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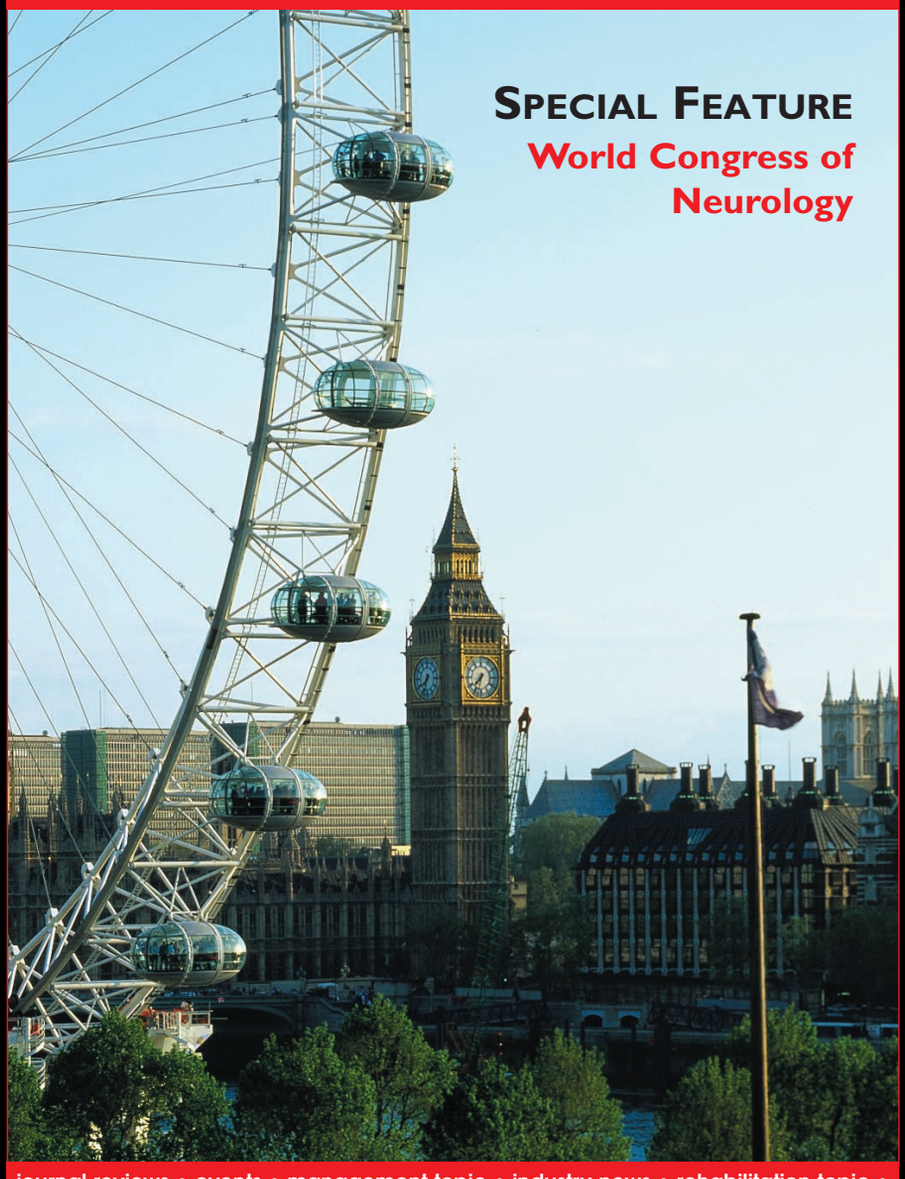
ACNR

Advances in Clinical Neuroscience & Rehabilitation



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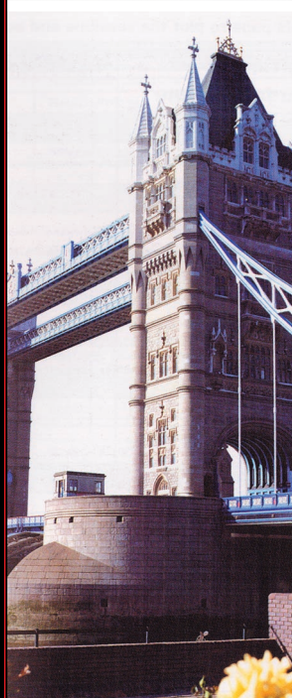

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† Benamer H *et al*. Accurate differentiation of Parkinsonism and Essential Tremor using visual assessment of ^{123}I-FP-CIT SPECT imaging: the ^{123}I-FP-CIT Study Group. Movement Disorders 2000;15:503-510

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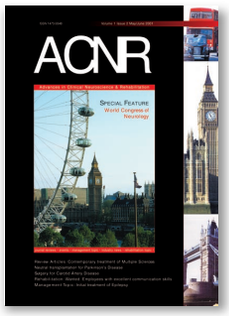
Roger Barker is editor of Advances in Clinical Neuroscience & Rehabilitation (ACNR), and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. He trained in neurology at Cambridge and at the National Hospital in London. His main area of research is into neurodegenerative and movement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

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

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

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



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Features

Regulars

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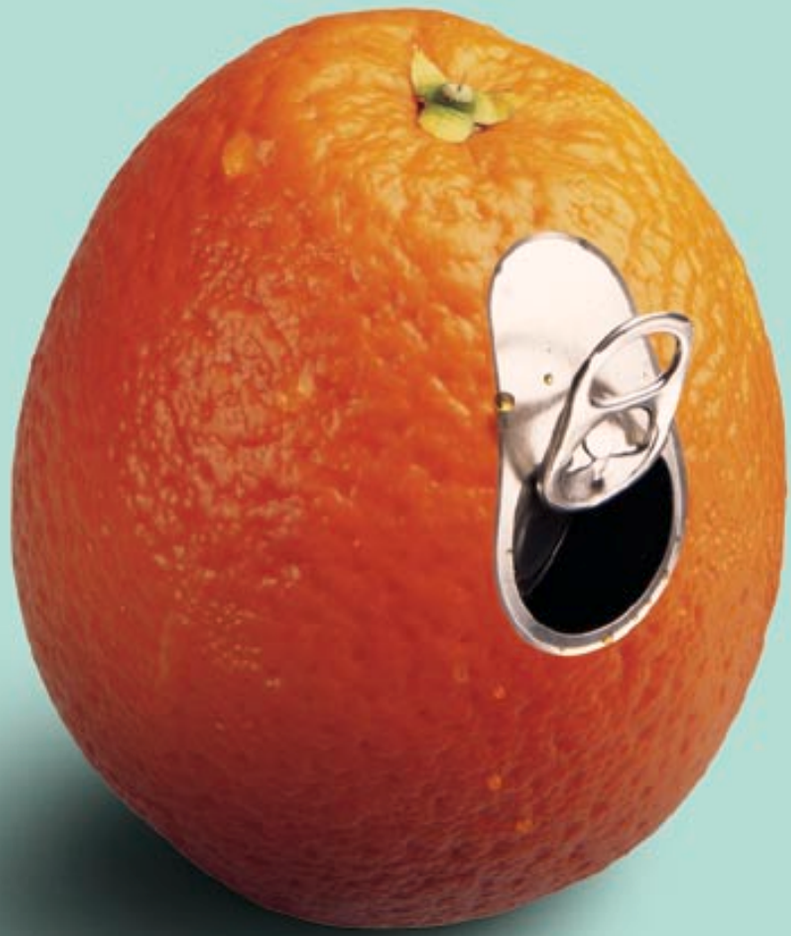
The Treatment Of Epilepsy

Has Evolved



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From the Editor...

I hope you enjoyed the first issue of ACNR, which we feel adopts a unique approach by virtue of its scientific and topical insights to clinical neuroscience and neurology. The second issue continues with the topical and practical themes that characterised the first issue. Thus there are reviews on stroke and surgery, which is currently entering a period of redefinition, as well as a review on the new and most effective therapies in MS.

However, a major new development that has arisen since the last issue is the role for neural grafting in Parkinson's disease, which has implications for a range of other neurodegenerative conditions. This topic arose following the publication of a controversial US study lead by the neurosurgeon Curt Freed, in which new disabling side effects were reported - a side effect that made it to the front page of the New York Times and Guardian. This study therefore is reviewed in a special feature in which I try to highlight the different approach adopted by this study, and the dangers of taking experimental techniques into the clinic before fully evaluating them in the laboratory - a lesson that needs reiterating in an age of burgeoning cell therapies for a range of conditions including Parkinson's and Huntington's disease as well as stroke. This is further developed in the summary of a meeting chaired by Professor Tony Schapira on Parkinson's disease.

In this issue we have also continued our series on neuroanatomy and epilepsy as well as a review of the journals. This latter aspect has been changed in its presentation as it seemed to make more sense to do it by topic than by journal.

Finally, we have a rehabilitation article on speech therapy along with a list of conferences, including the forthcoming world congress of Neurology to be held in London. We are therefore fortunate to be able to include an article by James Toole, the current President of the World Federation of Neurology, outlining his vision for neurology and the way this is to be fulfilled in the forthcoming congress meeting.

We hope you enjoy this issue and as I stated in my last editorial, do contact us if you have any ideas or suggestions to improve and modify this publication.

Roger Barker
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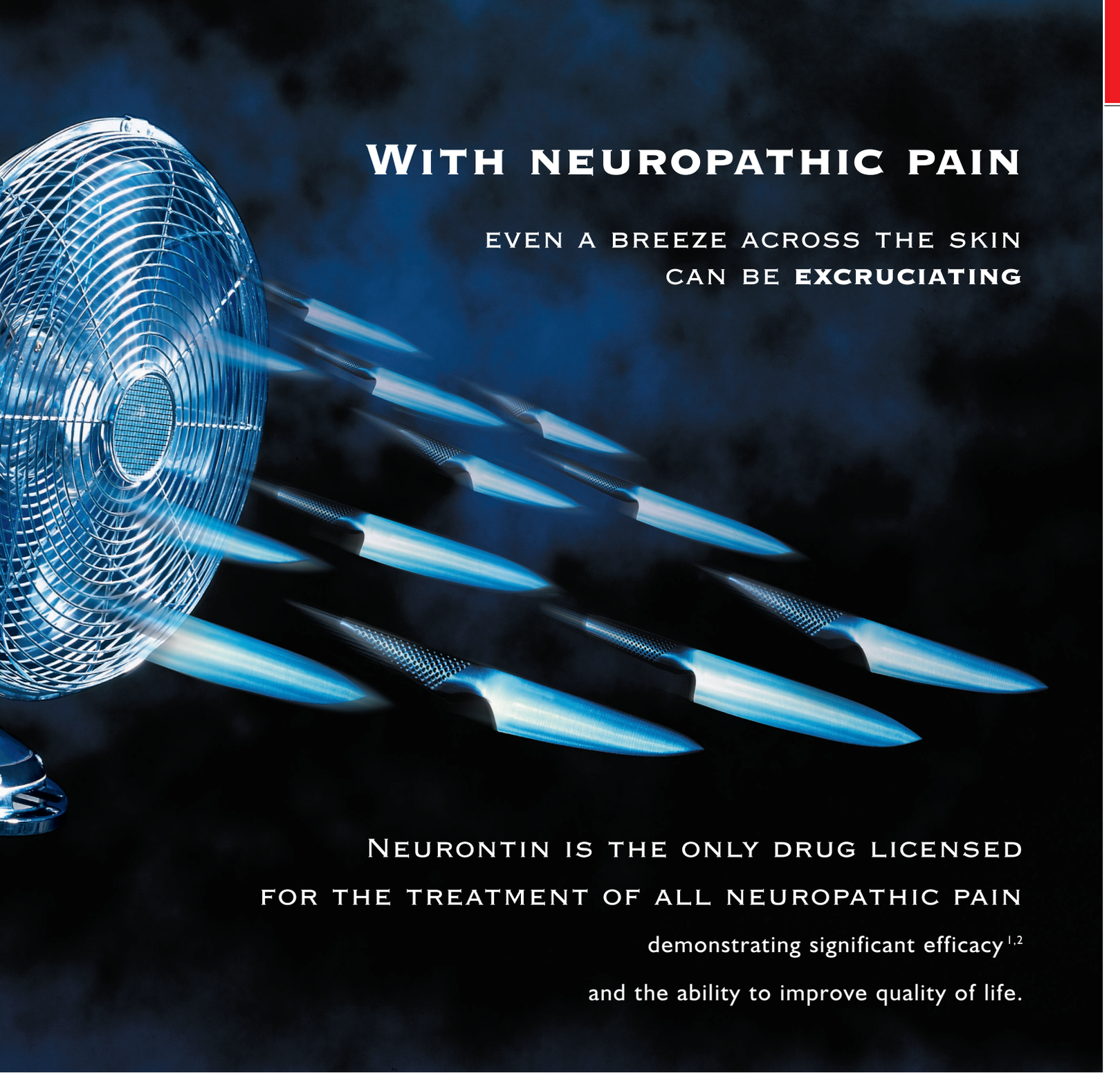

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References 1. Rowbotham M *et al.* JAMA 1998; **280:** 1837-1842. 2. Backonja M *et al.* JAMA 1998; **280:** 1831-1836.

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Contemporary treatment of multiple sclerosis

Introduction

Notwithstanding its long history and high profile, and despite enormous sums of money expended in research, and the countless therapies which suppress the often rather unfaithful animal models of this disease, multiple sclerosis continues to defy successful treatment: interventions which dramatically influence the course remain evasive[1]. Partly this reflects the complexity of the disease process and the inaccessibility of the tissue involved, and an important reason for attempting to understand mechanisms of myelin injury is to predict and design logical strategies for treatment. In the meantime, the potential impact of symptomatic treatment in patients with chronic multiple sclerosis cannot be exaggerated. In this brief review, therapies which compensate for or suppress symptoms, those currently available which are intended to influence the course of the disease, and experimental and future options, will be surveyed.

Symptomatic treatments

Whilst neither prevention nor cure appear remotely imminent, symptomatic therapies can offer an impact on many patients' quality of life enormously superior to any of the currently available disease-modifying agents[2,3].

Urinary frequency, urgency and urge incontinence are among the most troublesome and distressing complaints, and often respond well to anticholinergic treatment[4,5]. These drugs do, however, carry the risk of inducing retention either acutely, in patients whose symptoms paradoxically reflect a flaccid paretic bladder, or chronically, where a small volume of residual urine is no less attractive to microbes than any other pool of nutrient-rich, heated, stagnant water. At the very least, catheterisation to measure residual volume is mandatory before exhibiting anticholinergic drugs. Nocturnal doses can help allow a decent night's sleep, as can nocturnal nasal anti-diuretic hormone analogues (DDAVP)[6].

Where hesitancy or retention is the principal problem, intermittent self-catheterisation (by patient or carer) is often successful. Indwelling catheters are less satisfactory - encumbering, prone to infection, and rarely guaranteed not to leak - though superior to nothing at all when circumstances dictate. Suprapubic catheterisation may be better. Faecal incontinence[7], fortunately not common, is as dispiriting to the patient as it is difficult to treat. After excluding constipated impaction with overflow incontinence, most would advocate anti-cholinergics, but these are infrequently of great value.

