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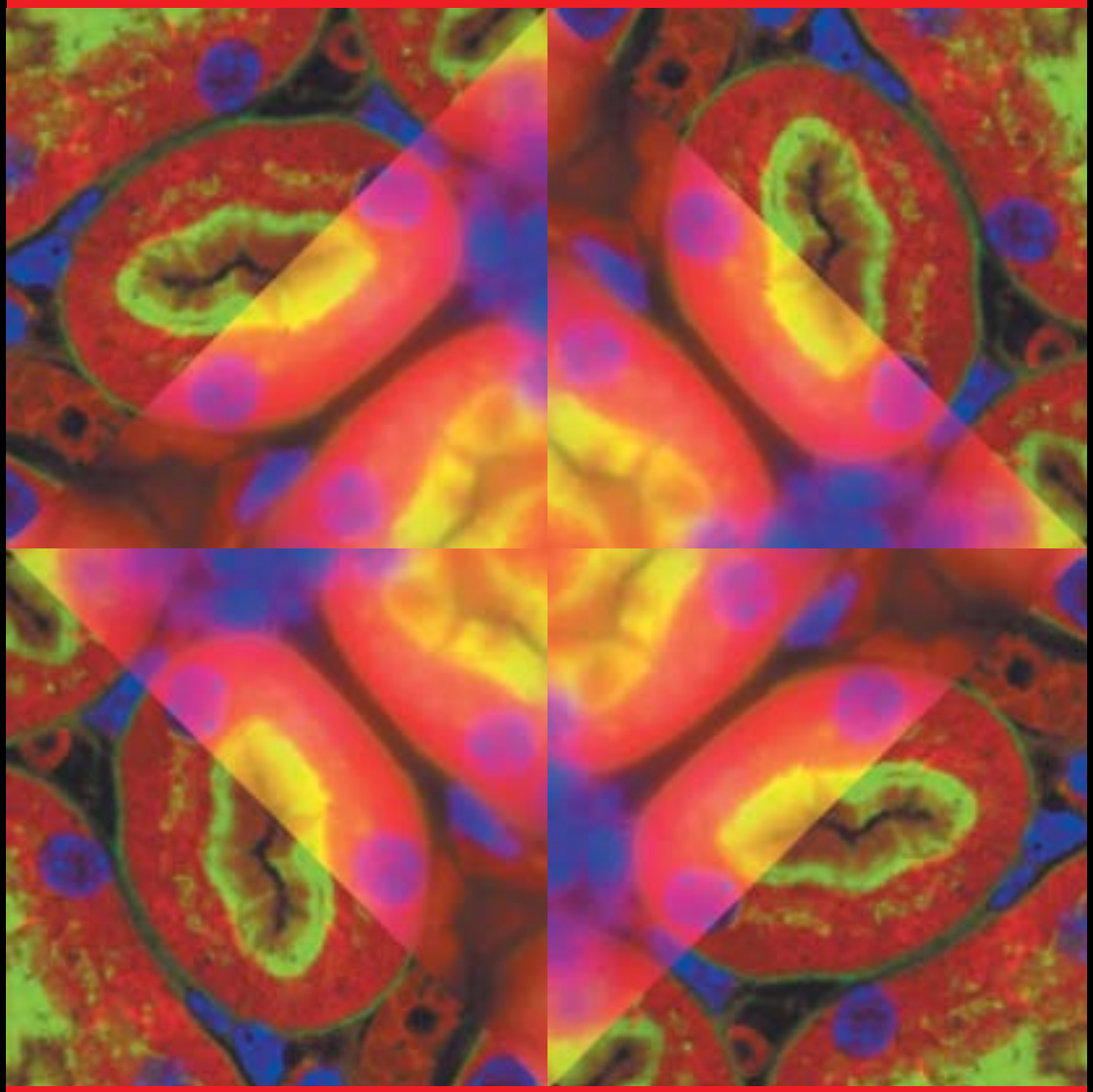
ACNR

Advances in Clinical Neuroscience & Rehabilitation



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

Review Articles: Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa; Neurological complications of Behçet's syndrome
Management Topic: Muscle ion channel diseases
Rehabilitation Article: Domiciliary ventilation in neuromuscular disorders - when and how?
WIN BOOKS: See page 5 for details

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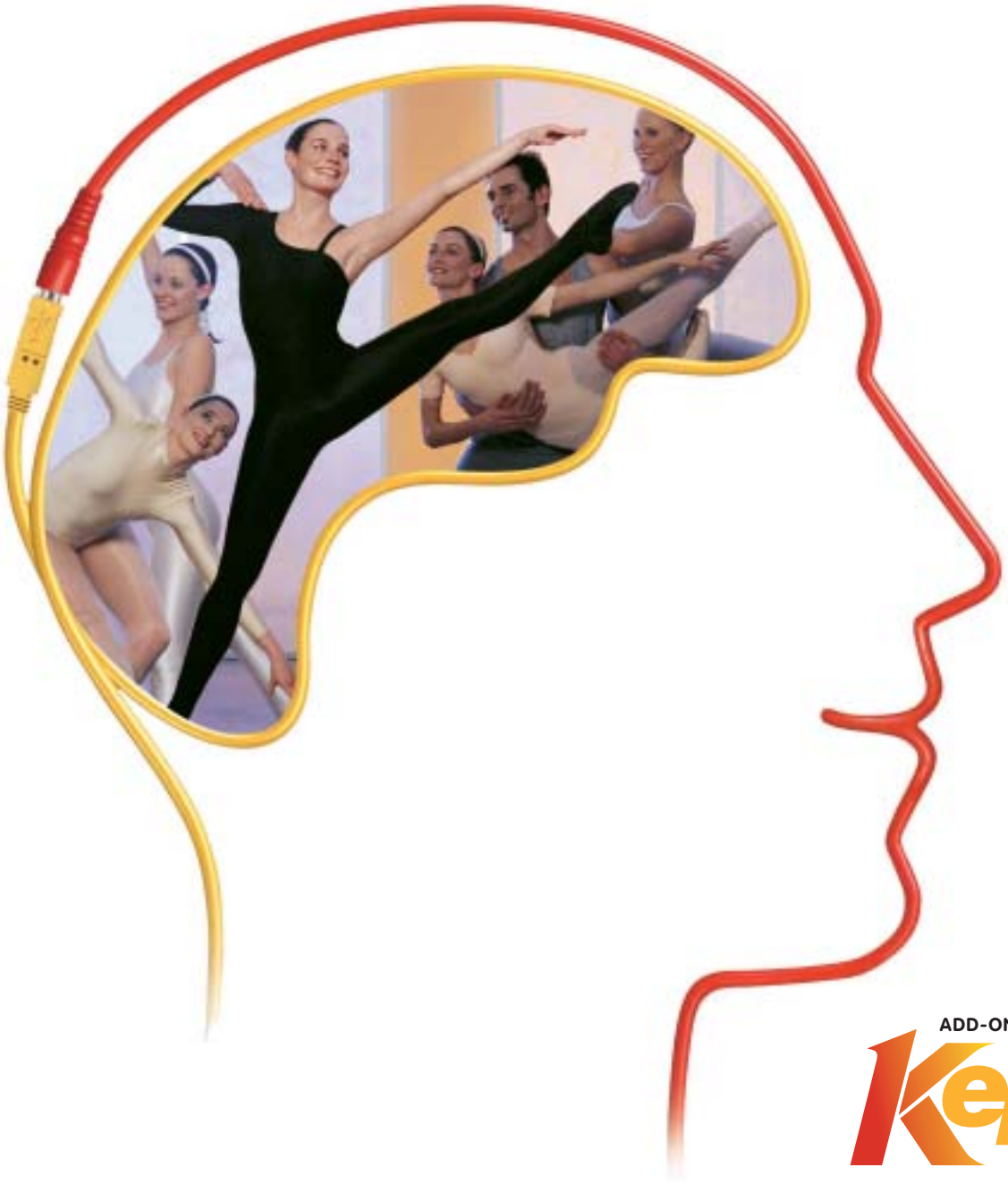

