the evolutionary change from monkey to human spatial awareness processing has been to lateralise it to the right temporal lobe rather than move it from the temporal to the parietal lobe. **-AJC**

Karnath HO, Ferber S, Himmelbach M.

Spatial awareness is a function of the temporal not the posterior parietal lobe.

NATURE

2001 Jun 21;411(6840):950-3

'Mind the doors please' - Virtual reality wheelchair training for patients with unilateral neglect

Patients with unilateral neglect take many weeks to rehabilitate, are prone to accidents and have difficulty achieving independence in daily life. A group from California has developed an imaginative and safe aid to improving wheelchair mobility in such patients. A computer assisted and virtual reality system of training in which images are projected onto a large (8x6ft) area of wall is used. Patients are trained on a hierarchical series of modules that are designed to improve scanning to the left space, decrease attentional pull to the right and improve visuospatial planning.

Webster *et al* tested their training protocol on 20 patients with left unilateral neglect and compared performance of these patients with 20 previous patients who had not experienced the computer assisted training. The patients who training with the computer and virtual reality simulation performed significantly better on a wheelchair obstacle course than the control subjects. They also had fewer reported accidents during their hospital admission.

Webster *et al* acknowledge the limitation of using a retrospective group as control subjects. This study is exciting because it demonstrates that wheelchair mobility and safety in neglect patients can be improved with tasks that do not require wheelchair propulsion. This means that training can begin before patients are ready to self propel in wheelchairs. Although it will be some time before virtual reality is in common use in rehabilitation. **-AJT**

Computer assisted training for improving wheelchair mobility in unilateral neglect patients.

Webster JS, McFarland PT, Rapport LJ, Morrill B, Roades LA, Abadee PS.

ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION

2001: 82: 769-75

COGNITIVE NEUROLOGY

'Stroop effect' is related to a specific pattern of frontal lobe damage rather than frontal damage per se.

The Stroop test is one of the most widely utilised paradigms in neuropsychological testing. The classic version of the test consists of three conditions: the first requires the subject to read colour words, written in black; the second requires the naming of coloured patches using the colours identified by their written names in the first condition and the third condition requires naming the colour of ink in which a colour word is printed when the colour is incongruent with the name (e.g. 'red' printed in the colour green). The test results in the general pattern of results where word reading is performed the fastest, colour naming is slower and the incongruent condition takes the longest time to complete. The great interest in this paradigm lies in the disproportionately impaired performance of various patient groups in the incongruent condition ('Stroop effect'). Performance of this aspect of the test is likely to depend heavily on intact frontal lobe function and functional neuroimaging has proposed a variety of key frontal lobe regions. In this study, Stuss *et al*, report a series of fifty-one patients with focal brain lesions (37 frontal, 14 posterior) and compared their performance on the Stroop test with 26 normal control subjects.

These investigations confirmed that only the group with frontal lobe lesions demonstrated a significant Stroop effect, with no effect seen in any patient with a posterior lobe lesion. Analysis of the frontal lobe lesion patients revealed that only 12 of the 37 had performed poorly on the incongruity aspect of the test. Comparison between impaired and non-impaired groups of frontal lobe lesion patients showed no difference between any demographic variables or neuropsychological measures. Thus Stroop effect was not related to frontal lobe damage in general, nor by undifferentiated unilateral or bilateral lesions. Patients with frontal lobe pathology were slower across all conditions of the task however; patients with superior medial frontal lesions (usually bilateral) did show an exaggeration of the Stroop effect. This region maps to the supplementary motor area bilaterally and is thought to be an important intersection between neural pathways receiving afferent subcortical activation pathways and projecting bilaterally to frontal cortex and striatum.

Greater understanding of the pathophysiological changes underlying this neuropsychological tool may allow for future therapeutic modulation of neurotransmitter systems (e.g. dopaminergic) to improve the cognitive deficit observed across a variety of neurological conditions. **-SJGL**

Stroop performance in focal lesion patients:dissociation of processes and frontal lobe lesion location.
Stuss DT, Floden D, Alexander MP, Levine B, Katz D
NEUROPSYCHOLOGIA
2001:39:771-786

Midlife systolic blood pressure and serum cholesterol linked to development of Alzheimer's disease

Previous studies have linked midlife blood pressure and serum cholesterol to the development in later life of Alzheimer's dementia, suggesting a possible vascular role in the pathophysiology of the disease. In this paper Kivipelto *et al* have performed a longitudinal population based study in Finland assessing both men and women to evaluate the role of these risk factors in this context. They identified a cohort of 1449 patients, mean age 71.3 years (65-80y) who had previously assessed between 1972-1987 when their mean age was 50.4years (40-64y). They were assessed by means of questionnaire, clinical examination and laboratory measurements. A diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition with diagnosis of Alzheimer's disease being made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.