Sexual difficulties are not at all rare[5]. Commonly, psychological factors relating to self-image, depression, and confidence are paramount, and libido is rarely improved by sphincter inefficiencies. Professional counselling and good nursing care go far, but neurological deficits must be more specifically addressed. Loss of perineal sensation cannot be treated; lubricants may improve dyspareunia. Erectile failure often responds to the phosphodiesterase inhibitor sildenafil[8].

Spasticity and painful spasms commonly respond to tizanidine[9]; baclofen, dantrolene, and diazepam are also used. Pulsed intravenous methyl prednisolone can help[10], and gabapentin has an increasing role[11]. Clearly, excluding or treating precipitating factors, including bladder infections and pressure areas, precedes pharmacological treatment. In difficult cases, intrathecal baclofen has not (at least yet) gained widespread use; destructive surgery, usually with phenol, is as attractive as destructive surgery ever can be, but has a role (after a trial of blockade by a reversible local anaesthetic). Finally, botulinum toxin has considerable promise[12]. Sodium channel blockers have an increasing role in positive paroxysmal symptoms in MS[13].

Fatigue is common, and whilst amantidine and pemoline have been advocated, neither is overwhelmingly valuable. Serotonin uptake inhibitors have their advocates - on which point the importance of seeking and treating depression is often overlooked - and the narcolepsy drug modafinil has been subject to small but promising trials.

The profoundly disabling, violent ataxic ***tremor*** of chronic severe multiple sclerosis is enormously difficult to treat; drugs (primidone, propranolol, isoniazid) almost invariably fail. Thalamic stimulation has a limited role[14,15].

Acute relapse

The use of high dose intravenous corticosteroids steroids in multiple sclerosis has a significant evidence base, trials suggesting accelerated (but not quantitatively superior) recovery from acute relapses, and no overall influence on the subsequent course of the disease - hence their inclusion as a symptomatic, rather than disease modifying therapy[10,16]. Oral methyl prednisolone may have an equal effect[17]. (Initially, retrospective analysis of data from the Optic Neuritis Treatment Trial suggested that steroid treatment might delay the development of multiple sclerosis[18], but careful longer term analysis failed to confirm this[19].)

Treatments intended to modify the course of multiple sclerosis

Conventional wisdom holds that adverse effects outweigh the modest benefits variably reported for non-specific immune suppressants such as azathioprine and cyclophosphamide[20]. Azathioprine in particular, however, may offer benefits comparable to the newer and much vaunted immunotherapeutic agents, and perhaps should be more widely used[21].

Interferon (IFN)-ß

The role of IFN-ß in treating multiple sclerosis continues to provoke controversy, and a settled position has yet to emerge in the UK. Large scale trials have shown a common 30-35% reduction in exacerbation rate using either alternate daily sub-cutaneous IFN-ß1b (*Betaferon*; Schering[22], weekly intramuscular IFN-ß1a(*Avonex*, Biogen)[23], or thrice weekly sub-cutaneous IFN-ß1a (*Rebif*, Serono)[24]. None of these trials is methodologically faultless[25] - for example, in the first, one third of randomised patients dropped out before completion, and were not included in the analysis, and relapses were self-reported (80% of patients correctly guessing they were taking active drug), raising serious difficulties concerning blinding[25]. Nevertheless, the consistency of this reduction has convinced most neurologists. Relatively few side effects are seen - 'flu-like symptoms, depression and injection site skin reactions, including more serious skin necrosis in 5% of patients[26]. Neutralising anti-IFN-ß antibodies develop in many treated patients, apparently compromising efficacy.

Not surprisingly, this relapse rate reduction is also seen in patients treated after a single episode of inflammatory demyelination in whom MRI shows evidence of disseminated lesions: the reduction here translates into delayed second clinical (diag-

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nostic) episode[27]. Unfortunately, there appears not to be a comparable reduction in progression of disability. Initially, enthusiasm was generated by the first trial designed primarily to explore an effect on progression, which suggested a significant delay in the accumulation of disability in 718 patients with secondary progressive multiple sclerosis[26]. 16.7% of IFN-ß1b-treated patients were wheelchair bound at the end of the two-year treatment period (compared with 24.6% in the placebo group; p=0.0277). The mean EDSS (disability score) in the treated group did not, however, significantly differ from the placebo group after (or before) the treatment period.

A positive effect on disability progression as the primary outcome measure in a trial of intramuscular IFN-ß1a(Avonex, Biogen) in relapsing-remitting multiple sclerosis was also reported[23]. This study was prematurely terminated - only 172/301 patients completed two years, and of these, 18/85 of the treated group progressed, compared to 29/87 in the placebo group (p=0.07). The interpretation of this study was also complicated by unusually rapid progression of disability in the placebo group. Two other trials looking at disability in patients with secondary progressive multiple sclerosis, one with IFN-ß1a, one with IFNß-1b, have been reported (respectively at the Ninth Meeting of the ENS, Milan 1999, and the American Academy of Neurology, San Diego 2000) but not formally published in a peer-reviewed journal. In neither were significant differences between placebo and treated groups found in the primary outcome measure.

It is disappointing, but seems inescapable, that any major impact of IFN-ß on disability in secondary progressive multiple sclerosis - by which patients might mean reversing disability, or properly halting or even perhaps halving the rate of progression - has been excluded.

On a more positive (if perplexing) note, most trials have shown a clear impact on MR parameters of disease activity. This discrepancy between reduced inflammatory activity and continued progression is yet to be wholly resolved, but may relate to the presumed disease mechanisms - increasing evidence suggests that inflammation and demyelination underlie relapse, while accumulating axon loss provides the substrate for irreversible progressive disability[28,29]. The striking dissection of progression from inflammation achieved by the anti-leukocyte monoclonal antibody Campath-1H helps substantiate these clinicopathological correlations[30]: late axon degeneration may be determined by early, frequently repeated inflammatory episodes - also the most likely cause of persistent, unrepaired demyelination.

Cost-benefit analyses of IFN-ß in multiple sclerosis provide scant health economic support[31,32]. However to infer from these and the recent disappointing secondary progressive data that IFN-ß should be rejected, would be a mistake no less defensible than the understandable but often uncritical excitement stimulated in many (or most) quarters by the earlier relapsing remitting trial findings. Patients treated well into the course of secondary progression, when a long history of relapses and remissions may already have set the course for sustained, non-inflammatory axon degeneration, may stand to gain little from IFN-ß Treatment earlier in relapsing disease may better delay progression.

Other treatment approaches

Glatirimer acetate appears comparably to reduce relapse rate, and an effect on disability has been reported, though the number of patients treated in trials is far less than is the case for IFN-ß[33]. The same might be said of *intravenous immunoglobulin*[34,35], though so far, still fewer patients have been studied. Several larger trials are underway, and good evidence for its safety is emerging[36]. A pro-remyelination effect of IVIg, predicted from careful experimental studies[37], has not as yet been shown in patients[38,39]. *Mitoxantrone* is a cytotoxic agent, with significant cardiotoxicity, for which there is some evidence of efficacy in patients with aggressive disease[40,41]. *Plasma exchange* may also have a role in aggressive MS[42]. *Bone marrow transplantation* has its advocates[43,44], but many neurologists are reluctant to recommend a procedure carrying an established short-term mortality for a non-life-threatening disease.

Experimental therapies

As mentioned above, the humanised monoclonal Campath-1H, directed against the pan-T cell marker CD52, has been studied in small numbers of patients, in whom a near-cessation of inflammatory activity has been seen[30,45]. A proportion develop thyroid disease[46]; further studies are planned.

On the (dubious) assumption that TNF might be involved in tissue damage in MS (see Ref. 47 for review) , anti-TNF antibodies have been studied. Informatively but disappointingly, increased MRI lesion formation and clinical relapses after treatment were found[48,49]. Inducing immune tolerance, aiming to exploit linked or bystander suppression, might offer the prospect of safe, effective and specific immune control. Thus far, attempts have not been promising, one Phase II trial rather suggesting a pro-inflammatory tendency, another being suspended because of (non-neurological) hypersensitivity reactions[50,51]. Inhaled or intranasal antigen administration might offer certain advantages[52].

Finally, in addition to these attempts to halt inflammatory damage, experimental strategies for repairing myelin damage are being pursued[53]. The complexity of the timing and delivery of multiple growth factors mitigates against the rapid applicability of this approach, but the first clinical experiments implantating remyelinating glia - oligodendrocyte progenitors, Schwann cells, or glia from adult or fetal stem cells - are imminent.

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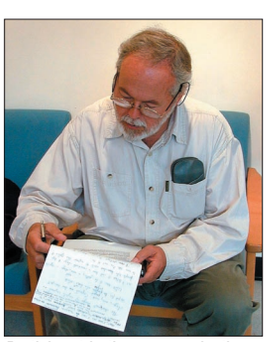
Wanted: Employees with excellent communication skills....

Speakability, the national charity working on behalf of people who have aphasia, estimate that 250,000 people in the UK have aphasia, and 20,000 people each year become aphasic. Thirty percent of strokes occur in people of working age, suggesting 6-7000 people under 65 become aphasic due to stroke each year. For many, their rehabilitation and access to speech and language therapy services will end within one year of their brain injury, never having had the opportunity to focus on strengthening the communication skills required for a work environment. But are people with aphasia capable of economic work, given appropriate therapy and support, or are services correctly given too low a priority to be funded from statutory services?

Early literature regarding the subject gave encouraging results. Hatfield & Zangwill (1975), described occupational resettlements for four people with severe dysphasia following strokes. The dysphasia was predominantly expressive in two cases and predominantly receptive in the other two. Three people were resettled in "gainful" employment and the fourth in sheltered occupation. All four patients attained a "very adequate" level of working efficiency, far greater than had been anticipated on clinical and psychometric grounds. Twenty six years later, although the return to work after stroke has been acknowledged as a critical measure of social restoration for people who have had a stroke, there has been little progress in the provision or evaluation of vocational rehabilitation for people with aphasia. Predictive models have found a negative association between return to work and aphasia following stroke(Black-Schaffer & Osberg 1990), but the prognosis for return to work after severe traumatic brain injury was not affected by presence or absence of aphasia (Gil *et al* 1996). So given that the literature is unconclusive regarding the potential people with aphasia have for returning to work, why are speech and language therapy services restricted in providing community services which will focus on peoples' communication skills for returning to work at a later stage?

It has been acknowledged that the treatment and research approaches for aphasia have arisen from a medical model which addresses only the affected individual and aims to reduce their language impairments. But in the past few years there has been a trend away from the medical model, towards the social model. Byng has described the social model as focusing not only on the individual with aphasia, but also on the ripple effect on the family, friends and wider society, and demonstrated the need for all intervention with people with aphasia to promote, directly or indirectly, healthy living with aphasia (Cameron 2000). The social model encourages the identification of barriers to aphasia, and the exploration of ways to lessen their effects so that the person with aphasia is enabled to adopt a lifestyle as part of the community. Since employment is one of the major community roles, perhaps the increasing use of a social model of aphasia will allow the development of vocational schemes to identify the specific communication barriers preventing people with aphasia from accessing work.



Participant in the communications group at the Bridge Project

In July, 2000, the Bridge Project undertook such a scheme at Sudbury with a European Social Fund "Contact" grant (Ritchie, 2000). The course was designed and conducted by a speech and language therapist (SLT), and aimed to provide functional communication strategies which would allow people with aphasia to access the work environment successfully. This included strategies for reading job adverts and writing a CV, application and other work style letters and documents, using software to assist spelling and word finding. Strategies for interview skills and social conversation as well as discussion on the public perception of people with aphasia were aso covered. The participants were individually assessed by the SLT and then all were treated in a group for $2^{1}/_{2}$ days a week for 10 weeks. In addition to linguistic assessments, they were rated by the therapist for impairment, disability, handicap and well being. Participants also self rated their communicative and some physical abilities on a 1-5 pictorial scale, at the beginning and end of the course. All participants' scores for impairment, disability and handicap improved, as well as those with lower initial well-being scores. Almost all the skills addressed on the course were self rated as improved, in contrast to the skills which were not addressed, which were unchanged.

This brief project has suggested that providing functional therapy for aphasia to young adults can improve the communication skills and confidence required for them to succeed in a vocational environment. This project did not have the scope to continue into job trials, but several members of the group are now ready for the sort of vocational schemes operated by organisations such as Leonard Cheshire Workability or the Shaw Trust.

From the comments received from participants, it is unlikely that a shorter programme would have achieved the same results, but it would be worthwhile investigating courses conducted by a therapy assistant or basic skills tutor working in conjunction with a qualified SLT. As the social model for aphasia treatment brings the focus of our services further into the community, and broadens the scope of SLT treatment programmes, there must be increased involvement of SLTs in the vocational rehabilitation of people with aphasia. Hopefully this can be facilitated through partnership between the voluntary sector, health and social services providers.

Author

Fiona Ritchie qualified in 1995 from Sheffield University, B.Med.Sci (Hons) as a speech & language therapist, followed by 3 years as a speech and language therapist at Medway Hospital, Kent, in the acute and community neurorehabilitation of young adults. She then moved to the Lewin rehabilitation Unit, Addenbrooke's Hospital, Cambridge in July 1999 to provide inpatient neurorehabiitation for young adults with acquired brain injuries. In Sept 2000 Fiona became the Clinical Service Manager and also still practicing as a speech & language therapist at the Oliver Zangwill Neurorehabilitation Unit, Ely. Her current research interest is the evaluation of SLT treatments in the rehabilitation of acquired dysarthria.

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Neural transplantation for Parkinson's Disease

- Where next after the American Study

Roger Barker

Parkinson's Disease is a common neurodegenerative disorder of the central nervous system, commonly affecting people in the fifth to seventh decades of life. The disease is characterised as a motor disorder, and whilst there are effective drug therapies early on, the disease is progressive and patients run into a number of problems not least motor fluctuations in response to this therapy. Therefore several different strategies have been developed for the treatment of these latter stages of the disease, including the possibility of deep brain stimulation and the use of neural transplants of embryonic dopamine cells.