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Date of preparation: January 2003.

Reference: 1. Cereghino J et al. Neurology 2000;55(2):236-242.

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This issue of ACNR sees us entering our third year of existence and continuing to link neuroscience to neurology and vice versa. The two review articles look at very different aspects of the CNS and disease, the first by Desmond Kidd reviews the neurological complications of Behcet's disease and the second by Mike Cheetham and Paul Chapple explores neurodegenerative processes through the study of retinitis pigmentosa.

Desmond Kidd has set about trying to explore this often thought of but rare disorder, through the recruitment of patients with the help of the British neurological surveillance unit, and through his work at tertiary referral centres. He then brings this personal experience into a survey of the literature to highlight what is known and not known about this condition. So, for example, he highlights that the evidence for a vasculitis in Behcet's is lacking and that drug trials in this condition are needed if we are to develop any rational approach to treating what often becomes a chronic, debilitating disorder.

Mike Cheetham and Paul Chapple have concentrated on looking at the molecular mechanisms underlying the photoreceptor degeneration that characterises retinitis pigmentosa (RP). Whilst this may be seen as a relatively specialised area with little clinical significance to most neurologists, the study of the processes underlying it may have wide-ranging implications for a whole host of common neurological disorders. These researchers have set about trying to unravel the intracellular processes causing RP, particularly concentrating on the interaction of mutant proteins with chaperones and chaperonins, whose normal role is to ensure the correct processing of proteins within the cell and by so doing protect it from damage. These proteins are also associated with the proteosome, which acts to remove misfolded or abnormally processed protein from within the cell. Disorders in these pathways have recently been thought to be important in the pathogenesis of a range of common neurodegenerative disorders such as Huntington's (see journal reviews) and Parkinson's disease. Thus by studying one system in one condition, inferences can be made that have wide-ranging implications for a host of other disorders, and this in turn may lead to common therapeutic strategies.

The rehabilitation article this month is written by John Shneerson and provides a marvellous overview of the use of ventilatory support in diseases of the nervous system. Alex Leff provides an interesting account on the rather obscure physician of the mid- to late 1800s, Thomas Laycock. Laycock was the first proponent of cerebral reflexes - actions which patients cannot restrain or modify and was also the first person to argue that the anatomical divisions of the CNS in humans is similar to that seen in other animals and forms part of a continuum. Alex Leff gives a beautifully clear account of his life and his contribution to neuroscience, as well as highlighting that he may have been a greater influence of neuroscience than people recognise, through his teaching of Hughlings-Jackson.

We also have our usual collection of regular articles. Wojtek Rakowicz and Mike Hanna conclude the superb series on muscle disease with a beautiful summary of a complex area, this time channelopathies. It is a shame that this is the last in the series, as they have been a real highlight of recent issues – we move on to movement disorders next with David Burn opening the bowling on the approach to such a patient.

Brian McNamara takes on the common peroneal nerve (CPN) and foot drop – a condition which often presents diagnostic problems. Whilst we all confidently tell medical students how to distinguish foot drop in a CPN palsy from a radiculopathy, we often find ourselves in clinic struggling to distinguish between the two (or perhaps it is just me!). Brian takes his usual no-nonsense approach to this issue through his neurophysiological eyes and provides a useful summary, including many sentences telling us very appropriately what steps we need to take to unravel the cause of this common problem. Malcolm Steiger and Hiliary Tyne continue the series on apomorphine, this time outlining the role of the neurologist and the need to educate patients and public alike about this drug and its efficacy, and Tipu Aziz and Dipander Nandi present their results for the neurosurgical treatment of patients with intractable pain. We have our usual journal and book reviews, as well as conference reports. So another packed issue, hopefully of the kind of articles that you want to read (DO fill in the readers questionnaire included with this issue), but if not let us know! Oh yes., and don't forget the web site is now up and running, so why not visit *www.acnr.com* when you next have 5 minutes to spare?

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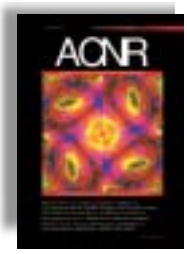

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Neurological complications of Behçet's syndrome

Dr Desmond Kidd is a Consultant Neurologist at the Royal Free Hospital, London. He trained in Belfast, St Thomas' and the National Hospitals. His research interests involve the natural history and pathophysiology of Neurosarcoidosis and neurological complications of Behçet's syndrome, and Neuro-ophthalmology.

Introduction

Behçet's syndrome is an episodic disorder of unknown aetiology or pathogenesis characterised by recurrent oral and genital ulceration and panuveitis. Skin involvement manifest as erythema nodosum, pustular eruptions or pseudofolliculitis, is common and pathergy occurs in some 50% of cases. An oligoarthropathy of large joints (knees, ankles and shoulders) can also be a feature of the illness along with lung, gastrointestinal and renal involvement, although this is rare. Malaise, fatigue and loss of weight are frequent associated symptoms[1].

