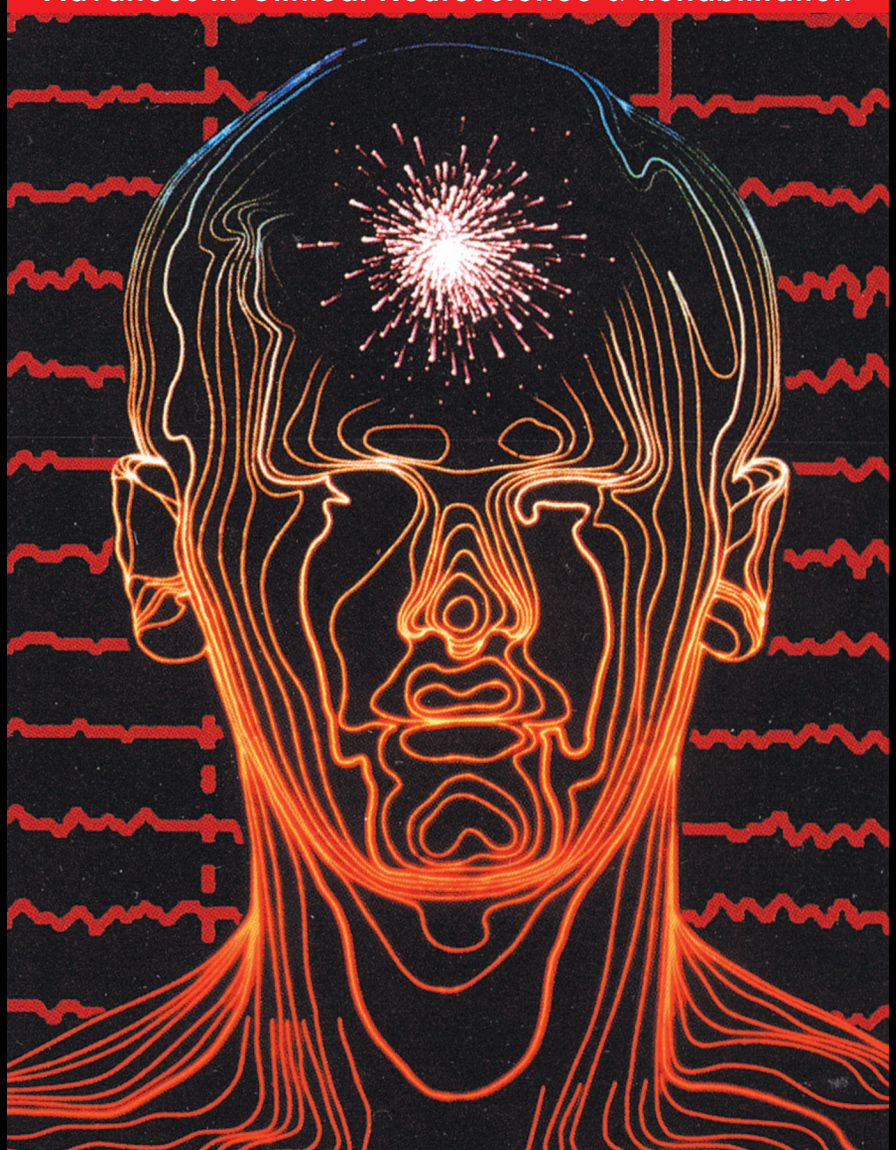
ISSN 1473-9348 Volume 1 Issue 5 November/December 2001

ACNR

Advances in Clinical Neuroscience & Rehabilitation



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

Review Articles: How to assess reports of clinical results
Ethical barriers in research into diseases of the human brain
Neuropsychiatry of Huntington's disease
Rehabilitation Article: The practicalities of treadmill training for non-ambulant hemiplegic patients
Management Topic: Management of refractory epilepsy

THE TRUTH BEHIND THE MASK

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

Now the truth is out. Nycomed Amersham are proud to announce the first and only approved nuclear imaging product in Europe to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's disease, Multiple System Atrophy and Progressive Supranuclear Palsy.

DaTSCAN

IOFLUPANE (^{123}I)

The images are easy to read and available the same day. DaTSCAN™ gives you clear diagnostic pictures that provide accurate visual differentiation of Parkinsonian Syndromes from Essential Tremor.

Currently, diagnostic methods rely on the use of clinical criteria, with formal confirmation only possible at post mortem. DaTSCAN can reduce the time required to reach a diagnosis. With 97.5% sensitivity†, you can be more confident than ever that your diagnosis is correct and that the medication you prescribe will have the desired effect.

DaTSCAN – another major step forward in the partnership of success between Neurology, Geriatrics, Nuclear Medicine and Nycomed Amersham.

Further information from: Zilla Moore,
zilla.moore@uk.nycomed-amersham.com

AMERSHAM HEALTH

Abbreviated Prescribing Information
Presentation: Vials containing 185 MBq ioflupane (^{123}I) at reference time.
Uses: Detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian Syndromes in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease (PD), Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP). DaTSCAN is unable to discriminate between PD, MSA and PSP.
Dosage and Administration: DaTSCAN is a 5% (v/v) ethanolic solution for intravenous injection and should be used without dilution. Clinical efficiency has been demonstrated across the range of 111-185 MBq; do not use outside this range. Appropriate thyroid blocking treatment must be given prior to and post injection of DaTSCAN. SPECT imaging should take place 3-6 hours after injection of DaTSCAN. DaTSCAN is not recommended for use in children or adolescents. For use in patients referred by physicians experienced in the management of movement disorders. See SPC.
Contraindications: Pregnancy and in patients with hypersensitivity to iodide or any of the excipients.
Precautions: Radiopharmaceuticals should only be used by qualified personnel with appropriate government authorisation and should be prepared using aseptic and radiological precautions. DaTSCAN is not recommended in moderate to severe renal or hepatic impairment.
Interactions: Consider current medication. Medicines that bind to the dopamine transporter may interfere with diagnosis; these include amphetamine, benzotropine, buproprion, cocaine, mazindol, methylphenidate, phentermine and sertraline. Drugs shown during clinical trials not to interfere with DaTSCAN imaging include amantadine, benzhexol, budipine, levodopa, metoprolol, primidone, propranolol and selegiline. Dopamine agonists and antagonists acting on the postsynaptic dopamine receptors are not expected to interfere with DaTSCAN imaging and can therefore be continued if desired.
Pregnancy and Lactation: Contraindicated in pregnancy. Information should be sought about pregnancy from women of child bearing potential. A woman who has missed her period should be assumed to be pregnant. If administration to a breast feeding woman is necessary, substitute formula feeding for breast feeding.
Side Effects: No serious adverse effects have been reported. Common side effects include headache, vertigo and increased appetite. Exposure to ionising radiation is linked with cancer induction and a potential for hereditary defects and must be kept as low as reasonably achievable.
Dosimetry: Effective dose from 185 MBq is 4.35 mSv.
Overdose: Encourage frequent micturition and defaecation.
Legal category: Subject to medical prescription (POM). Consult full SPC before prescribing. Further information available on request.
Marketing Authorisation number: EU/1/00/135/001
Basic NHS price: £420
Date of Preparation: July 2000
Nycomed Amersham plc., Amersham Place, Little Chalfont, Buckinghamshire, England HP7 9NA. www.na-imaging.com

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

contents

november/december 2001

This issue has an emphasis on clinical trials. Peter Rothwell, director of the Oxford Stroke prevention Research Unit, critically assesses how to interpret clinical trial results. This is especially helpful as big trials are often so influential in governing clinical practice, and to the uninitiated it is often difficult to know how to interpret large clinical trials and meta-analyses. It is therefore useful to have the view of an expert, so that we can all critically review what is being claimed in the publication of trial results.

This article is followed by a personal view from Professor Charles Warlow on the new data protection legislation and where it will lead and what it will mean for epidemiological research. This article is a transcript of the talk he delivered to the British Association science festival in September, and plots a course through his medical history and removed organs to the heart of the problem with data protection and clinical research. This is an issue that all of us should have an opinion on, as it will impact on anyone doing clinical research by restricting access to medical information. This will be felt most in epidemiological studies, where knowing incident and prevalent cases forms the backbone of much research and without which the work is ultimately built on shifting sand. As Professor Warlow points out, protecting information on patients is clearly essential but the way in which this has been implemented seems to have been poorly thought out, especially given the excellent record of confidentiality that exists in medical research.

Following on from our article in the last ACNR on cognition in Huntington's disease, we have an article from the same authors on the neuropsychiatric problems of this disorder. We also have our regular articles. Mark Manford takes us through status epilepticus and Alasdair Coles treats us to the painful topic of the spinothalamic tracts. We have a number of conference reports including the annual Neuroscience for Clinicians meeting held in Cambridge and organised by Professor Alastair Compston, and the neuroimmunology conference held in the heartland of this journal, Edinburgh. We also have a summary of the recent ABN held in Durham. Finally we also have our regular review of the journals.

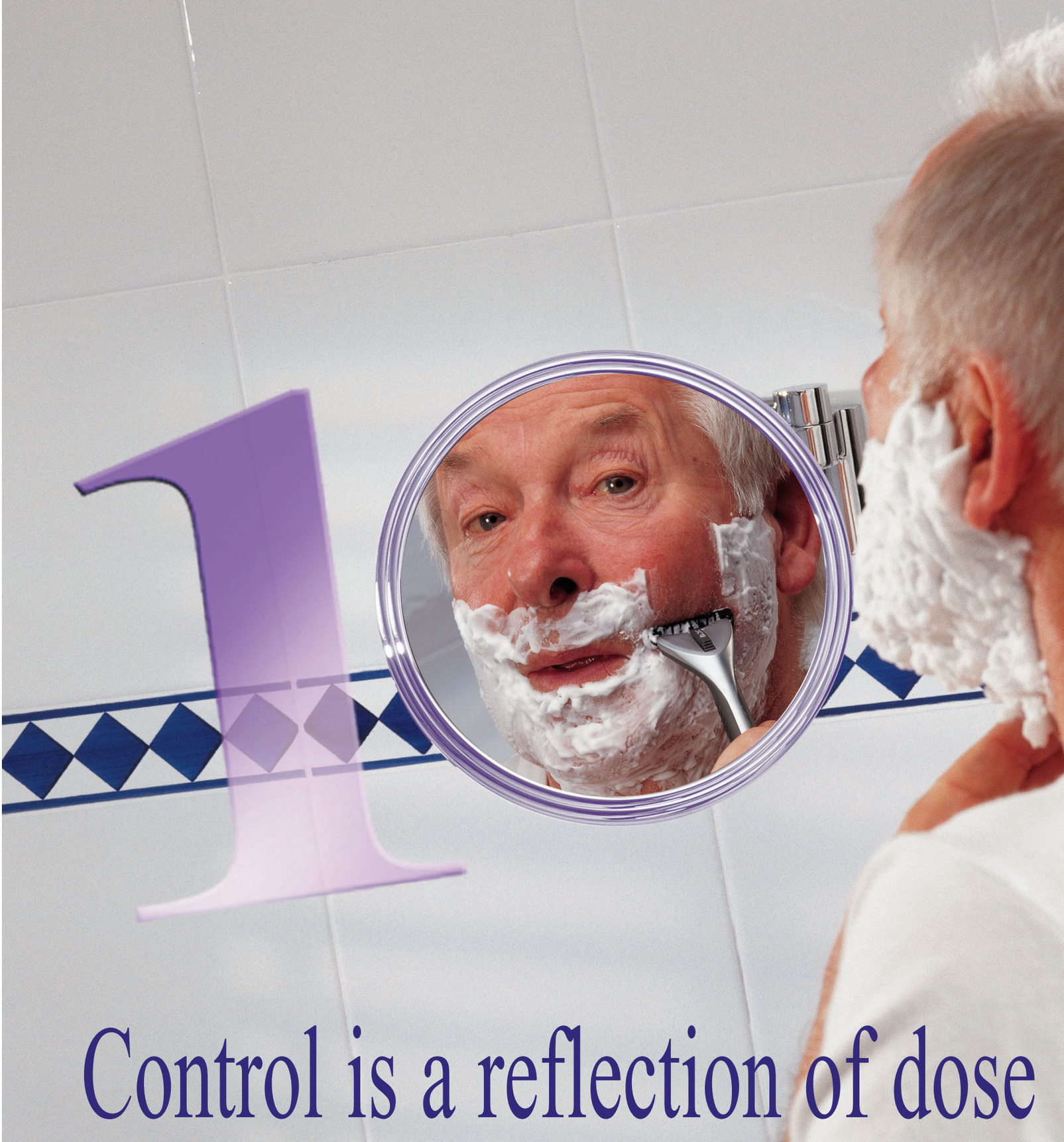
So there it is for another issue, if you have any ideas or thoughts on how to improve the journal (if that is possible!) or would like to suggest an article and author then do let us know. Finally many of you will be pleased to know Alasdair Coles has agreed (or been forced) to join me as Co-editor of ACNR.

Roger Barker, Editor
AdvancesinCNR@aol.com

Features

Regulars

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



Control is a reflection of dose

Move up to 10mg at 6 months

With ReQuip, stepping up the dose steps up the control.

In a landmark 5 year study[1] recently published in The New England Journal of Medicine, the full benefit of ReQuip was achieved in the upper dose range.

At 6 months the average dose was over 10mg/day.[2]

Dosage should be titrated against efficacy and tolerability.

REQUIP
ropinirole

TO START WITH AND STAY WITH

Editorial Board and regular contributors

Roger Barker is co-editor in chief of Advances in Clinical Neuroscience & Rehabilitation (ACNR), and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. He trained in neurology at Cambridge and at the National Hospital in London. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

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

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

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

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

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

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

How to assess reports of clinical results

Author

Dr Peter M Rothwell PhD MD MRCP

Peter Rothwell is an MRC Senior Clinical Fellow and Consultant Neurologist at the Radcliffe Infirmary, Oxford. He is Director of the Stroke Prevention Research Unit, funded by the MRC and The Stroke Association. Research interests include risk factors for ischaemic stroke, and the biology and management of carotid disease.

In recent years there has been a substantial increase in the number of randomised controlled trials (RCT) of treatments in neurology. This is a brief review of some of the questions to ask when assessing a report of an RCT. More detailed reviews are available elsewhere[1,2].

Was it randomised?

Randomisation (an experimental approach) has two main advantages over a non-randomised comparison (an observational approach). First, it ensures that clinicians do not know which treatment the patient will receive, and cannot select certain types of patients for one particular treatment. Second, it tends to result in an equal balance of baseline risk across the treatment groups. The importance of randomisation is not that no worthwhile observations can be made without it, but that major biases can occur in non-randomised comparisons. This is illustrated by a recent non-randomised comparison of the effect of aspirin dose on the operative risk of carotid endarterectomy (table 1, see facing page) which showed a clinically and statistically significant lower operative risk in patients on high dose aspirin (1300 mg) vs low dose aspirin (325mg or less)[3]. A subsequent RCT[4], performed to confirm this observation, showed that high-dose aspirin was, in fact, harmful (table 1). It is likely that the non-randomised comparison had been biased by unmeasured differences between the patients in low-dose and high-dose aspirin groups.

How was randomisation performed?

It is important that the method of randomisation is actually random. Treatment allocation according to day of the week, date of birth, date of admission, or alternate cases, is not random. The investigator will often know what treatment the patient will get if they enter the trial and so these methods are open to bias. Randomisation must be based on tables of random numbers or computer generated random allocation. It is also important that randomisation is secure.

Central telephone randomisation is preferable to other methods, such as sealed envelopes containing the treatment allocation.

Was it a pragmatic trial or an explanatory trial?

Whether the results of a trial can be applied in routine clinical practice depends on the type of trial. Explanatory (phase II) trials measure the effectiveness of treatment, whereas pragmatic (phase III) trials measure the usefulness of treatment. A treatment may be effective, but may not be useful because it is too poorly tolerated, too expensive, or too complex to administer. Explanatory trials are often small, include only a tightly defined group of patients, and frequently have non-clinical (surrogate) measures of outcome. Pragmatic trials seek to measure the usefulness of treatments in situations which, as far as possible, mimic normal clinical practice.

Can I apply the results to my clinical practice?

The results of an RCT may not be directly applicable to clinical practice. For example, a trial of carotid surgery might be confined to a small number of highly experienced surgeons with very low complication rates, or a trial of anticoagulation to prevent stroke might insist on much more frequent testing of the INR than is possible in clinical practice. In both cases, the risks of treatment are likely to be greater in everyday clinical practice.

Were the treatment groups balanced?

Details of the important clinical characteristics of the patients should be reported by treatment group. If a prognostic variable is particularly important, a relatively minor (and not necessarily statistically significant) imbalance between the treatment groups may have a major effect on the trial result.

How were patients selected, and what were the exclusion criteria?

The inclusion and exclusion criteria of a trial define the type of patient to whom the results can be extrapolated. Criteria can be much more exclusive than they seem. For example, the exclusion criteria of a recent trial of thrombolytic therapy for acute ischaemic stroke were so specific that only 0.4% of a typical population of stroke patients would have been eligible[5]. Even when the limit on time from stroke onset was ignored this only rose to 4%. In another acute stroke trial, one centre screened 192 patients over a two-year period, and found only one patient who could be randomised[6]. This is an extreme example, but trial entry rates of 10-20% are very common. Ideally, all trials should report the proportion of potentially eligible patients that were actually entered into the trial.

It is also important to check whether or not there are specific groups of patients to whom the results cannot be extrapolated. For example, trials of antiplatelet drugs often exclude patients with any history of upper gastrointestinal symptoms, no matter how mild or how long ago, in order to reduce the side-effects and risks of treatment. However, the results are then only applicable to about 50% of the patient population.

Was the trial sufficiently powered?

Sample sizes in RCTs in neurology may need to be large, either because treatment effects are relatively small, or because the progression of disease is slow (table 2, see facing page). The risk of getting the wrong result when a trial has an inadequate sample size is illustrated in figure 1. In this trial, there was consider-

Figure 1.

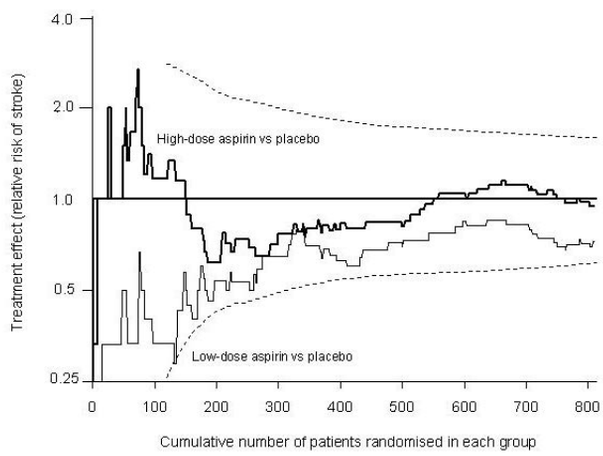


Figure 1: The evolution of the estimate of treatment effect in the UKTIA-Aspirin Trial (high-dose aspirin vs low-dose aspirin vs placebo in patients with TIA or minor stroke). The treatment effect calculated at each point is based on the outcomes at final follow-up for patients randomised to that point. The dashed lines represent the level at which the apparent treatment effect approached statistical significance at the P=0.05 level.

TOPAMAX® Abbreviated Prescribing Information.
Please read Summary of Product Characteristics before prescribing.
Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. **Uses:** Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. **Dosage and Administration:** Oral administration (not to be chewed). Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Renal disease may require a dose modification. Children 2 to 16: Approx. 5 - 9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1 - 3 mg/kg.
Sprinkle Capsules should be taken whole or sprinkled on a small amount (teaspoon) of soft food and swallowed immediately. **Contra-indications:** Hypersensitivity to any component. **Precautions and Warnings:** May cause sedation; so caution if driving or operating machinery. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen).**Side Effects:** Abdominal pain, ataxia, anorexia, CNS side effects, diplopia, fatigue, nausea, nystagmus, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis. **Pharmaceutical Precautions:**
Tablets: Store in a dry place at or below 25°C.
Sprinkle Capsules: Store below 25°C.
Legal Category: POM
Package Quantities and Prices:
Bottles of 60 tablets. 25 mg (PL0242/0301) = £22.02, 50 mg (PL0242/0302) = £36.17; 100 mg (PL0242/0303) = £64.80; 200 mg (PL0242/0304) = £125.83. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.88, 25 mg (PL0242/0349) = £25.32, 50 mg (PL0242/0350) = £41.60.
Product licence holder: JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE HP14 4HJ UK
Date of text revision: August 2000
APIVER250800

Date of preparation: July 2001
01759

JANSSEN-CILAG Ltd

TOPAMAX®
topiramate

Because life without seizures is so much better.

A FIRST CHOICE ADD-ON THERAPY FOR MOST SEIZURE TYPES

Table 1. The relationship between aspirin dose and the risk of stroke and death within 30 days of carotid endarterectomy in a non-randomised comparison within the NASCET trial[3], and in a subsequent randomised controlled trial[4].

	Operative risk of stroke and death			
Aspirin dose:	< 650mg	>650mg	Relative risk	P
NASCET	7.1%	3.9%	1.8	<0.001
ACE	3.7%	8.2%	0.45	0.002

Table 2. Effect of sample size on the reliability of the result of a trial of a hypothetical neurological treatment which is assumed to reduce the risk of a poor outcome by 20%, from 10% to 8%.