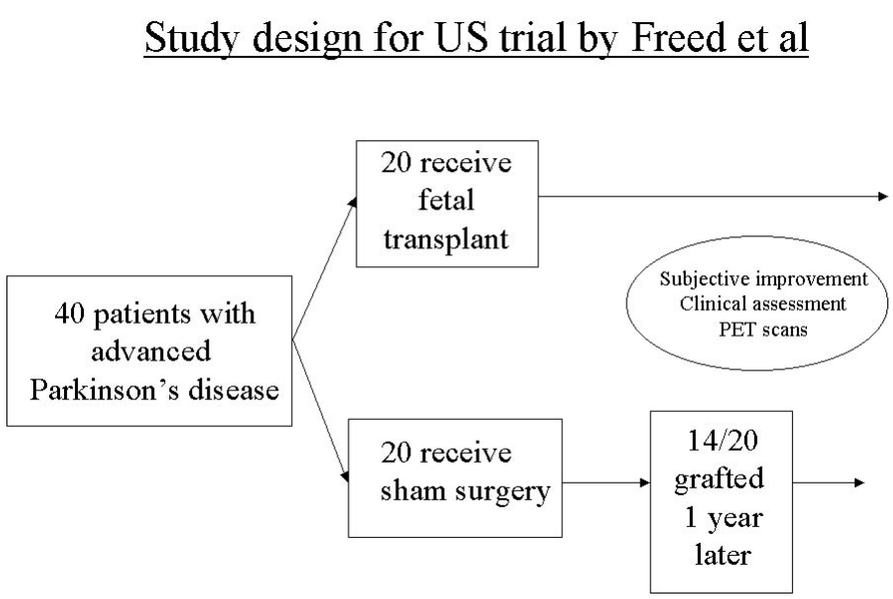
The use of embryonic dopamine cells was first pioneered some twenty years ago in a number of animal studies. These studies clearly showed that if the embryonic dopamine cells were harvested at the time of their normal development, then they could survive transplantation into animal models of Parkinson's Disease, and extend axons into the host brain and receive appropriate connections from that same brain. They could also release dopamine and have a number of functional benefits to the animal on a variety of behavioural tests[1]. It was on this background that the first clinical trials of neural transplantation took place in the late 1980's most notably in Lund, Sweden. These transplants have continued over the last eleven years, and a total of seventeen patients have now been transplanted with good clinical benefits in the majority of patients[2]. This clinical improvement whilst not being seen in all areas of disease symptomatology has nevertheless correlated well with increased fluorodopa signal on PET scanning. Furthermore, one of these patients has recently been the subject of a detailed functional imaging study, 11 years after being transplanted[3]. This paper reveals that first of all the graft survives in the face of progressive disease as evidenced by the loss of signal of the patients own dopaminergic system and secondly that the release of dopamine from the graft occurs in a regulated fashion. A number of other centres have now replicated these studies, most notably those in Creteil in France and in Tampa in the US[4,5].

It therefore seemed that neural transplantation for Parkinson's Disease was a safe and effective therapy although still experimental, or at least that was the case until the recent paper by Freed and colleagues[6]. This study from Freed *et al* has raised new concerns about the use of this approach because of the adverse effects they reported including the development of runaway dyskinesia and dystonia. This aspect of the trial has caused much excitement in the media, although in the original paper the comments relating to this were much more measured in their content. Nevertheless the development of these side effects raises fundamental questions as to the use of this approach in Parkinson's Disease. However, the fact that these side-effects have only been seen in this study raises questions as to whether they are more related to the approach adopted by Freed *et al* than transplantation *per se*.

The trial design adopted by Freed *et al* involved recruiting forty patients with advanced Parkinson's Disease and randomising them to either receive a fetal dopamine transplant or a sham operation (see figure 1). The sham operation involved taking the patient to theatre, drilling burr holes in the frontal part of the skull and then pretending to implant the tissue. The procedure was so effective, that the patients themselves were unaware of whether they had had a transplant or not, as assessed by questionnaires immediately after the operation. The patients were then followed clinically, and using fluorodopa PET scans although the primary end point was a subjective one, 12 months post transplantation. After a year, those patients in the sham operated group were offered a transplant and fourteen of the twenty in this group were transplanted, whilst the other six did not as a result of the side effects that had developed in 5 of the grafted patients.

One of main conclusions of the study was that there is a significant placebo effect of the procedure and furthermore the benefits of grafting seemed more successful in younger patients (those <60 years of age). Indeed of the thirty-four patients that completed the trial, nine noted improvement and five developed dyskinesias and dystonia off medication. Two patients died during the trial, neither of which was related to the transplant procedure itself, and at post mortem these patients were found to

Table 1.



have low numbers of surviving dopamine cells as compared to other post mortem studies from patients reporting significant clinical and imaging improvement[7] . The development of these dyskinesias and dystonias has not been seen in other studies, although some of the Swedish patients have developed a degree of dyskinesias off medication several years after grafting.

This trial adopted by Freed *et al* has though used a radically different techniques to other studies much of which have never been validated experimentally. In particular, this trial has:

- Used less tissue than other transplant trials in that they use two embryos per side of the brain, whereas in the more successful Swedish study up to three to five fetuses have been used per striatum.
- The tissue was stored up to a month prior to implantation, which is much longer than any other centre.
- The tissue was prepared in a unique "noodle" fashion, unlike the cell suspension/tissue pieces technique that has been used and experimentally validated by other centres.
- The transplant was done using a frontal trajectory which is different to that used in other centres.
- None of the patients received immunosuppression.

Whilst it is impossible to know whether the side effects seen in this trial relate to any or all of the above factors, it is probable that the transplants have led to great imbalances in dopaminergic innervation within the striatal complex, which in turn has led to the development of these major side effects. It is therefore clear that whilst the trial has produced adverse effects, this is more a consequence of the technique used than transplantation of embryonic dopamine cells for Parkinson's Disease. There is certainly no evidence for dopamine overgrowth as was suggested in some media reports, as the number of transplanted cells at post mortem in those that have died was much less than those seen in other studies.

So what does this study tell us and where does it leave this field of experimental therapeutics? First of all it highlights the dangers of going into clinical trials, without first validating the safety of the technique being developed, and also argues for extensive experimental studies before any clinical trials are undertaken. Furthermore whilst this trial has certainly put a dent in the use of neural tissue to repair the brain in Parkinson's Disease, it by no means derails the procedure as further studies have failed to show such adverse side-effects. Indeed this study like many others has shown that a significant number of patients benefit from the procedure. However, for those seeking a quick fix with either neural stem cells or other forms of cell replacement therapy, this study is a warning that until one has reliable and robust scientific and experimental data, the move to the clinical domain is not to be recommended.

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Surgery for Carotid Artery Disease

Background

The surgical procedure of carotid endarterectomy (CEA) - the removal of atheromatous plaque from the internal carotid artery origin via arterotomy - approaches its fiftieth anniversary. During this time the number of procedures has risen, fallen and risen again paralleling concerns about the validity and safety of the technique[1].

The large numbers of procedures being undertaken, often with reported complication rates of up to 20% during the 1970's and early 1980's prompted the European and North American symptomatic carotid endarterectomy trials[2,3]. A decade since their initial results were reported the salient findings are well known:

patients with mild (<30%) stenosis of the recently symptomatic ICA are harmed by surgery

patients with severe (>70%) stenosis of the recently symptomatic ICA in general benefit from surgery (absolute risk reduction for stroke of 9.6% [ECST] and 17% [NASCET]).

In addition, it has recently been suggested that:
some patients with 50-70% stenosis may benefit from surgery.

In applying these basic principles to routine clinical practice some important factors exist:

"Recently symptomatic" indicates a non-disabling carotid territory ischaemic stroke, carotid territory TIA (eye or brain) or retinal infarct within the past six months.

Clinical assessment should be undertaken by a medical practitioner with an interest and expertise in the selection of patients for carotid surgery, ideally operating within the setting of a fast-track cerebrovascular clinic. The greatest benefit of surgery is seen early after symptoms, borne out by the 20% stroke risk of a patient with a 90-99% ICA stenosis in the first year after a TIA or non-disabling stroke which falls to less than 5% after 3 years[4]. Many patients referred to such a clinic will have neurological disorders other than cerebrovascular disease and a neurologist is often best-placed to manage these[5,6]. Although patients were only randomised in NASCET and ECST if they had suffered symptoms within the previous 6 months it is reasonable to offer surgery up to a year later for patients with cerebral events.

Patients should be both fit for surgery, and willing to undergo surgery before expensive, time consuming and potentially hazardous (ie intra-arterial angiography) investigations are performed.

Screening for carotid artery disease should be performed using ultrasound, and if non-invasive imaging (ultrasound+/- MRA) is to suffice for the operative decision it must have been validated in that centre against the existing gold standard (intra-arterial angiography).

Magnetic resonance angiography is not an appropriate screening investigation. In ECST and NASCET percentage stenoses were estimated from angiograms. Failure to validate noninvasive techniques against angiography may deny some patients the benefit of surgery and expose some patients to the risks of surgery when thay may not benefit anyway. Since the methods of measurement of stensosis in ECST and NASCET were different (for a given stensosis the former giving a "tighter" estimate), it is neceassary for any centre to standardise its measurements according to either ECST, NASCET, or the "common carotid" method[7].

Carotid endarterectomy should be performed by a surgeon with a sufficiently large practice to enable continuing technical proficiency in the procedure, and operative complications must be open to prospective audit.

Once complication rates exceed those of ECST (7.5%) and NASCET (5.8%) all benefit is rapidly lost and harm results.

"Best medical therapy" must persist throughout the assessment period and after surgery.

Lifelong antiplatelet therapy, anticoagulation for atrial fibrillation, control of hypertension, hypercholesterolaemia and diabetes, and advice regarding smoking is crucial.

Since the publication of the final results of ECST[4] and NASCET[8] there have been many further analyses of either subgroups from the individual trials or using data pooled from these and other studies:

30-70% disease

Patients with symptomatic ICA stenosis of 30-50% do not benefit from surgery. Males with 50-69% stensosis and ipsilateral cortical cerebral ischaemic probably do benefit from surgery (absolute risk reduction of any stroke or death 9%). Women with 50-69% stensosis or males with 50-69% stenosis who have suffered lacunar or retinal ischaemic events do not benefit[9].

Gender

The risk of surgery is higher in women than men. In order to trade off the higher operative risk the stroke risk without surgery must be greater (presence of tighter stenosis, cerebral symptoms).

Cerebral versus retinal symptoms

The risk of stroke is higher after cerebral than retinal ischaemia[10]. When analysed according to severity of stenosis patients with severe (>70%) ICA disease and recent symptoms (cerebral and/or retinal) clearly benefit from surgery. However when analysed according to symptom type, subgroup and pooled data analysis of ECST and NASCET suggest that patients with ocular symptoms only (particularly females) may not benefit overall, despite the presence of a high grade stenosis[9].

Lacunar versus presumed embolic stroke

Although the mechanism of lacunar infarction does not directly relate to the existence of ipsilateral ICA stensosis, small vessel and large artery disease share exactly the same risk factors and therefore commonly coexist. Initial subgroup analysis of ECST data raised the possibility that patients with lacunar syndromes may not benefit from surgery[11] however subsequent analysis of ECST and NASCET confirms benefit in the presence of ipsilateral high grade disease[9].

Pseudo-occlusion

Patients with pre-occlusive or pseudo-occlusive lesions of the ICA with significant reduction in diameter of the distal ICA are probably at lower risk of

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stroke than previously believed (as low as 8% over 5 years[12]. In some of these patients technically adequate surgery is prohibited due to the inability of the surgeon to gain a satisfactory distal endpoint to the endarterectomy. Given the low stroke risk with medical therapy it seems reasonable not to offer surgery to this group if the procedure would be technically difficult or the end result unsatisfactory.

In basing one's practice it is important not to lose sight of the questions ECST and NASCET set out to answer, ie within the groups of randomised patients what was the surgical risk, what was the long term risk of stroke following surgery, and what effect does endaraterectomy have on long term non-disabled survival? These questions were posed for each category of stenosis (mild, moderate and severe).

The subsequent analyses have been usful in identifying higher (males, cerebral events) and lower risk groups (ocular symptoms) within each category of stenosis and aid the clinician in presenting the evidence for (or against) endarterectomy. Thus a female with a single ocular event and other comorbidity may now be presented slightly different advice as may a male with severel recent cerebral events and a 60% stenosis.

ECST and NASCET have demonstrated the importance of patient related factors (age, sex, type of symptoms) and their interplay with the severity of ICA stenosis. The behaviour of an atheromatous plaque and its influence on the brain and eye is unlikely to be related to how much it narrows an artery alone; factors such as plaque morphology, ulceration, overlying thrombus etc may be just as important. These may help explain the variation in clinical features and natural history of different patient groups.

Complications of CEA

Stroke, myocardial infarction and vascular death are the feared complications of CEA. Higher risk groups are[13]:

- Cerebral versus retinal symptoms
- Women
- Age >75yrs
- Systolic BP >180
- Presence of peripheral vascular disease
- Ipsilateral siphon and/or external carotid stenosis
- Contralateral ICA occlusion

Asymptomatic disease

When the American Asymptomatic Carotid Artery Study was published[14] there was an immediate paradox. Patients with asymptomatic disease of only 60% appeared to benefit from CEA whereas symptomatic patients with 60% stenosis did not.

The demonstration that some symptomatic patients with 50-69% stenosis (males, cortical ischaemia) benefit alleviates part of the paradox, together with the fact that the surgical complication rate in ACAS was only 2.3%.

The risk of stroke ipsilateral to severe asymptomatic disease is only 2% per annum and any modest benefit of surgery is not evident until 2-3 years post-operatively (having traded the operative risk versus the natural history). Approximately 50-80 patients with asymptomatic disease require surgery to prevent one stroke (versus 5-8 with symptomatic severe disease).

A European study continues to provide further evidence for or against surgery for asymptomatic disease. In the meantime endarterectomy for asymptomatic disease is not recommended routinely[15]. Some patients however do wish to be considered for surgery (usually the younger ones) and here a bald description of the current data usually enables them to decide if they still wish to proceed. The identification of higher risk asymptomatic groups (possibly according to sex, age, presence of "silent" infarcts on neuroimaging, plaque morphology, collateral flow pathways and cerebrovascular reserve etc) will enable better informed decisions to be taken.

Carotid endarterectomy and coronary artery bypass surgery

For patients with symptomatic carotid and coronary artery disease the options are either a combined or a staged procedure. All reports of combined procedures are observational and open to the usual criticisms (reporting and selection bias etc). Coronary artery surgery in general should not precede carotid surgery for symptomatic disease because of an unexpectedly high risk of stroke during the former[16]. Whether carotid surgery precedes coronary surgery or whether a combined procedure is performed will depend on local expertise and experience.

When *asymptomatic* carotid disease coexists with symptomatic coronary disease it seems reasonable to advise treating the patient's problem rather than performing a prophylactic endarterectomy and thus exposing the patient to the higher risks of either a staged or two separate procedures.