In total, forty-eight cases of Alzheimer's disease were identified. All of these cases had generalised or medial temporal atrophy on magnetic resonance scans whereas none showed appreciable vascular pathology. People with raised systolic blood pressure (>160 mm Hg) or high serum cholesterol concentration (>6.5 mmol/l) in midlife had a significantly higher risk of Alzheimer's disease in later life, even after adjustment for age, body mass index, education, vascular events, smoking status, and alcohol consumption, compared with those individuals with normal systolic blood pressure (odds ratio 2.3, 95% confidence interval 1.0 to 5.5) or serum cholesterol (odds ratio 2.1, 1.0 to 4.4). Participants with both of these risk factors in midlife had a significantly higher risk of developing Alzheimer's disease than those with either of the risk factors alone (odds ratio 3.5, 1.6 to 7.9). Diastolic blood pressure in midlife had no significant effect on the risk of Alzheimer's disease.

The results presented here emphasise the clinical importance in the aggressive management of these risk factors during midlife and highlight a possible vascular role underlying pathophysiology in this common neurodegenerative condition. **-SJGL**

Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study.
Kivipelto M, Helkala E, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A.
BRITISH MEDICAL JOURNAL
2001:322:1447-1451

MULTIPLE SCLEROSIS

Chlamydia pneumonia and multiple sclerosis

Pierre Marie, a pupil of Charcot, was perhaps the first person to suggest an infective aetiology for multiple sclerosis and there have been no end of candidate pathogens proposed since then. Most recently, attention has turned on Chlamydia pneumoniae, an organism that was first identified in 1986 and is established to be pathogenic in atherosclerosis. In 1999, Sriram and colleagues found Chlamydiae pneumoniae DNA in a high percentage of patients with multiple sclerosis, but not controls, by polymerase chain reaction. However replication of this finding by other laboratories has proved controversial.

A group from Lubeck in Germany have published a study in Annals, which may illuminate the controversy. They found C. pneumoniae DNA in the CSF of 21% of 58 multiple sclerosis patients and none present in 67 healthy controls. But 43% of 47 patients with other neurological diseases were also positive for C. pneumoniae in the CSF. Gieffers *et al* then examined peripheral blood mononuclear cells in some of their patients, because anything up to 50% of healthy blood donors may be positive for C. pneumoniae by PCR. Of 6 multiple sclerosis patients with positive CSF, 2 had positive blood C. pneumoniae and, of 10 patients other

neurological diseases, 8 had positive blood. In those patients with paired CSF and blood results, it may be that Chlamydial DNA had simply leaked across a disrupted blood-brain-barrier and its presence was an epiphenomenon of the disease process. But, the devil's advocate might say, the data is also consistent with the possibility that failure to clear C. pneumoniae from the CSF, having eliminated it from the blood, is seen in the majority of patients with multiple sclerosis.

The controversy is further fuelled by a study by Lenz and colleagues from Detroit. They looked for sequence similarity between C. pneumoniae proteins and myelin basic protein. They found a 20-mer peptide from one C. pneumoniae protein that shares a 7-aa motif with a critical epitope of myelin basic protein (rat MBP 68-86). They injected this C. pneumoniae peptide, with complete Freund's adjuvant, into Lewis rats and found that it produced typical EAE, with perivascular cuffing and parenchymal mononuclear cell infiltration on pathology (but not demyelination). The implication is that immune responses against C. pneumoniae can induce central nervous system inflammation in laboratory animals- in which case why not in man? **-AJC**

Gieffers J, Pohl D, Treib J, Dittmann R, Stephan C, Klotz K, Hanefeld F, Solbach W, Haass A, Maass M.
Presence of Chlamydia pneumoniae DNA in the cerebral spinal fluid is a common phenomenon in a variety of neurological diseases and not restricted to multiplebsclerosis.
ANNALS OF NEUROLOGY
2001 May;49(5):585-9

Lenz, D, Lu L, Conant S, Wolf N, Gerard H, Whittum-Hudson J, Hudson A., Swanborg, R.
A Chlamydia pneumoniae-Specific Peptide Induces Experimental Autoimmune Encephalomyelitis in Rats.
JOUNRAL OF IMMUNOLOGY
2001 167: 1803-1808

★★★ RECOMMENDED

Early intervention with interferon in suspected Multiple Sclerosis: Treatment or Prevention?

Earlier treatment in suspected multiple sclerosis (MS) would seem to be important in preventing conversion to clinically definite MS (CDMS), but currently little evidence confirms this logical notion. In an attempt to address this issue the multi-centre ETOMS (Early treatment of Multiple Sclerosis) study group undertook a randomised double blind placebo controlled trial of interferon after first presentation of neurological events, in patients with MRI findings strongly suggestive of multiple sclerosis. With 154 patients assigned to receive 22mcg of Interferon beta 1a (now generally considered a low dose) and 155 patients assigned to receive placebo injections, follow up for 2 years was undertaken. 34% in the treatment group developed CDMS, which was significantly less (p=0.047) than the 45% in the placebo group. It took 569 days for 30% of the interferon group to develop CDMS, which differed significantly (p=0.034) from the placebo group. Annual relapse rate and lesion burden on MRI were also significantly less in the treatment group. The EDSS score did not differ, but this was to be expected at such an early stage in the disease. These findings taken with results from the CHAMPS (Controlled High-risk Subjects Avonex Multiple Sclerosis Prevention Study) study suggest interferon has positive effects on clinical and MRI outcomes in suspected MS. But the ultimate targets of intervention on the long-term course of MS should be the prevention of the onset of progression and reduction in disability. Given the short follow up times this can not be fully assessed in these studies and will require further information, which may become available on these patients due course. As it now stands 6 years of treatment would be required to prevent one relapse, which would be hard to justify in the current funding environments. **- TH**