Total Patients	P*	Trial Power (%)	Comments on Trial Size
200	0.99	1	Completely hopeless
400	0.98	2	Still hopeless
800	0.96	4	Completely inadequate
1,600	0.90	10	Still inadequate
3,200	0.75	25	Not really adequate
6,400	0.43	57	Barely adequate
12,800	0.09	91	Probably adequate
20,000	0.01	99	Definitely adequate

* probability of failing to achieve p<0.01 significance if true relative risk reduction is 20%.

able variability in the apparent effect of treatment until several hundred patients had been randomised. If the trial had been small, misleading trends in treatment effect could easily have been reported.

Was the trial stopped early?

A trial may need to be stopped early if a treatment has serious adverse effects, or if there is clear benefit. However, as is seen in figure 1 the chance fluctuations during the early stages of a trial can easily reach statistical significance at the p=0.05 level. If the stopping rule is based on a p-value of 0.05, it is quite possible that the trial will be stopped early, and the wrong conclusions drawn. Stopping rules should be based on significance levels of p<0.01 or less, and the evolving results should be assessed on only a limited number of pre-specified occasions.

Was follow-up sufficient?

It important that the trial follow-up is sufficient to provide data on the usefulness of a treatment over a clinically relevant time period. For example, RCTs of new anticonvulsant drugs often have only a few weeks follow-up. This is insufficient to judge whether or not the treatment is clinically useful.

Was a surrogate outcome used?

Surrogate outcomes (e.g. infarct size on CT brain scan in an acute stroke trial, or MRI activity in multiple sclerosis) are often used to assess the effects of treatments. They can be useful in explanatory trials because they may be more sensitive to the effects of the treatment than clinical outcomes, and they are readily assessed blind to treatment allocation. However, they do not measure clinical effectiveness, and may sometimes be highly misleading. For example, a trial of three different antiarrhythmic drugs vs placebo after acute myocardial infarction assessed the frequency of ventricular extrasystoles on 24 hour ambulatory ECG monitoring[7]. All three drugs produced a substantial reduction in the frequency of extrasystoles, but the trial was subsequently stopped because of a major excess of deaths in the treatment group (33 vs 9, p=0.0003). Similarly, reduced bone density, which is known to be a useful marker for risk of fractures, was used as a surrogate outcome in a trial of sodium flouride in women with osteoporosis[8]. Sodium flouride produced a highly statistically significant, and apparently clinically important, increase in bone density. However, further follow-up revealed a 30% increase in vertebral fractures and a three-fold increase in non-vertebral fractures in the sodium flouride group.

Was outcome assessment blind?

There are two main reasons for blinding the trial clinicians. Firstly, so that the use of non-trial treatments and interventions is not influenced by a knowledge of whether or not the patients received the trial treatment. Secondly, so that clinicians are not biased in their assessment of clinical outcomes. The potential for bias depends on the subjectivity of the trial outcome. Biased assessment of neurological impairment and disability was clearly demonstrated in a multiple sclerosis trial in which blind and non-blind outcome assessment produced very different results[9]. Trials with blind assessment should also report whether or not blinding was effective. Non-blind trials should report data on non-trial treatments given to patients during follow-up to ensure that these were not biased.

Were serious complications of treatment included in the main outcome?

Some treatments have serious complications which should be included in the primary outcome, rather than relegated to a table of "side-effects" e.g. life-threatening gastrointestinal bleeding in trials of antiplatelet agents and anticoagulants.

Was the main analysis an intention-to-treat analysis?

The primary analysis in any RCT should be an intention-to-treat analysis i.e. patients remain in the treatment group to which they were originally randomised, irrespective of the treatment they eventually received. The alternative, an efficacy analysis (an analysis which is confined to patients who complied with the randomised treatment), is prone to bias. This was illustrated by the Coronary Drug Project[10], an RCT comparing several different lipid-lowering regimens with placebo following myocardial infarction. By intention-to-treat analysis, the five year mortality in the clofibrate group was 20.0% versus 20.9% in the placebo group. However, when patients who complied with treatment in the clofibrate group were compared with non-compliers the results seemed to suggest that there was a treatment effect: five year

mortality was 15.0% in the compliers versus 24.6% in the non-compliers. Perhaps clofibrate was beneficial. However, the same analysis in patients in the placebo group showed exactly the same trend: 15.1% mortality in compliers versus 28.2% mortality in non-compliers. The apparent effect of clofibrate in the treatment group was simply a bias due to the fact that patients who do not comply with treatment tend to have a worse prognosis.

Were any patients excluded from the main analysis?

It is common in reports of RCTs to find that a certain number of the patients who were randomised are excluded from the final analysis. A common reason for exclusion is that following randomisation it was found that a number of patients did not actually fit the eligibility criteria; so called protocol violators. However, the interpretation of what is a protocol violation can be rather subjective, and since the decision will often be made towards the end of the trial, and may not be blind to outcome, it is open to abuse. For example, 71 of 1629 patients randomised in a trial of an antiplatelet agent following myocardial infarction were excluded from the final analysis, apparently because they did not meet the eligibility criteria[11]. It subsequently transpired that there was a large excess of deaths in the exclusions from the treatment group compared with the placebo group[12]. Exclusion of these patients led to a bias which had contributed to the statistically significant apparent benefit in the treatment group. A second trial failed to confirm any benefit.

How many patients were lost to follow-up?

Another important potential cause of bias in the analysis of trial results is loss of patients to follow-up. Just as patients who comply with treatment are different from patients who do not, patients who are lost to follow-up are usually different from those who remain in the trial. For example, it may not be possible to contact patients because they are either incapacitated in some way, or even dead. It is therefore very difficult to interpret the results of a trial with significant loss to follow-up.

References

1. Friedman LM, Furburg C, DeMets DL (1996). *Fundamentals of clinical trials*, 3rd ed. St Louis, MS: Moseby.
2. Collins R, Peto R, Gray R, Parish S (1996). *Large scale randomised evidence: trials and overviews*. In: Weatherall D, Ledingham JGG, Warrell DA, eds. Oxford Textbook of Medicine. Oxford; Oxford University Press.
3. North American Symptomatic Carotid Endarterectomy Trialists' Collaborative Group (1998). *The final results of the NASCET trial.* N Engl J Med; 339: 1415-25
4. Taylor DW, Barnett HJM, Haynes RB *et al* (1999). *Low dose and high dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial.* Lancet; 353: 2179-84.
5. Jorgensen HS, Nakayama H, Kammersgaard LP *et al* (1999). *Predicted impact of intravenous thrombolysis on prognosis of general population of stroke patients: simulation model.* BMJ 1999; 319: 288-89.
6. LaRue LJ. Alter M, Traven ND *et al.* (1988) *Acute stroke therapy trials: problems in patient accrual.* Stroke; 19: 950-954.
7. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *Preliminary report: effect of encainide and flecainide on mortality in a randomised trial of arrhythmia suppression after myocardial infarction.* N Engl J Med 1989; 321: 406-412.
8. Riggs BL, Hodgson SF, O'Fallon WM *et al* (1990). *Effect of flouride treatment on fracture rate in postmenopausal women with osteoporosis.* N Engl J Med 1990; 322: 802-9.
9. Noseworthy JH, Ebers GC, Vandervoort MK, Farquhar RE, Yetisir E, Roberts R. (1994) *The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial.* Neurology;44:16-20.
10. Coronary Drug Project Research Group (1980). *Influence of adherence to treatment and response to cholesterol on mortality in the Coronary Drug Project.* N Engl J Med; 303: 1038-41.
11. Anturane Reinfarction Trial Research Group (1980). *Sulfinpyrazone in the prevention of sudden death after myocardial infarction.* N Engl J Med; 302: 250-56.
12. Temple R, Pledger GW (1980). *The FDA's critique of the Anturane Reinfarction Trial.* N Engl J Med; 303:1488-92.

Correspondence Address

Peter Rothwell, Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.
Tel: 01865 224237, Fax: 01865 790493
E-Mail: peter.rothwell@clneuro.ox.ac.uk

Ethical barriers to research into diseases of the human brain

This article by Professor Charles Warlow is a transcript of a lecture he gave at the British Association Science Festival this September in Glasgow. We have decided to include it in its entirety because of its importance to research in this country, especially epidemiological studies. The implementation of the new Data Protection Act has important consequences to all those involved with clinical research and whilst the article represents the personal views of Professor Warlow, it nevertheless highlights a number of issues that are relevant to all practising neurologists and associated specialists. - RB

Introduction

I must confess three conflicts of interest. Firstly, I am a doctor. We doctors are under attack as never before, by the media, by politicians, by patients and their organisations, and by ethicists. We are said to be incompetent, paternalistic, unable to adapt to new information and new ways of working, and some are even murderers. So I feel undervalued, threatened and vaguely anxious. I am defensive. Maybe I should retire a bit early. Secondly, I do research, not with molecules, test tubes or rats, but with people who are usually but not always patients. But we researchers are mistrusted, we exploit our patients, we recruit them into research projects for our own financial and academic gain without telling them. We cheat, we lie, we are fraudulent. Again, I feel threatened and definitely anxious. I am more defensive. Maybe I should give up research and do commercial practice instead. And thirdly, I have been a patient. My health was certainly threatened and sometimes I felt more than just anxious. Very likely I will be a patient again. So rather than being defensive, about being a patient as well as a doctor and researcher, I will exploit my third conflict of interest and tell you how medical research is obstructed by people who, although not representing patients, believe they have our patients' best interests at heart. But the ethical barriers these people construct to protect my privacy and rights are wrecking the research that will help me, and thousands of patients like me. I will tell you four stories about me the patient, the first three true, the last imaginary.

Author

Professor Charles Warlow is Professor of Medical Neurology in the University of Edinburgh, having previously been in the Department of Neurology, Radcliffe Infirmary, Oxford. He leads a large research team into clinical aspects of stroke and its management, as well as having more general interests in neuro-epidemiology and clinical trials. He was, for instance, one of the main forces behind the MRC European Carotid Surgery Trial whose final results were reported in the Lancet in 1998. He is the principal author of one of the major stroke textbooks (Stroke: a practical guide to management. See our book review on page 35). Charles Warlow is currently President of the Association of British Neurologists.

The appendix story

In 1966 I developed appendicitis and the offending vestigial organ was removed and put into a pot of formalin. As you know, partly thanks to recent media coverage, pathologists tend to keep removed organs, they might be useful in the future, one can't tell at the time. But, even long before the Alder Hey business of retained body parts of dead children which led to a wholesale clearing out of retained organs all over the country, it was not that easy to keep things in pots. They took up too much space. But some places managed, and just suppose my appendix, and others, is still there in Cambridge where I left it. And further suppose that today researchers into variant Creutzfeldt-Jakob Disease (CJD) want to find out, in their search for the origins of what may become a public health disaster of unimaginable proportions, whether the infectious particles called prions - the presumed cause - were actually around long before the Bovine Spongiform Encephalopathy (BSE) epidemic in cattle in the 1980s. Maybe variant CJD is nothing to do with BSE, maybe British beef is OK after all, maybe variant CJD was there all along and we could prove that by finding the offending prions in the appendix long before there were any brain symptoms. The quickest and easiest way would be to look in retained appendices like mine, and to link the patient names to the centrally held death certificates. Have there been more deaths due to CJD in those with, compared to those without prions? But this research can no longer be done. Retained organs have been cleared out, maybe including my old appendix, because we the patients were not asked for our permission to have our organs retained - a scandal we are told. The real scandal is that I have not been asked if my potentially useful appendix can be destroyed. In truth, I don't much care what happens to my discarded organs, but I do care about the witch hunt against pathologists who have material which may lead to us all being healthier if it can be exploited by bone fide medical research.

But, irrespective of the retained organs hooha, this research cannot now be done because we patients had not been asked our consent for our medical records - personal data - to be used for some future, and at the time, impossible-to-specify medical research. The 1998 Data Protection Act has done in that sort of opportunity. Although the Act does not apply to dead people, the researchers do not know who is dead and who isn't when they examine the medical records from 35 years ago. So, this research avenue is blocked by the current obsession with patient confidentiality. What if there were prions in some appendices? What if those patients with prions had given blood which we could find out, and might give blood again? And what if that blood causes CJD which we could also find out if we looked at the medical records of the blood recipients, albeit without their consent - consent to be scared witless that they might develop an incurable disease? I would sue for causing anxiety if anyone told me that I might develop an incurable disease which no one could prevent. Far better the researchers find out without bothering me. But no, I have to be told or the research has to be done another way, or we give up on blood transfusion from UK donors at enormous cost and inconvenience to us all - perhaps unnecessarily. Today, the ethical imperative enshrined in personal data protection ignores the other side of the coin, responsibility to society and the greater good. The most eminent epidemiologist in the UK, Richard Doll, who discovered the link between smoking and lung cancer, and his longstanding colleague Richard Peto, put this point rather well. "The right to medical care should generally continue to include the responsibility to allow the information gained in its course to be used for others who develop a similar disease, or are at risk of developing it".

In fact the Data Protection Act is probably not all that restrictive, but it has been interpreted as being so, albeit with different consequences. In England, legislation was rushed through Parliament just before the last general election. Section 60 of the Health and Social Care Act 2001 allows the Secretary of

State to sanction the use of patient data in the public interest but the bureaucracy and expense required for researchers to gain permission will be enormous - the red tape will kill off the research before it even starts. No mechanism to do this seems to be in place. Research using medical records will shudder to a halt. In Scotland, the Confidentiality and Security Advisory Group for Scotland (CSAGS) means to recommend to Ministers that "unless data is acceptably anonymised, informed consent must be obtained before processing". This will wreck medical research. Actually, although the Data Protection Act states that any use of personal identifiable data relating to the "physical or mental health or condition" of a living individual requires their informed consent, it adds an or - or that the "processing is necessary for medical purposes", and this does include research. However, the Act has been interpreted very differently by different bodies who offer conflicting guidance - some insist that consent must be obtained for every research use of personal data unless they are anonymised. But this is often impractical, expensive, or plain impossible. If patients are to be followed up, one needs to know who they are! One has got to look at the records for things like past exposure to medications, for example the oral contraceptive in a study of leg vein thrombosis in air travellers. The most important guidance for doctors comes from the General Medical Council (GMC) but even here there is confusion. The GMC do sanction the use of medical records where "you are satisfied that it is not practicable" to obtain consent and it is in the public interest to do so, but patients still have a right to object. Not only would the research be jeopardised if a lot of patients objected, but the door seems open to litigation against bone fide medical researchers.

The broken leg story

Second story. In 1993 I broke my leg, conveniently for the ambulance not up the mountain but - ridiculously - at the bottom, in the car park. It was straightened out and an alloy pin put down the middle of my tibia, where it still is. It is not at all clear whether that pin should come out. This would require a few days in hospital, an anaesthetic, possibly bone infection, and certainly some time hobbling around afterwards. Best avoided, unless...unless what? Who knows, but might that alloy gradually degrade, might some particles get into my brain, might that cause me to get unsteady on my feet, is my own increasing but still minimal unsteadiness due to natural ageing or that old metal pin? Should all such pins come out forthwith from thousands of limbs around the world? Seems a reasonable question to me, the patient. So a researcher might want to contact me and others like me to ask about my balance and compare our answers with those whose pins have been removed. To do so, the researcher would need to get my name from the Stirling Royal Infirmary and that would require the permission of my surgeon. But he is retired now, possibly gone to Saudi Arabia to earn lots of money for all I know, possibly dead. First obstacle. But even with the surgeon's permission, the researcher cannot look at my medical records without my permission too which at the time I was not asked. The Data Protection Act seems to require it now according to many authorities, including the CSAGS in Scotland. Second obstacle. So the researcher needs to find me, and I have moved twice since 1993. Third obstacle - check. Even trickier, the hospital refuse to give the researcher my name without my permission. Final obstacle - check mate, end of research, we don't know what to do about the pins, and I the patient lose out because some busybody is protecting my privacy which, for medical research, I would be happy to give up. Who asked my opinion as a patient? Nobody.

The colon cancer story

Third story. In 1995 my cancerous colon was removed. Suppose some researchers had been looking at the genes in my personal bit of cancer (assuming the pathology department retained my colon, which might not happen now given the witch hunt). They would like to know (and so would I) if a particular gene abnormality is associated with a high risk of a secondary growth in my brain. To do that, they need to follow up hundreds of people like me to find out. They could do so rather easily in Scotland where you can track the same person from each hospital in-patient episode to their eventual death certificate. It would be easy to track me and my fellow cancer patients until we had a brain secondary, and then compare our genetic abnormalities with the other colon cancer patients who did OK. Impossible now, without my permission. None of my personal details can be released, not even my name. Even if the researchers could get my name from the records system, find me years later, and ask for my consent I might be already dead, I might be difficult to find, I might be in the midst of a recurrence and not too keen to fill in a questionnaire, I might be chronically anxious and so terrified of any recurrence that any reminder would make me suicidal, I might have emigrated because I felt so well, or I might be on a cruise enjoying the last days of my life. There are all sorts of reasons for the researcher not to be able to find all us colon cancer patients, and to find out how we are, without using hospital information systems. But maybe the researcher has a go but he will never find us all so long after surgery. However, say he discovers that a gene abnormality seems to be associated with brain secondaries. But this could be complete nonsense if more of those without than with the gene abnormality were actually very well and couldn't be followed up because we had moved cheerily away. Or, the other way round, the researcher finds no association although there really is one, because more of those with than without the genetic abnormality are away on that terminal cruise and cannot be traced. Conclusions based on data from incomplete follow up of patients to relate some baseline factor to their eventual outcome are likely to be biased. We have no idea which way any bias goes, and how big it is, and so our conclusions are unreliable, possibly dangerously wrong. How irresponsible can you get? But tough, patient rights stop these lines of research. Responsibilities are for someone else to worry about. But I the patient am incensed that research cannot be done on my disease using my records, even without my consent. In the future, at every point they encounter the health care system, it is likely that patients will be asked if their records can be used for research. The systems to do this are far from up and running, to work they will have to be enormously expensive taking resources away from the clinical service. What happens if a patient changes their mind, how are refusers to be reliably identified as they pass through the health system (a black spot on their forehead)? And another thing, as a cancer patient, I am incensed that all the UK Cancer Registries may have to close down such is the obsession with patient confidentiality.

My objections, as a patient and as a researcher

These three stories illustrate how medical research is obstructed by the current demand that to look at patient records always requires the patient's consent, either at the time when the records were made or later, and moreover - in some instances - the patient's explicit consent for a specific research project, not blanket consent for any research. Consent is compulsory in the Scottish CSAGS document. There is no waiver. How ridiculous can you get? Why can't my records be used by any bone fide researcher who is interested enough in my disease to help me, or at least others with my disease? Who do I the patient com-

plain to about this nonsense? Of course if the privilege of looking at patient records had been frequently abused, there would be cause for alarm. But it hasn't. How many of you know of any case where confidential patient records have been given to a third party by a researcher? Last October, a British Medical Journal editorial asked the very same question, and no one has come up with an example. Of course, research should be carefully designed, thought about by researchers and their peers, and passed by a research ethics committee. But it is totally impractical to ask every patient at every medical contact for their permission for their records to be used for research - maybe - at some later date. Even if it was practical, and here we are on more dangerous ground, why should some patients opt out of research on just their records which would be in the public interest? We are not talking about the use of personal data to track our buying habits in Tescos, nor where we last used our mobile phone, we are talking about our health. Of course patients have rights, but rights come with responsibilities, and we all have responsibility to the society that looks after us when we are sick. We benefit from the fruits of medical research when they apply to us personally. Do these "you are not looking at my notes" patients understand what they are doing by denying access to their medical records for bone fide well constituted medical research in everyone's best interest? What right have those opting out to obstruct the public interest for their own selfish ends? If they had received a bottle of blood contaminated by CJD, and if there turned out to be a way of preventing infection because all those appendices had given us a clue, should the opters out benefit from this information? Is it OK if the results of research based on the records of the other people who do consent are then applied to the benefit of the objectors? Not in my book. Perhaps the objectors would like several bottles of blood?

"These three stories illustrate how medical research is obstructed by the current demand that to look at patient records always requires the patient's consent, either at the time when the records were made or later, and moreover - in some instances - the patient's explicit consent for a specific research project, not blanket consent for any research... How ridiculous can you get?"

The stroke story

Now I am going to imagine that one day, like my mother, I have a stroke and am rushed to hospital where a stroke team is waiting to give me the best possible care. They are doing research too, and are testing a treatment which may - just may - reverse my stroke and restore me to normal. But there are risks, it may - just may - kill me. They need to know, and so do future stroke patients, whether the benefits are worth the risks. The only way to find out reliably is by randomly allocating hundreds of patients like me to either the new treatment as well as the current best care, or to the current best care alone and seeing how we get on. Half the patients get the new treatment with its benefits and its risks, whatever they both are and whatever the balance between them turns out to be. The other half get the current best care and lose out on any benefits of the new treatment if there really are any, but also avoid the risks. This is a randomised controlled trial. Remember at this stage no one knows what the balance of risk and benefit is for me in particular with my stroke, and nor for stroke patients in general. But, after the trial, we will all know whether future patients like me are, on average, benefited or harmed by the new treatment and clinical practice can be altered appropriately.