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Initial treatment of epilepsy

Mark Manford

- **The patient** must be involved in any decisions and needs to be committed to treatment in order for it to be effective. Once anti-epileptic drug treatment is started, it is likely to be continued for a number of years.
- Most clinicians in the UK do not treat a single unprovoked seizure.
- The patient's **age** influences the diagnosis, the recurrence risk and the hazards of seizures. A **child** with a benign, self-limiting benign focal epilepsy syndrome may suffer more from antiepileptic drugs (AED) than from occasional seizures. Focal epilepsy in the **elderly** usually recurs and the morbidity of falls due to seizures is likely to be much higher than in younger patients, as is the morbidity of medication.
- Lifestyle modification may be considered rather than AED in selected cases (table 1)

Table 1: Lifestyle factors in the treatment of epilepsy

Factor	Comment
Sleep deprivation	Common trigger in IGE
Alcohol withdrawal	Common trigger in IGE
Illicit drugs	Cocaine and amphetamines are main culprits
Dietary factors	Rarely relevant
Herbal remedies	May be anticonvulsant or proconvulsive in aromatherapy doses
Photosensitivity	Common in IGE. Specific avoidance may be needed as not always responsive to AED
Psychological stress	May affect epilepsy but if a strong association consider non-epileptic seizures

Factors weighing against medication

- **Very mild seizures** such as auras with no evidence of functional impairment may be left untreated.
- **Very infrequent** seizures pose a difficult problem. It is often unclear whether treatment is having any impact.
- **The teratogenicity** of many anti-epileptic drugs may make some women decline treatment if they are planning a family, when they would otherwise wish to be treated.
- **Adverse effects** or concern over potential adverse effects may cause some patients to decline treatment, especially as treatment is long-term.
- **Acute symptomatic** seizures due to a non-recurring cause eg. acute renal failure, have the lowest risk of recurrence. Medication may be required to stop seizures in the acute phase but may be withdrawn early with a low risk of seizure recurrence.

Factors in favour of medication

- **Severe seizures**, prolonged seizures, seizures with severe injury or a history of status epilepticus, weigh heavily in favour of treatment.
- **Frequent seizures** usually require treatment unless they are very mild.
- **Sudden death in epilepsy** (SUDEP) is most commonly associated with young patients with severe epilepsy, but apparently well-controlled patients may be found dead in bed.
- Occupation involving public performance or driving is often in favour of treatment.

Which medication to treat the epilepsy?

General Principles

- **Seizure-freedom** can be achieved for 60-70% of patients with the first medication tried. Selection of AED is currently based on incomplete evidence. A multicentre study in the UK is currently comparing different drugs in newly diagnosed epilepsy.
- **Syndromic diagnosis** gives the best chance of finding an effective medication. The first stage is to distinguish between **focal** and **generalised** epilepsy.
- **Rarer syndromes**, usually arising in childhood may need specific AED.
- **Within epilepsy syndromes**, some drugs are effective only for specific seizure types, and these need to be categorised for each patient.
- **Adverse effect profile** may be the key factor in the choice of AED in situations where there is no clear evidence of differences in efficacy between drugs.
- **Gender** influences drug choice: interactions with oral contraception and teratogenicity are specific to women.
- **Medical conditions** such as renal or hepatic disease may affect choice of medication.

Spectrum of AED efficacy (table 2)

- **Broad spectrum drugs** have some efficacy across a broad range of focal and generalised epilepsy syndromes. They include valproate, lamotrigine, topiramate and felbamate (not available in the UK).
- **Focal epilepsy drugs** are primarily useful in focal epilepsy and may be helpful for tonic clonic seizures of IGE but often make IGE absences or myoclonus worse. These drugs include carbamazepine, phenytoin, oxcarbazepine, gabapentin, vigabatrin and tiagabine.
- Drugs for **specific seizure types** in IGE include ethosuximide for absences and piracetam for myoclonus. Clonazepam is also most useful for myoclonus but is often used more widely. They are rarely used as monotherapy.

AED for idiopathic generalised epilepsy

- **Valproate** is active against all IGE seizure types probably rendering 80% of patients seizure-free. Doses are commonly of 600-1500mg.

Table 2. Anti-epileptic drugs (AED) currently used as first line therapy

AED	Indication
Acetazolamide	-
Carbamazepine	Focal epilepsy
Clobazam	-
Clonazepam	-
Ethosuximide	IGE absences
Felbamate	-
Gabapentin	Focal epilepsy
Lamotrigine	Broad spectrum
Levetiracetam	-
Oxcarbazepine	Focal epilepsy
Phenobarbital	Broad spectrum
Phenytoin	Focal epilepsy
Piracetam	-
Tiagabine	-
Topiramate	Broad spectrum[1]
Valproate	Broad spectrum
Vigabatrin	-
Zonisamide	-

(1 Use as first line treatment is under investigation)

- **Lamotrigine** is useful for treating IGE. Absences and tonic clonic seizures are often well controlled but in my experience, myoclonus responds less well. The dose required for adults may be as little as 100mg per day but is sometimes 150-400mg. It is easy to use in monotherapy.
- **Valproate versus lamotrigine.** Valproate may cause weight increase and possibly menstrual irregularity. This has led some clinicians to favour lamotrigine as first line. Valproate is teratogenic but whether lamotrigine is less teratogenic in humans is not yet established.
- **Topiramate** may have a role treating in IGE but is not yet considered first line.
- **Phenobarbital** is an effective drug in IGE but has more sedative adverse effects than most newer drugs.

AED for focal epilepsies

There is even less information to guide choice of medication in the treatment of focal epilepsies. The overall success of treatment of focal epilepsy is less than for generalised epilepsy. The de novo patient probably has a no better than 50% chance of achieving seizure-freedom, excluding children with the benign partial epilepsies of childhood.

First line drugs in the treatment of focal epilepsy

- **No consistent differences** in efficacy as monotherapy have been proven between carbamazepine, valproate, phenytoin, phenobarbital and lamotrigine.
- **Carbamazepine** is standard medication for treating focal epilepsy in the UK. This is best introduced gradually (100mg per week) and given as the slow-release preparation, to minimise adverse effects.
- **Oxcarbazepine** is closely related to carbamazepine but has much less enzyme-inducing tendency. It is favoured to carbamazepine in some parts of Europe but has only recently become available in the UK.
- **Lamotrigine** is gaining in popularity as a broad spectrum first line treatment.
- **Lamotrigine versus carbamazepine.** Lamotrigine was comparable to carbamazepine in a monotherapy study. Dropouts in the lamotrigine arm were more commonly due to lack of efficacy, those in the carbamazepine arm were due to adverse effects. Carbamazepine is an enzyme inducer, affecting the oral contraceptive pill and other medications. It has a definite but probably fairly low rate of teratogenicity; the effect of lamotrigine remains uncertain.

Table 3. Drugs in focal epilepsy

Drug	Advantages	Disadvantages
Carbamazepine	Long-established and effective	Adverse effects in dose titration period, enzyme induction
Oxcarbazepine	Established in Europe, less enzyme induction and possibly less adverse effects than CBZ	Hyponatraemia is common in at risk patients eg. those on diuretics
Lamotrigine	Lower adverse effects than CBZ	May be slightly less efficaceous than carbamazepine
Phenytoin	Widely used in USA	More adverse effects than other first line drugs. Difficult kinetics
Valproate	Similar efficacy in trials. Teratogenicity worries	Many clinicians feel less effective in clinical practice
Phenobarbitone	Efficaceous and cheap	More cognitive adverse effects

Table 4. Checklist of advice for patients newly diagnosed with epilepsy

Issue	Advice
Nature of epilepsy	Discuss consequences and realistic appraisal of risks, including SUDEP
Medication	Explain purpose, duration, nature and adverse effects
Driving	Banned from time of diagnosis; advise DVLA and insurance
Contraception	High dose pill with enzyme-inducing drugs (efficacy still reduced)
Pregnancy	Seek medical advice prior to conception. Preconception folic acid 5mg daily
Social	Limit alcohol. Review work environment for safety, review hobbies.
Carers	Advice on emergency seizure management

Further information

SANAD is a multicentre trial of standard verus new anti-epileptic drugs funded by NHS R&D. It is co-ordinated by Professor David Chadwick at the Walton Centre, Liverpool.
Tel. 0151 529 5461,
E-Mail. bessan-p@wcnn.co.uk

Useful Web Site

American Epilepsy Society at
www.aesnet.org/

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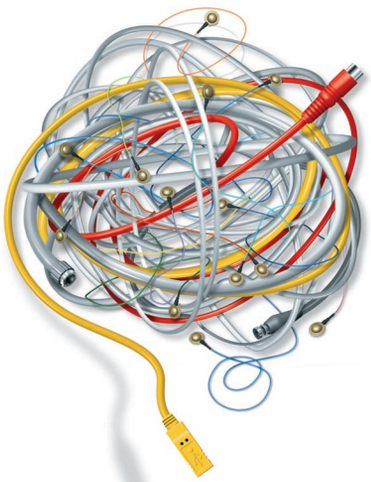
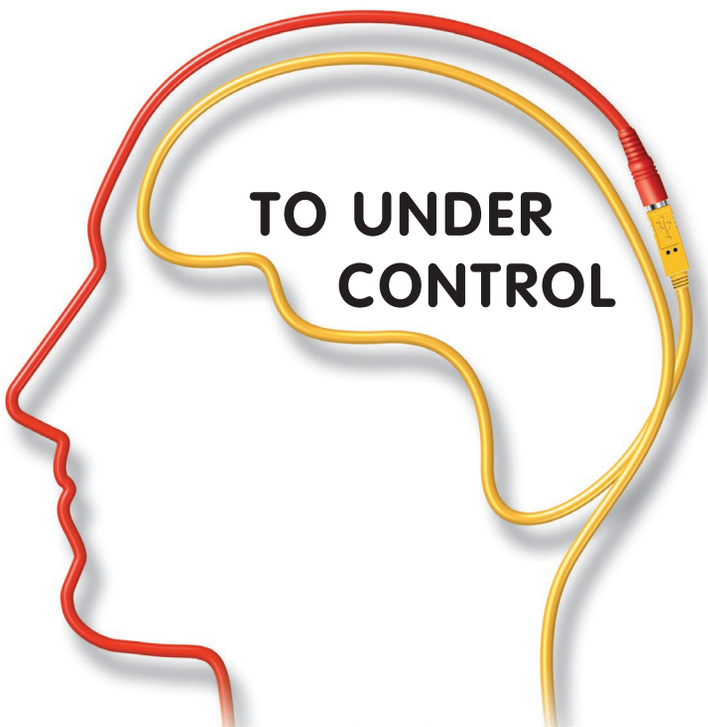
mark@mmanford.freeserve.co.uk

NEW 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)



NEW **ADD-ON THERAPY STARTS WITH**

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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.
Date of Preparation: October 2000.

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SIMPLIFYING SEIZURE CONTROL

World Congress of Neurology

Author

James Toole
President, World Federation of Neurology

Progress in neurology and neuroscience over the last decade has moved at an astonishing pace, yet most disorders of the brain and neuromuscular system continue to confound us. The World Congress of Neurology, organised by the Association of British Neurologists, will bring together more than 5,000 health professionals and representatives of interest groups from around the globe - a unique opportunity to share and exchange our knowledge in what remains one of the most important topics in medicine today - how the nervous system functions normally and how to prevent and treat its dysfunction.

This major event, initiated in 1931 and since 1957 held under the auspices of the World Federation of Neurology, takes place every four years. In 2001, it is being co-sponsored by the Association of British Neurologists, in association with the European Federation of Neurological Societies and the World Federation of Neurology. The World Federation alone has over 22,000 members from 86 countries, including 12,000 members of the EFNS from 38 countries.

Neurological disorders place an enormous burden on patients, their families, and society. Because people are living longer, the number of people likely to fall victim to stroke, dementia, and other diseases of the brain will increase, resulting in enormous new health care costs around the world. In addition, childhood developmental disorders, such as schizophrenia, brain injury, mental retardation, and consequences of malnutrition take their toll, not just on patients, but on their families and carers. However, there is gathering evidence that senility and cognitive decline can be delayed or prevented. It is a misconception to consider the brain "to wear out." Research on longevity is vital to pursue with life expectancy also on the rise. By the middle of this new century, the number of people over the age of 90 will have tripled[1,2]. Already in some countries, the economic burden of neurologic disorders of the elderly threatens to overwhelm health care facilities. Furthermore, there is increasing recognition that abnormal brain function in national and international leaders is one of the greatest threats to world peace and, therefore, public health.

The task we face in prevention, early recognition, and control of brain disease is monumental. But we should be encouraged by the remarkable advances made in just the last decade. For example, our understanding of normal brain development and function has increased significantly. Imaging technology has revolutionised diagnostic accuracy and the rapid testing of therapeutic compounds has enabled novel treatments, including methods to stimulate neuron regeneration. Most importantly, we are beginning to understand the neural basis of behaviour and to recognise "mental abnormalities" as brain and not mental disorders[3]. Meningitis, Creuzfeldt-Jacob disease (CJD), and multiple sclerosis are recognised as 'brain disorders' and as serious as AIDS or cancer. However, depression, eating disorders, and alcohol and other drug abuse are usually perceived by the public to be social problems and problems in living, rather than brain disorders[3].

It is hard to choose among the highlights of the exciting programme that the organisers have put together for the Congress but surely neuro-transplantation, prion disease and neurodegenerative diseases stand out, as do interventions for control of multiple sclerosis and epilepsy. Of course, neurological disorders and treatments differ around the world and to this end a series of symposia will take place where delegates can find out more about issues in Africa, Latin America, Asia and Oceania, and the Arab world, with a special emphasis upon vulnerable populations in developing countries.

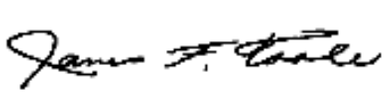
Each day, between Monday 18 and Friday 22 June, the scientific programme will focus on a theme that will inform delegates of mechanisms for disease prevention, treatment, and practical management issues. These daily themes are: stroke, dementia, epilepsy, multiple sclerosis, and neuromuscular disease. Parallel sessions will cover cognition, genetics, critical care and coma, neuro-oncology, spinocerebellar degeneration and a host of other subjects. The programme provides insights into clinical assessment and care of people with neurological disorders, including sleep disorders, communication abnormalities, and coma, among many others. We are particularly pleased that behavioural neurology, tropical diseases, and rehabilitation are integral in our scientific and education programmes.

Furthermore, brain experts can put their own brains to the ultimate test in the Neurological Tournament! Starting with multiple-choice questions on the first day, successful competitors will work their way towards the grand-finale on the final day of the Congress.

But the added value of the Congress must lie in continuous international networking for the future. Those of us dealing with the nervous system, either through clinical care or basic research, must take leadership roles in communicating around the world. No longer can we consider ourselves to be solely academics who educate fellow health professionals. We must also have outreach programmes for the public, in order to teach them about brain and nervous system health. People need to understand what the brain really does - that its billions of neurones, with their uncountable connections, control our thoughts, actions and bodily functions, and, through the brains of our leaders, the fate of our world. We know that malfunction leads to social disorder. We are witnessing in this new Millennium the changes in the structure of family life, the consequences of stress in work and the damage caused to society by mental illness[4].

Those concerned with the nervous system must collaborate continually with colleagues in other disciplines. For example, stroke affects the nervous system but is the result of vascular system disorders. Therefore, we should network more with vascular specialists. I take this opportunity to urge every one of you to become involved in outreach programmes. Let's help educate school children in the miracles of the brain and its functioning mind, so that we can work with the public to prevent mental illness.

Work and play hard while you are in London, one of the world's most vibrant cities. And when the Congress comes to an end, you will return home inspired and exhilarated by all you have discovered during this unique Congress.