Behçet's syndrome is most common in the countries around the eastern shores of the Mediterranean Sea and Eastern Asia. In Japan the prevalence was 7/10^5 in 1974[2] although in Turkey[3] in 1988 the prevalence was found to be higher in rural than urban areas at 37/10^5 *vs* 8/10^5 respectively. There has been only one published survey of the disease in the UK[4] in which the prevalence in part of Yorkshire was found to be 0.4/10^5, although more recently the prevalence in Hertfordshire[5] has been found to be higher at 5/10^5.

This latter study[5] identified a prevalence of neurological complications of 0.75/10^5, whilst previous studies, using retrospective data, have shown a much higher prevalence of neurological involvement at 5.3% to 25%[6-8], the latter figure being supported by an autopsy series in which 20% of 170 cases of patients with Behçet's syndrome showed pathological evidence for neurological involvement[9].

The diagnostic criteria[10] are summarised in the table and although it is specified that recurrent oral ulceration is a prerequisite, cases do exist in which pathologically proven Behçet's syndrome occurs without oral ulceration;. Nevertheless the criteria are said to exclude only 3% of patients in whom recurrent oral ulceration is not a feature.

Clinical syndromes

Neurological involvement occasionally arises at the time of first presentation of the systemic disease[12] and more rarely precedes it[12,14], but typically presents during the course of established disease. These neurological syndromes occur either as a result of the development of inflammation within the central nervous system – so-called parenchymal involvement – or as a result of vascular complications within the nervous system.

The neurological syndrome which develops most frequently is due to a lesion within the brain stem[11,12], and accounts for 25%-50% of all parenchymal lesions in large published series[11,12,14,15]. This often arises in the midbrain or pons (figure) with the patient developing a subacute ophthalmoplegia with ataxia. Involvement of the medulla is less common and whilst isolated cranial neuropathies also occur[11], optic neuropathy is rare.

Hemispheric involvement due to inflammatory infiltration of white and grey matter structures may lead to hemisensory symptoms or hemiparesis but only a minority of patients develop seizures[13]. A subacute encephalopathy frequently complicated by psychosis may also arise.

Spinal cord involvement may be severe with transverse myelitis or with partial involvement and an isolated sensory syndrome. Involvement of muscle, peripheral nerves, and nerve roots with a polyradiculopathy have all been reported, although these are rare features of this condition (reviewed in [11]).

Symptoms of meningitis are more rare than was once thought; isolated aseptic meningitis arose in only 4/50 patients in one series[11] and 3/40 in another[14], but headache and photophobia often precede and coexist with the symptoms of the lesion. Indeed headache is an exceedingly common symptom which is independent of vascular complications (see below) and the presence of abnormalities on MRI scans[21]. The headache syndrome is typically migrainous in nature with a high prevalence of visual and sensory aura[22].

Vascular complications as a result of dural venous sinus thrombosis occur in about 16% of cases[11,12,14,15,16], and is found in 80% of cases with isolated intracranial hypertension[17-19] and the CSF is in general inactive[11]. Arterial thrombosis is more rare, and aneurysm formation has been reported[20].

Investigation results

MRI findings show a close clinico-radiological correlation[23] with a single lesion being the most common abnormality seen. Frequently the lesion diminishes strikingly in size following treatment and recovery[24] .

The cerebrospinal fluid is often abnormal during an acute attack with a raised protein and a CSF leucocytosis which can be in excess of 100 cells per ml. Neutrophils are common early in the illness, with lymphocytes predominating later[11,12]. Oligoclonal bands are not found.

Neuropathology

The neuropathology is of a chronic meningoencephalitis, with inflammatory cell infiltration and circumscribed

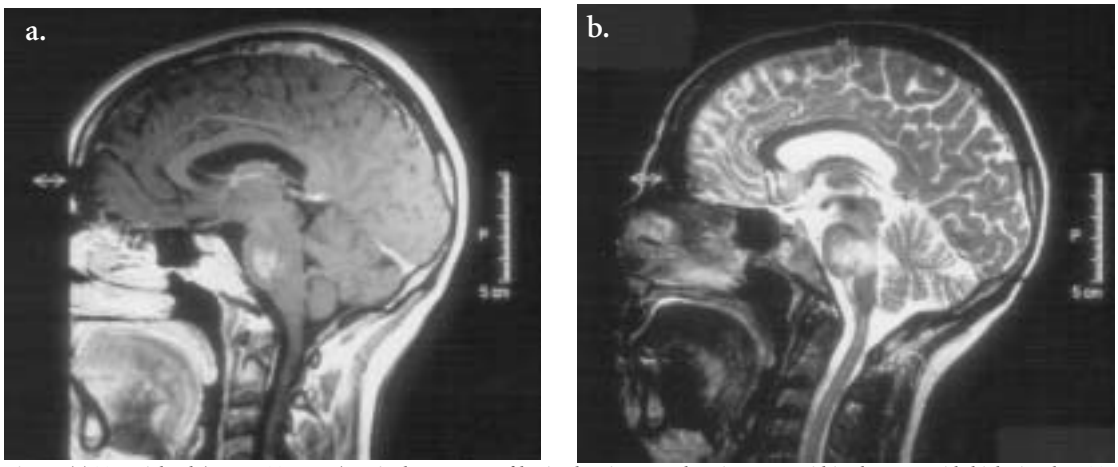
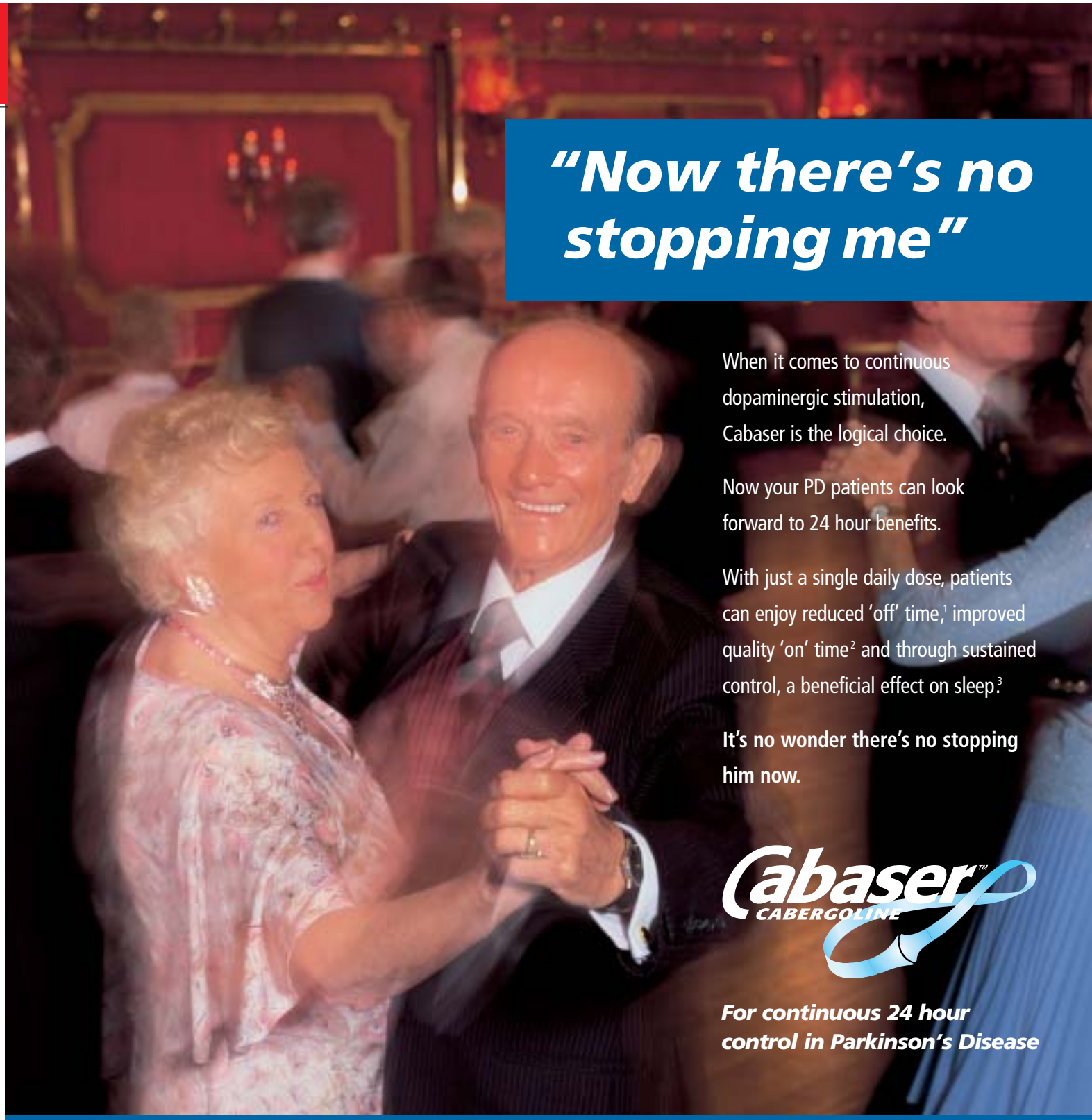