Effect of early interferon treatment on the conversion to definite multiple sclerosis: a randomised study.
Comi G, Fillipi M, Barkhof F, Durelli L, Edan G, Fernadez O, Hartung HP, Seeldrayers P, Sorensen PS, Rovaris M, Martinelli V, Hpmmes OR, and the Early Treatment of Multiple Sclerosis Study Group.
LANCET
(2001);357: 1576-82

Preventing multiple sclerosis.
Ebers G.
LANCET
(2001);357: 1547

Cigarette Smoking and Incidence of Multiple Sclerosis

The causes of multiple sclerosis remain unknown although both genetic and environmental factors such as viruses are likely to play a role in the development of the disease. Epidemiological studies continue to play an important role in attempting to identify possible risk factors.

This paper presents data from the ongoing Nurses Health Studies (NHS) I and II, in which exposure data has been collected prospectively from over 230,000 US women. Every 2 years follow up questionnaires are used to update exposure assessments and identify incident diagnoses, with written confirmation of diagnoses being sought from the subject's specialist physician.

Three hundred and fifteen "definite" or "probable" diagnoses of MS were identified from these studies during follow up to 1995. Analysis with adjustment for age, latitude of residence and ancestry, has shown a significantly

Complimentary Journals Reviewed

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

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

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

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

increased relative rate of MS (1.6) for current smokers compared to never smokers. This was consistently found in both of these studies individually and when the data were pooled. When the analysis incorporated the number of pack-years smoked before the diagnosis, a significant dose-response effect was also observed, but the relative rate of MS for past smokers was not significantly increased. Although significant, the magnitude of the increased risk of MS in these studies due to smoking is small. Previous prospective cohort studies have also identified increased risks for MS among smokers but with only borderline significance. Restriction of analysis to only "definite" cases of MS, or further adjustment for alcohol, caffeine intake or Body Mass Index exerted little change on the results, which excludes false association due to some, but not all possible confounders.

Although by no means proof of a cause and effect relationship, these studies raise the possibility that the small positive association between smoking and MS is real. Possible mechanisms include immuno-modulation by nicotine or tobacco glycoprotein, direct CNS toxicity, or increased permeability of the blood brain barrier.**-TF**

Cigarette Smoking and Incidence of Multiple Sclerosis.
Hernan MA, Olek MJ, Ascherio A.
AMERICAN JOURNAL OF EPIDEMIOLOGY
2001:154:1:69-74

EPILEPSY

★★★ RECOMMENDED

Looking beyond the hippocampus

Hippocampal atrophy can be detected preoperatively in 85% of patients with mesial temporal epilepsy. Proving the presence of hippocampal disease is a challenge in the remaining 15% and methods such as magnetic resonance spectroscopy and T2 relaxometry may increase sensitivity. There is increasing evidence however, that mesial temporal epilepsy is not just a disease of the hippocampus. Ultrastructural studies have shown there are also dysplastic changes elsewhere within the temporal lobes. Moran *et al* compared the volumes of different temporal lobe structures ipsilateral and contralateral to the affected hippocampus to volumes in normal controls. They found an average volume reduction of 13% in the temporal cortex ipsilateral to hippocampal volume reduction, which averaged 38%. The greatest reduction was in the temporal pole. Bernasconi *et al* studied patients with TLE but no evidence of reduction in hippocampal volume on MRI. They found a 20% reduction in entorhinal cortex volume ipsilateral to the TLE focus. These patients went on to have temporal lobe surgery and despite the normal hippocampal volumes, the great majority had histological evidence of mesial temporal sclerosis. Taken together these studies show that TLE is not restricted to the hippocampus and extrahippocampal atrophy can be a marker of hippocampal disease, even when the hippocampus itself appears normal. To what extent the extratemporal cortex is involved in the generation of seizures is unclear but the best seizure outcome is obtained if entorhinal cortex as well as hippocampus is resected. These findings will help chip away at the numbers of patients with no structural imaging abnormality prior to temporal lobe epilepsy surgery, but they are very time-consuming and can only be performed in some centres.
- MRAM

Extrahippocampal temporal lobe atrophy in temporal lobe epilepsy and mesial temporal sclerosis.
Moran N, Lemieux L, Kitchen N, Fish D, Shorvon S.
BRAIN
2001;124:167-75

Entorhinal cortex atrophy in epilepsy patients exhibiting normal hippocampal volumes.
Bernasconi N, Bernasconi A, Caramanos Z, Dubeau F, Richardson J, Andermann F, Arnold D.
NEUROLOGY
2001;56:1335-39

NEUROPHYSIOLOGY

Nerve conduction studies and carpal tunnel syndrome, an old controversy laid to rest?