The researchers have consulted far and wide with other researchers and doctors, the research has been approved by numerous research ethics committees up and down the land, and it has been funded by the Stroke Association, the main charity in the field. But, all these well meaning people trying to do their best for me and other stroke patients are obstructed by those who say that to protect my rights as an incapacitated adult I must have the research explained to me, including the risks, and that I must consent to being in the trial. But the stroke has rendered me unconscious and - to add to the dilemma - let me tell you that the new treatment is unlikely to work unless it is given within three hours of stroke onset, the sooner the very much better. My stroke started two hours ago. What is the researcher supposed to do? Ask my partner for her approval? She may be dead. Ask my brother? He could be in Australia. Ask my children? On holiday. Anyway, the assent of someone for research on me is not, in English law, regarded as my consent, although this has never been challenged. So far, research ethics committees have taken a pragmatic view and randomised trials involving assent are quite common. In Scotland, however, the new 'Adults with incapacity (Scotland) Act 2000' - designed to protect the rights of incapacitated adults - will stop randomised trials in emergency situations. Because, in Section 51 we are told that "before any research involving an adult is undertaken consent must be obtained from the adult's proxy or next of kin". But, all this could easily take far too much time - "time is brain" is the current slogan and I will have run out of both. So no trial can be done, and we will never know if the new treatment works or not. As a potential stroke patient, I am incensed but the Act is the law now, at least in Scotland. I wonder what other stroke patients have to say? Have they been consulted? I doubt it.

Perhaps the new treatment could be tried just on those able to consent to enter the trial? Yes, but they would have mild strokes and it may be that for them the hazards of the treatment are greater than the benefits because they may recover without the treatment, unlike the unconscious patient at death's door. Could the research be done on rats? No, they are different to humans. Could the research be done in countries with a laxer attitude to patient protection? Of course not, it would be outrageous to do research elsewhere just because it is unacceptable here. It has to be done here and now in suddenly incapacitated patients. It is the same problem for patients who drop unconscious in the street with a cardiac arrest, or who have a severe head injury. Are they to be denied new treatments because the research to test new treatments is impossible because of the ethical and legal obstructions? Whose side are the obstructionists on? What right have they to deny my right to have treatments tested on me for the benefit of others with my disease, and the rights of those future patients too?

A possible solution

So what can we do about unconscious patients, or others unable to give their own consent to enter a randomised trial in an emergency situation? Waiver of consent is really the only solution, at least unless assent can be obtained very quickly from a close relative and is regarded as sufficient, as it now is in Scotland. This waiver of consent - and wherever possible deferred consent at a later more reflective time - now happens

in the USA but only if the trial has been carefully vetted by peers and a research ethics committee, and has been disclosed to and approved by the community, and the results eventually made public. Earlier this year the New England Journal of Medicine published a trial showing that cooling down acute head injured patients did not work. In the words of the editorialist "This study would never have been completed without the provision that waived the requirement to obtain consent for the enrolment of 38% of the patients," and he later remarked "The period during which an intervention is likely to be effective is short, and by the time consent is obtained by traditional means the treatment may be futile". So where does that leave testing emergency treatments in acute stroke, head injured and cardiac arrest patients in Scotland? I fear nowhere, the research will stop. I am told it is unethical.

I believe that as well as waiver of consent for emergency treatment trials we should involve patients much more explicitly in agreeing that the trial should be done in the first place and helping in its design. For stroke we should and could - and indeed have - talked with stroke patients and with older people who are the type of person who may have a stroke. I value these people's views more than any number of ethicists, lawyers, politicians and media commentators. Those of us involved with research must try again and again to explain what we are doing, why, and how it really is for the greater good. Let the objectors come and talk with real patients and ask them what they think, not to some university or Fleet Street crony. Let them try getting full frontal informed consent from a sick patient frightened out of their mind that they are about to die and who is barely competent to understand anything very much - waiver of consent is surely the kinder and more appropriate option if no proxy is instantly available. Mind you, the ethicist would demand that we first get the patient's consent to be approached by anyone other than the doctor!

We researchers do not benefit anyone by backing off, throwing away usefully retained organs, ignoring the public health gold mine in patient medical records, and abandoning randomised controlled trials in unconscious patients.

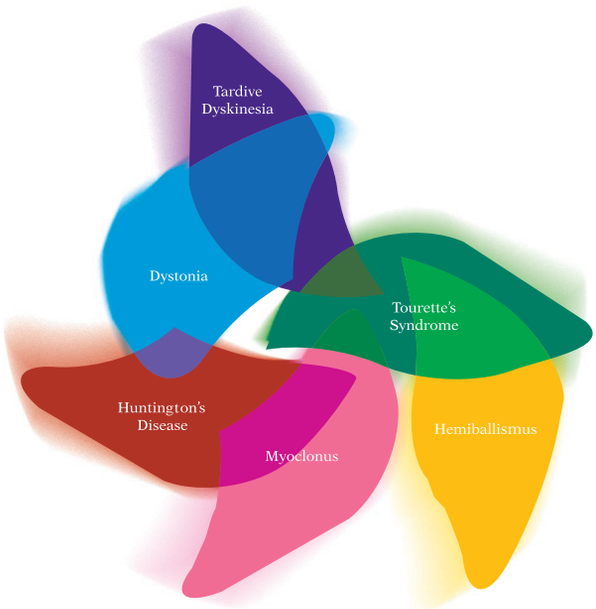
> "How many of you know of any case where confidential patient records have been given to a third party by a researcher? Last October, a British Medical Journal editorial asked the very same question, and no one has come up with an example."

Wasting time

In this current climate of suspicion of doctors and our research, and of litigation and recrimination which leads to defensive and so bad, risky and expensive medicine, we must be open and we must explain. We must defend our position to all comers. It may not seem very professional to grapple with the media, most doctors hate it. If ethicists and others dominate the airwaves it is because we doctors are not prepared to get in there and debate the issues. Of course all this wastes doctor and researcher time. This is not what we are paid to do, it is our evening and weekend work not the daytime work of the journalist and ethicist. One of our research fellows has wasted weeks wading through the ethical swamps trying to get an innocuous research project agreed, funded and done in Scotland. Just getting ethics committee approval required literally more than an arm and a leg - you don't believe me? The overwhelming red tape required nearly 6000 sheets of A4 paper and that weighed 27kg! Understanding the 1998 Data Protection Act has been a nightmare and I don't think we do yet. Certainly others have not succeeded because gathering together, reading and trying to make sense of all the guidance from august bodies based on the Act reveals inconsistency and confusion. Another colleague has wasted weeks trying to explain to civil servants and politicians that the Adults with Incapacity (Scotland) Act will stop all randomised trials in acute stroke, head injury and cardiac arrest.

Trying to repair the damage to medical research - and to the health of patients like me - by those who have the best interests of us patients at heart, but who simply have not thought through the consequences of their actions, has been and still is a huge waste of time. It is dispiriting for us doctors and researchers. We should be doing medicine and research or at least fighting other more important battles - medical fraud, bribery dressed up as marketing, and the over-influence of pharmaceutical companies on medical research. But those are other stories. In the meantime we are kept far too busy dealing with the ethical barriers which obstruct bone fide - and ethical - medical research. We doctors, we researchers and we patients have grounds for complaint.

What do these movement disorders have in common?



They *all* respond to Xenazine™ 25[1]

tetrabenazine

Although the diagnosis of a hyperkinetic movement disorder can be devastating, help is at hand in the form of Xenazine™ 25, an established agent with proven efficacy in the suppression of involuntary movements.[1-5] Xenazine™ 25's benefits include excellent, sustained response and good tolerability.[1] What's more, Xenazine™ 25 has an indication for patients with tardive dyskinesia.[1,4,5] So consider Xenazine™ 25 for *your* patients – it could well prove to be the right move.

Xenazine™ 25
tetrabenazine
movement through choice

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.

References: 1. Jankovic J, Beach J. *Neurology* 1997;48:358-362. **2.** McLellan DL et al. Lancet 1974;1:104-107. **3.** Shoulson I and Goldblatt D. Neurology 1981;31:79. **4.** Ondo WG, Hanna PA, Jankovic J. *Am J Psychiatry* 1999;156:1279-1281. **5.** Watson MWB, Skelton D, Jamali F. *Can J Psychiatry* 1988;33:11-13.

Cambridge LABORATORIES
Serving the needs of Healthcare Specialists

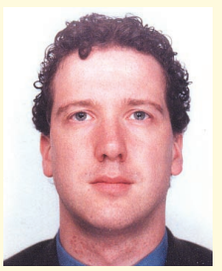
Deltic House, Kingfisher Way, Silverlink Business Park, Wallsend, Tyne and Wear NE28 9NX. Tel: 0191 296 9300 Fax: 0191 296 9368
www.camb-labs.com

CL/TET019

Neuropsychiatry of Huntington's disease

Author

Dr John D C Mellers is a consultant psychiatrist in the Neuropsychiatry Unit at the Maudsley Hospital and at the Royal Hospital for Neuro-disability, London.



Niall Pender is a Neuro-psychologist 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 Neuro-psychology 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.

Emotional and behavioural changes are often the earliest clinical manifestation of Huntington's disease (HD) and may precede more obvious signs of dementia and movement disorder by several years. Up to 40% of patients with HD are likely to be misdiagnosed initially as having a primary psychiatric disorder[1]. Neuropsychiatric problems have a profound impact on quality of life for the individual with HD and are probably the most distressing aspect of the disease for families and care providers. An understanding of these problems and an informed approach to their management is therefore critical for anyone involved in the care of patients and families affected by this devastating disorder.

Personality Change

The early emotional, behavioural and cognitive changes in HD are best understood as a frontal disconnection syndrome. Although pathological abnormalities are relatively confined to the basal ganglia, in particular to the corpus striatum in the early stages of the disease, cell loss in these areas is associated with disruption of cortical pathways. A wave of cell loss begins within the caudate, starting antero-medially and spreading ventro-laterally. Thus the first cortical areas affected are frontal and personality changes are the conspicuous clinical feature. The earliest change is often emotional with irritability and a reduced tolerance of frustration. While triggers for outbursts of anger often remain easily identified the episodes become increasingly explosive and disproportionate. They also become more difficult to defuse and carers learn that it is better to walk away from an argument than try to resolve it. Irritability and emotional lability are often accompanied by impulsivity and disinhibition - the so-called pseudopsychopathic syndrome of frontal lobe impairment, associated with impairment in the orbitomedial prefrontal cortex[2]. This may co-exist with the contrasting pseudodepressive state of apathy and self-neglect (thought to be more closely associated with dorsolateral prefrontal dysfunction). Irritability and apathy are more common in HD compared with Alzheimer's disease, each symptom occurring in 60 and 50% of HD patients respectively[3]. Similar figures were obtained more recently using the Neuropsychiatric Inventory[4]. As the disease progresses, intellectual impairment dominates the clinical picture. Mental slowness, perseveration and impairments of judgement, reasoning and planning contribute to behavioural problems. The patient's mental and behavioural repertoire becomes increasingly narrow. Agitation and aggression in the latter stages of the disease often arise in the context of fixed preoccupations that are not amenable to explanation or reassurance. Patients sometimes appear to become stuck in a perseverative loop in which they dwell endlessly on a particular worrying issue leading to a vicious circle of mounting distress driven by seemingly inescapable, repetitive negative cognitions.

Affective Disorder

Estimates of the prevalence of affective disorder in HD vary widely depending on the patient sample studied and the diagnostic criteria used. Up to 40% of patients will suffer a significant episode of depression at some stage in the course of their illness[5,6,7]. Hypomania (and mania) are seen in between 5 and 10%[8]. Anxiety disorders are common but their prevalence has not been systematically studied. As with personality changes, depressive episodes may occur before other signs of the disease are present, leading some to stress biological aetiological factors. However, as with other neuropsychiatric problems in HD (and indeed in other neurological conditions), a multifactorial aetiology must be considered. Living with the risk of developing HD and witnessing parents or siblings develop the disorder obviously represents a significant predisposing stressor for depression even when the individual themselves is asymptomatic. The development of more obvious clinical symptoms and the individual's growing realisation that they are affected often coincides with the stresses of early adult life, including marriage, the responsibilities of a family and establishing a career. The indirect social consequences of the disease, such as marital breakdown, unemployment, and estrangement from family and social supports, contribute further as precipitating and maintaining factors for emotional problems in HD.

Suicide

The risk of suicide is greatly increased in HD and up to 6% of patients with the disorder will take their own lives, at least a 4 fold increased risk compared with the general population. Suicide rate is increased not just in those with the disease but also in family members regardless of their risk status[9]. Others have found that the single most predictive factor against suicide was having children[10]. Factors associated with an increased risk were being unmarried, living alone, having a family history of suicide and having no contact with others suffering from HD. These findings emphasise the tremendous importance of social supports for patients with the disorder.

Psychosis

Psychotic disorders resembling schizophrenia occur in between 3 and 12% of patients[11]. Psychotic states with prominent persecutory delusions but relatively little in the way of hallucinations or other psychotic symptoms, referred to in the earlier literature as atypical psychosis, may be more common than schizophrenia-like states but prevalence is difficult to establish. In the more advanced stages of the disease a comprehensive assessment of mental state is often very difficult and it may not be possible to elucidate clearly the nature of abnormal experiences or beliefs. In some cases psychosis can only be inferred by observations of behaviour.

Management

Cognitive impairment and communication difficulties may make psychiatric assessment difficult in HD[12]. Patients may deny they are ill. Sometimes this reflects loss of insight as part of a psychotic illness, but more often it is better understood as a form of intense self-deception, perhaps facilitated by subtle cognitive impairments and temperamental changes. An informant history is very important, especially if there is any suggestion of risk. On occasions detention and treatment under the Mental Health Act (MHA) may be required. Unfortunately in clinical practice there is still a reluctance to use the MHA in patients with HD because

the illness is seen as neurological rather than psychiatric or because it is untreatable. When patients with HD develop psychosis there is seldom a debate. But even when behavioural problems arise as a direct result of the dementing process, in the absence of any secondary psychiatric disorder, there should be no doubt that the patient does indeed suffer from a mental disorder within the meaning of the MHA and that compulsory assessment and or treatment may be indicated if there are compelling reasons in the interests of the patients health or safety or for the safety of others. In this context it is important to recognise that nursing care may be regarded as treatment within the meaning of the MHA.

Treatment starts with explanation and many families are greatly helped simply through a medical understanding of the changes in behaviour and personality they see. Contact with specialist services is ideal but their availability is highly variable from one region to another. Unfortunately the existence of such services depends more on the interests of local consultants than on any strategic service planning. Patients with HD pose the familiar challenge of patient groups affected by joint mental and physical problems in that psychiatric services lack the resources to deal with physical disability and services for the physically disabled complain of an inability to effectively engage mental health services. In this country the Huntington's Disease Association plays an invaluable role in providing information both to affected families and to professionals who have not encountered the disorder before. They are also able to advise on referral to specialist services at all stages of the illness.

Neuropsychiatric pharmacological treatment in HD has recently been reviewed[13]. The empirical evidence for individual treatments is scant and the literature consists mainly of case reports and small case series. In general, the indications for treating psychiatric syndromes are as they would be in the absence of HD, the choice of drug being dictated by side-effect profile, in particular by the likelihood of exacerbating physical symptoms of the disorder.

1. Antidepressants are effective and the modern generation of compounds are better tolerated than tricyclics. The anticholinergic effects of the latter are particularly problematic as they may exacerbate cognitive impairment. However, some of the less selective modern compounds, for example sertraline and venlafaxine in higher doses, have a prominent dopaminergic action and may result in an unacceptable exacerbation of involuntary movements. ECT is effective and well tolerated in severe depression.

2. Conventional antipsychotic agents are effective in the treatment of psychosis but carry the theoretical risk of exacerbating involuntary movements in the longer term through tardive dyskinesia. For this reason atypical agents are probably the treatment of first choice in psychosis. The appetite stimulation and weight gain associated with olanzapine that is usually regarded as an adverse effect may be beneficial in patients with HD.

3. Treatment of aggression must focus on the underlying causes: antipsychotics are indicated where aggression arises in the context of psychosis, antidepressants where the patient is depressed. Where aggression occurs in the context of dementia and organic personality change there is a largely anecdotal literature describing the use of beta-blockers, SSRI antidepressants, anti-epileptic drugs, lithium, neuroleptics and benzodiazepines. It is doubtful whether any of these drugs have an effect on aggression over and above a general sedative action. The exceptions to this are beta-blockers and SSRI's, neither of which are sedative, but the evidence of their efficacy is sparse and in both cases there are reports of paradoxical exacerbations of agitation.

In a similar manner there are little data available on psychological treatments for challenging behaviour. In the early phases psychological management techniques such as Cognitive Behavioural Therapy can be useful in enabling the individual to cope with the condition. However, as the patient's cognition deteriorates, their thinking becomes more rigid and perseverative and insight diminishes the use of such techniques becomes limited. Behavioural techniques such as differential reinforcement within the context of a planned behavioural treatment regime may also be helpful. Furthermore, emergency response strategies as such as antecedent control and stimulus change can enable the safe management of challenging behaviour using positive approaches[14].

Summary

Patients with HD present with many complex and challenging behaviours that require careful and balanced management. Such treatment must be applied with knowledge of the progression of the condition and an awareness of the associated impairments. One must balance the necessary treatment of one set of difficulties with the possible exacerbation of others. Impairments in communication, cognition and movement increase the difficulty of diagnosing and treating such difficulties. However, the appropriate and timely treatment of neuropsychiatric conditions can improve the daily functioning in patients with an apparently deteriorating condition.

Acknowledgements:
Niall Pender is supported by a grant from the Neuro-disability Research Trust.

References

1. Dewhurst, K. Oliver, J. E; McKnight, A. L. (1970) *Socio-psychiatric consequences of Huntington's disease.* British Journal of Psychiatry, Vol. 116 (532), 255-258.
2. Lishman, W.A. (1997). *Organic Psychiatry. 3rd edition.* Blackwell Scientific Publications. Oxford: UK.
3. Burns, A., Folstein, S., Brandt, J., Folstein, M., (1990). *Clinical assessment of irritability, aggression, and apathy in Huntington and Alzheimer disease.* Journal of Nervous & Mental Disease, Vol 178(1), 20-26.
4. Paulsen, J.S., Ready, R.E., Hamilton, J.M., *et al.*, (2001). *Neuropsychiatric aspects of Huntington's disease.* Journal of Neurology, Neurosurgery and Psychiatry, 71, 310-314.
5. Shiwach R. (1994). *Psychopathology in Huntington's disease patients.* Acta Psychiatrica Scandinavica, 90(4), 241-6.
6. Folstein, S. E., Leigh, R. J., Parhad, I. M., Folstein, M. F. (1986). *The diagnosis of Huntington's disease.* Neurology, Vol 36(10), 1279-1283.
7. Troster, A.I. (1999). *Movement and demyelinatng disorders. In P.J. Snyder and P.D. Nussbaum (eds).* Clinical Neuropsychology: A pocket handbook for assessment. American Psychological Association. Washington: UK
8. Mendez MF. (1994). *Huntington's disease: update and review of neuropsychiatric aspects.* International Journal of Psychiatry in Medicine, 24(3), 189-208.
9. Di Maio L. Squitieri F. Napolitano G. *et al.*, (1993). *Suicide risk in Huntington's disease.* Journal of Medical Genetics, 30(4), 293-5
10. Lipe H. Schultz A. Bird TD. (1993). *Risk factors for suicide in Huntington's disease: a retrospective case controlled study.* American Journal of Medical Genetics, 48(4), 231-3.
11. Morris, M., Scourfield, J. (1996). *Psychiatric aspects of Huntington's disease.* In P.S. Harper (ed.). Huntington's Disease. 2nd edn. W.B.Saunders Co. UK: London
12. Purdon, S.E., Chase, T. Mohr E. (1996). *Huntington's Disease.* In J.G. Beaumont, P.K. Kenealy, M.J.C. Rogers (Eds). The Blackwell Dictionary of Neuropsychology. Blackwell Publishers: UK.
13. Leroi I. M. M. (1998). *Treatment of the psychiatric manifestations of Huntington's disease: a review of the literature.* Canadian Journal of Psychiatry, 43(9), 933-40.
14. Donnellan, A.M., LaVigna G., Negri-Shoultz, N., Fassbender, L.L. (1988). *Progress without punishment.* Teachers College Press: NY

Management of Rational epilepsy

Mark Manford

About two thirds of patients with epilepsy will respond to first line treatment. For the remainder there are three considerations:

- Is the **diagnosis correct?** Misdiagnosis is common - 20% of refractory patients. The diagnosis needs to be fully re-evaluated. Non-epileptic seizures either alone or in association with epilepsy need to be considered. If necessary a referral should be made for video-EEG-telemetry
- What is the **epilepsy syndrome?** This determines choice of medication.
- If the epilepsy is focal, might there be a **surgical target?**

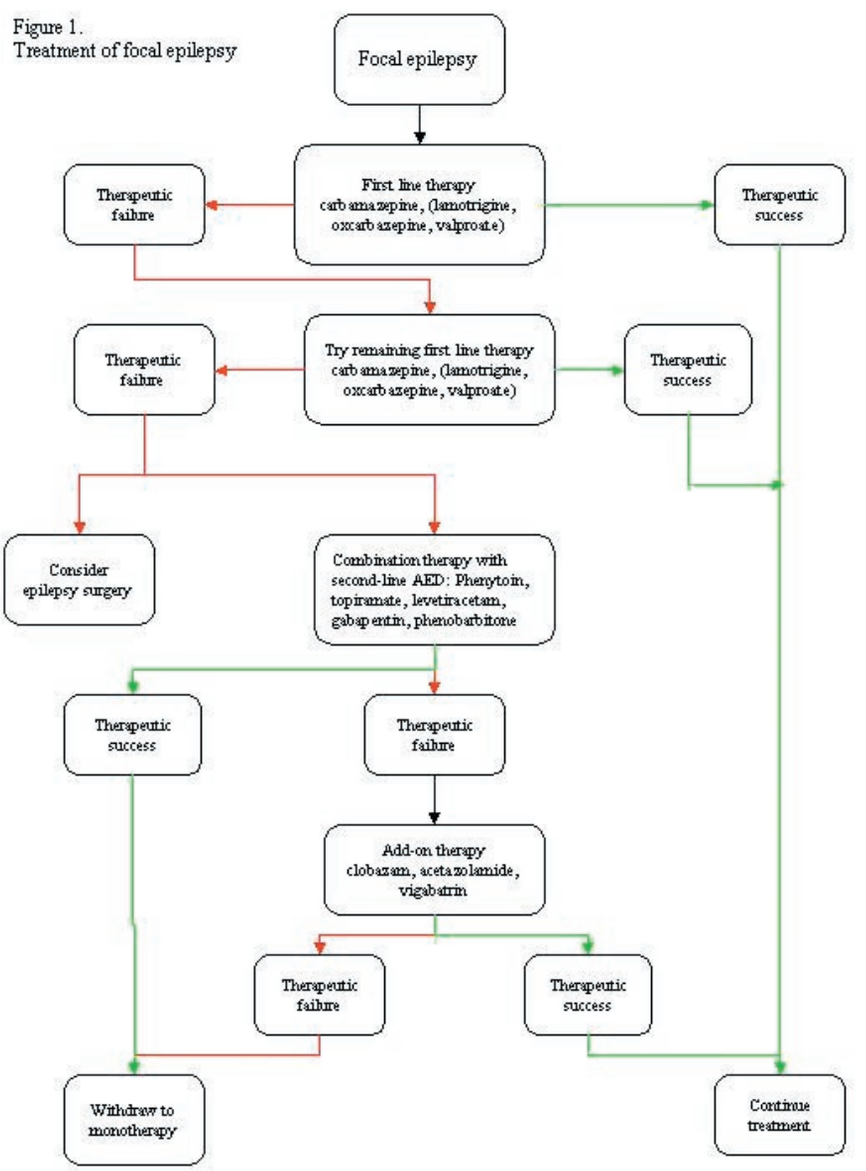
When first-line treatment fails:

1. Try an alternative first-line drug, determined by the epilepsy syndrome (table 1). Figure 1 shows a scheme to consider medication in focal epilepsy, which forms the greatest proportion of refractory epilepsy. A good method of changing medication is by crossover, with simultaneous introduction of the new drug and withdrawal of the old drug. This avoids unnecessary polypharmacy and reduces the risk of adverse effects with the new drug, which are likely to be greater if it is added in to an existing AED at high doses. An alternative method is to add the new AED and then if it is successful, withdraw the old one. This allows one to establish whether it is the new AED alone or the combination that is of value, but is more likely to end in polytherapy.
2. When monotherapy options have been exhausted, AED can be added that are licensed only for add-on. If these are successful, then again withdrawal to monotherapy can be attempted in the understanding that this is an unlicensed indication.