Figure: (a) T1 weighted (490ms, TE 20ms) sagittal MRI scan of brain showing an enhancing mass within the pons with high signal on T2 weighted images (TR 2000ms, TE 130ms) (b).



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areas of necrosis with loss of all tissue elements, accumulation of lipid-laden macrophages and gliosis[25]. There is a marked infiltration by neutrophils and eosinophils as well as lymphocytes, and there is at times marked axonal degeneration within lesions[26]. No evidence for vasculitis has been found in this or other pathological studies aside from one report of fibrinoid necrosis within small post-capillary venules. This was not however seen in adjacent arterioles[27].

Natural history and prognosis

Four papers provide reasonable details on the natural history of the disorder; which taken together reviews 454 patients seen over ten years[11,12,14,15]. The majority (77%) had parenchymal disease in which there was involvement of the brain, brainstem or spinal cord. 41% had only single attacks[11,15], most others went on to have further attacks or to develop a progressive disease course (some 25%), often with superimposed relapses[11,12,15], although approximately 10% of patients present with a primarily progressive disease course, without relapses. Others have "silent" lesions; patients without symptoms of neurological involvement who nonetheless have abnormal neurological signs which are not attributable to an alternative disease process (about 20% in one series)[12].

The prognosis in this condition seems to be related to number of attacks, the degree to which recovery occurs with each attack, whether there is brainstem involvement and the presence of a progressive disease course[12,15]. In two studies[11,12] CSF white cell count at the time of presentation was correlated with subsequent outcome, although this remains unproven.

In one series the median time to death or dependent disability in those followed for three or more years was only 115 months[12], although in another[15] the ten year survival was 96%.

The prognosis for neurological complications related to vascular disturbances is in general much better; those presenting with intracranial hypertension on its own when treated tend not to develop recurrences, nor do patients with vascular occlusive complications. Formerly it appeared that such patients did not develop other neurological complications and vice versa but new data suggest that patients may at different times develop both forms of neurological complication and indeed some may present with parenchymal and vascular complications simultaneously (Al-Araji and Akman-Demir, personal communications).

Table: International Study Group for Behçet's disease (ISG) criteria; patients who fulfil these criteria must have two or more of the features noted.

Recurrent minor or major aphthous or herpetiform ulceration of the mouth	
plus	recurrent genital ulceration
	erythema nodosum
	pseudofolliculitis
	papulopostular eruption
	aceiform nodules
	positive pathergy test
	anterior or posterior uveitis
	retinal vasculitis

Treatment

No reasonable treatment trial has been carried out for any neurological complication of the syndrome, however uveitis has been studied carefully, and there are many histological and immunological similarities. These studies have shown that use of corticosteroids is often helpful but that other immunosuppression is usually also required. Azathioprine, methotrexate, Cyclosporin A, Chlorambucil and Cyclophosphamide have all been used with success in ocular complications. More recently Interferon⁄ 2a[28] and infliximab[29] have been used with success even in patients seemingly resistent to other immunosuppressants. These two new drugs are currently being tested in large blinded trials in Europe and the US.

Concluding comments

Neurological complications of Behçet's syndrome are rare; the majority arise as a result of inflammation of parenchymal structures, the others as a result of vascular complications. Most patients recover well and suffer only single attacks although others develop increasing impairments due to repeated attacks and/or to a progressive disease course. Immunosuppression can stabilise the disease in some but not all patients. Further studies are required which identify more clearly the pathophysiology of neurological involvement in this uncommon condition.

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Looking at protein misfolding neurodegenerative disease through retinitis pigmentosa

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Dr Mike Cheetham, Senior Lecturer, Institute of Ophthalmology, UCL, developed his interest in molecular chaperones and neurodegeneration whilst doing his PhD with Professor Brian Anderton on the molecular biology of Alzheimer's disease. He has been at the Institute of Ophthalmology since 1995 and now researches the role of chaperones in retinal degeneration.