Most neurophysiology journals have at least one paper on carpal tunnel syndrome in each edition, so yet another paper on carpal tunnel syndrome tends to attract a 'so what' response. However Jeremy Bland's enormous (n=3336) and thorough clinical study of the subject is essential reading for anyone involved in the treatment of carpal tunnel syndrome. He examined the role of nerve conduction studies in predicting the outcome of surgical decompression. He found that those patients with absent sensory and motor responses from the median nerve tended to respond poorly, suggesting that in these patients the damage to the median nerve may be irreversible. Patients with normal responses or mild abnormalities tended to do badly also, implying that this group contains a significant number of false positives. Those patients with moderate abnormalities had a very good surgical outcome, this may be due to a combination of a treatable neuropathy and a low number of false positives. Nerve conduction studies were of greater predictive value than pre-operative symptom score, this is very reassuring for those of us who believe that nerve conduction studies should be an essential part of the pre-operative evaluation of anyone with suspected carpal tunnel syndrome. **- BMcN**

Bland J. ***Do Nerve conduction studies predict the outcome of carpal tunnel decompression?***
MUSCLE AND NERVE
July 2001; 24:935-940

Functional MRI and simultaneous EEG

One of the difficulties with EEG is that while the clinical correlates of many sorts of abnormal EEG activity are well described, the pathophysiological mechanisms that produce these EEG features are not. A possible solution to this problem is to combine EEG with other means of studying brain function such as functional MRI. Unfortunately this is easier said than done, MRI scanning tends to produce horrendous EEG artefacts, also timing the scanning to correlate the scanning period with the precise period of abnormal EEG activity can be a logistical and computational nightmare. Baudewig *et al* present a simple approach to these problems that allowed them to correlate EEG recordings with fMRI bold responses in a patient with generalised epilepsy. The precise details of the study are not important, however this and other recent reports show that combined EEG and fMRI studies are becoming technically possible which has exciting implications for the clinical application of EEG. **- BMcN**

Simulaneous EEG and functional MRI of Epileptic activity: a case report. **Baudewig J, Bittermann HJ, Paulus W, Frahm J.**
CLINICAL NEUROPHYSIOLOGY
July 2001;112:1196-2000.

MOVEMENT DISORDERS

★★★ RECOMMENDED

Alpha-synuclein and parkin: a new understanding of their role in Parkinson's Disease

The recent identification of genetic defects in families with Parkinson's Disease has spurned a great deal of exciting new research into the possible aetiology and pathogenesis of the much more common sporadic form of the disease. The two most well-characterised genetic causes of PD are those relating to mutations in alpha-synuclein in two large kindreds with autosomal dominance inheritance and the young onset autosomal recessive forms of the disease with mutations in parkin. In the former, Lewy bodies are present whilst in the latter no such structures have yet been identified. In this paper Shimura *et al* have now identified a protein complex in the normal human brain that includes parkin which is bound to a novel glycosylated form of alpha-synuclein (alphaSp22) - a binding that cannot be achieved when mutant parkin is used. Thus in the presence of a parkin mutation, alphaSp22 accumulates, and this in turn leads to cell death. This paper therefore is important in linking these well-characterised genetic causes of PD together in a pathogenic cascade, which may shed new light on mechanisms of dysfunction in the sporadic cases of this common disease **-RAB**

H.Shimura, MG Schlossmacher, N.Hattori *et al.*
Ubiquitination of a new form of alpha-synuclein by parkin from human brain: Implications for Parkinson's Disease.
SCIENCE
2001: 293: 263-269

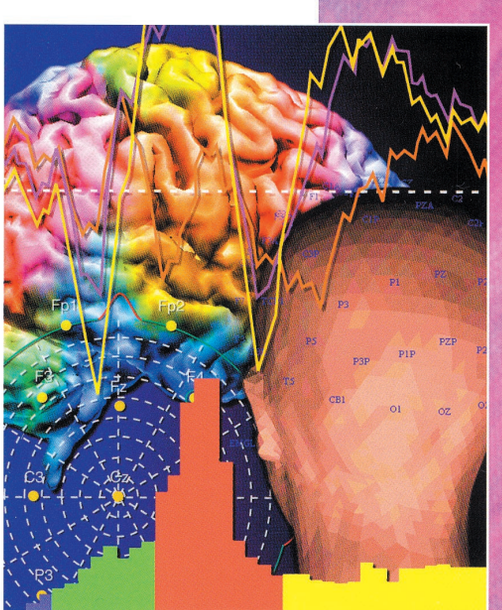
STROKE

★★★ RECOMMENDED

The cause of spontaneous cervical artery dissection?