Rational polytherapy is an attempt to predict which AED combinations are likely to be more helpful and which should be avoided. There are too many potential combinations to get the information from clinical trials.

- The most logical combinations of drugs are those used to treat different seizure types in idiopathic generalised epilepsies (table 1).
- **Combinations of enzyme-inducing** drugs often leads to erratic blood levels and it may be difficult to achieve satisfactory levels of both drugs e.g carbamazepine and phenytoin.
- Combining drugs with **similar mechanisms** of action may be expected to give additive adverse effects with little therapeutic benefit eg. gaba-ergic AED gabapentin and tiagabine may increase sedation and weight gain.
- Adding an **enzyme-inhibiting** drug such as valproate may inhibit the metabolism of other drugs (especially lamotrigine), rendering them toxic. Anticipatory changes in drug dosages and AED blood levels before and after making the change, may be appropriate.
- Adding an **enzyme-inducing** drug may reduce the efficacy of existing medication, leading to worsening of seizures. Anticipatory increases in existing AED may be appropriate.
- **Pharmacodynamic interactions** may cause adverse effects without any major change in blood levels. Many AED may cause sedative or cognitive adverse effects that can be reduced by a small reduction of concomitant medication during initial dose titration.
- **Lamotrigine** titration rates and maintenance doses are heavily dependent on concomitant therapy. In monotherapy its half-life is around 20 hours and therapeutic doses are usually 150-400mg daily. With **concomitant valproate** its half-life is around 60 hours and therapeutic doses are usually 100-300mg per day. With concomitant enzyme-inducing drugs, its half-life is around 10-15 hours and therapeutic doses are usually 300-800mg per day.
- **Informing the patient** enhances compliance. Without prior warning they reasonably blame the new medication for any problem and stop it rather than modifying previous medications.

Figure 1.
Treatment of focal epilepsy



Selecting patients for epilepsy surgery

- Epilepsy is generally considered refractory after **failure of 2-3 AED** (figure 3). The earlier appropriate patients are treated surgically, the more likely the psychosocial consequences of the epilepsy will be reversible. One should aim for surgical treatment within 2-3 years of diagnosis where possible.
- The principles of selection of patients for resective epilepsy surgery are:

1. The epilepsy must come from a **single brain region.**
2. Resection of that region must not result in **unacceptable neurological deficit.**
3. The patient must be **psychiatrically** able to tolerate the investigation for surgery, surgery itself and the lifestyle changes imposed by a sudden transition to seizure-freedom.

- The presence of a relevant **neuroimaging abnormality** is the most important prognostic factor for epilepsy surgery but highly specialised neuroimaging may be needed to identify it.
- **Mesial temporal sclerosis** is the commonest surgically treatable cause of epilepsy but needs **special MRI analysis** used in epilepsy centres to find it. Clues to the presence of mesial temporal sclerosis include: childhood onset epilepsy; focal temporal lobe seizure pattern; a history of severe febrile convulsions and focal temporal EEG changes.
- Other treatable causes include **foreign tissue lesions and developmental abnormalities** which usually require specialised neuroimaging.

Figure 2. Selection of patients for epilepsy surgery

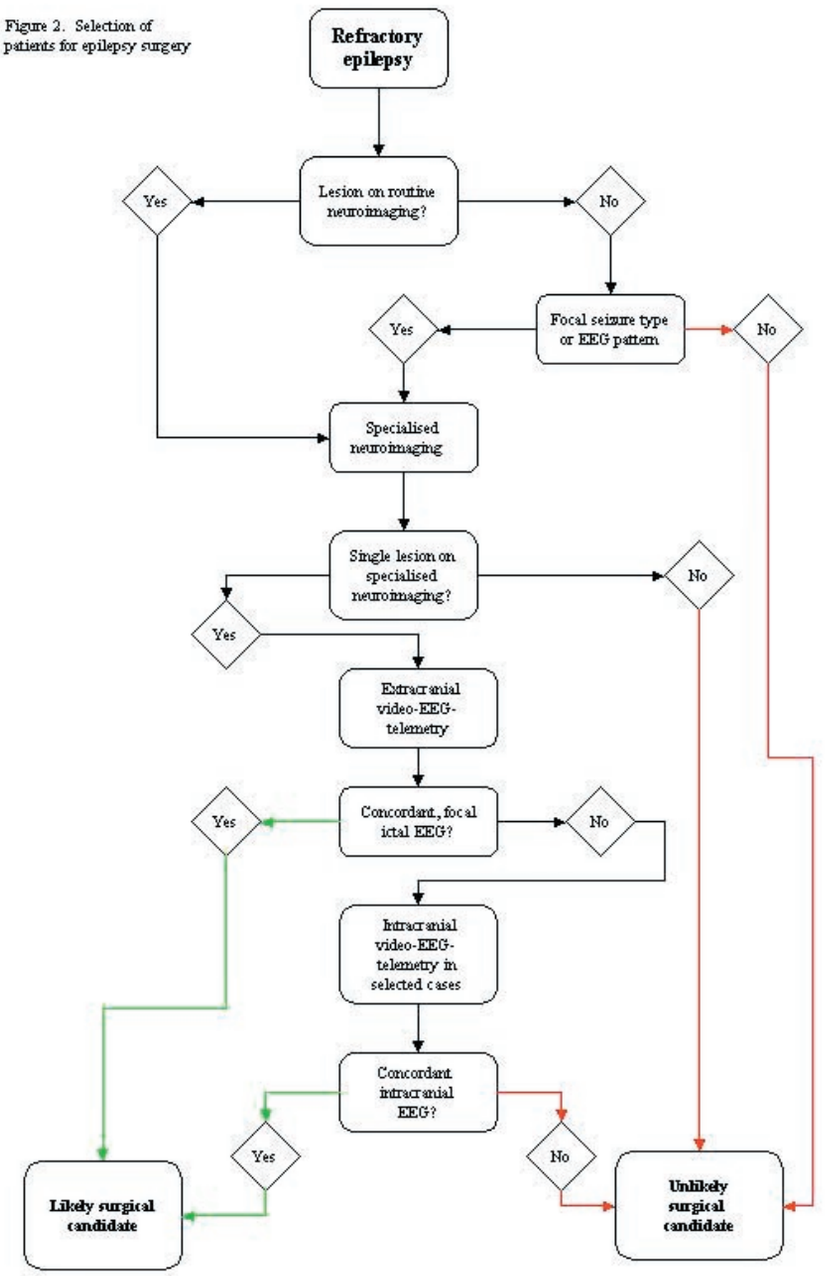


Table 1. Rational drug combination

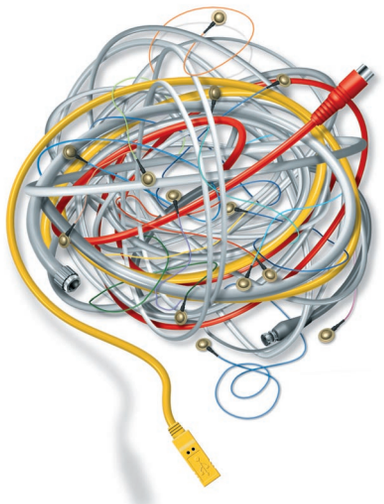
	Clobazam	Ethosuximide	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Piracetam	Tiagabine	Topiramate	Valproate	Vigabatrin
Carbamazepine		2		1,2,3		2,3*		1,2,3	2		1	1	
Clobazam							3			3			3
Ethosuximide			2			2	2	2		2			2
Gabapentin						4	2,3		2	2,3			2,3
Lamotrigine						1,2,3		1,2,3				1	
Levetiracetam									2				
Oxcarbazepine								1,2,3	2				
Phenobarbital								1		3	1	3	3
Phenytoin									2			1	
Piracetam										2			2
Tiagabine													2,3
Topiramate													
Valproate													
Vigabatrin													

Combination not recommended
Combination in generalized epilepsy
Combination in focal epilepsy
Combination in myoclonic epilepsy
Broad spectrum combination

1. Pharmacokinetic interaction
2. Illogical combination
3. Additive adverse effects likely

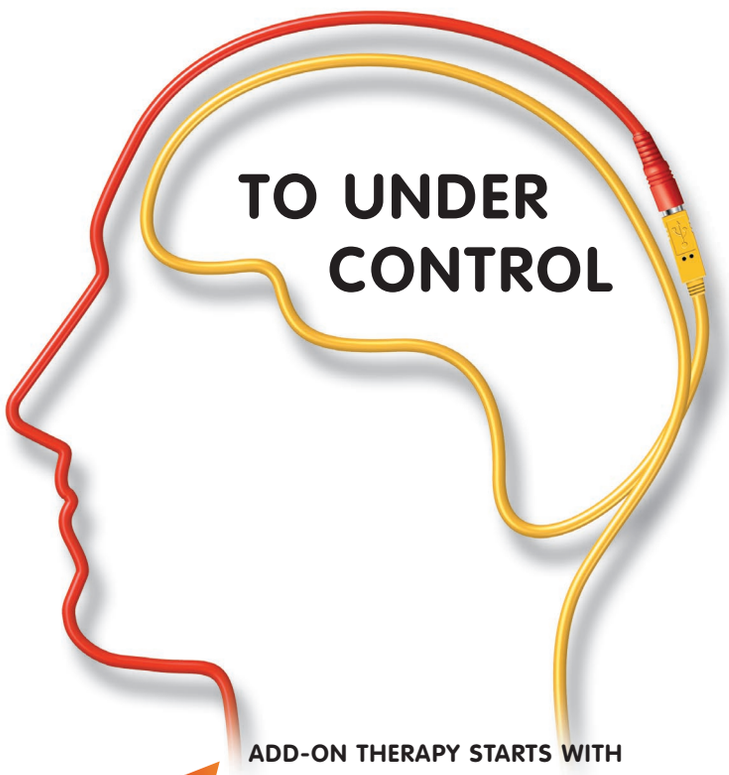
* Despite this being an apparently illogical combination, one study has shown benefit from this combination

ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS



FROM UNCONTROLLED...

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



ADD-ON THERAPY STARTS WITH

Keppra® levetiracetam

KEPPRA® Prescribing Information:
Presentation: Keppra 250 mg, 500 mg and 1,000 mg film-coated tablets containing 250 mg, 500 mg and 1,000 mg levetiracetam respectively. **Uses**: Adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy. **Dosage and administration:** *Adults and adolescents older than 16 years:* The initial therapeutic dose is 500 mg twice daily which can be started on the first day of treatment. Depending upon clinical response and tolerance the dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increments or decrements every two to four weeks. *Elderly:* Adjustment of the dose is recommended in elderly patients with compromised renal function. *Children (under 16 years):* Not recommended. *Patients with renal impairment:* Adjust dose according to creatinine clearance as advised in SPC. *Patients with hepatic impairment:* No dose adjustment with mild to moderate hepatic impairment. In patients with severe hepatic impairment and creatinine clearance <70 ml/min a 50% reduction of the daily maintenance dose is recommended. **Contraindications:** Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. **Warnings and special precautions for use:** If discontinuing treatment reduce dose gradually as advised in SPC. **Interactions:** Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel) or levels of luteinizing hormone or progesterone. Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. **Pregnancy and lactation:** Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, *e.g.* driving vehicles or operating machinery. **Undesirable effects:** The most commonly reported undesirable effects are somnolence, asthenia and dizziness. In the pooled safety analysis there was no clear dose-response relationship but incidence and severity of the central nervous system related undesirable effects decreased over time. Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: Very common (>10%): asthenia and somnolence. Common (between 1%–10%): accidental injury, headache, anorexia, diarrhoea, dyspepsia, nausea, amnesia, ataxia, convulsion, depression, dizziness, emotional lability, hostility, insomnia, nervousness, tremor, vertigo, rash and diplopia. **Legal category:** POM. **Marketing Authorisation numbers:** 250 mg x 60 tablets: EU/1/00/146/004. 500 mg x 60 tablets: EU/1/00/146/010. 1,000 mg x 60 tablets: EU/1/00/146/024. **Basic NHS cost:** 250 mg x 60 tablets: £27.00. 500 mg x 60 tablets: £49.50. 1,000 mg x 60 tablets: £94.50.
Further information is available from: UCB Pharma Ltd., 3 George Street, Watford, Herts WD18 0UH. Tel: 01923 – 211811 or e-mail medicaluk@ucb-group.com
Date of Preparation: October 2001.

References:

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

UCB-K-01-87

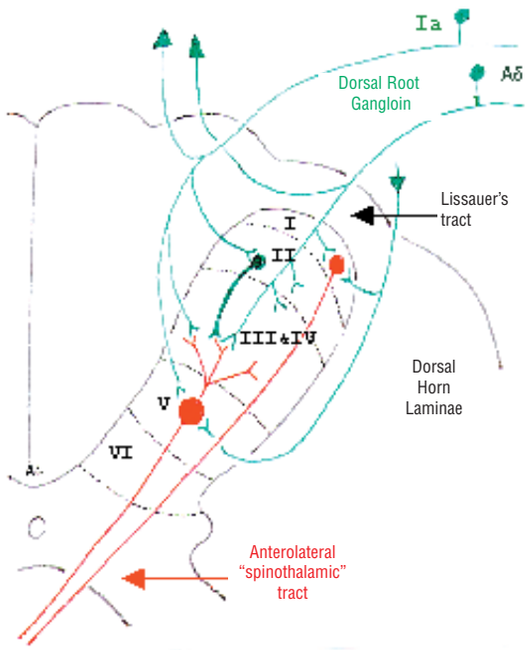
ucb Pharma

SIMPLIFYING SEIZURE CONTROL

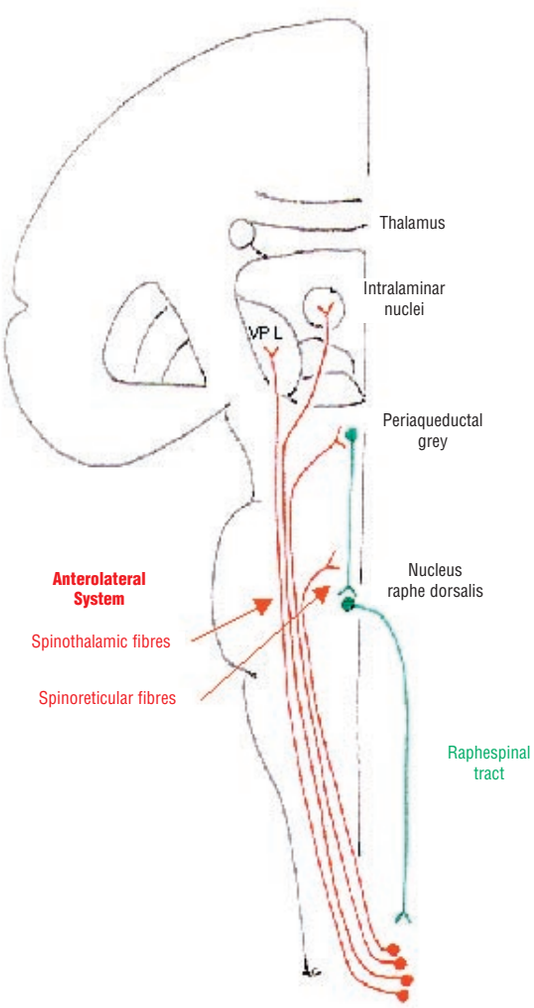
Pain Pathways

Alasdair Coles

The Basics. Pain is a perception and not a sensation. The same stimulus can elicit different levels of pain depending on context. To some extent this modulation of sensation is reflected in the anatomy of the pathways that subserve noxious sensation. They relay onto neurons in the dorsal horn that cross the spinal cord at the same level of entry and ascend in the contralateral "anterolateral system" to terminate in the reticular formation, mesencephalon, hypothalamus and thalamus. (The term "spinothalamic tract" should strictly only be used for the latter pathway, but tends to be used for all). At the level of the spinal cord there are several mechanism to modulate the firing of this anterolateral system. Study of a surgical treatment for pain, anterior cordotomy, reveals subtleties of the pain pathways.



Afferent Pain Fibres. Myelinated Aδ, and unmyelinated, fibres carry impulses from noxious stimuli. Because they are smaller than primary somatic afferents, their conduction velocity is lower. They enter the spinal cord at their appropriate somatic level (in Lissauer's tract), but then send dorsal root collaterals up and down several segments in the dorsal horn before synapsing onto second order neurones using the following neurotransmitters glutamate, substance P and calcitonin gene related peptide.



Dorsal Horn Laminae

Myelinated Aδ, and unmyelinated, dorsal ganglion cells project mainly to Rexed's laminae I and V of the dorsal horn, but with minor contributions to laminae II, VI-VIII.

In the cat, there are some lamina I cells with small receptive fields that specifically respond to either noxious or thermal stimuli. The thermoreceptive cells project to the dorsomedial part of ventroposterior medical thalamic nucleus, whereas nociceptive cells project to the ventro-posterolateral nucleus. These pathways may provide the sensory-discriminative aspects of pain. However other lamina I cells are less modality specific and project to sites outside the thalamus. For instance, in the cat, three times as many lamina I neurons project to periaqueductal grey than to thalamus.

Laminae IV-VI neurones have larger receptive fields and respond to both noxious and innocuous stimuli. Laminae VII-IX cells have still larger (often bilateral) fields and respond to a wide variety of stimuli. These neurones project to the reticular formation and intralaminar nuclei of the thalamus, perhaps subserving the emotional-affective component of pain.

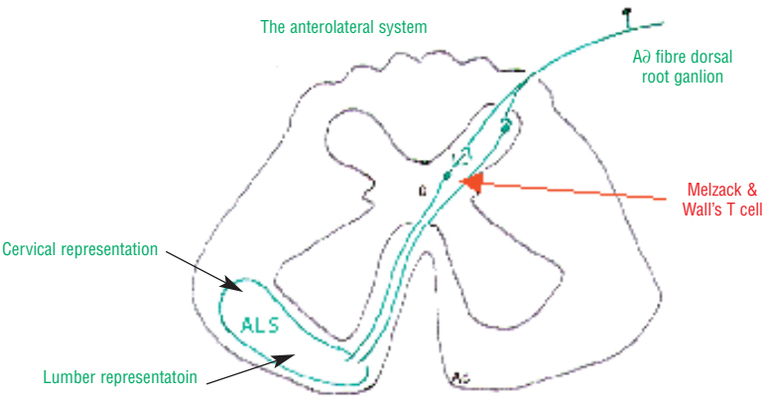
Crossing of the ALS. Fibres of the ALS move anteriorally from their origin in the dorsal horn to cross in front of the anterior commisure and lie in the anterolateral white matter tracts.

Projections of the ALS:

- Reticular formation (from which relay neurones ascend to the thalamus) as spinoreticular fibres.
- Periaqueductal grey, which relay down to the nucleus raphe, magnus, and from there back down to laminae I, II and V of the dorsal horn in the raphespinal tract.
- Thalamus, in the intralmainar nuclei, VPL and parts of the posterior thalamus.