Characteristics of Retinitis Pigmentosa

Retinitis pigmentosa (RP) describes a genetically heterogeneous group of retinal dystrophies that are characterised by progressive degeneration of photoreceptor cells in the retina (see RetNet, http://www.sph.uth.tmc.edu/RetNet/disease.htm). RP is the most common cause of inherited blindness, and is estimated to affect one in every 4000 individuals. For recent reviews of RP and related retinal degenerations see[1,2].

Patients with RP lose vision because of the death of both rod and cone photoreceptors. The disease is thought to primarily compromise the function of rod photoreceptors and ultimately triggers apoptosis of these neurons. As rod cell death progresses, cone cell viability is reduced and further photoreceptor cell death occurs. Clinical examination by electroretinography reveals a reduced response from rod photoreceptors (the dim light or 'scotopic' response) early in disease and later a defect in the cone photoreceptors (the daylight or 'photopic' response), confirming rods as the primary site of pathology. As the disease progresses examination of the retina typically shows pigmentation in a 'bone-spicule' pattern, pallor of the optic disc and narrowing of retinal blood vessels.

There is a large diversity in the function of the gene products that have been implicated in RP, which reflects the complexity of the retina and photoreceptor specialisation. These include genes encoding proteins of the phototransduction cascade (for example, rhodopsin; the subunit of rod cyclic GMP phosphodiesterase; the subunit of the rod cyclic GMP-gated channel and arrestin). RP genes also encode structural proteins of the photoreceptor disc outer segment, (RDS-peripherin and Rom 1); components of the retinoid cycle; extracellular matrix proteins; proteins involved in cell adhesion; and transcription factors (CRX, NRL and TULP1). The disease also occurs as a component of syndromes such as Bardet-Biedl[3] and Usher's[4]. In Usher's syndrome (types 1A and 1B) mutations in the genes for harmonin and myosin V11a affect hair cells of the inner ear and photoreceptors. Ubiquitously expressed RP proteins, which do not cause systemic disease, have also been identified. These include RP2, which is targeted to the plasma membrane. Mutations in RP2 which prevent this localisation cause an RP phenotype[5,6]. The role of RP2 in photoreceptors remains unclear, but it has been shown to have functional overlap with co-factor C a cellular chaperone involved in tubulin folding[7,8].

This review focuses on the most prevalent form of RP, which is caused by mutations in rhodopsin, the receptor responsible for dim light photoreception in the vertebrate retina. More than 150 distinct mutations in rhodopsin have been identified [OMIM 180380] which together account for 15% of all inherited retinal disease[9]. The majority of mutations in rhodopsin cause autosomal dominant RP.

Misfolding of rhodopsin; toxic proteins and aggregation

Rhodopsin, the prototypical seven transmembrane G-protein coupled receptor[10], consists of the apoprotein opsin covalently bound to the 11-*cis*-retinal chromophore. It represents a major protein product of rod photoreceptors and accounts for over 70% of the total protein in the outer-segments where rhodopsin dimers tightly pack the disc membranes[11].

Rhodopsin mutations can be divided into two categories on the basis of the mechanism of pathogenesis. Mutations at the C-terminus of the protein interfere with its normal targeting to the photoreceptor outer-segment12, whereas mutations in the transmembrane, intradiscal or cytoplasmic domains result in the misfolding of the protein13. The first misfolding mutation identified in rhodopsin (also the most frequent ADRP mutation in the US population) is a proline to histidine change at residue 23 (P23H). Studies in cultured cells have revealed that misfolded rhodopsin (P23H) undergoes retrotranslocation from the endoplasmic reticulum (ER) and degradation by the ubiquitin-proteasome system14,15. Saturation of the normal proteolytic machinery causes misfolded ubiquitinated rhodopsin to accumulate in pericentriolar cytoplasmic inclusion bodies, known as aggresomes14,15 (Figure. 1). The formation of aggresomes has been shown to be dependent on transport of misfolded proteins by dynein dependent retrograde transport on microtubules16.

The aggregation and deposition of abnormal protein has recently been identified as a common characteristic of a broad range of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), prion encephalopathies and polyglutamine diseases such as Huntington's disease (HD)[17,18]. Pathogenic mutations are associated with a toxic gain of function in polyglutamine diseases[19] and some other protein misfolding diseases. We have proposed that misfolded rhodopsin also acquires a gain of function that leads to cell death[9]. The role of aggregated protein deposits in disease pathogenesis is unclear and there has been considerable debate whether they are pernicious, coincidental or beneficial and this is also the case for rhodopsin aggregates and inclusions.

The cellular molecular chaperone machinery plays a vital role in the cellular

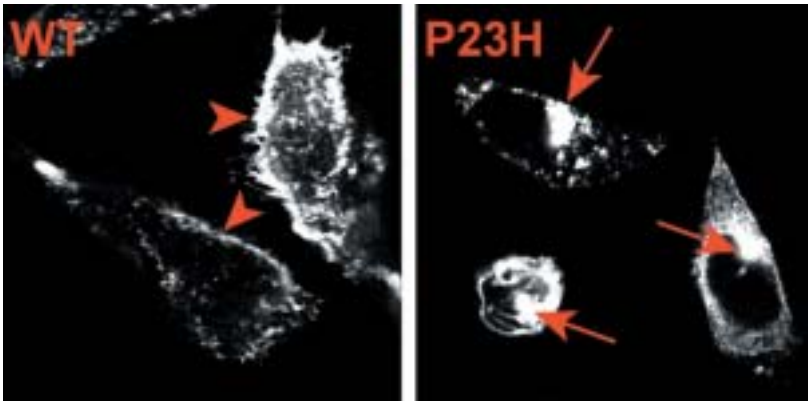

Figure 1. Comparison of the localisation of wild-type rhodopsin and rhodopsin with the misfolding mutation, P23H, in cultured neuronal cells. Wild type protein translocates to the plasma membrane (arrowheads), whereas protein with the P23H mutation forms inclusion bodies, known as aggresomes (arrows).

response to misfolded proteins[20] and have been shown to play a critical role in several neurodegenerative disorders[21]. Molecular chaperones and components of the ubiquitin-proteasome degradation system are present in the aggregates of misfolded protein. Molecular chaperones are known to be involved in rhodopsin folding in *Drosophila* and have been shown to be present in rhodopsin aggresomes[9,14].