Increasingly, cervical artery dissection is being recognised as a cause of stroke, especially in young patients. Sometimes this follows obvious blunt or rotatory trauma to the neck. But more intriguing is the cause for dissection in non-traumatic cases. This study from Heidelberg and Düsseldorf suggests that such patients have a previously undescribed disorder of collagen. They examined 65 patients with non-traumatic cervical artery dissection. More than one vessel was involved in 22 patients and recurrent dissections in another 7. In six patients there was a first-degree family history. Angiographic signs of fibromuscular dyplasia were seen in four patients. Three patients had clinical signs of a connective tissue disorder (one was marfanoid, another had hyperextensible joints and the last had pseudo-molluscoid scars at the elbows). The important point is that all patients had a skin biopsy and 36 were abnormal (with no abnormalities found on 10 controls). There were defects of elastic fibres or collagen that, when severe, resembled those found in Ehlers-Danlos syndrome type II or III. The questions this study raises are: what is the cause of the collagen defect in these patients and what can be done to reverse it? **-AJC**

Brandt T, Orberk E, Weber R, Werner I, Busse O, Muller BT, Wigger F, Grau A, Grond-Ginsbach C, Hausser I.
Pathogenesis of cervical artery dissections: association with connective tissue abnormalities.
NEUROLOGY
2001 Jul 10;57(1):24-30



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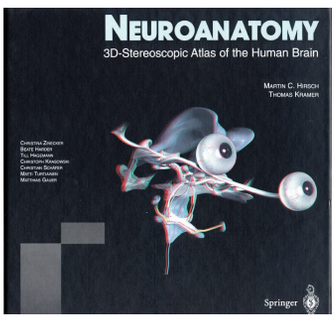
Neuroanatomy 3D stereoscopic atlas of the human brain

"In neurology a knowledge of the anatomical basis is perhaps of greater importance than in any other field of medicine". So wrote Alf Brodal in the first edition of his wonderful book Neurological Anatomy (1943). Few contemporary neurologists would take issue with his thesis, but they might with his exposition. For his book contains dense text and sparse figures. Yet illustrations have been the key to most people's understanding of the complex three-dimensional geometry of the nervous system: from Christopher Wren's mighty depictions of Thomas Willis' and Richard Lower's dissections in the seventeenth century to the elegant line drawings of John Patten in Neurological Differential Diagnosis. Hirsch and Kramer, together with a computer image company called interActive Systems GmbH, have produced an entirely novel and entertaining way of depicting the brain. They have used the scorned cinematic technology of the 60s and 70s, that famously brought us "Jaws III": the red/blue stereoscopic image. In the back of this otherwise handsomely Springer-produced book is a cardboard pair of red/blue spectacles through which to view the plates. Without the glasses they appear as slightly smudged images with blue and green haloes. (For instance, look back at the cover of the last issue of Advances in Clinical Neuroscience and Rehabilitation, which shows two alarming free-floating eyes). With the glasses on, the figures take on an eerie life. Mamillary bodies hover above the page. The cerebellar cortex gracefully fades into the distance. Tracts in the brainstem weave complex paths in and out of focus. It is all tremendous fun. Most chapters are arranged as virtual dissections, with structures gradually peeled off in successive plates. Combined with the stereoscopic glasses, this is an excellent way of appreciating the three-dimensional brain.

It does not end there though. Also at the back of the book is a CD-ROM, on which the same images can be found (and once again must be viewed through the flimsy specs). Wonderfully, the images can be rotated and tipped this way and that, so that the enthusiast can gorge on the intricacies of neural architecture. Manipulating the pictures of the cerebral circulation, for instance, helps considerably to understand all those angiographic views. The reviewer spent several happy hours touring the Circle of Willis and the pons. This is definitely an atlas: in the book (but annoyingly not in the CD-ROM) the structures are labelled but there is no explanatory text. This is not therefore the place to learn neuroanatomy. Frustratingly, using the CD-ROM, it is not possible to magnify the images, which are sometimes too cramped to be easily discriminated. But for those with some knowledge already, who are eager to piece it together, this is a delight and a pleasure. And for only £33, it is a real bargain. -AJC



Authors: Hirsch and Kramer
Published by: Springer Verlag
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Price: £33