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2. Office of National Statistics, UK, 1999.
3. The Public Perception of Brain Disorders. European Dana Alliance for the Brain (Gallup1998)
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WORLD CONGRESS OF NEUROLOGY

EARL'S COURT, LONDON 17-22 JUNE 2001

PROGRAMME AT A GLANCE

Date	Main Theme of the Day	Other Topics
Mon 18 June	Stroke	Cognitive neurology Neurogenetics Pain Neuropsychiatry Genetic neuropathy Neurodegeneration Pan African symposium Neurotoxicology Botulinum toxin Neuro-urology and sexual dysfunction
Tues 19 June	Dementia	Stroke treatment Headache Inflammatory neuropathy Myasthenia CSF History of clinical diagnosis Epilepsy genetics Pan American symposium Infectious diseases and tropical neurology Motor neuron disease
Weds 20 June	Epilepsy	Neurotransplantation Prion diseases Interventional neuroradiology Pan Arab symposium Neurorehabilitiation EMG Cochrane Neurological Network Neuro-otology Autonomic disorders
Thurs 21 June	Multiple sclerosis	Movement disorders Parkinson's disease Muscle disease: genes and proteins Pan Asian & Oceanic symposium Spinocerebellar degeneration Swallowing and gastro function Adolescent neurology Neuro-epidemiology Alzheimer's disease: neuro-imaging Genetics of mitochondrial disorders
Fri 22 June	Neuromuscular disease	Critical care and coma Neuro-oncology Advances in neuroimaging EFG Neuro-ophthalmology Neurological disease in women Neurosonology Sleep disorders

Servier Satellite Symposium

Monday 18th June, 12.00-1.30 pm, Hall 1, Earls Court 2

Title:	**PROGRESS Study Results and Implications**
Co-Chairs:	Charles Warlow (UK) & Marie-Germaine Bousser (FRANCE)
Programme PART 1	PROGRESS rationale, results and clinical implications *35 minutes*
Introduction	Charles Warlow (UK)
Background to PROGRESS	Bruce Neal (AUSTRALIA)
PROGRESS results	Stephen MacMahon (AUSTRALIA)
Clinical Implications of PROGRESS	John Chalmers (AUSTRALIA)
PART 2	Panel Discussion
Moderator	John Chalmers (AUSTRALIA)
Panel participants	Charles Warlow (UK) Kennedy Lees (UK) Philip Bath (UK) Geoff Donnan (AUSTRALIA) Marie-Germaine Bousser (FRANCE) Stephen MacMahon (AUSTRALIA) Bruce Neal (AUSTRALIA) Christophe Tzourio (FRANCE)
Conclusion	John Chalmers (AUSTRALIA)

For information contact Servier Laboratories, Fulmer Hlal, Windmill Road, Fulmer, Slough, SL3 6HH.
Tel. 01753 662744, Fax. 01753 666262

Events Diary

We would like to thank Novartis for sponsoring this page. 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 June 4th, 2001.

2001

May

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

Innovative Treatment Strategies with Trileptal
14 May, 2001; Buenos Aires, Argentina
Sam Barnes, Novartis Pharmaceuticals, Tel. 01276 692255.

10th European Stroke Conference
16-19 May, 2001; Lisbon, Portugal
Eurocongressos, R. Francisco andrade, 4 P-1700-198 Lisboa, Tel. 00351 21 847 2577, Fax. 00351 21 847 37 46,
E-Mail. Eurocongressos@mail.telepac.pt

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

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

June

ECNR Seventh Cycle: First Course Brain
1-5 June, 2001; Cambridge, UK
Dr Wendy J. Taylor/Dr H. Rolf Jäger, National Hospital for Neurology & Neurosurgery, Lysholm Radiological Department, Queen Square, London WC1N 3BG. Tel. 0207 837 7660, Fax. 0207 278 5122, E-Mail
w.taylor@ion.ucl.ac.uk,
r.jager@ion.ucl.ac.uk

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

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

Fifth European Skull Base Society Congress
15-17 June, 2001; Copenhagen, Denmark
5th ESB Congress, Copenhagen Secretariat, ENT Dept, Gentofte University Hospital. Tel. 0045 397 73833, Fax. 0045 39777634,
E-Mail. Injo@gentoftehosp.kbhamt.dk

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

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

Trileptal, Rationale & Potential Role for its use beyond Epilepsy
18 June, 2001; London, UK
Sam Barnes, Novartis Pharmaceuticals, Tel. 01276 692255.

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

The Role of Levetiracetam in Epilepsy Treatment
20 June, 2001; London, UK
Info: UCB Pharma on Tel. 01923 211811 or E-Mail. Medcaluk@ucb-group.com

July

17th Congress of the International Association of Gerontology
1-6 July, 2001; Vancouver, Canada
Congress Secretariat, Gerontology Research Centre, Simon Fraser Unversity at Harbour Centre, 515 West Hastings Street, Vancouver, BC, Canada V6B 5K3. Fax. +1 (604) 291 5066, E-Mail. iag_congress@sfu.ca, www.harbour.sfu.ca/iag/

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

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

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

August

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

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

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

September

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

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

4th Advanced Rehabilitation Course
4-7 September, 2001; Nottingham, UK
Anne Warner, University of Nottingham, Tel. 01332 625680,
E-Mail. Anne.warner@nottingham.ac.uk

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

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

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

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

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

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

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

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

October

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

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

November

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

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

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

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

December

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

2001

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

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

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

Parkinson's Disease Nurse Specialist Association Annual Conference

Leeds, 29-31 March, 2001

The PDNSA conference hoped to enable delegates to recognise some of the pieces of the puzzle of Parkinson's Disease and also to keep abreast of professional issues in specialist practice.

The key note speaker was Jacki Handley, the first PD Nurse Consultant in England, who explained how the role of Nurse Consultant is the next step in providing further effective services to this patient group. Dr David Burn, Consultant Neurologist, then gave a very informative presentation on differential diagnosis of PD from a clinical perspective and reviewed other conditions that may masquerade as PD.

The committee of PDNSA, looking from left to right: Liz Scott, Oxford; Lynn Osborne, London; Sarah Morgan, Kingston; Carolyn Noble, Peterborough; Alison Dick, Belfast; Audrey stainton, Cumbria; Sandra Christou, Leeds.

The next two speakers described how to recognise the conditions of Multiple System Atrophy and PSP with management strategies for the problems for those who face these diseases and their carers. The last speaker, Dr Tim Harrower, Wellcome Clinical Research Fellow & Hon Neurology Registrar, gave an insight into stem cells as replacement therapy for Parkinson's Disease. He discussed the recently published trials undertaken in the USA and commented that stem cells could represent one of the biggest steps in refining the procedures involved in transforming neural transplantation into a safe and accessible treatment.

The afternoon was given over to workshops giving a platform to share good practice with members of the Multi Disciplinary Team with topics as varied as Neuropsychiatry, Physiotherapy, SAL T, Bladder Management, Nutrition & Occupational Therapy.

Mary Baker focused on the needs of the patient during her presentation

The second day opened with a presentation by Mary Baker, Chief Executive of the PDS of the UK and President of the European PD Association who focused on the needs of the patient and the importance of this. She emphasised that populations are living longer, and that with old age comes frailty and more evidence of long-term neurological disorders. There is the urgent need to focus on families affected by neurological disorders so that needs can be met appropriately.

Dr Doug McMahon, Consultant Physician, demonstrated in his talk how modern technology in the form of a PD Integrated Care Template can produce useful evidence around the core clinical information on PD in a clinical database. This can be modified according to local needs and resources therefore hopefully improving patient care. The following two sessions were of importance to the predominantly nurse audience, discussing professional regulation and Nurse Prescribing.

The remaining presentations were the results of two very different projects, the first a Complementary Therapy project carried out by a group in Cumbria. The final presentation informed the delegates of the results of the Association's Survey on Nurse Prescribing, the resultsof which are to be published and have been forwarded to the Department of Health.

Delegates commented that the conference was well organised, presentations were excellent with interesting, relevant and informative content.

The PDNSA would like to thank DuPont Pharma the main sponsor, and every one who supported this conference.

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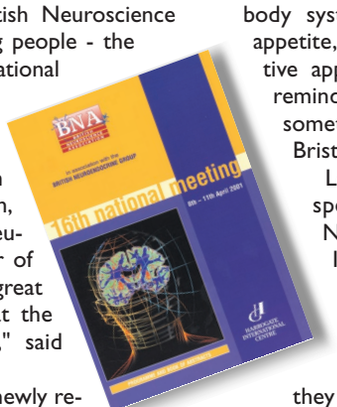
One of the great strengths of the British Neuroscience Association is its membership of young people - the rising stars of British neuroscience. The national meeting in Harrogate proved the point.



Over 600 people attended the meeting where delegates enjoyed a varied and exciting scientific programme. Topics ranged from synaptic plasticity to genomics and cognition, from neurogenesis to maternal bonding to neuronal ageing.. The BNA welcomed a number of well-known international speakers. "It was great to see some of the 'big names' speaking at the same symposia as our younger members," said BNA President, Nancy Rothwell.

This year the BNA joined forces with the newly renamed British Society for Neuroendocrinology. Neuroendocrinologists are driven to understand whole body systems such as body clocks, hormone cycles and appetite, and the symposia generated discussion on integrative approaches to neurosciences. "Perhaps this meeting reminded the more traditional neuroscientists that there is something below the neck," said Michael Harbuz from Bristol University.

Looking beyond laboratory and clinical sciences, some special events were organised. 'Teaching of Neuroscience', 'Careers in the Pharmaceutical Industry' and 'Public Awareness of Science' - all had a full house.

"Networking, of course, is the added bonus of a successful conference, bringing together people from different fields of neuroscience, whether they are established experts or students just beginning their careers," said Professor Rothwell.

For further information see www.bna.org.uk/harrogate2001

Current advances in Parkinson's Disease: challenges and developments

York, March 11-12, 2001

The last few years have seen important advances in the understanding and treatment of Parkinson's Disease (PD) and the insights gained may also have a useful spillover into the understanding of other neurological conditions.

Throughout the course of this meeting it became clear that PD is probably more accurately described as Parkinson's Syndrome as there is certainly more than one cause, often several, and clear biochemical differences in each manifestation of the condition although the clinical features are usually similar.

Aetiology

In his round up of recent advances in the genetic understanding of PD, Professor Tony Schapira concluded that the most common cause is likely to be a genetic susceptibility to certain environmental agents. Those with younger onset PD are much more likely to have a significant genetic component, but this factor does not reduce the occurrence of a genetic susceptibility to environmental factors in later onset PD.

Recently established agents with a causative influence on PD include rotonene, a complex I mitochondrial inhibitor, which in rat models was also linked with the production of lewy bodies.

Rare causes of PD are purely genetic (mutations of the alpha-synuclein gene, mutant Parkin gene) all of which produce selective dopamine cell death in the substantia nigra by different mechanisms. Cellular studies on these proteins suggest that idiopathic PD may represent an abnormality in protein handling which leads to the misfolding of proteins or the wrong disposal of them (as in Huntington's or Alzheimer's Disease).

Imaging

One of the biggest problems with PD is in diagnosis and Professor David Brooks presented evidence of recent advances in imaging techniques using SPECT and PET scanning that could make accurate in vivo diagnosis a real possibility.

Surgery

Surgical therapy for PD is a rapidly expanding area in the management of severe PD and Professor Warren Olanow pointed out that it is still only recommended when other treatments have no benefit. Pallidotomy and thalamotomy are well documented techniques, they are extreme in traumatic effect and are currently being overtaken by deep brain stimulation (DBS) as the treatment of choice. The benefits of DBS include the fact that it is not necessary to make a disruptive lesion, the stimulation can be adjusted, and it does not preclude the use of neuroprotective drugs if some should be developed which require the pallidus or thalamus to be intact. However, there is a need to replace the battery under anaesthetic, it is extremely expensive to carry out, and there are only a limited number of sites with the necessary expertise to perform it. On foetal nigral transplantation he noted that despite the recent reports of failure in US trials, trials in Sweden demonstrate that the procedure can successfully re-innervate the striatum (see review on page 11).

Levodopa

The mainstay of treatment for the symptoms of PD remains drug therapy and levodopa has been used in this context for over 30 years. Professor William Koller, in assessing the strengths and weaknesses of this 'gold standard' drug noted that after the 'honeymoon period' of effective response to levodopa, the well documented long-term side-effects of levodopa use would affect 50% of patients within five years of therapy. These effects include dyskinesias, mental status changes and motor fluctuations. He speculated that the complications were likely to be caused by the following toxic aspects of levodopa: that it impairs the mitochondrial respiratory chain; increases lipid peroxidation; is toxic to cultured dopamine neurones; and is converted to dopamine oxidation products. Professor Koller concluded that, as one of the goals of therapy is to prevent these long-term problems, the use of dopamine agonists is now the most widely recommended first-line treatment, pointing out that biological rather than chronological age should be the reason for choice of treatment.

Beyond levodopa

The short half-life of levodopa (1.5 hours) is implicated in the increased risk of developing disabling dyskinesias. Dopamine agonists directly stimulate dopamine receptors and have a much longer half-life (ropinirole 6-8 hours, pramipexole 8-12 hours and pergolide 7-16 and cabergoline 63-68 hours). Professor Schapira, in his assessment of post-levodopa therapy, commented that they can be used as mono or adjunct therapy, they may delay or reduce motor fluctuations and may even have a neuroprotective and possibly antidepressant effect. Professor Schapira challenged the current assumption that when patients presented with the first non-disabling symptoms of PD it was best not to treat with medication. He assessed the potential neuroprotective action of the agonists, and of selegiline, a potent MAOI. From laboratory studies, the potential neuroprotective effects of dopamine agonists could be caused by the fact that they increase dopamine turnover (which can decrease free radical toxicity), have anti-oxidant effects and are levodopa sparing.

Emerging use of dopamine agonists

Professor Jean Hubble concurred that the greatest challenges in the treatment of PD are 'how to treat those with no definable disability?', and 'what to use as a first-line treatment as the disease progresses and an intervention is needed?', concluding that dopamine agonists currently appear to be the most useful. She illustrated the facts that dopamine agonists are rarely, if ever, associated with dyskinesias and that agonists may delay or postpone motor complications.

Assessing studies on a third dopamine agonist, cabergoline, Dr Ray Chaudhuri, was at pains to point out that the treatment of PD should be holistic, taking into account quality of life issues, particularly those connected with the nocturnal problems associated with the condition. Between 75 and 90% of PD patients have sleep dysfunction, including insomnia, sleep fragmentation and sleep akinesia. Such nocturnal symptoms are a major cause of morbidity in PD and have severe ramifications for daytime quality of life. Dr Chaudhuri found that cabergoline's long half-life (63-68 hours) meant that up to 90% of patients in trials at his centre found it improved their night-time symptoms and morning dyskinesia.

Non-dopaminergic complications

The non-dopaminergic complications in PD reflect a widespread degeneration in brainstem nuclei. Depression is a major complication that does not respond to dopaminergic therapy in a satisfactory way and Dr David Burn commented that whilst markedly different prevalence figures are reported the mean figure is likely to be around 46%. This is much higher than in age-matched controls and there is also some suggestion that depression may actually precede the physical symptoms and diagnosis of PD in 25 to 30% of patients.