Improving rhodopsin folding; molecular chaperones a potential therapy

The common characteristics of neurodegenerative protein misfolding diseases suggests parallel approaches to treatment based on an understanding of the normal cellular mechanisms for disposing of unwanted and potentially toxic proteins[18]. The role of chaperones in correct protein folding and protein degradation clearly identifies their manipulation as a potential therapy for RP. In cellular models of polyglutamine disease overexpression of members of the Hsp70 and Hsp40 families of chaperones have been shown to suppress the toxicity and aggregation of polyglutamine containing proteins. We have recently identified a member of the Hsp40 family of chaperones (HSJ1b) which has a neuronal expression pattern and is enriched in photoreceptor inner-segments, the site of rhodopsin biogenesis. HSJ1b is localised to the cytoplasmic face of the endoplasmic reticulum and will thus encounter cytoplasmic domains of rhodopsin *in vivo*. We tested whether HSJ1b could enhance the folding of mutant rhodopsin. In fact the chaperone caused wild type rhodopsin to be retained in the ER and increased the incidence of aggresome formation for both wild type and P23H rhodopsin (Chapple and Cheetham, submitted). These data provide evidence that cytoplasmic chaperones can influence the folding and processing of rhodopsin. Understanding the specialised chaperone networks within photoreceptors will be essential to exploit the potential of cellular chaperone machines to manipulate the folding of normal and mutant rhodopsin.

Several pharmacological agents have been identified that can manipulate chaperone expression/function, such that gene transfer mediated overexpression may not be required to use chaperones in RP therapies[9]. As cell death in RP, and many other neurodegenerations, is via apoptosis[22], it is tempting to speculate that blocking a caspase cascade or similarly disrupting cell death pathways may be of therapeutic benefit. Chaperones play an important role in many cellular signalling pathways and could also provide a mechanism for suppressing signalling cascades which lead to apoptosis[21].

In addition to manipulating molecular chaperones, there is the potential to manipulate protein folding by 'chemical chaperones' or stabilise protein structures using ligands. Indeed, the folding of mutant rhodopsin has been improved by the natural ligand retinoids. The addition of 11-*cis*-retinal and 9-*cis*-retinal to T17M mutant opsin expressing cells has been shown to improve folding[23].

We have also shown that addition of 9-*cis*-retinal to cultures expressing P23H mutant opsin improves the amount of opsin that reaches the plasma membrane, whilst having no effect on K296E mutant opsin[14]. Addition of a modified retinoid, 11-*cis*-7-ring-retinal, has also been shown to improve the folding of rhodopsin containing the P23H mutation[24]. These data suggest that retinoids may be used as 'chemical' chaperones that can stabilise the folding of mutant opsins shifting the equilibrium away from aggregation and towards functional protein. High doses of vitamin A have already been shown to be of some therapeutic benefit in RP[25].

This clinical trial, however, was not focused on patients with misfolding mutations in rhodopsin and if it had been the clinical outcomes might have been even better. Further investigation of methods to stabilise and promote the correct folding of mutant rhodopsin, either through chemical chaperones or molecular chaperones, may lead to novel therapies for protein misfolding diseases which can be tested on the most accessible part of the CNS, the retina.

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Muscle ion channel diseases

The inherited muscle ion channel diseases (muscle channelopathies) are a group of disorders of skeletal muscle membrane excitability characterised by variable muscle stiffness and/or intermittent weakness. Myotonia is a common but not universal feature of these disorders which are nevertheless distinct from the myotonic dystrophies (Table 1). External and environmental factors can be important triggers to attacks or lead to worsening of symptoms and may include alterations in serum potassium levels, reduction in ambient temperature and muscle activity, particularly when followed abruptly by rest. Common muscle channelopathies are the result of chloride, sodium and calcium channel dysfunction and are therefore amenable to therapeutic interventions.

ABBREVIATIONS USED IN THIS ARTICLE

MC	myotonia congenita
PMC	paramyotonia congenita
PAM	potassium-aggravated myotonia
HyperPP	hyperkalaemic periodic paralysis
HypoPP	hypokalaemic periodic paralysis

Presentations

MYOTONIA AND PARAMYOTONIA

Myotonia is the phenomenon of delayed relaxation of skeletal muscle following voluntary contraction (see Box below). Affected individuals may report muscle **stiffness** or an **inability to relax** their muscles after contraction. Stiffness may be mildly worse in the cold or after prolonged periods of rest but diminishes with repeated muscle contractions, the so -called **warm-up phenomenon**.

The classic clinical findings are an **inability to relax** after prolonged contraction (eg handgrip) and **percussion myotonia**, spontaneous muscle contraction after direct percussion (eg abductor pollicis brevis). **Lid-lag** may be seen on suddenly looking downwards after prolonged upwards gaze. These findings become less marked with repetition but reappear after rest.

In contrast to myotonia, muscle stiffness in **paramyotonia** is precipitated rather than ameliorated by exercise. This is the opposite of the warm-up phenomenon in myotonia (hence *paradoxical* myotonia or *para*myotonia). Paramyotonia is also particularly temperature-sensitive. Marked exacerbation by cold and exercise is useful clinically in distinguishing paramyotonia from myotonia.

WEAKNESS

Episodic weakness is seen in many of the muscle channelopathies and is a hallmark feature of the periodic paralyses. Individuals may experience not only **generalised limb** weakness but also single limb, hemibody or very focal muscle weakness. Bulbar and respiratory musculature are either spared or insufficiently affected to be clinically significant.

Attacks of weakness most commonly occur in the morning after **waking from sleep** but can be **triggered** by stress, fasting (sodium channelopathies) or a carbohydrate meal (hypokalaemic periodic paralysis). Exercise followed by rest is a potent trigger for attacks of weakness in all forms of periodic paralysis. Cold exposure can trigger an episode of weakness in the periodic paralyses and, particularly dramatically, in paramyotonia congenita.

Depressed tendon reflexes during an attack are an important clinical pointer to the organicity of 'generalised limb weakness' caused by periodic paralysis. Some patients with periodic paralysis develop a fixed myopathy which can be significantly disabling. A mild fixed weakness can develop in patients with myotonia congenita and paramyotonia congenita.

MUSCLE HYPERTROPHY

Muscle hypertrophy is a characteristic feature of myotonic disorders and is a direct result of muscle overactivity. This is very different from the muscle pseudohypertrophy seen in some of the dystrophinopathies: the 'true' hypertrophy of myotonic disorders results in increased muscle strength. Some individuals are able to participate in sports requiring strength rather than speed or endurance (eg Thomsen-type myotonia).