Beta-interferon and Glatiramer turned down by NICE

On the 7th of August, the National Institute of Clinical Excellence (NICE) published a "provisional appraisal determination" that the NHS should not use beta-interferon and glatiramer (Copaxone®) in multiple sclerosis. Most neurologists were surprised by the decision and certainly many patients have been disheartened. In theory this document is just the basis for final consultations with interested parties, who are asked to submit their responses by 11 September, after which NICE will make a formal guidance to the NHS. But it would be very surprising if new facts emerged to shake NICE's argument which is based on the balance of clinical efficacy and cost-effectiveness. NICE accepts that the beta-interferons and glatiramer reduce the frequency of relapses in multiple sclerosis by about 30%. They acknowledge that treatment of relapsing-remitting patients, but not those in the progressive phase, may delay disability progression. However NICE noted that all current trials were short-term and the long-term effect of treatment was unknown. This analysis of the drugs' effectiveness was compared to their cost: for an annual treatment £6,650 (glatiramer), £7,259 (Betaferon), £9,061 (Avonex) and £9,088-£12,068 (Low/High doses of Rebif). The tool for working out cost-effectiveness was the QALY (quality-adjusted life year): a unit of quality of life that was derived from the Kurtzke EDSS scores in the published literature. Although the NICE committee acknowledged problems with using QALYs, they found no suitable alternatives. At the start of NICE's consultation process, estimates for the use of the beta-interferons varied between £10,000 and £3 million per QALY. So the committee commissioned its own estimates. Schering and Biogen provided supplementary data; TEVA (who make glatiramer) and Serono did not. NICE concluded that, over a five-year period, the cost per QALY of treatment of multiple sclerosis with beta-interferon and glatiramer ranged from £380,000 to £780,000. They judged this to be too high. There was a caveat for those patients already on one of these drugs; their treatment could be continued until they meet one of the ABN criteria for withdrawal.

Whatever the rights and wrongs of this decision, it is a brave one. Perhaps only the British health system could take such a stance. Prescribing of the "ABCs" (beta-interferon and glatiramer) in the US is rampant and certainly has drifted outside all prescribing guidelines. Even before this decision, beta-interferon use in the UK was the lowest in Europe. The ball is back in the pharmaceutical court: if the cost of these drugs was reduced the QALY equations might tip in favour of prescribing them. -AJC

Ruling heightens concerns for people with MS

Biogen, the maker of Avonex® (Interferon Beta 1a), has called on the Secretary of State for Health to overturn the provisional determination published by NICE on the use of beta interferons in England and Wales, and to stand by the promise of the NHS to ensure that "no-one will be denied the drugs they need."

According to Biogen, the effectiveness of beta interferons in MS is now overwhelming. Beta interferons are widely used in the treatment of MS in every developed country except the United Kingdom. Since NICE began their lengthy appraisal, a number of major trials have been presented and published confirming the effectiveness of beta interferons.

A spokesperson for Biogen said "It is plainly in the interest of people with MS for NICE to conclude this exercise once and for all. Approval of these drugs would allow British patients to enjoy the benefits enjoyed by MS patients throughout the rest of the developed world."

For further information contact Biogen, Tel. 01628 501000.

APO-go (apomorphine)

Britannia Pharmaceuticals Ltd have re-branded their apomorphine range, with the introduction of 2ml and 5ml APO-go ampoules.

APO-go is used in the treatment of Parkinson's Disease and provides additional or alternative benefit for those individuals who have found that each dose of their existing treatment has become shorter and who are experiencing 'wearing off', or very sudden and unpredictable 'on-off' fluctuations.

Britannia has developed, with the assistance of the Italian company, Cane, the APO-go Pump, which is used to administer a continuous infusion of apomorphine.

The APO-go pump is small and "state of the art". It is discreet to wear and once programmed with the dosage details, it is simple to use.

For further information contact Britannia Pharmaceuticals Ltd on Tel. 01737 773741, Fax. 01737 773973.

Activity monitor for use in neurological research and clinical assessment

The Actiwatch-Neurologica®, recently exhibited by Cambridge Neurotechnology Ltd at the World Congress of Neurology, is one of a series of ultra-lightweight activity monitors designed to be worn by people of all ages, typically on the wrist. An accelerometer measures movement.

Each monitor is easily programmed via a Reader connected to a PC with data transferred by telemetry and then analysed by specific software. As well as monitoring general activity levels, tremor levels and duration can be detected, and data collected on the periodicity and frequency of specific movements.

The applications for Actiwatch - Neurologica® include use in the detection and assessment of tremor and dyskinesias associated with Parkinson's Disease and other movement disorders. Also in the monitoring of the effectiveness of different treatment regimes, and the effects of drugs on the CNS system, as well as in stroke rehabilitation programmes.

For further information contact Dr Caroline Reynolds, Business Development Manager, Cambridge Neurotechnology Limited, Upper Pendrill Court, Papworth Everard, Cambridge, CB3 8UY. Tel. 01480 831223, Fax. 01480 831733, E-Mail. carolinereynolds@camntech.co.uk

4-year roll over in the brain injury lottery

The Government's response to the HSC report into rehabilitation following head injury was described recently as "Complacent, ambiguous and very disappointing" by Headway.

Graham Nickson, Policy and Campaigns Manager, said, "Although action is promised by 2005 with the implementation of a national service framework (NSF) there is nothing in the Government response to tackle the problem which exists now of the lottery of care or rehabilitation services across England for people who survive a head injury. Early, appropriate and well resourced rehabilitation following head injury is vital if patients are to maximise their recovery and reintegrate into their community".