Dr Burn said it was likely that the development of depression in PD relates to changes in mesencephalic monoamine neurones; remote changes in basotemporal limbic regions; and secondary involvement of serotonergic neurones. Thus SSRIs and the NARI reboxetine have shown significant benefits in treating the depression in PD patients, and in addition the dopamine agonist pramipexole may have some antidepressant effects.

Finally Dr Burn also discussed the pedunculopontine nucleus (PPN), which has important reciprocal link with the subthalamus and is involved with locomotion and linked with the initiation of programmed movement, plus maintenance of gait.

Professor Tony Schapira, Chairman

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60 Cranmer Terrace
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Brain & Spinal Injury Charity
Hope Hospital
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"First Floor, 32 Market Place"
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www.bsrm.co.uk/

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

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

The European Dana Alliance for the Brain
Vicarage House
58-60 Kensington Church Street,
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W8 4DR
Tel: 020 7937 7713
Fax: 020 7937 4314

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5 Coates Place,
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Tel: 0131 226 5458

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48 Govan Road
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Tel: 01422 823508

Head Injuries Trust for Scotland (HITS)
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Oxgang Road
Grangemouth FK3 9ET
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King Edward Street
Nottingham NG1 1EW
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Fax: 01159 121011
www.headway.org.uk

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www.mssociety.org.uk

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www.erg.ion.uci.ac.uk/NSE.home/

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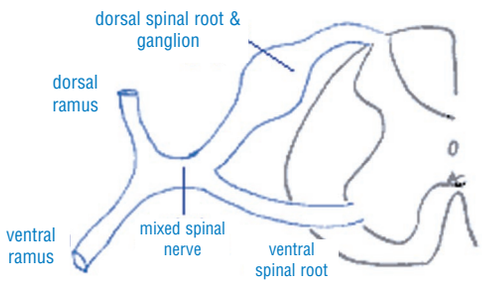
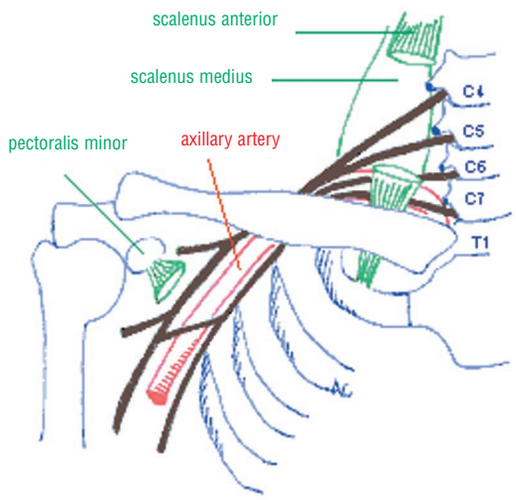
The Brachial Plexus

Alasdair Coles

The basics. The brachial plexus is the mesh of nerves in the neck that is formed by interconnections of the C5-T1 roots. From it emerge all the nerves to the arm including the median, radial and ulnar. The plexus innervates all arm muscles, except for trapezius and levator scapula, and all the skin of the arm except the axilla (intercostobrachial nerve), the area just above the shoulder tip (supraclavicular nerve) and dorsal scapular area (dorsal rami). The most common lesions of the brachial plexus are of its trunks, which cause deficits that appear as multiple root lesions.



The roots of the plexus are quite different from the spinal roots. The plexus roots are formed by the ventral rami of the mixed spinal nerves; the dorsal rami go on to supply muscles and skin of the posterior neck. Each ventral ramus receives a branch from the corresponding sympathetic trunk ganglion; in addition the T1 ventral ramus contributes preganglionic sympathetic fibres to the inferior cervical ganglion.

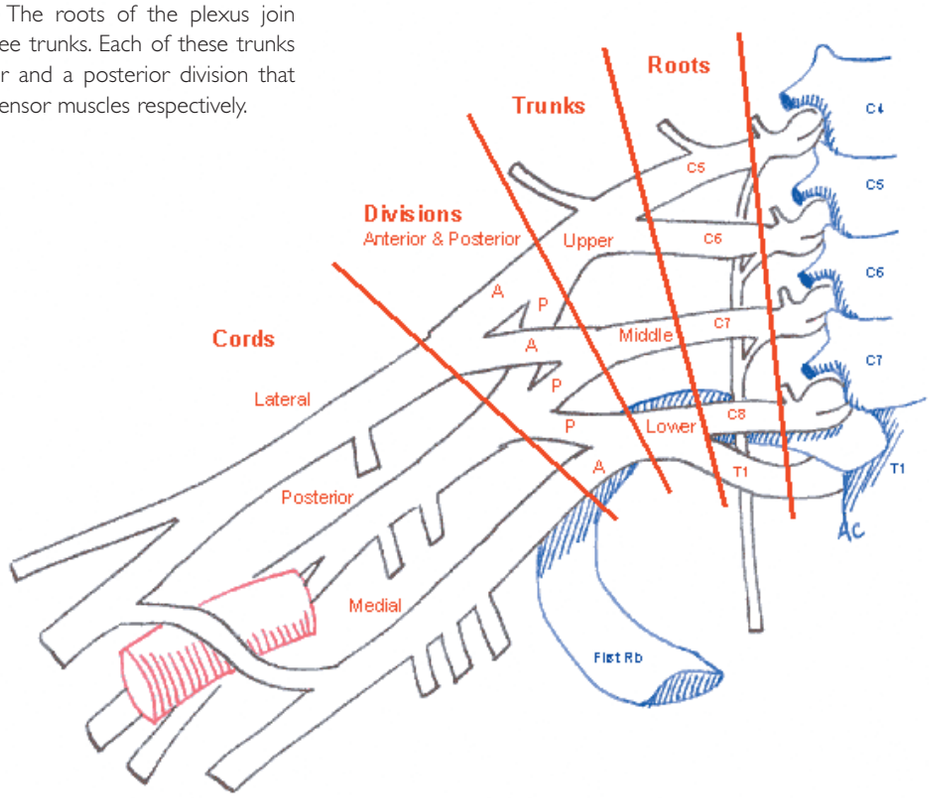


The roots of the brachial plexus emerge anterior to scalenus medius and posterior to scalenus anterior, both of which are deep to sternocleidomastoid. They form **trunks** which lie in the posterior triangle of the neck. These divide to make anterior and posterior divisions which squeeze through the small space behind the clavicle and the first rib, close to the axillary artery. The divisions reassemble to form cords which lie alongside the axillary artery, and are close to the glenohumeral joint and the axillary lymph nodes.

Usually the brachial plexus is supplied by C5-T1, but a **pre-fixed plexus** may arise from C4-8, and a **post-fixed** from C6-T2. Rarely is a brachial plexus made up of more than five root segments.

Trunks & Divisions. The roots of the plexus join together to form three trunks. Each of these trunks splits into an anterior and a posterior division that supply flexor and extensor muscles respectively.

The Cords are the longest part of the brachial plexus and are named in relation to the axillary artery. The anterior divisions of the upper and middle trunks unite to form the lateral cord and the anterior division of the lower trunk becomes the medial cord. The posterior cord is formed from all three posterior divisions.



Statistically, most brachial plexus lesions (and certainly the non-traumatic causes) affect the supraclavicular portion of the plexus and cause multiple root syndromes. Partial upper plexus syndromes are described here, although lesions of all three trunks are common. The cords are less often damaged and the divisions even less so, being well protected under the clavicle.

Posterior Cord Palsy

Cord lesions appear as complex multiple nerve palsies. They are caused by trauma: road accidents, falls and gun-shot wounds. Usually all three cords are involved; if only one is involved, it is often the posterior cord.

The clinical signs of a posterior cord palsy are:

- weak shoulder abduction, extension, internal and external rotation.
- weak forearm, hand and finger extension
- absent triceps reflex
- sensory deficit small: over deltoid and base of thumb

Erb-Duchenne Palsy (Upper Trunk, C5/6)

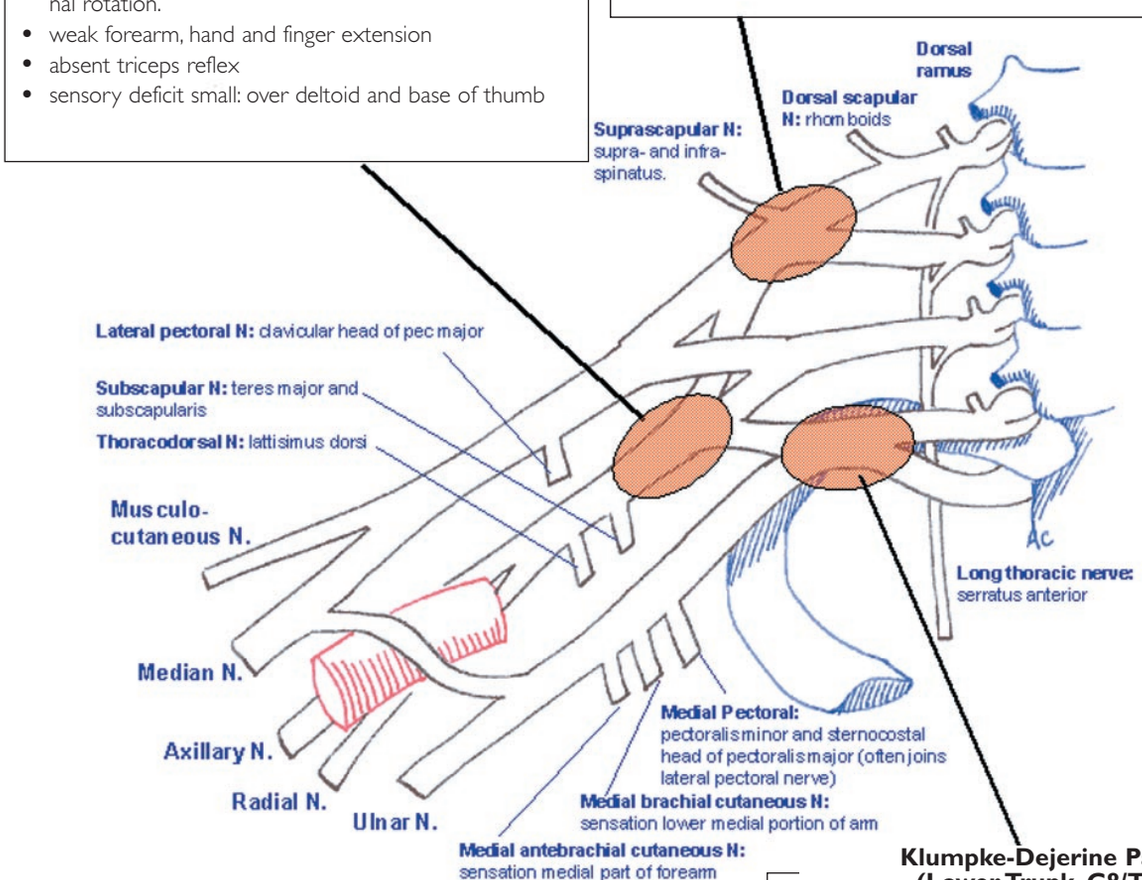
This is the most common single brachial plexus lesion and is due to

- partial traction injuries,
- traumatic delivery, 'obstetric paralysis',
- neuralgic amyotrophy (Parsonage-Turner syndrome)
- rucksack palsy

The clinical signs are:

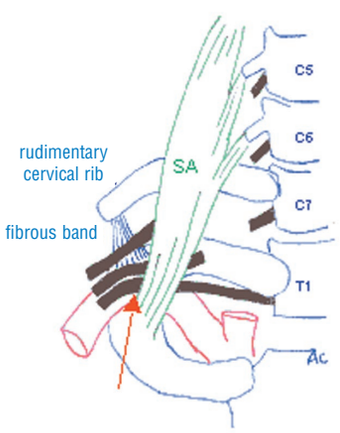
- flaccid shoulder girdle (except some extension from deltoid)
- elbow hangs extended and pronated,
- thus the arm assumes the "waiter's tip" position
- absent biceps and brachioradialis tendon reflexes
- sensory deficit from the postero-lateral upper arm down the radial side of the forearm.

The exact position of the lesion may be extrapolated by examining for sparing of the long thoracic, dorsal scapular or supraspinatus nerves.



The **Neurogenic Thoracic Outlet Syndrome** occurs with cervical ribs. A complete cervical rib may fuse with the first thoracic rib, or a fibrous band will join a rudimentary cervical rib to the first thoracic rib.

The effect of this is to put traction on the lower trunk as it comes over the first thoracic rib behind scalenus anterior (SA): (➛).



Klumpke-Dejerine Palsy (Lower Trunk, C8/T1)

These lesions occur characteristically in the

- neurogenic thoracic outlet syndrome,
- metastatic plexopathy,
- Pancoast syndrome,
- following a median sternotomy

The signs are:

- wasted medial forearm and claw hand
- weakness of all ulnar muscles
- weakness all intrinsic hand muscles
- Horner's syndrome
- All reflexes present (except finger jerks)
- Sensory deficit along medial aspect of the arm and 4th and 5th fingers

REFERENCES:
Dyck, Thomas, Griffin, Low, Poduslo. Peripheral Neuropathy 3rd Ed (1992) WB Saunders, pp 911-947
http://www.eatonhand.com/ner/ner006.htm

With thanks to Simon Shields and especially to Andrew Larner.

EDITOR'S CHOICE

MULTIPLE SCLEROSIS

Vaccinations do not cause Multiple sclerosis (MS) relapses

This study, and its companion article in the same issue of NEJM, brings to an end decades of concern about the risks of vaccination in multiple sclerosis. Using the European Database for Multiple Sclerosis (EDMUS) patients who had a neurologist confirmed relapse between 1993 and 1997 after being relapse free for 1 year at least were studied. Vaccination details were gathered telephonically and confirmed by medical records. 643 patients met the inclusion criteria and 15% had had a vaccination in the 12 months immediately prior to the relapse. The overall relative risk of developing a relapse in the 2 months following a vaccination was 0.71. There was no significant difference between patients with relapses vaccinated in the 2 months immediately prior to the relapse as compared to 4 other previous two month periods. Tetanus, hepatitis B, and influenza vaccination did not produce any increase in the specific risk of a relapse. Vaccinations should not be avoided in patients with MS because of an unjustified fear of precipitating a relapse. ***-TH***

Vaccinations and the risk of relapse in multiple sclerosis.