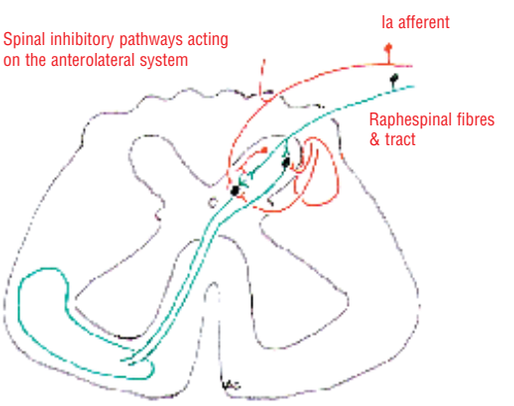
Somato-topography of the anterolateral system. Most textbooks say that, as new fibres join the anterolateral system as it ascends the cord, so fibres from the lumbar cord are pushed dorsally. Recent reports in monkeys however indicate that spinothalamic neurons from lumbar cord ascend in increasingly ventral position as new fibres enter dorsally.

A few weeks ago, Patrick Wall died at the age of 76. He studied medicine at Oxford, but worked throughout his life in the USA. With Ron Melzack he pioneered pain research, at all levels. In 1965 they published their famous "spinal gate control theory".



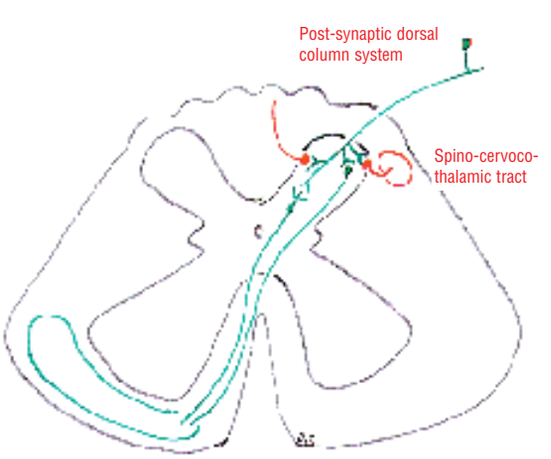
Melzack & Wall's Gate Control Theory (1965)

Melzack and Wall proposed that there was modulation of pain impulses at the level of the spinal cord. Specifically they proposed there were "T-cells" that received excitatory input from unmyelinated and Aδ fibres (transmitting noxious stimuli) and inhibitory input from large afferent fibres (carrying impulses from discriminative senses) as well as descending raphespinal tracts. The output of this summation of influences on the T cells was transmitted caudally to be appreciated as pain. A prediction of this model is that if noxious stimuli are accompanied by other cutaneous sensations, the perception of pain will be reduced. This is the basis for the automatic rubbing a painful area, and also for the introduction of transcutaneous electric nerve stimulation (TENS) which has an established role in pain control. The gate control theory has been enormously fruitful but remains a theory. Many of its components remain unproven.



Minor spinal pain pathways

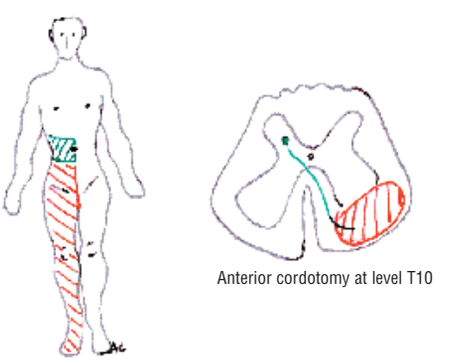
Some patients do not experience complete pain relief after anterior cordotomy. This can be explained by the presence of minor pain pathways, not normally regarded as prominent in man although they are in smaller animals. First, Aδ collaterals ascend the cord in the dorsal columns in the post-synaptic dorsal column system. Second, in the dorsolateral region of the lateral funiculus there is an ascending Spino cervico-thalamic tract.



Sensory loss following anterior cordotomy

Much useful information on the pain pathways has been gained from careful observation of the effects of anterior cordotomy (especially by PW Nathan). This operation is designed to relieve intractable pain by severing the anterolateral system.

Typically there is a level of complete loss of pain and temperature sensation. However, just above this there is an area of reduced noxious and temperature sensation. This is explained by the fact that Aδ fibres have collaterals that supply the dorsal horns immediately above and below their spinal segment. So, in the case of a T10 anterior cordotomy, the T9 spinothalamic complex has lost the input of T9 callaterals that descend to lower spinal levels before crossing and the T10/11 complex receives fibres that ascended to T9 in the dorsal horn before crossing.



References

W Nathan, Smith & Deacon. The crossing of the spinothalamic tract. Brain (2001), 124, 793-803

Melzak & Wall. (1965) Pain mechanisms: a new theory. Science 150: 9719

The practicalities of treadmill gait training for non-ambulant hemiplegic patients

Gait training with partial body weight support for brain and spinal cord lesions was first described by Sherrington in 1910[1], when he studied the reflexes of cats. He noted that they could learn to walk in a rather automatic fashion, but their balance did not recover: "the performance of mere stepping movements as exhibited by the decapitate preparation is amplified in the decerebrate preparation into the performance of actual walking and running - imperfect it is true, especially in regard to equilibrium, the regulation of which is almost entirely wanting, but nevertheless amounting to a certain measure of effective locomotion." Practical physiotherapy manuals of gait training with body weight support were published in the 1950s[2], but this technique went out of fashion until scientific papers describing physiological experiments and controlled trials, initially in spinal cord injured and subsequently hemiplegic humans were published[3,5] in the last 10 years, and summarised by Dobkin[6].

Edgerton[7] emphasised that the effect of training was limited to the specific task: spinal cats trained to step can step, but not stand: those trained to stand can stand, but not step. Human comparisons of muscle activity have shown a similar distinction: relatively normal patterns of activity during gait in hemiparetic muscles despite loss of response to a perturbation of standing balance[8,9]. This suggests that to get better at walking, patients should practice walking, and they may find it easier to activate the affected muscles in this task than in static balancing. Conventionally, and from practical necessity, hemiplegic patients have been taught to stand and keep their balance before they begin stepping, but body weight support allows patients who cannot stand, balance or walk unaided to practice stepping movements. The continuous movement of the treadmill encourages more automatic stepping, and reduces the need for patients to actively and consciously initiate each step from a standing start.

Patterns of muscle activation and movement in patients walking on the ground and on the treadmill are generally similar, with treadmill gait tending to be more symmetrical[10,11]. The use of hand rails and degree of body weight support has a large impact on amplitude of muscle activation and energy expenditure.

Our experience of treadmill training is based on studies funded by the Stroke Association into gait training of hemiplegic patients who either could not walk independently, or who could only walk short distances. We sought to reproduce Hesse's dramatic 1995 study[4], in which the majority of 9 non-ambulant patients, whose walking ability had been static during the preceding 3 weeks with regular physiotherapy, learnt to walk independently after 25 treadmill sessions. The mean interval after stroke in that study was 17 weeks, but it was 17 months in our group, and we did not see functional benefit which would justify the therapeutic input[12]. Muscle tone did not increase. We felt the results reflected the different intervals since stroke onset, and recommended that treadmill training of patients who require hands on help to walk on the ground would be most appropriate during the initial period of intensive rehabilitation. Our subsequent very encouraging experience with more acute patients has confirmed this view.

Author

Kate Kendrick is Superintendent Physiotherapist in the Lewin Stroke and Rehabilitation Unit, Addenbrooke's NHS Trust, Cambridge. She conducts Stroke Association funded research into treadmill training.

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

Techniques and equipment

Most cheaper treadmills are designed for fast walking and running, and may overheat, stall or burn out when used with high loads at slow speeds e.g. 0.8 kph. Our Powerjog worked reliably, but the side rails got in the therapists way and prevented sideways access to the treadmill. Ideally they would be removable. The overhead support must be able to catch the patient if they fall and take all their weight, and secondly be able to provide controlled lift without impeding normal pelvic movement. We used nylon loops designed for catching falling climbers and a set of wall mounted Winchester weights and pulleys suspended from a ceiling mounted hoist. Ceiling and wall mounted supports do not impede side access to the patient, which is a problem with some commercially available floor standing systems, but do make it impractical to move the support to another part of the gym. A home made system should be called a "support" and not a "hoist", as hospital insurers and medical engineering departments have very stringent criteria for hoists which it would be very expensive to meet. Descriptions and recommendation for treadmill training equipment have been published[13,14].

Several types of harness are commercially available: they support body weight through broad padded straps around the proximal thighs when standing erect, unlike unmodified parachute or climbing harnesses which force the subject to adopt a more seated posture. Ideally it would be possible to put these on while still sitting in the wheelchair, and then hoist the patient up onto the treadmill, but this was rarely possible and the therapists had to provide all assistance.

In general, the physiotherapists facilitate weight transference, foot placement and hip extension on the treadmill in the same way as they would if the patient was walking on the ground. One therapist was positioned behind the patient with their hands on the pelvis, and the other sat or kneeled on the ground and lifted, dorsiflexed and placed the hemiplegic foot as necessary. This was very hard work and the height of the treadmill and position of the hand rails made access difficult. All therapists developed back pain, and the duration of training sessions for non-ambulant patients was usually limited by the endurance of the foot therapist rather than the patient. Some patients preferred to have their hemiplegic hand strapped to the handrail in front of them, but they were discouraged from taking weight through their arms on side rails, as this interfered with their gait pattern. Some patients continued to use ankle foot orthoses to overcome low tone foot drop.

While ground ambulant stroke patients may benefit from walking on a treadmill with little physical assistance, treadmill training of non ambulant patients is labour intensive, and carries a significant risk of back and shoulder pain among therapists. The duration of each treatment session may be limited by the therapists exhaustion, while the patient may be prepared to continue. To overcome these two problems Hesse *et al* have developed a free standing gait trainer[15] which moves the patient's feet and pelvis and provides body weight support. This allows one thera-

pist to supervise in place of two doing physically demanding and repetitive work and, if shown to have similar functional benefit as treadmill training, would overcome this useful technique's main difficulties.
(http://www.reha-hesse.de/ewelcome.html).

A patient using the Gait Trainer.

References

1. Sherrington CS. *Flexion reflex of the limb, crossed extension reflex and reflex stepping in standing,* J. Physiol. 1910; 40, 28-121
2. Hollis M and Roper MHS: *Suspension therapy* 1958
3. Hesse S, Bertelt C, Schaffrin A, Malezic M, Mauritz KH. *Restoration of gait in non ambulatory hemiparetic patients by treadmill training with partial body-weight support.* Arch Phys Med Rehabil. 1994;75:1087-93
4. Hesse S, Bertelt C, Jahnke MT, Schaffrin A, Baake P, Malezic M, Mauritz KH. *Treadmill training with partial body weight support compared with physiotherapy in non ambulatory hemiparetic patients*. Stroke 1995; 26: 976-81
5. Visintin M, Barbeau H, Korner-Bitensky N, Mayo NE. *A new approach to retrain gait in stroke patients through body weight support and treadmill stimulation.* Stroke 1998; 29:1122-8.
6. Dobkin BH. *An overview of treadmill locomotor training with partial body weight support: a neurophysiologically sound approach whose time has come for randomised trials*. Neurorehab and Neural Repair 1999;13: 157-165.
7. Edgerton VR, Roy RR, Hodgson JA, Prober RJ, De Guzman CP, De Leon R, 1992, *Potential of adult mammalian lumbosacral spinal cord to execute and acquire improved locomotion in the absence of supraspinal input.* J. Neurotrauma, 9 (Suppl.1), S119-128
8. Brunt D, Vander Linden DW, Behrman AL. *The relation between limb loading and control parameters of gait initiation in persons with stroke,* Arch Phys Med Rehab 1995; 76: 627-34
9. Kirker SGB, Simpson DS, Jenner JR, Wing AM. *Stepping before standing: hip muscle function in stepping and standing balance after stroke.* J Neurol Neurosurg Psychiatry 2000; 68:458-464.
10. Nilsson L, Carlsson J, Danielsson A, Fugl-Meyer F, Hellstrom K, Kristensen L, Sjolund B, Sunnerhagen KS, Grimby G. *Waking training of patients with hemiparesis at an early stage after stroke: a comparison of walking training on a treadmill with body weight support and walking training on the ground.* Clin Rehab 2001; 15: 515-527.
11. Hesse S, Konrad M, Uhlenbrock D. *Treadmill walking with partial body weight support versus floor walking in hemiparetic subjects*. Arch Phys Med Rehabil 1999 80:421-7
12. Jenner J, McGlashan K, Kendrick K, Holt R, Kirker S. *Treadmill training with partial body weight support for poorly or non-ambulant chronic stroke patients*. Stroke Association Annual grant holders meeting 2001.
13. Norman K, Peppin A, Ladouceur M, Barbeau H. *A treadmill apparatus and harness support for evaluation and rehabilitation of gait.* Arch Phys Med Rehab 1995;76;772-78.
14. Wilson MS, Qureshy H, Protas EJ, Holmes SA, Krouskop TA, Sherwood AM. *Equipment specifications for supported treadmill ambulation training.* J Rehabil Res Dev 2000; 37:415-22
15. Hesse S, Uhlenbrock D, Sarkodie-Gyan T. *Gait pattern of severely disabled hemiparetic subjects on a new controlled gait trainer as compared to assisted treadmill walking with partial body weight support.* Clinical Rehabilitation 1999; 13: 401-10.

Treadmill training.

Correspondence Address

Catherine Kendrick
Box 185, Physiotherapy Department, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ. E-Mail: ckendrickphysio@yahoo.com

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 December 7th, 2001.

2001

November

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

Anticonvulsants, Pregnancy and the Child
7 November, 2001; London, UK
Conference 2000,
Tel. 01691 650290,
Fax. 01691 670302,
E. denise@conference2000.co.uk

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

MS 2001- The Way Ahead, MS Research Trust Fifth Annual Conference
11-13 November, 2001,
Harrogate, UK.
Tel. 020 8772 1551,
Fax. 020 8772 1552,
E. MS2001@packerforbes.co.uk

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

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

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

Royal Hospital for Neurodisability Open Day
22 November, 2001; London, UK.
Chloe Hayward, Tel. 020 8780 4561, E. chayward@royal-neuro3.demon.co.uk

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

BSRM Autumn 2001 Meeting
26-27 November, 2001;
Manchester, UK
Sandy Weatherhead, BSRM,
Tel/Fax. 01992 638865,
E. admin@bsrm.co.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
Maria Rivera, Tel. 001 860 586 7505, Fax. 001 860 586 7550

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

December

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

2002

March

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

April

3rd World Congress in Neurological Rehabilitation
3-6 April, 2002; Venice, Italy
Aristea, Tel. 0039 06 844 98364, Fax. 0039 06 844 98332, E. neu-rorehab2002@aristea.com

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

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

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

British Neuropsychological Society Spring Meeting
24-25 April, 2002; London, UK
www.hop.man.ac.uk/bns,
Tel. 0161 275 3401

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

May

XIV International Neuro-Ophthalmology Society Meeting
5-8 May, 2002; Buenos Aires, Argentina
Fax. 0054 11 4331 0223,
E. 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. Motesz@elender.hu

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

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

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

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

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

June

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

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

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

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

August

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

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

September

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

October

5th European Congress on Epileptology
6-10 October, 2002; Madrid, Spain
E.epicongress@eircom.net.

2nd Latin America Committee for Treatment & Research in MS (LACTRIMS)
9-12 October, 2002; Monterrey, Mexico
www.lactrims2002.com.mx,
E. lactrims@hsj.com.mx

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

November

Parkinson's Disease & Movement Disorders
10-14 November, 2002; Florida, US. Tel. 001 414 276 2145, Fax. 001 414 276 2146, E. info@movementdisorders.org

Residential Meeting of the Section of Rehabilitation and Social Psychiatry
15-16 November, 2002;
Newcastle, UK
Tel. 020 7235 2351,
E. rcpsych@rcpsych.ac.uk

Association of British Neurologists Meeting

12th-14th September 2001, Durham

The timing of the World Congress of Neurology event in London, coupled with the immense effort involved in its organisation, meant that this was a rather unusual year for the Association of British Neurologists (ABN). Instead of the normal twice-yearly gatherings, the ABN meeting in Durham was the only one to be based on 'home soil' in 2001. Professor Charles Warlow presided over the meeting, which, to the relief of the local organisers, headed by Dr Niall Cartlidge, was very well attended. The conference dinner was held in Durham Castle.

The theme of the Scientific Symposium, held on the first afternoon, was Parkinson's disease. This mixed scientific advances with practical advice. The session clashed with the traditional ABN golf match, held at Brancepeth, and won by Dr Timothy Walls. There was some consolation to those whose consciences took them to the auditorium rather than the first tee to hear the heavens open mid-way through the afternoon!

After a brief but interesting session on Dementia and Psychiatry on the Thursday morning, there followed a new departure for the ABN, an Interactive Educational Symposium. This feature was coordinated by Dr Geraint Fuller and was undoubtedly extremely popular, judging by feedback forms. The interactive component meant that the audience could respond to various clinical scenarios with key-pads. An audiovisual team that were on top of their game collated the answers immediately and this information, relayed back to the audience, formed the basis of ensuing debate and discussion. An acute onset headache (could it be a sub-arachnoid haemorrhage?), blackouts (fit or faint), episode of optic neuritis (do you tell the patient they may develop multiple sclerosis?) provided the clinical material for the session, in which Richard Davenport, Phil Smith, Jacky Palace and Charles Warlow made notable contributions. (Geraint might have an alternative career in "The Weakest Link"!).

Thursday afternoon and Friday were then mainly devoted to the more traditional presentation format, with sessions on Stroke and Parkinson's disease, Epilepsy, Tumours and Migraine and Muscle and Mitochondria. Many devotees of demyelinating disease had travelled to Dublin for the competing ECTRIMS meeting, hence the lack of a session on this topic. There was the usual eclectic mixture of leading edge scientific work and clinical observations presented by the ABN speakers. Space for the discussion of the five best posters is also an essential feature of the ABN, in recognition of the wide range of topics covered by the posters, their scientific content and the effort involved in their production, which is clearly considerable in the majority of cases.

Durham Castle, venue of the conference dinner.

Finally, mention must be made of the clinicopathological conference (CPC), organised by Paul Reading, with Ralph Gregory as the discussant. It is rumoured that both went for a "bonding" game of golf prior to the CPC and that the final diagnosis was never discussed! To the independent observer, it seemed that it was 'honours even', in that Ralph performed extremely well under pressure (he had been heard to say beforehand "It's so easy, I don't know how I'll be able to spin it out"!), while Paul, with a satisfied smile, saw Ralph come only close to the final diagnosis of Actinomycosis! Peter Goulding came up with the correct answer from the floor to win the CPC audience prize.

As one of the local organising team, it is a little difficult to be objective as to how the meeting in Durham was perceived by others. Overall, however, we tried to provide something for everyone, with a blend of old and new ideas, crammed in to two and a half days. There just never seemed to be enough time to catch up on all the news with colleagues from around the country!

David Burn,
Newcastle-upon-Tyne

17th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)

12 -15 September 2001, Dublin , Ireland

Although heavily overshadowed by the tragic events unfolding in the United States this conference still managed to provide an interesting forum for the analysis of current immuno-modulating therapies, potential new therapies including non-drug related rehabilitation techniques, unusual presentations and new insights into the pathogenesis of MS.

Several sessions were dedicated to analysing the use of interferons and glatiramer acetate. The general consensus was that these immuno-modulating agents do have an effect on the number of clinical relapses and on MRI show a decrease in T2 lesion load throughout the relatively short trials to date. However their effect on the most disabling progressive phase of the disease is disappointing. Of four large but again relatively short trials the EUSPMS, SPECTRIMS, NASPMS and IMPACT, only the European study showed a beneficial effect on delaying disability as measured by deterioration of one point on the widely accepted Expanded Disability Status Score (EDSS).

Amongst the most intriguing presentations were talks by Prof Kappos (Basel, Switzerland) on the evidence for a significant effect on disability by disease modifying drugs. He challenged the sensitivity of the EDSS as a scale for efficacy and quality of life whilst also presented compelling data from several trials demonstrating decreases in relapses, delay in onset of clinically definite MS if treated early and MRI lesion load.

Prof George Ebers (Oxford, UK) then discussed the weakness in efficacy data from published randomised clinical trials in MS. He emphasised the difference between effectiveness and efficacy, outlining that for a drug to be effective it should achieve what it was intended to do. For MS this would be an impact on the long-term natural history measured as an effect on hard outcome measurements and that "surrogate markers need not apply". To follow on from this Prof Ebers presented unpublished retrospective data, also presented in two posters from London, Ontario by Prof GPA Rice and Dr S Karlik on patients who had

been on Betaseron for a mean duration of 12 years. Although this study includes only 15 patients, Prof Ebers stressed that it was the first study to address the crucial question of effectiveness of interferon and that further studies were crucial. Only MRI data was presented, the patients on long-term Betaseron had a dramatic reduction in T2 lesion burden but absolutely no change in the degree of brain atrophy (probably a better indicator of overall disability). I eagerly await the results of the changes in the EDSS in these patients versus controls.

Newer treatments such as Mitoxantrone were also discussed. Mitoxantrone now has FDA approval in MS for patients with increasing disability in SPMS or to decrease the relapse frequency in RR or SPMS. Although limited studies are available in the effectiveness of mitoxantrone it is still widely used in Europe. Unfortunately it can only be given short-term with a lifetime accumulative dose of 140mgm^2. Several posters demonstrated its relative safety and proposed effectiveness although I was struck by the lack of controls used in these studies.