"The Government response perpetuates the lottery by creating a four-year roll over until 2005, when the NSF will ensure legally enforceable minimum standards are in place across England." Headway wants the Government to address the following points immediately:

- Research to establish the prevalence of head injury across the country.
- social services departments to adopt a separate category of user group of people with complex neurological conditions, recognising head injury as a separate disability and so design services which address their real - rather than perceived - needs
- improve the quality of information offered to people who survive a head injury, their families and carers and professional clinical and social care staff.

For further information contact Headway on Tel. 01159 240800.

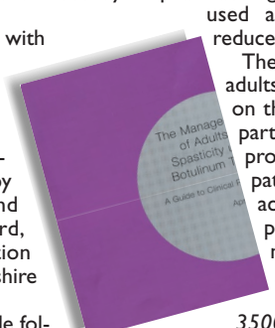
FREE RESOURCE

Management of adults with spasticity

New guidelines to improve the outcome for people with spasticity were launched recently at the RCP in London.

'The Management of Adults with Spasticity using Botulinum Toxin: A Guide to Clinical Practice' was produced by an eminent panel comprising specialists from neurological rehabilitation, neurology, physiotherapy and occupational therapy and chaired by Dr Anthony Ward, Consultant in Rehabilitation Medicine at the North Staffordshire Rehabilitation Centre.

Spasticity often occurs in people following stroke, traumatic brain injury and in moderate to severe multiple sclerosis.



Botulinum toxin is an innovative treatment in the pharmacological management of spasticity, and if used appropriately, has the potential to reduce the cost burden.

The guide will assist clinicians treating adults with spasticity by providing guidance on the correct use of botulinum toxin, as part of an overall patient management programme. It also aims to ensure all patients treated with botulinum toxin achieve optimum benefit when used as part of a co-ordinated multi-disciplinary approach.

For a free copy of the guidelines contact Radius Healthcare, Tel. 01932 350006, Fax. 01932 353336, E-Mail. Enquiries@radiushealthcare.co.uk, or return the reader enquiry form enclosed with this magazine.

New fever control technique reduces nurse workload in neuro ICU

A new medical technique to protect critically-ill patients from developing harmful fever is also helping to reduce the workload on nurses in Neuro ICU.

The revolutionary intravascular products developed by Alsius Corporation of California allow doctors to closely control the core temperature of their patients - particularly critical for patients with stroke, brain trauma or other severe neuronal injury, who commonly experience elevated temperature or 'fever'.

The use of the Cool Line™ catheter in conjunction with the CoolGard™ temperature management system provides a quantum leap over conventional methods of fever management that are primitive, labour-intensive and of limited effectiveness.

According to Trina Cunningham, Neurosurgery Nurse Coordinator at John Hopkins Hospital: "Our temperatures are on a constant monitoring schedule with the CoolGard™, so the nurse doesn't have to be at the bedside every hour, or every 30 minutes, taking the temperature."

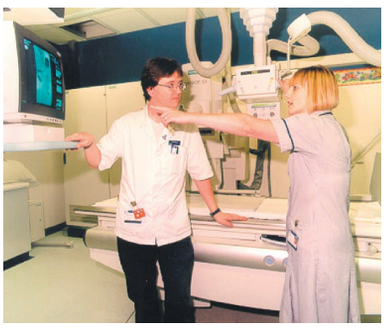
Aslius Corporation is the worldwide leader in the development of intravascular temperature control systems. The systems have received CE Clearance in Europe and are currently investigational in the US.

Alsius Corporation, 15770 Laguna Canyon Road, Suite 150, Irvine, California USA 92618. www.alsius.com

Siemens supplies X-ray equipment for new Bristol Children's Hospital

The X-ray department at the new Bristol Royal Hospital for Children was recently commissioned with the installation of new General X-ray and Digital Fluoroscopy facilities.

The new Siemens SIRESKOP SX Digital Fluoroscopy unit incorporates many of the dose saving features relevant for a dedicated Paediatric Department. The combination of 'Carevision' low dose pulsed fluoroscopy together with 'Careprofile' collimation without radiation, Carewatch dose display and 'Carefilter' automatic copper filtration adaptation depending on the patient size and the new 'Harmonization' feature, all contribute to the resultant lower doses now achieved with excellent image quality.



Pictured alongside the new fluoroscopy facility at the Bristol Children's Hospital are: (L to R) Mark Waterhouse, Radiographer and Donna Dimond, Superintendent Radiographer.

The department also houses two new MULTIX TOP general x-ray units one with the new ORBIX TOP isocentric skull unit.

For further information contact Siemens Medical Solutions, Tel. 01344 396317, Fax. 01344 396337. E-Mail. bellm@plcbrk.siemens.co.uk

Sheffield hunts for better diagnosis of brain disorder

Sheffield is leading a new study designed to help medics more accurately diagnose Parkinson's Disease. Lead researcher Professor Paul Griffiths, head of neuroimaging at the University of Sheffield, says, 'The exact cause of the illness is still unknown, and as yet there is no accurate way of diagnosing whether a living patient has PD. Only a post-mortem can define the disease.'