Confavreux C, Suissa S, Saddier P, Boudres V, Vukusic S for the Vaccines in Multiple Sclerosis Study Group.
NEJM
2001:344:319-26

★★★ RECOMMENDED

Axons die early in multiple sclerosis

Multiple sclerosis lesion burden as measured on conventional T2-weighted MRI of the brain correlates poorly with disability. MRI is nevertheless being increasingly used as a surrogate marker of disease activity in the context of treatment trials and carries increasing weight with the drug licensing authorities. There is a need therefore to find MR techniques that reflect the different pathological processes underlying the MS lesion and hence improve the correlation between MR and disability. MR spectroscopy allows the measurement of N-acetyl aspartate (NAA) concentrations within the brain. NAA is located almost exclusively within the neurons and axons of the adult brain; reduced concentrations have been found by MR spectroscopy in both acute and chronic MS lesions, most likely reflecting axonal dysfunction and loss. Axonal loss is probably the main determinant of irreversible disability in MS. Di Stefano performed MR spectroscopy on 88 patients with clinically definite MS. They used a large voxel incorporating a high proportion of the supratentorial white matter. They demonstrated significantly lower NAA/creatine ratios in patients compared with controls, even in those with short disease duration or minimal disability. The result supports the findings of pathological studies suggesting axonal loss occurs early in the course of the disease, not only within MS lesions but also more diffusely within the normal appearing white matter. The correlation with disability was much weaker for patients with more advanced disease. The authors argue that the appearance of axonal loss at an early stage supports early treatment with disease modifying agents. This remains to be established. MR assessment of axonal loss, be it by MR spectroscopy or especially by measurement of atrophy, will however play an increasingly important role in treatment trials in the future. ***-JT***

Evidence of axonal damage in the early stages of multiple sclerosis and its relevance to disability.

Di Stefano N, Narayanan S, Francis GS, Arnaoutelis, Tartaglia MC, Antel JP, Matthews PM, Arnold DL.
ARCHIVES OF NEUROLOGY
2001: 58: 65-70

★★★ RECOMMENDED

STROKE

Is thrombolysis safe and feasible outside of a clinical trial?

Recombinant tissue plasminogen activator (rTPA) is licensed in the USA and Canada for use within three hours of acute ischaemic stroke. It may soon gain a European licence and lead to a huge shift in the culture of acute stroke care this side of the Atlantic, although initially fewer than 10% of stroke patients will be eligible. Can rTPA be used safely and effectively within stringent regulations outside of a trial? Prospective series from the USA (eg STARS Study, JAMA 2000: 283: 1145-1150) suggest that results similar to the NINDS trial can be achieved in experienced centres. Here the median time from onset to treatment was 2 hrs 44 mins amongst 389 patients, and the rate of symp-

tomatic intracranial haemorrhage was only 3% (versus 6% in NINDS). However, there were protocol violations in 127 patients (33%), mainly treatment beyond the three hour time window, treatment with anticoagulants within 24 hours of rTPA and treatment despite a systolic blood pressure greater than 185. Conversely other studies have suggested that rTPA use outside of a clinical trial increases the number of complications and poor outcomes. In the Cleveland study (JAMA 2000: 283: 1151-1158) the rate of symptomatic haemorrhage was 16% and half the patients violated agreed protocols. However, fewer patients were treated than in the STARS experience (n=70) and it is likely there exists a significant learning curve in selecting, triaging and investigating patients. Thus as more patients are treated, the better the results might become.

In this study, a group from Indianapolis describe their experience of 50 patients treated in 10 major hospitals in Indiana. These patients were accrued over an 18 month period, thus each hospital treated only a handful of patients. 70% of patients were treated by a general neurologist (mean delay in starting rTPA from stroke onset was 44 mins), 25% by a stroke neurologist (mean delay 86 mins) and 6% by emergency physicians (mean delay 141 mins). Protocol violations were seen in 8 patients (16%); none of these were due to delay in treatment, instead they were use of anticoagulants, coexisting clotting abnormalities, recent prior stroke or head trauma, and uncontrolled hypertension. The risk of all types of haemorrhage was significantly greater amongst protocol violators (75%) than non violators (12%). Among those patients treated according to NINDS criteria, cerebral haemorrhage rate (5%) was similar to that seen in the NINDS study.

The authors emphasise that most patients were treated by general rather than stroke neurologists and that the former were mainly based in private practice. They do not mention what proportion of all strokes seen were eligible for treatment (no doubt very small). Besides attention to the three hour time window, they highlight the importance of avoiding uncontrolled hypertension and concomitant anticoagulants when treating acute ischaemic stroke with tPA. They could not determine which protocol violation carried the highest risk of adverse events but suggested that, when strict protocols are closely followed, thrombolysis can be a safe and effective treatment for acute cerebral infarction. **- *PM***

Protocol violations in community-based rTPA stroke treatment are associated with symptomatic intracerebral haemorrhage.

Lopez-Yunez AM, Bruno A, Williams LS *et al*.
STROKE
2001: 32; 12-16

COGNITIVE NEUROLOGY

Identifying early Alzheimer's disease

Evidence from clinical, neuroimaging and histopathological studies has indicated that Alzheimer's disease (AD) has a preclinical phase which may extend for many years. Identifying this preclinical phase not only elucidates the natural history of AD, but may also provide opportunities for therapeutic intervention. Bäckman *et al* report a Swedish study that aimed to determine the course of the preclinical episodic memory deficit in AD. As part of the Kungsholmen project, a longitudinal population-based study in a Stockholm parish, measures of episodic memory (free recall of word lists and recognition of words) and short term memory (forward and backward digit span) were made in 120 subjects on three occasions, three years apart, over a period of six years. Fifteen individuals developed AD after six years of follow-up. Compared to the non-demented group, the incident AD cases showed poorer global cognitive function (on the Mini-Mental State Examination) and their performance was worse on both free recall and recognition, differences that were evident at both 6 and 3 years before diagnosis. There were no group differences on forward or backward digit span. There was no evidence of a selective decline in the AD group between the six and three year time points, suggesting relative stability of preclinical deficits. These findings are consistent with a long and detectable preclinical phase in AD. The difficulties in transferring information from temporary to permanent representations are consistent with early hippocampal pathology, as also demonstrated by histopathological and neuroimaging studies. The relative stability of the preclinical phase, at least until its later stages, may have therapeutic implications, suggesting that early interventions are the most likely to be helpful. **- AJL**

Stability of the preclinical episodic memory deficit in Alzheimer's disease.

Bäckman L, Small BJ, Fratiglioni L
BRAIN
2001:124(1):96-102

MOVEMENT DISORDERS

Involuntary movement disorders following thalamic stroke

Delayed onset of involuntary movements following thalamic stroke was first reported by Dejerine and Roussy in 1906 ("Dejerine-Roussy syndrome"). Although many other cases have been reported, large study groups with control populations have not. This observational follow-up study from South Korea reports on 93 patients with thalamic stroke seen by one neurologist over a period of 57 months, 35 of whom developed involuntary movements, 58 of whom did not. Demographic factors, risk factors and site of lesion (posterolateral thalamus) were similar in the two groups. Patients developing involuntary movements were more likely to have haemorrhagic lesions (all due to hypertension), and more severe initial hemiparesis and sensory loss compared to the control group. The involuntary movements observed were complex, involving arm and fingers more than leg and feet, and encompassing dystonia, athetosis, chorea, with or without action tremor and jerky myoclonus; isolated tremor was not seen. Dystonia/athetosis/chorea was closely associated with position sensory loss (hence appropriately designated "pseudochoreoathetosis"); tremor/myoclonus was associated with cerebellar ataxia. Thus, it seems that damage to the lemniscal sensory pathway, the cerebello-rubrothalamic tract and the pyramidal tract are required for the development of post-thalamic

stroke involuntary movements. Unbalanced but successful recovery of motor function, with development of pathological neuronal circuitry, may account for the delayed onset of the movements. **-AJL**

Delayed onset mixed involuntary movements after thalamic stroke. Clinical, radiological and pathophysiological findings.

Kim JS
BRAIN
2001:124(2):299-309

MUSCLE

Another sad episode in attempts to treat inclusion body myositis

The histology of muscles affected by inclusion body myositis (IBM) shows, as the name suggests, inflammatory cells yet it is unresponsive to immunosuppessants. Nonetheless, this team from the NIH have persisted with immunotherapies of IBM. They had previously shown minor improvements in muscle strength following treatment with intravenous immunoglobulin (IVIG). They now report their attempt to accentuate this positive effect by adding corticosteroids. They performed a double-blind trial of prednisolone with or without IVIG treatment over three months in 36 patients. There was no difference between the groups. Given that previous experience had shown steroids to be ineffective in this condition, this not only proved that steroids do not add to IVIG's effect, but brought into question the previous positive result with IVIG alone. Perhaps the inflammation in IBM is in response to the muscle injury rather than its primary cause. All rather disappointing really. ***-AJC***

A controlled study of intravenous immunoglobulin combined with prednisolone in the treatment of IBM.

Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K and Cupler E.
NEUROLOGY
2001: 56: 323-327

EPILEPSY

Causes of epilepsies: Insights from discordant monozygous twins

Genetic studies of epilepsy from Berkovic's group have provided a rich seam of data on inherited aspects of epilepsy. Here they studed 12 pairs of monozygous twins, where only one of the pair had epilepsy. They made a syndromic diagnosis in each, investigated them with MRI and EEG, and looked for aetiological factors. Eight pairs had epileptogenic MRI lesions. In four of these, there was a history of major acquired insults such as prolonged febrile convulsions associated with mesial temporal sclerosis. In four others, the lesions were not associated with any clear history; one had bilateral subependymal heterotopia, which may be due to an inherited mutation (usually X-linked dominant), but, as her mother and her twin had normal MRIs, it was probably due in her case to a somatic mutation. The final four twins had normal MRIs and no relevant antecedent history. Of these, two had classical childhood epilepsy and one was thought to have familial temporal lobe epilepsy. This study shows that the majority of discordance in the expression of epilepsy between monozygotic twins is due to the exposure of only one twin to an acquired aetiological factor. Of equal interest however, is the discordance between identical twins of epilepsy syndromes that are thought to be genetically determined. The authors consider environmental factors and somatic mutations as potential explanations for this observation. ***-MM***

Causes of epilepsies: Insights from discordant monozygous twins.

Briellmann RS, Jackson GD, Torn Broers Y, Berkovic SF.
ANNALS OF NEUROLOGY
2001;49:45-52

NEURO-OPHTHALMOLOGY

Acute ophthalmoparesis: "Miller Fisher minus"

Neurologists are all familiar with the triad of ophthalmoplegia, ataxia and arreflexia that constitute the Miller Fisher syndrome, in which IgG antibodies to the ganglioside GQ1b are found with high sensitivity. These antibodies have also been found in Bickerstaff's brain stem encephalitis suggesting that there may be a spectrum of associated disease. Yuki and colleagues draw attention to the opposite end of the clinical spectrum. They reviewed the clinical findings of 340 consecutive patients whose serum contained significant titres of anti-GQ1b antibodies. They identified 21 patients in whom there was ophthalmoparesis without ataxia. Seventeen had some preceding illness (sore throat, upper respiratory tract infection, fever or gastroinestinal illness). The commonest pattern was of limitation of abduction. Vertical gaze palsy was less common. Five patients had unilateral involvement. Internal ophthalmoplegia was not found. Some patients had limb paraesthesiae. Four had bilateral facial weakness, two mild bulbar involvement. Tendon reflexes were variable. Cerebrospinal fluid was normal in most cases. The authors state that anti-GQ1b antibodies are a more useful test in acute ophthalmoparesis than CSF analysis. However, a diagnosis based on antibodies is usually made long after therapy has been initiated. This is probably reflected in the various treatments used (plasmaphoresis, intravenous immunoglobulin and steroids). Prognosis was not discussed (but was presumably favourable).***-JT***

Acute ophthalmoparesis (without ataxia) associated with anti-GQ1b antibody. Clinical features.

Yuki N, Odaka M, Hirata K.
OPHTHALMOLOGY
2001: 108: 196-200

INTENSIVE CARE

Tuning in whilst in coma

Relatives are often encouraged to talk to patients in a coma, on the basis that personally meaningful stimuli are more likely to arouse them than background noise or neutral conversation. This study provides evidence to support this practice. Mazzini *et al* report on the effects of different stimuli on long-latency auditory evoked potentials in 21 comatous patients after traumatic brain injury. These long-latency responses are recorded at between 70 and 500 ms after the presentation of a sound stimulus and are thought

to be generated by cortical auditory processing. The patients heard three stimuli: tones, an insignificant word and their name spoken by a relative. The evoked responses were compared with outcomes at 6 and 12 months. The latency of the negative potential at around 100 ms was associated with recovery measured by various rating scales. The patients with response latencies that were similar to normal recovered better than those with longer latency responses. The correlations were highest with the responses to the patient's name. These results suggest that patients are more likely to register hearing their name spoken by a relative than less meaningful stimuli. Perhaps this will be of comfort to those who are maintaining a one sided conversation. **-AJT**

Long-latency auditory-evoked potentials in severe traumatic brain injury.

Mazzini L, Zaccala M, Gareri F, Giordano A, Angelino E.
ARCHIVES PHYSICAL MEDICINE AND REHABILITATION
2001: 82 (1): 57-65

REHABILITATION

Rehabilitation for people who do not know they need it

After head injury patients are often unrealistic about their abilities. It is difficult to rehabilitate patients with such lack of self-awareness. They are unlikely to be motivated to change and may put themselves and others at risk by their behaviour. Abreu *et al* report an Occupational Therapy project in which self-awareness regarding performance on daily living tasks was examined and a model of self-awareness was tested. They compared the level of confidence that 55 head injury patients had in their ability to perform dressing, meal planning and money management tasks, with their actual performance as judged by two experienced therapists. Not surprisingly the head injury patients anticipated their abilities to be higher than the clinician's ratings of actual performance. However when it came to predicting how task performance might affect ability to live life, patients who reported being aware of changes in behaviour that might affect task performance showed no more agreement with the therapists than those who were unaware. Therefore it should not be assumed that patients who have an awareness of impairments that might affect task performance will be able to foresee the type of difficulties that they will encounter in everyday life. Maybe those who had awareness of deficits after brain injury were still hopeful of recovery to normal or perhaps the awareness of a deficit and experiencing problems does not readily translate to making realistic predictions about functioning in everyday life. The authors are cautious about rejecting the hierarchical nature of developing self-awareness after head injury and would like to verify the validity of their questions to patients and try additional means to test the hierarchy. This line of enquiry is important for therapists who are currently struggling to work with people who do not recognise the need for rehabilitation and will ultimately help them to develop new and effective approaches to treatment. **-AJT**

Levels of self-awareness after acute brain injury: how patients' and rehabilitation specialists' perceptions compare.

Abreu B C, Seale G, Scheibel R S, Huddleston N, Zhang L, Ottenbacher K J.
ARCHIVES PHYSICAL MEDICINE AND REHABILITATION

★★★ RECOMMENDED

PRION DISEASE

A new marker for transmissible spongiform encephalopathy (TSE)

Now that BSE has reached Europe, there is even more demand for a rapid easy test of prion infection. Neuropathological examination is not straightforward and waiting for laboratory animals to succumb to an inoculation of nervous tissue is time-consuming. Gino Miele and colleagues at the Roslin Institute in Scotland have come up with a novel technique for diagnosing transmissible spongiform encephalopathies. It is based on a comparison of 10,000 mRNA transcripts in the spleens of healthy animals and those infected with TSE. They identified one transcript that was significantly reduced in spleen from scrapie-infected mice and showed this to have sequence homology with a novel molecule named "erythroid differentiation-related factor" (EDRF). Surprisingly, in humans EDRF is not found in the brain but only in blood and bone marrow, where prion infectivity has never been found. The link between prions and erythroid precursors is intriguing; for the moment, the important point is there is now a straightforward diagnostic test of TSE: a Northern Blot using cloned EDRF as a probe ***-AJC***

A novel erythroid-specific marker of transmissible spongiform encephalopathies.