Chloride channelopathies

The primary membrane defect in myotonia congenita (MC) is reduced chloride conductance. Mutations in the *CLCN-1* gene encoding the ClC-1 muscle voltage-gated chloride channel can give rise to allelic disorders with autosomal dominant or recessive modes of inheritance. It is interesting to note that recent evidence suggests the myotonia in myotonic dystrophy is caused by altered expression of the same chloride channel secondary to abnormal RNA aggregation.

MYOTONIA CONGENITA

Becker-type myotonia (recessive MC) is more common and is usually more severe. Muscle stiffness may be worse in the cold, although never to the extent seen in paramyotonia, and improves with exercise. Onset is usually in the

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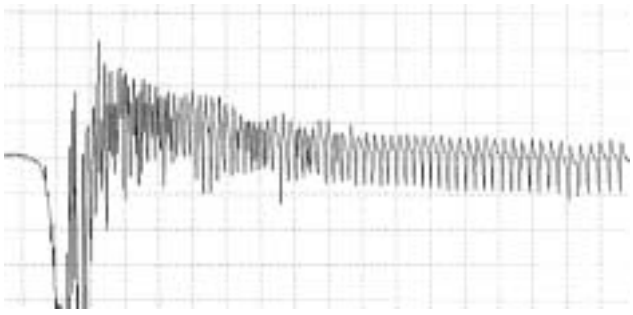
MYOTONIA



A characteristically waxing and waning myotonic waveform. This particular discharge is made up of positive sharp waves.

The morphology of myotonic discharges can be of fibrillation potentials (spikes) or positive sharp waves (see waveform). This allows the source generator to be identified as muscle as distinct from spontaneous activity arising in the motor nerve which has the morphology of a *motor unit* action potential. *Neuro*myotonia, caused by abnormal firing of the *motor nerve*, bears some clinical resemblance to myotonia (stiffness, delayed muscle relaxation, 'true' muscle hypertrophy). However, the shape and frequency of discharges in neuromyotonia are easily differentiated from myotonic potentials in the EMG laboratory.

Normal muscle at rest is electrically silent outside the end-plate zone. Electrophysiological myotonia is caused by spontaneous repetitive discharges of a single *muscle fibre*. Myotonic discharges have a waxing and waning quality that gives rise to the characteristic "dive-bomber" or "chain-saw" sound heard in the EMG laboratory. They are a defining feature of both the dystrophic and non-dystrophic myotonic myopathies (Table 1) but they may also be found in acid maltase deficiency, polymyositis and centronuclear myopathy.

DR. ALOIS ALZHEIMER

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Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** ***Pregnancy.*** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. ***Lactation:*** Excretion into breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine -type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £68.32. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £95.76. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** January 2002.

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DYSTROPHIC MYOTONIC MYOPATHIES	*myotonia*	*periodic weakness*	*potassium sensitivity*	*progressive weakness*	*distinctive features*
*non-primary channelopathies**					
MYOTONIC DYSTROPHY	+	-	-	+	extramuscular features
PROXIMAL MYOTONIC MYOPATHY	+	-	-	+	extramuscular features
MYOTONIC CHANNELOPATHIES *(non-dystrophic)*					
*chloride channelopathies**					
RECESSIVE MYOTONIA CONGENITA (BECKER'S-TYPE)	+	(+)	-	(+)	lower limb onset
DOMINANT MYOTONIA CONGENITA (THOMSEN'S-TYPE)	+	-	-	-	generalised onset
sodium channelopathies					
PARAMYOTONIA CONGENITA	+	+	-	-	extreme cold sensitivity
HYPERKALAEMIC PERIODIC PARALYSIS	+	+	+	(+)	triggered by fasting
POTASSIUM-AGGRAVATED MYOTONIA	+	-	+	-	triggered by potassium ingestion
NON-MYOTONIC CHANNELOPATHIES					
potassium channelopathy					
ANDERSEN'S SYNDROME	-	+	+	-	cardiac/dysmorphic features
calcium channelopathies					
HYPOKALAEMIC PERIODIC PARALYSIS	-	+	+	(+)	triggered by carbohydrate ingestion
MALIGNANT HYPERTHERMIA	-	-	-	-	triggered by anaesthetic agents

Table 1: Inherited muscle ion channel diseases and related disorders

**NOTE: The myotonia in the myotonic dystrophies appears to result from altered expression of the muscle voltage-gated chloride channel. Chloride channelopathies can occasionally be associated with a dystrophic biopsy.*

second decade and the condition progresses slowly over years. The lower extremities are affected first, giving rise to a disproportionate figure with calf and gluteal muscle hypertrophy but relatively poorly developed neck and shoulder girdle muscles. Grip and percussion myotonia and the lid-lag phenomenon are easily elicited. **Thomsen-type myotonia** (dominant MC) develops in infancy or early childhood with a generalised onset in the limb girdles, calves and facial muscles.

MC is distinguished from myotonic dystrophies by the absence of extramuscular features and the lack of prominent weakness (Table 1). Distinguishing dominant and recessive forms of MC depends on both the distribution of symptoms and the examination of all family members but may be difficult. While later in onset, the recessive form is usually more disabling and may exhibit the following features: (1) more severe myotonic stiffness; (2) episodes of focal short-lived weakness precipitated by sudden movements after a period of prolonged rest; (3) minor distal wasting and weakness.

Sodium channelopathies

Mutations in *SCN4A* gene encoding the Skm-1 skeletal muscle voltage-gated sodium channel can cause four different skeletal muscle channelopathies paramyotonia congenita (PMC), hyperkalaemic periodic paralysis (HyperPP), hypokalaemic periodic paralysis (HypoPP) and occasionally potassium-aggravated myotonia (PAM), although HypoPP is more commonly the result of mutations in the skeletal muscle calcium channel (see below). PMC and HyperPP may occur in the same kindred. The diseases are inherited in an autosomal dominant fashion, usually with complete penetrance.

PARAMYOTONIA CONGENITA

Symptoms of PMC start in infancy and primarily affect bulbar, facial, neck and hand muscles. In contrast to myotonia, stiffness can be precipitated by exercise and is often followed by a period of true weakness. Cold sensitivity is typically much more extreme than in myotonia. Characteristic presentations include blepharospasm after prolonged crying and tongue stiffness after eating an ice cream. Symptoms of paramyotonia are usually static through life but attacks of weakness and hyperkalaemia may appear during adolescence.