He adds, 'Current techniques - in which medics carry out an assessment based on a set of clinical criteria - mean that almost one in five patients are wrongly diagnosed with PD when they have another condition with similar symptoms such as multiple system atrophy (MSA).'

A good reliable diagnostic technique is therefore needed and a new two-year study funded by Action Research is designed to do just that.

The researchers will be looking at how much iron might play a role in the illness. Iron is essential for a number of brain processes but increased levels may be damaging to the individual, resulting in neurodegeneration.

The Action Research team will carry out a series of tests using brain scanning to determine whether iron content in the brain can be used as a 'measuring stick' to assess PD progression.

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

UK Launch of Dendron (GmbH) embolisation coils

Dendron GmbH. of Germany has launched its product range of embolisation coils and accessories into the UK market.

Dendron (originally EFMT) has been manufacturing the coils for ten years and was previously an EEC funded research company looking into the treatments for AVMs and various types of aneurysms.

The German company was recently privatised in order to allow it to concentrate on expanding the international markets for the coils. "There has previously only been one main supplier for these embolisation coils" said Ian Graney, Managing Director of Neurotechnics Ltd, the exclusive UK & Ireland distributor of the coils. "We are now in a position to offer the customer a wide choice of the highest quality EEC manufactured product at a very competitive price, which can only serve to help the NHS in meeting its' challenging funding goals for the future." Mr Graney went on to add that "Further unique products are planned for release towards the end of this year that will add to the neuro Radiologists armoury and Neurotechnics plan to be a key supplier in this marketplace within 24 months".

For further information contact Ian Graney on Tel. 01844 260777, Fax. 01844 260778.

Consensus reached on Riluzole cost-effectiveness

Positive NICE guidance has confirmed that riluzole is cost-effective in the management of patients with ALS / MND. However, there has been debate as to what is the true figure of cost-effectiveness (measured as cost per quality adjusted life year (QALY)). The ratio has ranged from £34,000 to £58,000 at the upper level (based on the Health Technology Assessment report), and £16,500 to £20,904 at the lower level (based on the manufacturer submission).

At the recent International Health Economics Association (IHEA) meeting in York, Stirling Bryan (a co-author of the HTA report that estimated the ratios at the higher level) stated that having incorporated the long-term evidence for riluzole (48 months), their revised estimate of the cost per QALY was between £16,500 and £20,000. This is now consistent with the manufacturers evaluation.

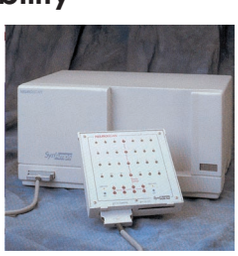
Along with the impressive survival advantage that riluzole offers (an additional 3 to 6 months over best supportive care), the consensus on cost-effectiveness provides stronger support for prescribing.

The NICE guidance on riluzole (Rilutek) and the HTA report are available at www.nice.org.uk.

For further information contact Aventis Pharma on Tel: 08705 239604.

SynAmps: speed, power and flexibility

Combining the flexibility of software with the power and speed of the latest electronics, SynAmps is a software-programmable amplifier capable of true DC or AC recording. Each unit is an integrated physiological data acquisition system that can be configured for 8,16, 24 or 32 channels and includes ultra-low-noise amplification, 16-bit analogue-to-digital conversion, and digital filtering. Multiple units can be interconnected or 'daisy-chained' together to provide synchronised acquisition for up to 256 channels.



SynAmps contains the analogue components needed to amplify low-level neurophysiological signals and the digital components required to log external events and digitise, DC-correct, digitally filter and transfer data to a host computer. With its distributed processing approach, SynAmps can acquire data in discrete epochs at rates of up to 20 KHz per each of 32 channels, 50 KHz per each of 8 channels, or 100 KHz per each of 4 channels.

It performs simultaneous sampling via multiple individual sample-and-holds, thereby assuring zero phase error across all channels. This is a significant problem that most multi-channel systems do not address.

For more information contact MedTech Systems Ltd, Tel. 01306 627171, Fax. 01306 627141, E-Mail. Miguel@medtechsystems.com.
See also our advertisement on page 27.

Prescribing information

Lamictal (lamotrigine)

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

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

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

Contra-indications: Hypersensitivity to lamotrigine.

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

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

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

Legal category: POM.

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

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

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

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

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

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GlaxoSmithKline

GEN 26792-ALP/May 2001

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Imagine you're a woman diagnosed with epilepsy.

There are certain things you need to be assured of before starting monotherapy.

Will it affect my periods? Will I put on weight?

Unlike some other therapies, Lamictal can offer the reassurance a woman seeks.

Lamictal does not interact with the contraceptive pill.[1,2]

It is not associated with cosmetic side effects or menstrual disorders.[3-5]

Lamictal causes significantly less sedation than carbamazepine[6,7] and phenytoin.[8]

In addition to these benefits – essential to women – it still provides the effective seizure control you expect.[6-8] What other AED can offer a woman so much?

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lamotrigine

Epilepsy treatment with women in mind