Results presented from a questionnaire on immunosuppressive treatment in MS was most striking for its low response rate (27%). France had the highest number of MS patients having been treated with immunosuppresants (32.5%), with Scandinavia having the lowest levels (1.8%). The UK was towards the lower range with 4.2% of MS patients receiving immunosuppressive therapy. The most common drug to be used worldwide was Azathioprine followed variably by Cyclophosphamide, Mitoxantrone and Methotrexate. There was a call for the establishment of an International Co-operation on Immunosuppressive Therapy (ICIT) to create an order on usage, and to organise clinical trials for these therapies.

A whole session was dedicated to bone marrow transplantation in MS. New control trials are beginning to study the effectiveness of bone marrow transplantations in severe MS. Previous experience presented from Greece and the Czech Republic indicated high mortality rates of between 2 and 5% that raised the issue of the ethics behind such studies. Overall MS patients who had received transplants had been in the EDSS range of 6 to 8 and post transplant the majority had not further significantly deteriorated. However neither had they improved.

Other sessions concentrated on rehabilitation and pathogenesis in MS. In brief, rehabilitation methods developed in stroke patients such as stimulation or inhibition therapies may provide relief for MS sufferers. Accumulating evidence demonstrates both remyelination and remodelling occurs in MS indicating that the adult CNS retains a certain degree of plasticity. My impression from these sessions was that MS contains several components, an early auto-immune phase precipitated by various genetic or environmental aetiologies followed by a slow, uncharacterised neurodegenerative process with neuronal loss and axonal damage. This would explain why immunomodulating drugs may be effective in the early phase of MS but do not have an impact on the long-term prognosis. It appears essential that further long-term data on the effectiveness of the immunomodulators in MS is provided to ensure firstly the cost effectiveness and secondly to establish whether by partially inhibiting the immune phase they are not having long-term deleterious actions.

Dr David A Cottrell,
Newcastle upon Tyne.

International Society of Neuroimmunology Sixth International Congress

3-7 September, 2001, Edinburgh, Scotland

The International Society of Neuroimmunology meets for an international conference every three years. The fact that this is only its sixth meeting betrays the novelty of the discipline of neuroimmunology. But, as this conference revealed, it is expanding aggressively, straying far outside the traditional immunological domains of myasthenia gravis and multiple sclerosis into degenerative diseases, epilepsy and movement disorders. For instance, among the many presentations of unpublished work, were two nice preliminary studies from Gavin Giovannoni's (London, UK) group showing the presence of anti-basal ganglia antibodies in 50/72 children with Tourette's syndrome and 19/20 patients with acute Sydenham's chorea (and none in appropriate controls). Showing that such antibodies are pathogenic is the next step and has never been more elegantly done than by Jack Griffin's peripheral nerve group at Johns Hopkins, studying the acute axonal motor form of Guillain-Barre, which is associated with antibodies against the GD1a ganglioside. They implanted hybridomas secreting anti-GD1a antibodies into normal mice and found this causes Wallerian degeneration and some demyelination, without T cell infiltration. Another elegant study on the pathogenesis of autoantibodies came from Robert Darnell, (Rockefeller University, New York) on POMA (Paraneoplastic Opsoclonus, Myoclonus, Ataxia syndrome) that is seen in association with gynaecological or small cell cancer. Antibodies from patients with this syndrome bind to a novel family of proteins called Nova, which are RNA binding proteins. Disruption of Nova1 causes failure of alternative splicing of glycine inhibitory molecules. So Nova-1 knock out mice show loss of inhibition of motor neurons with symptoms similar to those seen in the patients. Less secure is the pathogenic role of anti-glutamate 3 receptors in Rasmussen's encephalitis. Levite (Weizmann Institute) has always proposed that these antibodies are pathogenic, for which she presented some tissue culture evidence. But a group in Milan showed that such antibodies were found in 4/11 Rasmussen's patients with and 27/76 patients with non-Rasmussen's epilepsy.

A major theme of this conference was the importance of activated macrophages in some diseases. In particular, and this is a relatively new concept, such primed macrophages have been shown to cause damage without being part of a classical inflammatory lesion. For instance, Hugh Perry (Southampton) has studied a model of prion protein scrapie disease in mice. Here activated macrophages, but rarely lymphocytes, are found in the brain. If these animals are exposed to LPS (mimicking a Gram negative infection), these primed macrophages secrete excessive IL-1 and the animals have increased "sickness behaviour". This may perhaps explain why the behaviour of patients with degenerative diseases (in which one also finds primed macrophages) deteriorates so much with intercurrent infections. J Mcarthur (Johns Hopkins) presented a hypothesis for the pathogenesis of HIV dementia, based on the established finding of activated monocytes (macrophages) in the peripheral circulation. He suggested that these activated macrophages crossed the blood-brain-barrier by diapedesis (that is by without BBB disruption) and there release inflammatory mediators, which cause astrocytosis and neuronal death by apoptosis. But they must also cause some reversible reduction in neuronal function, as early HIV dementia may be partially reversed by highly active retroviral therapy.

There was a refreshing friendliness and candour about this meeting. For instance, Cedric Raine (Albert Einstein, New York), President of the International Society of Neuroimmunology, cheerfully took Hugh Perry to task about the use of the word "inflammation" to describe immune responses consisting only of

activated macrophages in the absence of the lymphocytes and neutrophils of the classic inflammatory response. The importance of this dispute is that physicians need to be educated that not all that is described as "inflammatory" will respond to conventional immunosuppressants. There was polite tolerance of idiosyncratic views, such as those of A Ebringer, from King's College, who believes that spongiform encephalopathies are not due to prion protein deposition but to acinetobacter infections (associated also with multiple sclerosis, he claims).

Cedric Raine (left) outgoing President of the International Society and Angela Vincent (right) who takes over the reins.

Adriano Aguzzi's (Zurich) group has done outstanding work on the spongiform encephalopathies. At this meeting he reported that prion protein enters the body via the 'M' cells of the intestinal epithelium. His group has shown that prion protein infectivity is crucially dependent on the presence of B cells in the periphery and the accumulation of prion proteins in the follicular dendritic cells of the lymphoid organs. Over-expression of prion protein leads to an anti-B cell autoimmune response. Aguzzi hypothesised that prion protein may enter and infect the sympathetic nerves innervating these lymphoid organs and travel from there to the brain. As evidence his team have found that sympathectomised mice have delayed infection.

This was Cedric Raine's last function as President of the International Society of Neuroimmunology. He hands over the reins to Angela Vincent (Oxford), part of the UK team (John Greenwood, Sandra Amor, John Fazakerly, David Baker) who organised this conference. The dynamic and exciting range of talks at this meeting was a tribute to them both.

Alasdair Coles, Cambridge

Neuroscience for Clinicians 11 - The Scientific Basis of Neurology

September 3-5 2001, Cambridge, UK

The 11th Neuroscience for Clinicians meeting again allowed neurologists in both clinical and academic posts to gain an overview and insight into the latest developments in modern neuroscience. The meeting was held in the beautiful surroundings of Jesus College, Cambridge, and attracted a wealth of expert speakers, from both scientific and clinical backgrounds. No less than nine professors spoke on their subjects of interest over the three days.

The course was structured, incorporating development of the nervous system, cell biology, mechanisms of neuronal signalling, neural systems, cognition and neurodegeneration. We were also reminded of the work of our predecessors in a wonderfully entertaining history of neuroscience presented by Professor Glickstein.

Professor Copp from the Institute of Child Health opened the meeting with an overview of the clinical disorders which may result from aberrant neural tube development, closure or neuronal migration. He went on to describe the role of folate in prevention of spina bifida and also a folate-resistant form of spina bifida, which may be ameliorated by manipulation of inositol and protein kinase C pathways.

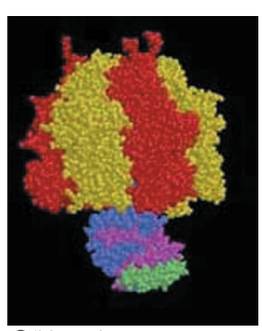
Professor Parnavelas reviewed the migration of cortical pyramidal neurons and interneurons, followed by Dr Sarah Guthrie discussing the range of axon guidance molecules involved in chemo-attraction and repulsion of the neuronal growth cone. In particular she presented her work on hepatocyte growth factor and its role as a chemo-attractant factor within the developing CNS.

Olfactory Ensheathing Cells (OECs) are the only PNS cells that can survive within the CNS, and as such are a source of interest in the repair of damaged CNS neurons, in particular following demyelination. Dr Susan Barnett described the factors and media which are required to allow proliferation and differentiation of these OECs into either Schwann cell-like or Astrocyte-like cell lines.

Professor O'Keefe from University College London brought techniques of cognitive science into the 21st century with the description of virtual mazes based on computer games. Patients with specific memory deficits were asked to explore this virtual world and were then tested on their recall of the features within the maze. These experiments have shown the importance of the right hippocampus in "allocentric spatial memory" ie the relationship of objects to each other, and the inferior parietal cortex in "egocentric memory" ie the relationship of objects to oneself.

The highlight of the meeting must be the presentation by the Nobel prize winner Sir John Walker. He presented the discovery of the rotatory mechanism by which the enzyme "ATP synthase" functions in order to generate ATP. The accompanying figure (below right) demonstrates the F_1 subunit of ATP synthase in which there is rotation of the *γ*-subunit relative to the *α*,ß ring, driven by a flux of H^+ down a proton gradient.

Dr Michael Hastings discussed the role of the genes 'per' and 'cry' responsible for the control of the circadian rhythmicity, in particular their differential expression in response to light. He discussed possible concerns relating to junior doctors who undergo frequent changes in working hours, and how disruption of circadian rhythms may affect performance.



© 'Nature'

In the field of neurodegeneration, Dr Tolkovsky described the importance of the mechanism of neuronal injury, which dictates whether damage can be reversed by the use of caspase inhibitors. Professor Bates from King's College described the use of transgenic mice in Huntington's disease, and the possible reversibility of both pathology and functional deficit that can be obtained by manipulation of the abnormal gene.

Overall, this meeting yet again reinforced the importance of basic science in the understanding of the brain and eventually treatment of neurological disease, and was made special by the high calibre of the invited speakers. As always Jesus College provided a delightful venue for the Annual NFC Dinner, and we are grateful to Professor Compston who again organised this splendid occasion, and to the Guarantors of Brain who provided sponsorship for the event.

Tom Foltynie and Meena Jain, Cambridge

EDITOR'S CHOICE

PARKINSON'S DISEASE

Deep Brain Stimulation in Parkinson's Disease (PD)

With the realisation of the universal benefit of levodopa the use of surgery in the treatment of PD was relegated to the extreme periphery of PD management. However despite the overwhelming benefit of levodopa and dopamine agonists in the management of early stage PD, a need for good treatment later in the disease to relieve some of the complications of treatment and symptoms due to the progression of the disease is required. Surgical treatment has therefore been reconsidered in patients with advanced PD. But this reconsideration occurs with far greater understanding of the circuitry involved in developing the symptoms in PD and technical advances in stereotactic neurosurgery and implantable electrically active devices. Currently surgical intervention involves either surgical destruction or electrical stimulation, which is less destructive and partially reversible on stopping stimulation. Two sites for surgical manipulation have emerged as being reasonably safe and beneficial in preliminary studies, the globus pallidus pars interna (GPI) and the subthalamic nucleus (STN), whilst thalamotomy has fallen by the wayside because of comparative lack of global benefit. Thalamotomy has beneficial effect in treating tremor but none of the other features of PD.

This multi centre study involving most of the significant centres and figures involved in PD research assessed the benefit of bilateral stimulation of either the STN (n=96) or the GPI (n=38) in patients with advanced PD (UPDRS between 40 and 70), in a prospective, limited double blind crossover study. Because the design did not involve randomisation direct comparisons between these two groups was not possible. Not all of the assessments were strictly blinded and crossover does not mean that electrodes were exchanged between the STN and GPI but rather that the stimulators were turned on and off in different sequences at times of assessment which occurred preoperatively, at 3 months and at 6 months. For STN stimulation at 3 months the median motor score improved 49% ($p<0.001$) and time in the on state at six months improved from 27% to 74% ($p<0.001$). For the stimulation in the GPI motor score improved 37% and time spent in the on improved from 28% to 64% ($p<0.001$for both comparisons). Furthermore significant improvement in activities of daily living, tremor, dyskinesia were recorded for both techniques and rigidity and bradykinesia in the STN technique.

Overall intracranial haemorrhage occurred in 7 patients and infected leads in 2 patients. The overall significant benefit of bilateral stimulation of the STN and GPI should translate into increased use of these techniques (with a suggestion of better effect in STN stimulation) but the underlying mode of action still needs to be defined. ***-TH***

Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease

The Deep Brain Stimulation for Parkinson's Disease Study Group

NEJM 2001;345:956-63

NEUROLOGICAL INFECTIONS

HIV and motor neuron disease

In 1985, a NEJM report first speculated on an association between HIV infection and a disorder that resembled amyotrophic lateral sclerosis (ALS). This paper is the fullest description yet of this syndrome and makes a strong case for a real association. It is based upon a huge personal series of HIV neurology cases. Antoine Moulignier, from a Tropical Diseases unit in Paris, has seen 1700 patients with neurological syndromes due to HIV from 1987 to 2000. Six of these had an ALS like syndrome. All were very comprehensively investigated for alternative causes (to the extent of bone marrow aspirates for occult lymphoma, for instance). All patients had low CD4+ counts (86/ml on average) and a detectable serum HIV load. In three patients the CSF viral load was measured and was high. 5 patients presented with involvement of only one limb, but there was progression to other sites shortly thereafter. Physical and neurophysiological examination was entirely typical for ALS, satisfying El Escorial criteria. However the patients were younger (mean age 34) and had more rapidly progressive syndromes than wild-type ALS. The direct association with HIV infection is best illustrated by the response to anti-retroviral treatment: two patients improved and two others returned to normal, but subsequently the ALS symptoms re-emerged as CD4+ counts began to drop again. The pathogenesis of this syndrome is obscure; the authors have excluded a known opportunistic infection and HIV is not found in motor neurons.
In the same issue of Neurology there is a case report from New York of a 32 year HIV positive old woman with an ALS syndrome that resolved completely on antiretroviral treatment and remained well four years later. -***AJC***

Moulignier A, Moulonguet A, Pialoux G, Rozenbaum W.
Reversible ALS-like disorder in HIV infection.
NEUROLOGY
2001 Sep 25;57(6):995-1001
MacGowan DJ, Scelsa SN, Waldron M.
An ALS-like syndrome with new HIV infection and complete response to antiretroviral therapy.
NEUROLOGY
2001 Sep 25;57(6):1094-7

Five year sequelae of infant meningitis

Meningitis in childhood has its highest incidence during the first year of life and much is known about its immediate mortality and morbidity. However, there is a paucity of reliable data from large prospective studies on the longer-term outcomes of this infection.

In this study, Bedford *et al* have conducted a detailed analysis of the sequelae occurring in a cohort of children aged 5 years who suffered meningitis during the first year of life. They identified children who were diagnosed with meningitis in infancy from a prospective national study carried out in England and Wales between 1985 and 1987. In addition they identified a cohort of matched controls and targeted general practitioners and parents with detailed questionnaires about the children's health and development.

In total 1584 children who had suffered meningitis in infancy and 1391 controls were included in this research. The results showed that meningitis in infancy has serious consequences. Of those cases surviving the acute attack, 2% died before the age of 5 years. In those children surviving to 5 years there was a 10-fold increase in the risk of severe or moderate disability compared to the control group. This was reflected in the significantly higher frequency of neuromotor disabilities, seizure disorders, hearing problems, ocular or visual problems, speech or language problems, behavioural problems and the increased need for non-mainstream schooling. Furthermore, neuromotor and seizure disorders were significantly higher in those children diagnosed as having meningitis during the neonatal period compared to those diagnosed after the first month of life. Disability also seemed to relate to the causative organism, with Streptococcus pneumoniae having worse outcomes compared to Haemophilus influenzae and Neisseria meningitides infection.

This study confirms the severity of this disease and its longer-term sequelae, raises clinical awareness and should assist in prognosis in such cases. It is also important to note that since these cases were identified, clinical management has probably changed with third generation cephalosporins now forming the mainstay of acute treatment, as opposed to the previous regimes, which would have seen a much greater use of penicillin and chloramphenicol. Thus a future study may serve to illustrate effectiveness of treatment in this relatively common condition. -***SL***

Meningitis in infancy in England and Wales: follow up at 5 years.
Bedoford H, de Louvois J, Halket S, Peckham C, Hurley R, Harvey D.
BRITISH MEDICAL JOURNAL
2001:323:533-536

ALZHEIMER'S DISEASE

★★★ RECOMMENDED

Probably pathological protofibrils

Put simplistically, there are two conflicting theories as to the pathogenesis of Alzheimer's disease: the accumulation of amyloid ß-peptide into amyloid deposits or the presence of excessive *tau*. The former has gained considerable support from the finding that some mutations in the amyloid precursor protein (APP) cause rare familial forms of Alzheimer's. APP is a large molecule, which is cleaved by three enzymes (*a,ß,y*-secretase) to give the smaller amyloid ß-peptide, which is normally 40 amino acids long. The *presenilin* mutations disrupt APP processing close to the *y*-secretase site and cause overproduction of an elongated form of amyloid ß-peptide, called Aß42. These peptides form fibrils and accumulate into the senile plaques characteristic of Alzheimer's. An intermediate form of fibril formation is known as protofibrils; they may themselves cause neuronal death. Similar protofibrils are formed by *a*-synuclein in early onset familial Parkinson's disease.

Curiously, mutations within that part of the APP gene encoding for the amyloid ß-peptide itself (such as the Dutch mutation) tend to give cerebral amyloid angiopathy rather than Alzheimer's disease. However a Swedish group has described, for the first time, such a mutation that does cause familial Alzheimer's without the features of amyloid angiopathy. They have nicknamed it the Arctic mutation (because it is found in kindreds in northern Sweden). At first glance, the biology of the Arctic mutation seems to buck the trend. Patients with this mutation have reduced levels of Aß42 in their serum. So how do they develop Aß42 amyloid plaques? It turns out, from this elegant study, that the mutation accelerates the rate at which Aß42 forms protofibrils and hence excessive Aß42 deposition.

There are drugs that can reduce protofibril formation. Would they help the Arctic patients? Much more critically, have the authors discovered a general mechanism of Alzheimer's and Parkinson's disease toxicity -and therefore a therapeutic target? ***-AJC***

Nilsberth C, Westlind-Danielsson A, Eckman CB, Condron MM, Axelman K, Forsell C, Stenh C, Luthman J, Teplow DB, Younkin SG, Naslund J, Lannfelt L.
The 'Arctic' APP mutation (E693G) causes Alzheimer's disease by enhanced Abeta protofibril formation
NATURE NEUROSCIENCE
2001 Sep;4(9):887-93

HUNTINGTON'S DISEASE

★★★ RECOMMENDED

A clinical trial of coenzyme Q10 and remacemide in Huntington's disease.

Huntington's disease (HD) is an inherited disorder in which the expression of mutant huntingtin leads to selective neuronal loss, especially in the striatum. As a result patients present typically in middle-age with a combination of abnormalities including a movement disorder, cognitive decline and psychiatric problems. At the present time treatments are symptomatic and there are no therapies that are known to affect the natural history of this condition, although several possible candidate treatments are emerging from laboratory based work using transgenic mouse models of HD. The Huntington Study Group (HSG) in the US involves 43 centres and over 200 personnel and by recruiting large cohorts of patients aims to address questions of disease progression, presentation and therapy. This recent publication is the result of a trial in which 247 patients with early HD were recruited and randomised to receive either coenzyme Q10, remacemide hydrochloride, both or neither. The patients were then followed over a 30-month period with regular assessments to see whether these agents slowed the natural progression of the disease. Both drugs were selected following small pilot studies and based on the rationale that they should, relatively non-selectively, protect cells from stressful insults. At the conclusion of the study both drugs were well tolerated but neither had significantly altered the decline in disease, using the total functional capacity (TFC) measure of the UHDRS. However there was a trend to a slowing of TFC with coenzyme Q10 therapy. Whilst this was modest and not significant, it did suggest that this drug in combination with others may be capable of significantly slowing this condition, and is the first study to show any such effect. Thus this study will not alter our practice in HD, but does herald a new era in the approaches to treating this fatal condition. ***-RAB***

A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease.
The Huntington study Group
NEUROLOGY (2001)
57: 397-404

TRANSCRANIAL MAGNETIC STIMULATION

As good as a kick in the head?