Mile G, Manson J, Clinton M.
NATURE MEDICINE
2001: 7: 361-364

Complimentary Journals Reviewed

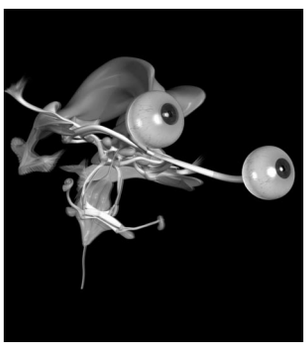
We would like to thank the following publishers who have provided us with complimentary review subscriptions to their journals. For subscription details please contact the relevant publisher direct.

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

3D Stereoscopic Atlas of the Human Brain



What is the function of the mammillary body?; Which information is passed through the cuneate fasciculus or the internal arcuate fibers?; Which hormones are produced by the paraventricular hypothalamic nucleus?; Which nerves and vessels run through the jugular foramen?; Which parts of the body are innervated by the accessory nerve?; Which cortical regions are affected by a dysfunction of the central sulcus artery?

These are questions to which a short, precise answer is seldom found in textbooks or other scientific works. According to Springer, these questions are answered in the Dictionary of Human Neuroanatomy. This is an atlas for anyone looking for precise and functional definitions of terms in the field of neuroanatomy, and is said to be absolutely essential for those studying neuroanatomy, and for quick reference. The stereo glasses for 3D effect enable you to see the brain in whole new dimensions using a 3D computer model.

The use of a complex, stereoscopic visualisation procedure presents the reader with a completely new insight into the human brain. In combination with the CD-ROM, which contains all 173 illustrations as rotatable 3D models, this book introduces an innovative quality into the conception of spatial structures.

For further information, please contact Sally Tickner at Springer-Verlag on Tel: 01483 414113 or E-Mail: sally@svl.co.uk

New Generation of PET Scanner

Siemens has commissioned a new generation of PET scanner based on the new scintillator crystal LSO. The new detector allows for much higher count rates than traditional BGO- or NaI based detectors, which in turn enhances image quality and increases patient throughput. With this scanner, a typical time for a whole body scan is reduced to 20 minutes, representing savings of 20-40 minutes over previous generations of PET tomographs.

This new tomograph also incorporates a number of features to enhance simultaneous image acquisition, processing and reconstruction. Innovative software facilitates more accurate image processing and faster data analysis.

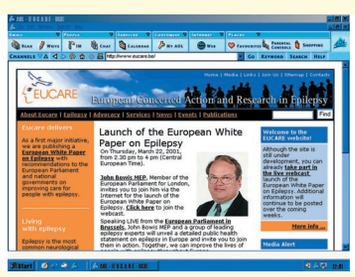
Designated the ECAT ACCEL, this tomograph is the first commercially available PET scanner to use LSO detection. It is a whole body positron emission tomography scanner that provides volume measurements of both metabolic and physiological processes. In the performance spectrum, it will enable routine clinical applications as well as advanced clinical or research projects, meeting the demands of most of today's clinical PET users.

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

The new Siemens' ECAT ACCEL positron emission tomograph that uses LSO crystal technology to improve both imaging quality and patient throughput.

European Parliament calls for action in epilepsy

Experts in epilepsy called upon members of the European Parliament, the public and the medical community to share their knowledge and unite in action to improve the lives of the six million people with epilepsy in Europe, with the launch of the European White Paper on Epilepsy on March 22.



The White Paper on Epilepsy, supported by EUCARE (EUropean Concerted Action and Research in Epilepsy), an educational initiative from UCB Pharma aimed at raising the profile of epilepsy across Europe, has been produced in a timely manner to take advantage of the European Parliament's new remit for Public Health.

Mr John Bowis, MEP for London and host of the White Paper launch meeting in parliament, stated, 'I am demonstrating my personal commitment by setting up 'Parliamentary Advocates for Epilepsy' a group of key MEPs specifically dedicated to bringing epilepsy to the forefront of parliamentary health issues, campaigning to improve existing legislation - particularly within the workplace'.

Eradication of Stigma, Discrimination in the Workplace, and Inadequate Research Funding were cited as three key focus areas requiring rapid improvement across Europe. The White Paper on Epilepsy is intended to be a platform on which local epilepsy programmes can be built.

For further information: www.EUCARE.be

Novel botulinum toxin for cervical dystonia

NeuroBloc® (5000 U/ml Botulinum Toxin Type B) is said to be the first treatment for cervical dystonia to contain the type B form of botulinum toxin.

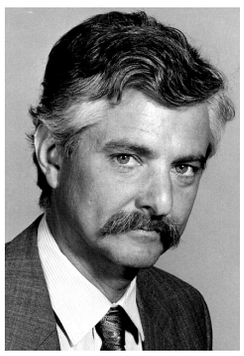
NeuroBloc offers patients with cervical dystonia effective, long lasting relief from painful muscle spasms in their neck and shoulders, whether or not they are resistant to the type A botulinum toxin widely used to treat this condition. In a recent survey carried out by the Dystonia Society, 8 out of 10 respondents had used botulinum toxin as part of their treatment. But 1 in 3 reported decreasing effectiveness or lack of benefit with repeated injections, and 1 in 12 had stopped treatment because of side effects.

By blocking release of a neurotransmitter in affected muscles at a different site from botulinum toxin A, NeuroBloc provides Britain's estimated 18,000 cervical dystonia patients with a much needed alternative treatment. Professor Andrew Lees, Consultant Neurologist at The National Hospital for Neurology and Neurosurgery, explained that the new type B form of botulinum toxin provides a valuable new option for the treatment of cervical dystonia. "Botulinum toxin has made a major difference to the way people with this debilitating disease live their lives, and the arrival of a long acting, easy to use type B toxin is an important advance for current and future patients," he said.

For further information contact Elan Pharma on Tel. 01462 707200.

A British Society of Neuro-otology

Dr Adolfo Bronstein is proposing to create a forum where clinicians and scientists from a variety of backgrounds can meet to discuss research into neuro-otology. The group will first meet on **Friday 15th of June,** with a view to forming a British Society of Neuro-otology. This date has been chosen to tie in with the World Congress of Neurology, where there are two separate sessions on neuro-otology as well as related topics on Eye Movement Disorders and Autonomic Function disorders.



Dr Adolfo Bronstein

Dr Bronstein says, "This should be a valuable meeting for all of us engaged in clinical or scientific research in neuro-otology and balance control.

I should be grateful to know who would be prepared to attend and who would like to present a research paper (15-20 minutes).

As there will be many eminent international neuro-otologists in London at this time, I am planning a guest lecture for this neuro-otology meeting."

For further information contact Dr Adolfo Bronstein, Hon. Consultant Neurologist. Tel: 0207 837 3611 x 4112, Fax. 0207 837 7281, E-Mail: dizzymrc@ion.ucl.ac.uk

New Working Party to promote Vestibular Rehabilitation

Chartered physiotherapists with a special interest in vestibular rehabilitation (VR) are meeting in May with the intention of forming a specialised clinical interest group.

The day bas been initiated by four physiotherapists who have been working together over the past 18 months to promote VR within the physiotherapy profession. They have produced an assessment and therapy handbook, due to be published shortly.

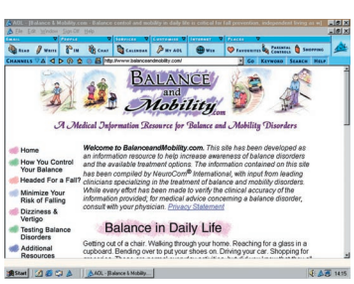
This book is designed for physiotherapists working, or interested, in vestibular rehabilitation, but who only have a basic knowledge of the subject.

The meeting, to be held in Birmingham, will be host to Professor Neil Shepard of the University of Pennsylvania, author of *Practical Management of the Balance Disorder Patient.* He will talk on VR with particular reference to physiotherapy assessment and management. It is hoped that this specially directed meeting will attract many of the physiotherapists nationwide, who have made contact with the working party, expressing an interest in VR and asking for support in this specialised area of work.

The meeting will be sponsored by SLE Diagnostics and details can be obtained from Fran Williams on 0208 681 1414.

Web Site for Patients with Balance Disorders

BalanceandMobility.com is an information resource for patients with balance and mobility disorders. The site, designed to increase public awareness, assists individuals suffering from imbalance or dizziness in understanding their problems and the available treatments. The site was developed with input from leading clinical specialists, and also contains educational information for medical professionals.



At least half of the US population will experience balance problems at some point during their lives, especially as they get older. Poor balance and fall related injuries account for a significant percentage of emergency room visits and medical expenditures per year. Unfortunately, many people suffering from balance problems find it difficult to receive an accurate clinical assessment of their problem and even more never receive adequate follow up and treatment.

BalanceandMobility.com explains the body's balance control system for patients and specifically addresses the risk factors associated with falling, as well as tips on how to minimise fall risk. The site reviews common balance disorders along with the different tests available that can help document a balance problem.

BalanceandMobility.com was developed by NeuroCom International, Inc. with input from leading clinical specialists. For further information visit www.BalanceandMobility.com and www.onbalance.com or call 001 503 653-2144.

A new NSF - implications for stroke care

New national standards of NHS care for patients over 65 have been published by the Department of Health. The NSF for Older People aims to ensure high quality care regardless of age and fair resources for conditions affecting the elderly. Stroke is one of just eight standards set by the document. The NSF highlights the need for specialist stroke units - latest figures show that around 75% of patients are not treated in such a facility.

The document lays down a plan of immediate stroke management including a brain scan within 48 hours and giving aspirin if haemorrhage is unlikely. It also highlights requirements for early and continuing rehabilitation. The NSF adds that secondary prevention measures should be initiated in hospital and refers to recent recommendations from the RCP. These include advice that all patients not on anticoagulation should be taking aspirin daily or a combination of low-dose aspirin and dipyridamole modified release. If aspirin intolerant an alternative anti-platelet agent should be used. The framework says that stroke teams should be led by a clinician with relevant expertise and should include a clinical specialist nurse, speech and language therapist, physiotherapist and occupational therapist, dietitian, clinical psychologist, pharmacist, social worker, stroke care co-ordinator and others. It recommends that stroke teams meet weekly and lists 13 fundamental training topics. By April 2003, every hospital is expected to deliver stroke care according to the RCP guidelines, with all stroke patients cared for in a specialised unit by April 2004.

The NSF for Older People is at www.doh.gov.uk/nsf/pdfs/nsfolderpeople.pdf

Print copies are available from DoH, PO Box 777, London SE1 6XH.

Seeking Solutions - Parkinson's Awareness Week 2001

Parkinson's Awareness Week (21-29 April) focused on Parkinson's Disease Society funded research. The PDS funds over £1.5 million annually towards research into the cause and cure of Parkinson's. A further £100,000 is additionally spent on welfare research affecting all aspects of living with Parkinson's - PDS is one of the largest organisations responsible for research into Parkinson's in the UK.

Seeking Solutions mainly concentrated on Gene Therapy, a new approach to treating medical conditions, which can be described as the use of genes as drugs. It works by introducing normal genes into people with certain disorders to overcome the effects of defective genes that may cause or have a part to play in the development of the condition. Gene therapy can also be used to treat disorders where the genetic cause is not known, or may not be caused exclusively by genetic defects, such as Parkinson's. Gene therapy is still in the early stages of research - it will be at least five years before it can be used in humans. Results on PDS funded research on Gene Therapy at Manchester University were published during Parkinson's Awareness Week.

For more information call 0800 378 378 or e-mail pr@parkinsons.org.uk

Prescribing information

Lamictal (lamotrigine)

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

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

Dosage and Administration: Initial dose and subsequent dose escalation should not be exceeded to minimise the risk of rash. *Monotherapy:* Initial dose is 25mg daily for two weeks, followed by 50mg daily for two weeks. Dose should be increased by a maximum of 50-100mg every 1-2 weeks until optimal response. Maintenance dose is 100-200mg/day in one dose, or two divided doses. *Add-on therapy: Adults and Children over 12 years:* To sodium valproate with or without ANY other antiepileptic drug (AED), initial dose 25mg every alternate day for two weeks, followed by 25mg/day for two weeks. Dose should be increased by 25-50mg every 1-2 weeks until optimal response. Usual maintenance dose 100 to 200mg/day in one dose, or two divided doses. To enzyme inducing AEDs with or without other AEDs (but NOT valproate), initial dose is 50mg daily for two weeks, followed by 100mg/day in two divided doses for two weeks. Dose should be increased by 100mg every 1-2 weeks until optimal response. The usual maintenance dose is 200 to 400mg/day given in two divided doses. *Children aged 2-12 years:* To be dosed on a mg/kg basis until the adult recommended titration dose is reached. Add-on to sodium valproate with or without ANY other AED, initial dose is 0.15mg/kg bodyweight/day given once a day for two weeks, followed by 0.3mg/kg/day given once a day for two weeks. Dose should then be increased by a maximum of 0.3mg/kg every 1-2 weeks until optimal response. Maintenance dose is 1 to 5mg/kg/day given in one dose, or two divided doses. Add-on to enzyme-inducing AEDs with or without other AEDs (but NOT valproate) is 0.6mg/kg bodyweight/day given in two divided doses for two weeks, followed by 1.2mg/kg/day for two weeks given in two divided doses. Dose should then be increased by a maximum of 1.2mg/kg every 1-2 weeks until optimal response. The usual maintenance dose is 5-15mg/kg/day given in two divided doses. The weight of the child should be monitored and the dose adjusted as appropriate. If the calculated dose is 2.5-5mg/day then 5mg may be taken on alternate days for the first two weeks. With the currently available 5mg tablet strength it is not possible to accurately initiate Lamictal therapy in paediatric patients weighing less than 17kg. *Elderly patients:* Treat cautiously. *Dose Escalation:* Starter packs covering the first four weeks treatment are available. When the pharmacokinetic interaction of any AED with Lamictal is unknown the dose escalation for Lamictal and concurrent sodium valproate should be used.

Contra-indications: Hypersensitivity to lamotrigine.

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

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

Side and Adverse Effects: With monotherapy: headache, tiredness, rash, nausea, dizziness, drowsiness, and insomnia. In addition with add-on therapy: diplopia, blurred vision, conjunctivitis, unsteadiness, GI disturbances, irritability/aggression, tremor, ataxia, agitation, confusion, halucinations and haematological abnormalities. Severe skin reactions including angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred rarely, with or without signs of hypersensitivity syndrome (including hepatic failure – see Precautions).

Legal category: POM.

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

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

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

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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.
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Before you treat her epilepsy, put yourself in these.

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

What other AED can offer a girl so much?

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