There has been an explosion in the use of transcranial magnetic stimulation to investigate cognitive function. The technique is roughly the same in most of these studies, you ask the subject to perform a particular task, you attempt to turn off the bit of brain that you are interested in by applying TMS and you see how well the subject performs at that task. Obviously these sorts of study complement neuroimaging techniques neatly, area X lights up during a task, so inhibiting area X with TMS ought to impair performance. The study by Mull and Seyal is fairly typical of the genre. They were directed to the role of the frontal cortex in working memory by results of PET, fMRI and spatial EEG studies. The patients were asked to perform a simple working memory task, a single pulse was then applied to the frontal region during the task, the authors found that the number of errors increased when TMS was applied to the left frontal area but not when the TMS was applied on the right. Unfortunately this paper is riddled with methodological errors, for instance control experiments were performed in the absence of TMS. Anybody who has had TMS will tell you that the noise and muscle twitch induced by TMS is enough to induce errors in any task. This type of experiment should be properly controlled with some form of 'sham' TMS. Similar errors taint much of the TMS literature; some of the results should be taken with a very large pinch of salt. However with more rigorously controlled studies TMS will be a useful tool for investigating cognitive function and a nifty foil to neuroimaging techniques. ***-BMcN***

Mull BR, Seyal M.
Transcranial Magnetic Stimulation of Left Pre-frontal Cortex Impairs Working Memory
CLINICAL NEUROPHYSIOLOGY
2001: 112 1672-1675

BRAIN INJURY

Hot Heads After Acute Brain Injury

In experimental models of ischaemic brain damage, cooling the brain improves outcome. Slowing down cerebral metabolism is presumed to be neuroprotective, and there is also evidence in acute stroke and traumatic brain injury (TBI) patients that hyperthermia correlates with poorer outcome. Avoiding fever is therefore generally advocated and accepted as a good thing, but direct clinical evidence of interventional efficacy is conflicting, perhaps because standard core body temperature has been measured. Rossi and colleagues from a Neurosciences ITU in Milan have studied differences between actual intracerebral (ICT) and core temperature (Tc) using very accurate thermistors mounted on intraventricular and Swan-Ganz catheters respectively. They correlated these with intracranial pressure (ICP) in a group of 20 patients mostly with either severe TBI or aneurysmal subarachnoid haemorrhage. They found not only that fever was extremely frequent but also that ICT was nearly always significantly higher than Tc. ICT was also more closely correlated with increases in ICP, and there was some evidence using intra-jugular oxygen saturation monitoring that this was less related to changes in cerebral metabolism than in cerebral blood flow itself. It remains to be tested whether avoiding rises in ICT will improve outcome, but perhaps keeping a cool head really is good for you, after all. ***- RJH***

Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage.
S Rossi, E Roncati Zanier, I Mauri, A Columba, N Stocchetti
JOURNAL OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY
2001:71:10:448-454

PERIPHERAL NERVE

One Lump or Two?

As every medical student knows, diabetes mellitus is one of the more common causes of neuropathy so a fasting or random blood glucose level is essential to the investigation of any neuropathy. There is also a group of patients who do not have frank diabetes mellitus but are labelled with what is known as impaired glucose tolerance. The precise definition of these entities tends to get diabetologists very hot under the collar. My layman's understanding of impaired glucose tolerance is that it includes patients with a normal blood glucose but an impaired response to a glucose load. So has this got anything to do with neuropathy? There are two studies in September's Muscle and Nerve that suggest that perhaps it does. The first (Singleton *et al.*) was a retrospective study that examined the records of 121 patients with idiopathic polyneuropathy, 25% of these patients fulfilled the definition of impaired glucose tolerance. Interestingly these patients tended to have a painful sensory neuropathy. A second similar study (Novella *et al.*) looked sequentially at patients who presented to a neuromuscular clinic with idiopathic polyneuropathy, 50% of these patients had some form of impaired glucose tolerance, 27% met the criteria for impaired glucose tolerance. Again these patients tended to have a painful sensory neuropathy. These studies leave plenty of unanswered questions, for instance how common is neuropathy in impaired glucose tolerance? However there is a fairly simple take home message, if there are no obvious causes of neuropathy it is worth doing an oral glucose tolerance test, after all it is an inexpensive and non-invasive test. ***-BMcN***

Singleton JR, Smith G, Bromberg MB. *Painful sensory polyneuropathy associated with impaired glucose tolerance.* MUSCLE AND NERVE 24, 1225-1229

Novella SP, Inzucchi SE, Goldstein JM. *The frequency of undiagnosed diabetes in patients with idionpathic sensory neuropathy.*
MUSCLE AND NERVE
24, 1225-1229

A new treatment of Guillain Barre: CSF filtration

None can deny the need for an improved treatment of Guillain-Barre; even with best management, some 10% of patients are unable to walk a year later. This group, from Ulm in Germany, have compared CSF filtration with plasma exchange in a randomised clinical trial of 37 patients. CSF is filtered by withdrawing 30 to 50 mLs CSF through a spinal catheter and then reinfused through a filter. At each session, this withdrawal and reinfusion is repeated up to six times. Such sessions are repeated for 5-15 consecutive days. There was no difference in clinical efficacy between the two treatments; six months on, 80% in each group could walk more than 5 metres unaided. CSF filtration was better tolerated; there was one case of pulmonary oedema and one of hypovolaemic shock in the plasma exchange group.

The investigators originally planned 40 patients in each study arm, but as IVIG became increasingly available recruitment tailed off and they had to stop the study prematurely. For this reason, the numbers are small and this study should not change practice. But it is interesting to speculate on how CSF filtration might be working. The autoimmune response in Guillain Barre is believed to be generated in the periphery and directed against peripheral nerve or root antigens. There is no evidence for intrathecal antibody synthesis. So why should sieving CSF help? In a Nature Medicine article last year, the same group

described a CSF pentapeptide, QYNAD, that blocks sodium channels and thereby blocks neuronal conduction. They showed in this study that CSF filtration transiently reduced CSF levels of QYNAD. All very intriguing. ***-AJC***

Wollinsky KH, Hulser PJ, Brinkmeier H, Aulkemeyer P, Bossenecker W, Huber-Hartmann KH, Rohrbach P, Schreiber H, Weber F, Kron M, Buchele G, Mehrkens HH, Ludolph AC, Rudel R.
CSF filtration is an effective treatment of Guillain-Barre syndrome: A randomized clinical trial
NEUROLOGY
2001 Sep 11;57(5):774-80

EPILEPSY

Epilepsy surgery: Research uses of the waiting list

How do you do a randomised study to prove the worth of surgery for temporal lobe epilepsy, when everyone knows it works and you cannot ethically randomise patients to no surgery? Normally it takes a year to work patients up for surgery. The authors split patients into two groups. A: standard workup then surgery after a year. B: fast-track with surgery within 4 weeks. The groups were compared over the next year: prior to surgery for group A and after surgery for group B. This gets round the problem of randomising patients to no surgery although follow-up is short.

In group A 8% became free of seizures impairing consciousness compared to 58% in postoperative patients. This, in fact, is less good than other non-randomised postoperative studies of temporal lobe epilepsy surgery. There were four post-operative complications, but only one death, a sudden unexplained death in a patient in the delayed surgery group. This study provides strong support for the role of temporal lobe epilepsy surgery in selected patients, but it is perhaps the design of the study that is particularly intriguing and may be applicable to other surgical techniques, especially in the NHS! ***- MM***

Wiebe S , Blume WT , Girvin JP , Eliasziw M for the effectiveness of surgery for temporal lobe epilepsy study group.
A randomized controlled trial of surgery for temporal lobe epilepsy.
NEW ENGL J MED 2001;345:311-8

Calcium Channel (P/Q type) mutation linked to a form of human epilepsy

As the field of channelopathies expands for the first time a human form of epilepsy has been associated with a mutation on the gene encoding the alpha 1 subunit of the voltage gated Calcium channel, which is found on chromosome 19. To date spontaneously arising murine mutations have been described with mutations in this gene which represent models of human absence epilepsy but up till now no human mutations in this gene have given rise to epilepsy but have rather been described as giving rise to familial hemiplegic migraine and episodic ataxia type 2. The case in which this mutation has been described has a complex phenotype with primary generalised epilepsy, episodic and progressive ataxia and mild learning difficulties. The mutation produces a stop codon producing complete loss of the C terminal, which is required for bind to the other sub-units which together usually form the pore region of this Ca Channel. The patient was found to be heterozygous for this mutation as all other described human Calcium channel (CACNA1A) mutations. This mutation was not found in the parents (paternity confirmed genetically) or 200 healthy controls and the patient is the only child so other cases as yet have not been described. Using sophisticated expression studies the role of the mutation in causing Ca Channel malfunction was confirmed. Furthermore this effect was defined as being a dominant negative effect. The importance of the ion channels in basic neurological function is once again underlined and the role of drugs modulating the function of these channels may provide new avenues of treatment for some cases of epilepsy. ***- MM***

Human epilepsy associated with dysfuntion of the brain P/Q-type calcium channel.
AnneJouvenceau, Louise Eunson, Alexander Spaushus, Venkataswaran Ramesh, Sameer Zuberi, Dimitri Kullmann, Michael Hanna
LANCET
2001;358:801-07

MULTIPLE SCLEROSIS

★★★ RECOMMENDED

Diagnostic criteria for multiple sclerosis

This paper presents the conclusions of the International Panel on Multiple Sclerosis (MS) Diagnosis, convened in London in July 2000. This is the first major review of MS diagnostic criteria since those of Poser *et al*. with which most neurologists will probably be familiar if not conversant, which were published in 1983 when use of MRI was still in its infancy.

The importance of demonstrating dissemination of lesions in time and space is reaffirmed, using either objective clinical evidence (symptoms alone are not enough), or clinical and supporting paraclinical evidence (MRI, CSF, VEP), the latter obtained using the highest quality, state-of-the-art technology. Specific MR imaging criteria, absent in Poser, are presented. Although the diagnosis can be made on clinical grounds alone (i.e. two or more attacks with objective clinical evidence of two or more lesions), more stringent additional criteria apply as the clinical evidence becomes weaker. Hence in clinically isolated syndromes (monosymptomatic presentation), the diagnosis of MS requires demonstration of dissemination in space (MRI, MRI + CSF) and time (2nd attack, clinical evidence of a second lesion). The diagnosis of primary progressive MS remains problematic, requiring evidence of dissemination in space (MRI, MRI + VEP) and time (MRI, clinical progression of disability over 1 year). No better explanation for the clinical and paraclinical abnormalities must be available.

The outcome of using these criteria will be a diagnosis of MS, "possible MS", or "not MS". Terminology familiar from the Poser criteria (e.g. clinically definite, laboratory supported) is dropped. The criteria aim to be of use to the practising physician as well as for research purposes. It seems likely that they will be widely accepted and supersede the Poser criteria.***-AJL***

McDonald WI, Compston A, Edan G *et al*
Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis
ANNALS OF NEUROLOGY 2001;50(1):121-127

Stereotactic surgery for tremor in multiple sclerosis

Many neurologists will have experienced the frustrating sense of therapeutic impotence when attempting to treat disabling tremor in patients with multiple sclerosis (MS). Although a number of drugs have been tried, such as carabamazepine, clonazepam, isoniazid, ondansetron, primidone and propranolol, and even limb weights, lack of meaningful benefit is not infrequent. Stereotactic surgery has also been used, intermittently, for many years in this situation, but few good prospective studies have been conducted, a deficiency partially answered by the current study. Of 46 MS patients assessed, 33 (= 72%) were excluded from surgery for various reasons. In the surgical group (n = 13), stereotactic lesions were made in the thalamus, zona incerta or subthalamic nucleus.

Assessments made 3 and 12 months postoperatively showed attenuation of contralateral upper limb postural and kinetic tremor in all cases, irrespective of lesion site, and in head tremor. Total tremor suppression was seen if preoperative tremor frequency was > 3Hz, but total suppression was never seen if tremor frequency was ≤ 3Hz. By 1 year, 7/11 survivors had reduced tremor-related disability.

Surgery was associated with significant morbidity: postoperative hemiparesis, seizures, fatigue, increased bladder dysfunction, and depression were reported. However, compared to control patients matched for duration and severity of MS (but not necessarily with tremor), there was no significant difference in the rate of disease progression at 3 and 12 months postoperatively.

Although numbers are small, and patient assessments were not blinded, nonetheless this is a significant study showing that stereotactic lesional surgery can be beneficial for MS tremor, but only for highly selected patient groups. Moreover surgery is not without concurrent morbidity, but this may be minimised, as selection criteria for the procedure are refined. It seems likely that stereotactic surgery will become part of the standard therapeutic approach to tremor in multiple sclerosis.***-AJL***

Alusi SH, Aziz TZ, Glickman S, Jahanshahi M, Stein JF, Bain PG

Stereotactic lesional surgery for the treatment of tremor in multiple sclerosis. A prospective case-controlled study.

BRAIN 2001:124(8);1576-1589

STROKE

★★★ RECOMMENDED

Levodopa boosts the effects of physiotherapy after stroke?

Enhancement of motor recovery may be brought about by an increased concentration of norepinephrine in the central nervous system. Animal models of stroke and some small clinical trials have shown that treatment with amphetamines, whose action is to release norepinephrine, is effective in improving motor recovery when combined with training or physiotherapy. However there seems to be little impetus in the UK for larger scale trials leading to their use in clinical practice.

Reluctance to use amphetamines may be because of the risk of physical and psychological dependence or because of potentially dangerous cardiovascular side effects. Is there a way to increase norepinephrine safely? A group in Munich have successfully tested a potential solution. Instead of amphetamine, Levodopa in combination with a decarboxylase inhibitor is used. Given orally, it is metabolised to dopamine in the brain and converted to norepinephrine.

However in the periphery metabolism of the norepinephrine is blocked by the decarboxylase inhibitor that does not cross the blood-brain barrier.

53 patients were enrolled to a randomised double blind trial. They were given single doses of 100mg levodopa or placebo before every session of physiotherapy for three weeks. For the following 3 weeks they had physiotherapy without drug intervention. At the start of treatment the two groups were similar except in side of stroke. A greater proportion of patients with right hemisphere strokes were in the placebo group.

Motor recovery was measured using the Rivermead Motor Assessment and was found to be significantly better after 3 weeks of levodopa than placebo intervention. The advantage was maintained at the end of the study, 3 weeks after levodopa was stopped.

These results are very promising. In their report the group put forward a number of possible mechanisms for levodopa's beneficial influence on recovery. Further work is needed to identify how it works. In the future will this method prove be an acceptable way to boost the effects of physical therapy? ***-AJT***

Effect of Levodopa in combination with physiotherapy on functional recovery after stroke: a prospective, randomised, double-blind study.

Scheidtmann K, Fries W, Muller F, Koenig E.

THE LANCET

2001: 358 September 8,2001: 787-790

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.

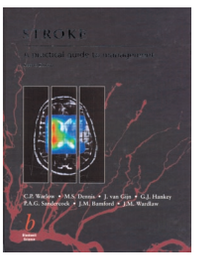
Cerebrovascular Diseases, Neuroepidemiology
S. Karger AG - Medical and Scientific Publishers,Allschwilerstrasse 10, CH - 4009 Basel, SWITZERLAND.
Tel. 0041 61 306 11 11, Fax. 0041 61 306 12 34, E-Mail. t.nold@karger.ch www.karger.com

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

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

Stroke: A Practical Guide To Management 2nd Edition



Authors: C P Warlow, MS Dennis, J Van Gijn, G J Hankey, PAG Sandercock, JM Bamford, J M Wardlaw
Published by: Blackwell Science
Pages: 804
ISBN No: 632054182
Price: £99.50

It is five years since the first edition of this benchmark book hit the scenes. Benchmark because it was a comprehensive textbook of cerebrovascular disease written by a close group of authors combining neurological, radiological and gerontological skills with pragmatism and common sense. The second edition is no different and is indispensable.

What makes this book so important is the clarity and structure with which it is written. The style is such that the reader could believe it is the writings of one individual, not seven, for it is not a book made up of individual chapters written by different contributors. The constant honing of all parts of the book until a consensus was reached was certainly worthwhile.

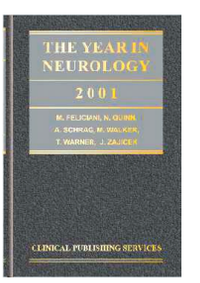
Approximately 800 pages and 18 chapters long, with clear text, tables, line drawings and photographs, the book can either be used for reference or for education and the personal development of a questioning approach to every vascular case one might come across. Rather than encouraging medicine by recipe the authors use their commanding knowledge of the clinical encounter and the weight (or sometimes lack of it) of evidence to enable the reader to make sensible clinical decisions.

Much of the fabric of the book (for example the sections describing clinical features, pathology etc) remain little changed but sections on treatments (post IST and post NINDS and ECASS thrombolysis trials) are updated. Given that five of the seven authors are neurologists one might have anticipated a slightly more comprehensive section on unusual causes of ischaemic stroke and cerebral venous thrombosis but I appreciate that far more readers of the book will be stroke physicians than stroke neurologists. The reader will also find copious references to take a topic further if necessary.

This book should be open on the desk (rather than hidden on a shelf) of all of us who see patients with cerebrovascular disease as a constant reminder to keep asking ourselves "What sort of stroke is it? What am I going to do about it? What caused it? How can I stop it happening again?"

Peter Martin,
Addenbrooke's Hospital

The Year in Neurology 2001



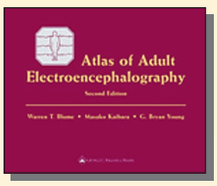
Authors: Feliciani, M; Lovestone, S; Quinn, N; Schrag, A; Walker, M; Warner, T; Zajicek, J.
Published by: Clinical Publishing Services Ltd
Pages: 400
ISBN No: 0-9537339-5-5
Price: £49.50

It is not possible for one person to read all the literature on a single neurological disease, let alone for the practising neurologist to keep abreast of developments across a range of diseases. For instance in the last eighteen months there have been (to consider some of the diseases covered in this book) 2129 papers relevant to multiple sclerosis, 2585 to Parkinson's disease, 4707 to Alzheimer's and 5171 to epilepsy (according to PubMed). Perhaps the best solution to this problem is a publication such as ACNR, which regularly provides reviews of major journals in the field. Another is the annual "digest" of important papers selected by a team of experts, such as this book. It has been developed, the publishers say, "to provide the reader with a concise focused resource of recent developments in the field" and promises to be the first of an annual series. The experts chosen to review the literature are mainly from the UK and will be reasonably familiar to those in their field. Their reviews are presented attractively in a format that is convenient for both reference and idle browsing. Each disease takes up a chapter, which consists of a brief overview followed by literature reviews arranged into sensible subtopics. Each chosen study is reviewed briskly, to a set template that clearly distinguishes findings from interpretation.

One can argue over the balance of the chapters: that on cervical dystonia is twice as long as that on multiple sclerosis for instance. And the reader looking for the most up-to-date account will be disappointed. Although published in November 2001, there are no contributions from the 2001 literature; all the papers reviewed are from late 1999 to 2000. This time lag is of course a problem with all book publishing (and where journals such as ACNR have the advantage). However this book has been produced remarkably rapidly, compared to many recent neurology texts; for instance the content of Clinical Trials in Neurology, edited by Roberto Guiloff and published in 2001, was written in 1997. This slight publication lag is a reasonable price to pay for an accessible and authoritative distillation of the recent neurological literature; and at £49.50 (US$80) has to be considered a bargain.

Alasdair Coles,
Cambridge

SAVE ON THE NEUROLOGY TITLES YOU *NEED*
WITH LWW & ACNR



ATLAS OF ADULT ELECTROENCEPHALOGRAPHY

Second Edition

Warren Blume, MD **& Masako Kaibara,** MD,

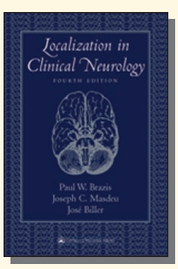
Electroencephalography (EEG) is the study of brain electrical activity and remains the primary diagnostic tool for epilepsy & seizure disorders. These disorders are the most common neurological disease as they affect over a million individuals.

Thoroughly revised and updated, this atlas remains a "must have" for anyone performing or interpreting EEGs in adults. This new edition shows readers how to maximise the usefulness of digital EEG and also features a special horizontal format, digital EEG and expanded coverage of subdural EEG and EEG in the ICU and 500 clear as well as easy to read EEG samples.

0-7817-2996-3 • 500 illus. • November 2001 • Hardback • 550 pages

Normal Retail Price: £120.00

ACNR Price: £108.00



LOCALIZATION IN CLINICAL NEUROLOGY

Fourth Edition

Paul W. Brazis, MD, **Joseph C. Masdeu,** MD **& Jose Biller,** MD,

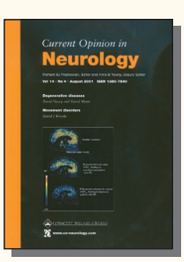
Clinical localization comprises a series of examination techniques where clinical signs and symptoms are used to determine the anatomical location of neurological disease. This updated fourth edition is still the most practical reference available on localization in clinical neurology.

Revised in it's format the book now includes more tables and illustrations to aid in accurate diagnosis as well as a more didactic approach to the emphasis of the importance of localization as a crucial tool in patient care. This is a "must have" book for neurologists, residents in training and for the shelf of every neurology department library since the book features concise but systematic explanations, easy to understand explanation of difficult concepts as well as full coverage of neurological signs ranging from obscure to the most common. Also there are now more tables and figures, a new introductory chapter and also a comparison of localization and imaging for accurate diagnosis.

0-7817-2843-6 • 100 illus. • September 2001 • Hardback • 512 pages

Normal Retail Price: £102.00

ACNR Price: £91.80



CURRENT OPINION IN NEUROLOGY

www.co-neurology.com

Editor: **Richard SJ Frackowiak**
Deputy Editor: **Anne B Young**

Current Opinion distills the massive amount of primary literature into reliable, concise and thoughtful analyses written by respected opinion leaders.

The entire discipline is covered within structured sections so that you receive a full update on all aspects of neurology every year.

Visit **www.co-neurology.com** for further information and to check out a sample issue.

ISSN – 1350-7540 • Individual subscription **$266**
(6 issues per year) includes online access.

LIPPINCOTT WILLIAMS & WILKINS
A **Wolters Kluwer** Company

To order any of the above publications or any other **Lippincott Williams & Wilkins** publications email ACNR Bookservice at **ACNRbooks@aol.com** or fax **0131 313 1110**

NEUROMUSCULAR DISEASES

Advances In Neurology, Volume 88

Rahman Pourmand, MD **& Yadollah Harati,** MD,

Neuromuscular disease is a major subspeciality within neurology and includes muscular dystrophy, myasthenia gravis, amyotrophic lateral sclerosis, diabetic neuropathy and other diseases. Some of these illness are rare while others more prevalent.

Together neuromuscular disorders account for half a million cases of neurological disease. This volume explains the recent breakthrough in a way that is clinically relevant. The book will be based on a symposium; with contributors being invited by the editors to contribute. All chapters will include sections on scientific advances, practical applications, treatment strategies and future directions. The book will feature chapters by internationally recognised experts and will include coverage of innovative diagnostic methods, new and effective therapies and new management strategies. Each of the chapters has three main sections – namely scientific background, practical application and future directions.

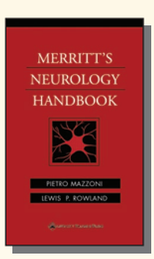
Contents

Advances in Neuromuscular Disorders: A Historical Perspective • Pathogenesis of Amyotrophic Lateral Sclerosis • Genetic Aspects of Amyotrophic Lateral Sclerosis • Motor Unit Estimate • Diagnostic Criteria and Outcome Measurement of Amyotrophic Lateral Sclerosis • Drug Therapy in Amyotrophic Lateral Sclerosis • Spinal Muscular Atrophies • Diabetic Neuropathy • Immune Mediated Neuropathies • Genetically Determined Neuropathies and Plexopathies • Neuropathic Pain • Myasthenia Gravis • Lambert-Eaton Myasthenia Syndrome • Congenital Myasthenia Syndrome • Metabolic Myopathies • Periodic Paralysis and Related Disorders • Idiopathic Inflammatory Myopathies • Dystrophinopathies • FSH Syndrome • Limb-Girdle Muscular Dystrophies • Myotonias • HIV Neuromyopathies • Critical Illness Neuromyopathies • INDEX

0-7817-3145-3 • 95 illus. • December 2001 • Hardback • 450 pages

Normal Retail Price: £128.00

ACNR Price: £115.20



MERRITT'S NEUROLOGY HANDBOOK

Pietro Mazzoni, MD, PhD **& Lewis P. Rowland,** MD,

Designed for portability and quick reference on the wards and in other clinical settings, this handbook presents the essentials of **Merritt's Neurology, 10th edition**. The book follows the text chapter by chapter and presents the key information on signs and symptoms, diagnostic tests, and neurologic disorders in an easy to scan numbered list format. This pocket sized reference is sure to be perfect for residents and practitioners needing clinical information from **Merritt's** but in a practical format for on the spot consultation. The book also features a bulleted outline format for quick information access that is keyed to the main text book by *SIGNS AND SYMPTOMS, DIAGNOSTIC TESTS AND NEUROLOGICAL DISORDERS.*

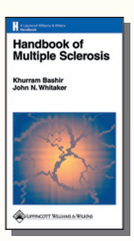
Contents

Symptoms of Neurological Disorders • How to Select Diagnostic Tests • Infections of the Nervous System • Vascular Diseases • Disorders of Cerebrospinal and Brain Fluids • Tumors • Trauma • Birth Injuries and Developmental Abnormalities • Genetic Diseases of the Central Nervous System • Disorders of Mitochondrial DNA • Neurocutaneous Disorders • Peripheral Neuropathies • Dementias • Ataxias • Movement Disorders • Spinal Cord Diseases • Disorders of the Neuromuscular Junction • Myopathies • Demyelinating Diseases • Autonomic Disorders • Paroxysmal Disorders • Systemic Diseases and General Medicine • Environmental Neurology • Ethical and Legal Guidelines • INDEX

0-683-30496-8 • 40 illus. • September 2001 • Paperback • 500 pages

Normal Retail Price: £34.00

ACNR Price: £30.60



HANDBOOK OF MULTIPLE SCLEROSIS

Khurram Bashir, MD **& John N. Whitaker,** MD,

A concise guide to the evaluation and management of patients with multiple sclerosis., this book's coverage will begin with clearly written reviews of the classification of human demyelinating diseases as well as the epidemiology, pathology and pathogenesis of human sclerosis. The authors will also explain the clinical symptoms and signs which occur during the course of the diseases and present guidelines for diagnostic workup and treatment and also offer specific recommendations for managing the physical and psychosocial aspects of multiple sclerosis.

0-7817-2754-5 • 36 illus. • November 2001 • Paperback • 288 pages

Normal Retail Price: £29.00

ACNR Price: £26.10

FOCUS ON PUBLISHERS

Need to keep updated? Here is the pick of latest publications

Expert advice in the Neurosciences

The most up-to-date knowledge on the applications of Transcranial Magnetic Stimulation is combined with essential background information in the forthcoming 'Handbook of Transcranial Magnetic Stimulation' (Pascual-Leone, Davey, Rothwell, Wasserman and Puri). Available in November 2001, this indispensable guide brings together the related basic science, fundamental principles and essential procedures of TMS, with current information on the technique. Expert authors provide reader-friendly guidance on this procedure for clinical and research-based neurologists, neurophysiologists, neuropsychologists and psychiatrists.

Other recent publications in this area include 'Parkinson's Disease in the Older Patient' - a practical guide to assessment and clinical management and the 4th edition of 'Uncommon Psychiatric Syndromes' - the definitive account of rare mental health problems.

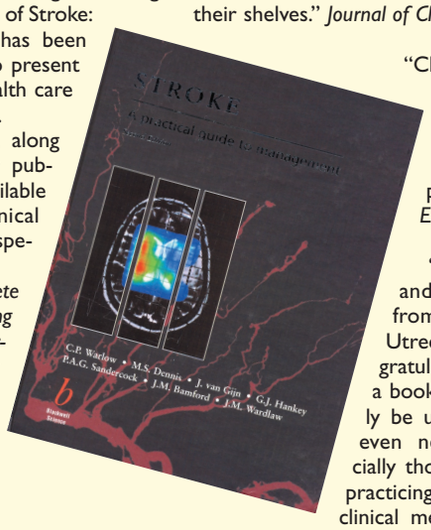
For more information on these, and other related publications from Arnold Publishers, contact E.Mail healthsci.marketing@hodder.co.uk or call 0207 873 6355 for a catalogue.

New Second Edition
Stroke - A practical guide to management

Presenting a unique approach to stroke, both from the uniformity and clarity of the style and the integrated clinical management which weaves together causation, presentation, diagnosis, management and rehabilitation, the second edition of Stroke: A practical guide to management has been extensively revised and expanded to present an authoritative reference for all health care professionals involved in stroke care.

This highly acclaimed textbook, along with a selection of other recently published titles in neurology, are now available to readers of Advances in Clinical Neuroscience and Rehabilitation at specially discounted prices.

To reserve your copies simply complete and return the order form accompanying the promotional leaflet inside this journal. Alternatively, contact the publisher Blackwell Publishing Tel: 01865 206233, Fax: 01865 206026, or E-mail: Medirect@blacksci.co.uk quoting reference Q/G00270/10.



Reviews of the First Edition ...

"This is an important book ...The authors deserve congratulations for their impressive achievement." *Neuroradiology*

"I cannot remember when last I read a book so clearly written and so well set out ... I can strongly recommend it to all those who deal with stroke. Neurologists, neurosurgeons, vascular surgeons and trainees should all have a copy of it on their shelves." *Journal of Clinical Neuroscience*

"Charles Warlow and his colleagues and pupils are to be congratulated on this original piece of work.'" *European Neurology*

"Charles Warlow and his colleagues from Edinburgh and Utrecht are to be congratulated on producing a book which will actually be useful to clinicians, even neurologists, especially those who believe in practicing properly scientific clinical medicine." *Journal of Neurology, Neurosurgery and Psychiatry*

"This book is probably already a classic and should be in every hospital library ...'" *Medicine Weekly.*

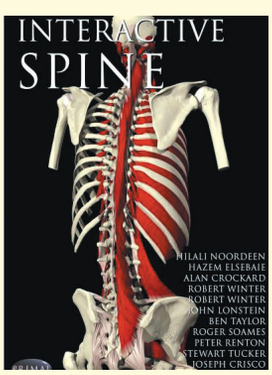
The Interactive Spine

Primal Pictures has announced the launch of its latest and most ambitious product to date. The Interactive Spine represents the world's first computer graphic model of the entire spinal column.

Primal Pictures is one of the world leading developers and publishers of 3D interactive anatomy software on CD-ROM and now on-line. The Interactive Spine features 3D computer graphic models of the spine, allowing users to rotate, select from a range of spinal models and peel away over 20 layers of anatomy from skin to bone! Full anatomy, pathology and radiology text is illustrated by hundreds of slides and video clips. The Interactive Spine is the ultimate resource for improving patient education, enhancing training sessions and transforming presentations.

Primal Pictures is offering ACNR readers a special offer price of £112.50 plus VAT and a 30-day no risk, money-back guarantee.

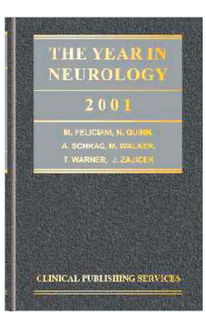
For further information contact Primal Pictures Ltd, 2nd Floor, Tennyson House, 159-165 Great Portland Street, London. W1W 5PA. Tel: 020 7637 1010, www.primalpictures.com



The Year in Neurology

Clinical Publishing Services Ltd has published its newest title, The Year in Neurology 2001. Providing the reader with a concise overview of the latest developments in neurology, the title provides evaluation and critical appraisal of the full range of recently published literature in the field. This year's volume covers Cervical Dystonia, Parkinson's Disease, Epilepsy, Alzheimer's Disease, and Multiple Sclerosis.

For further information on this and related titles, visit www.clinicalpublishing.co.uk, or contact the publishers at Oxford Centre for Innovation, Mill Street, Oxford, OX2 0JX, Tel: 01865 811116, Fax: 01865 251550 or E-mail: gresford@compuserve.com.



WIN A COPY OF THIS TITLE!!

Clinical Publishing and ACNR magazine are pleased to offer readers the chance to win a copy of The Year in Neurology.

To enter, all you have to do is fill in the short survey on the back of the reader enquiry/mailing sheet included with this magazine, and fax it to 0131 313 1110. If you don't have the insert sheet, just fax your details to the above number, marking your fax "YEAR IN NEUROLOGY COMPETITION".

New treatment for Schizophrenia

Rosemont Pharmaceuticals are pleased to announce the launch of Sulpor (200mg/5ml Oral Solution Sulpiride) as a licensed product for the treatment of chronic schizophrenia.

The initial dosage varies from 400mg to 800mg twice daily, depending on the condition being treated.

The product is available at a strength of 200mg/5ml in 150ml bottles (£27/150ml) and allows dosage flexibility to the prescriber. Sulpor has the same formulation as the Rosemont Sulpiride 200mg/5ml Oral Solution, previously supplied under its Specials manufacturers licence.

Sulpor is easy to swallow, sugar free in a suitably flavoured base, packaged in an attractive blue vignetted carton representing the Rosemont Central Nervous System therapeutic group, has easy to read pack information, and child resistant tamper evident closures.

Sulpor is available from all major wholesalers.

For further information, freephone 0800 919312, Fax. 0113 2460738.

New marketing manager for Oxford Instruments

Oxford Instruments Medical are pleased to announce Sue Maxwell as the new Marketing Manager for its Neurophysiology products. Sue takes global responsibility for the Medelec range of EEG, EMG and EP products as well as Oxford Instruments partnership with Compumedics for sleep diagnostic instruments.

Sue Joins OI from 'Integra Neurosciences' where for four years she was responsible for the international marketing for "Selector", an ultrasonic aspirator for the removal of tumours, and for European marketing for a variety of neurosurgical equipment and implants.

Prior to this Sue worked with Johnson & Johnson Professional as a Product Manager for Neuroendoscopy. Although starting originally in skin-related research, she progressed to the sales arena with Glaxo and Keymed (part of the Olympus group) before joining J&J.

For further information contact Oxford Instruments on Tel. 01483 770331.

Call to reassess the significance of NAbs in MS patients treated with Interferon-Beta

Researchers at ECTRIMS called for physicians and clinicians to recognise neutralising antibodies (NAbs) as a primary consideration when starting interferon-beta treatment for MS.

Evidence confirms that high levels of therapy-induced NAbs may reduce or abolish the efficacy of beta-interferon (IFN beta). Various studies presented at ECTRIMS demonstrate that the type of Interferon, dosage, dose frequency and route of administration may each influence the rate of NAb development. For example, IFN-beta 1a (Avonex) is administered once a week by intra-muscular injection and the incidence of NAb formation ranges from 2-8%. IFN-beta-1a (Rebif) is administered three times a week by sub-cutaneous injection and generates levels of Nabs from 15-30%. Finally, over 40% of patients receiving IFN-beta-1b (Betaferon) administered sub-cutaneously every other day will develop NAbs.

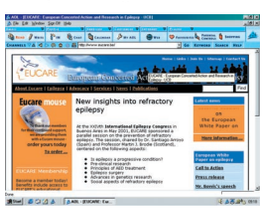
A clinical consensus also suggests that NAbs caused by any of these products are cross-reactive, so switching a patient to a less antigenic Interferon after NAbs have been generated may not overcome their negative effects. Clinical trials demonstrate that IFN-beta-1a (Avonex) is associated with the lowest incidence of NAbs and is the least immunogenic. Physicians and clinicians should therefore consider the long-term immunogenicity of NAbs as major criteria when initiating MS treatment to ensure continued therapeutic efficacy. Many ECTRIMS speakers also emphasised a vital need for standardised IFN-antibody measurements and ongoing NAb monitoring during treatment.

"The clinical impact of NAbs is not generally seen in the short-term since MS is a long-term chronic disease. Patients need to be followed up regularly for at least a year for the effects to be reliably detected," noted Dr Jeffrey Greenstein of the Temple University School of Medicine, Philadelphia, USA.

For further information contact Biogen on Tel. 01628 501000.

Web resource for epilepsy specialists

www.eucare.be (European Concerted Action and Research in Epilepsy) is dedicated to providing information and a contact point for epilepsy professionals, and to raising the profile of epilepsy across Europe through educational and political actions. It was initiated to coincide with the launch of the European White Paper on Epilepsy, enabling a live webcast of the event to reach a wide internet audience. This technique has also been used to transmit live webcasts of Eucare's satellite symposium at the WCN, and the parallel session 'Prevention of refractory epilepsy' at the International Epilepsy Congress. In addition to extending the live audience, webcasting allows Eucare events to be archived, then viewed by individuals at their convenience.



Free mouse! Registered members of Eucare can apply for the chance to receive the EUCARE mouse. See www.eucare.be for more details.

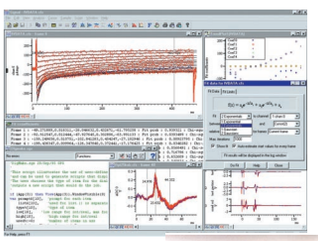
Gait Trainer GT I - the new development in gait rehabilitation

Modern concepts of motor learning favour a task-specific, repetitive approach, ie. if someone wants to re-learn walking, they have to walk. So far, conventional therapy requires the strenuous effort of up to three therapists to assist the gait of severely disabled subjects resulting in a non-sufficient (seldom more than 100 steps) and non-optimal practice. This is the reason for the design of the gait trainer: the harness-secured patient is positioned on two footplates, whose movements simulate stance and swing in a physiological manner, a drive supports the patient according to his abilities, and the highly relevant trunk movements are controlled phase-dependently. By themselves or with only a little help, wheelchair-bound subjects can thus practice up to 1000 almost natural steps per session. The gait trainer operates successfully in several European countries, improving gait ability in stroke, TBI, paraparetic, MS, CP and orthopaedic patients.

For more information contact Reha-Stim, Kastanienallee 32, 14050 Berlin, Germany, or use the reader enquiry service enclosed with this magazine.

Laboratory favourite gets power boost

The all-new Micro1401 Mk II from CED Ltd is an updated version of the Micro1401 data acquisition unit, used in thousands of life-science laboratories world-wide. The Micro1401 established itself as the standard laboratory interface, bringing versatility and reliability to research at an affordable price. Used with Spike2 and Signal software, the Micro1401 and its big brother the Power1401 gave the researcher unparalleled performance and ease-of-use for neurological, physiological, pharmacological and many other applications.



Now CED has updated the Micro1401 to bring even greater performance and value-for-money. A 16-bit 500kHz analogue-to-digital converter, built-in choice of USB or CED standard interfaces, option of expandable memory, multi-system synchronisation for large numbers of channels, expansion top boxes and downloadable firmware updates are just some of the new features available with the Micro1401 Mk II. CED Spike2 and Signal software means that the performance of the Micro1401 Mk II can be harnessed right away.

For further information contact Simon Gray, Cambridge Electronic Design Ltd, Science Park, Milton Road, Cambridge CB4 0FE. Tel. 01223 420186, E-Mail. simong@ced.co.uk

2001 IPA Service to the Field Awardee

Professor Raymond Levy has been awarded the Service to the Field Award from the IPA, to commemorate his lifetime contribution the field of Psychogeriatrics through his work for IPA, especially as president from 1995-1997. Professor Levy was the foundation Profesor of Psychiatry of Old Age at the Institute of Psychiatry, London, and is noted for his groundbreaking work on neuroimaging and cholinergic therapies in Alzheimer's disease.

From left to right: Alistair Burns, Edmond Chiu, Raymond Levy

He has mentored scores of psychogeriatricians on 5 continents.

Cooler future for brain-injury patients

European neurologists and neurosurgeons are at the forefront of treating patients with fever-related brain damage using a new technology that reduces core body temperature. Developed by Alsius™ Corporation, the technology features a heat-exchange catheter called the Cool Line™ which connects to a sophisticated temperature control Coolgard™ system.

Prof. Erich Schmutzhard

At the January 2001 ANIM meeting in Innsbruck, neurologists and intensive care clinicians from Leipzig, Innsbruck, and Vienna reported how Alsius' new approach showed signs of benefiting patients admitted into Neuro ICU with severe brain injury. Since then, physicians in Italy, Spain and Germany have been using Alsius™ technology.

Innsbruck neurologist Prof. Erich Schmutzhard has already successfully controlled fever in 50 patients and reported that 89% of patients treated had no temperature value over 38°C (or 100° F.). "The Alsius system is able to successfully control temperature because cooling takes place internally as opposed to conventional surface cooling methods such as ice packs or blankets," said Prof. Schmutzhard. "This is the future for treating critical care patients with neuronal injury".

Alsius technology has received CE clearance in Europe and is currently investigational in the US.

For further information, please contact: George Strang, Forth Medical Limited, Forth House, 42 Kingfisher Court, Hambridge Road, Newbury, Berkshire RG14 5SJ.

Unchain your workflow

The AXIOM Artis MP multi purpose X-ray system

Siemens Medical Solutions has introduced a new concept that improves the productivity of many radiographic procedures. Called AXIOM, the concept simplifies routine tasks and increases workflow by using advances in information technology techniques.

The AXIOM concept has been introduced because of the increasing need to bring down equipment life-cycle costs and improve operational productivity - notably the more efficient use of equipment and staff - by employing the latest advances in hardware and software. Making substantial improvements to image quality, ease of use, patient care and equipment connectivity, all the equipment variants in the AXIOM range make gains in these four key areas by combining advances in hardware with software. This improves image quality for quicker and more accurate diagnoses.

'Unchaining your workflow' improves productivity from diagnostics and therapy to continuing and ongoing care. This also means that x-ray systems and equipment can be 'seamlessly' integrated into a hospital network to facilitate faster data exchange not just between departments but, if necessary, between remotely located sites. Depending on requirements, images and data from other modalities and departments can be made available at the touch of a button. Such facilities not only promote faster therapeutic decisions, but also raise productivity.

For more information contact: Mike Bell, Siemens Medical Solutions, Tel. 01344 396317.

The British Neuroscience Association

'Towards a better understanding of the nervous system in health and disease'

The BNA is the fastest growing learned society, with nearly 2000 members, a rise of 40% since its relaunch as the BNA in 1997 from the former Brain Research Association. In addition to discounted journals and books and other occasional 'special offers', the benefits of membership now include the following: Reduced registration fees to the National Meeting and One-Day Symposia, and FREE admission to many events; Regular newsletter and other relevant mailings; Regular 'BNA News Email Alert' service; Student prizes, and bursaries for attendance at BNA and FENS meetings; Free on-line access to European Journal of Neuroscience; Concessionary (SFN membership rate) registration fees and sponsored abstract forms for Society for Neuroscience; Free advertising in 'BNA News Email Alert', the BNA Newsletter and on the BNA Website.

For further information contact membership@bna.org.uk, or see www.bna.org.uk. Membership application forms are also available from either of these sources, or from the BNA Conference Office c/o New Medical School, Ashton Street, Liverpool L69 3GE. Tel. 0151 794 4943/5449, Fax, 0151 794 5517. Membership fees are still only £45 per annum (full member), £15 per annum (student member)!

Prescribing information

Lamictal (lamotrigine)

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

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

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

Contra-indications: Hypersensitivity to lamotrigine.

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

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

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

Legal category: POM.

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

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

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

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

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

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

GlaxoSmithKline

GEN 26792-ALP/May 2001

Before you treat her epilepsy, put yourself in these.

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?

Lamictal™
lamotrigine

Epilepsy treatment with women in mind