HYPERKALAEMIC PERIODIC PARALYSIS

Patients with HyperPP have episodes of generalised weakness lasting minutes up to 1 hour beginning in the first decade of life. Attacks can occur on waking and can be precipitated by the cold, fasting, rest after exercise, emotional stress and potassium ingestion (eg fruit juices). Symptoms improve with an oral carbohydrate load, mild exercise and inhaled €-agonists. Bulbar and respiratory musculature is characteristically spared. Depressed deep tendon reflexes during an attack are a key clinical finding and the serum potassium is usually raised (4.5-8.0 mM) if it is measured early in an attack. Coexisting paramyotonia may be present.

POTASSUM-AGGRAVATED MYOTONIA

Some individuals with sodium channel mutations present with symptoms of myotonia which, unlike MC, are potassium-sensitive. Several variants of PAM (also known as sodium channel myotonia) have been described. The myotonia can be painful, can fluctuate and may be induced by exercise but the variants share the characteristic of being worse after potassium ingestion (eg fruit juices). Unlike other sodium channelopathies, however, there is no true weakness and symptoms are not usually worse in the cold.

Calcium channelopathies

Pathological mutations are recognised in two different muscle calcium channels. Mutations in the non-voltage-sensitive ryanodine receptor gene (*RYR1*) encoding a sarcoplasmic reticulum calcium channel involved in excitation-contraction coupling cause malignant hyperthermia

which can be associated with central core disease (cf. Rakowicz (2003): ACNR 2(6):11-13). Pathogenic mutations in the dihydropyridine receptor gene (*CACNA1S*) encoding the muscle voltage-gated calcium channel give rise to HypoPP. The disease is inherited with autosomal dominant inheritance but with reduced penetrance in women. Recently HypoPP has also been reported in association with mutations in exon 12 of the *SCN4A* gene encoding the muscle voltage-gated sodium channel.

HYPOKALAEMIC PERIODIC PARALYSIS

HypoPP is the commonest inherited periodic paralysis. As in HyperPP, episodes of weakness can be triggered by the cold, prolonged rest, rest after exercise and emotional stress but are usually of longer duration (hours to days). Unlike HyperPP heavy meals rather than fasting predispose the individual with HypoPP to an attack and there may be a characteristic history of weakness occurring on waking on the day after a large meal. Depressed deep tendon reflexes during an attack are a key clinical finding and the serum potassium is usually depressed (2-3 mM). Although attacks may be very mild and kindreds frequently include asymptomatic individuals, compromised respiratory function has occasionally been reported. The presence of even asymptomatic myotonia excludes the diagnosis of HypoPP.

An important differential diagnosis of HypoPP is **symptomatic hypokalaemia**. 'Secondary' HypoPP is seen most frequently in the context of treatment with potassium-wasting diuretics but can be the result of primary hyperaldosteronism, inadequate dietary intake, excessive potassium loss (sweat, gastrointestinal and renal) and chronic liquorice ingestion. Usually in symptomatic hypokalaemia the patient is persistently weak rather than experiencing attacks of weakness. In some Far-Eastern populations hyperthyroidism can lead to attacks of weakness with a depressed serum potassium concentration which are very similar to HypoPP but the cause is unknown.

Potassium channelopathies

Two muscle potassium channelopathies are now recognised. A rare form of HyperPP is described in association with mutations in the MinK gene. A more common potassium channelopathy is Andersen's syndrome caused by mutations in the *KCNJ2* gene encoding the muscle voltage-independent potassium channel Kir2.1.

ANDERSEN'S SYNDROME

The diagnosis of **Andersen's syndrome** is based on a triad of (1) periodic paralysis; (2) prolonged QT interval or ventricular arrhythmias; (3) dysmorphic features. The attacks of paralysis may be accompanied by a reduced, normal or raised serum potassium level. Cardiac involvement varies from the asymptomatic to cardiac arrest in childhood and requires close cardiological supervision. Dysmorphic features include short stature, low-set ears, hypertelorism, micrognathia, a short index finger and syndactyly of the toes. It is important to note that dysmorphic features may be subtle and that cardiac complications can present at any age. Therefore in any patient with periodic paralysis a careful search for dysmorphic features should be undertaken as well as a 12-lead ECG.

Investigations

LABORATORY TESTING

Serum CK may be mildly raised in many of the muscle channelopathies but is not diagnostically useful. Serum potassium levels during an episode of weakness may be depressed, normal or raised in potassium-sensitive disorders but should be normal in between attacks unless a secondary disturbance of potassium handling is present. Important secondary causes to consider include potassium-wasting diuretics, primary hyperaldosteronism, inadequate dietary intake, excessive sweating, diarrhoea, kidney dysfunction and chronic liquorice ingestion. A 12-lead ECG should be performed in every individual with periodic paralysis to exclude cardiac conduction defects. Muscle biopsy is generally not required although a lack of Type2B fibres is recognised in MC and slowly progressive proximal muscle weakness in HypoPP is accompanied by a vacuolar myopathy.

DNA-BASED DIAGNOSIS

DNA-based diagnosis is now the most rapid, accurate and safe method to achieve a diagnosis. An accurate genetic diagnosis is important not only to confirm a clinical diagnosis but also because it allows correct genetic counselling and guides therapeutic options. In the UK genetic diagnosis is now available for all the channelopathies described in this article (see Footnote).

NEUROPHYSIOLOGY

Nerve conduction studies are normal except for compound motor action potentials (CMAPs) which are depressed *during* an attack of periodic paralysis. Muscle fibre action potentials are generally normal but mild myopathic changes may be seen in Thomsen-type myotonia and late in the course of the periodic paralyses. **Myotonic discharges** are a cardinal feature of the myotonic myopathies (see Box), may be present in some cases of HyperPP and exclude a diagnosis of HypoPP. Initial transient dense fibrillations followed by electrical silence (prolonged contracture) on **muscle cooling** (20°C) are diagnostic of PMC. Changes in CMAP amplitude during and after short and prolonged **exercise testing** can be helpful in the diagnosis of MC and the periodic paralyses.

Treatments

Acute and prophylactic treatments can be used in the muscle channelopathies. Patients with mild MC may not require treatment. However, most MC and PMC patients will benefit significantly from antimyotonic treatment and in our experience the antiarrhythmic drug mexiletine is easily the most effective. Pretreatment ECG is important.

Acute attacks of HyperPP can be treated at onset with continued slight exercise or ingesting carbohydrates. Lifestyle preventive measures in HyperPP may be helpful. Prevention of attacks can usually be achieved with carbonic anhydrase inhibitors, either acetazolamide or dichlorphenamide. Thiazide diuretics may also be useful preventive agents. €-agonists such as salbutamol have a useful role to play in preventing HyperPP attacks in certain patients.

Mild attacks of HypoPP need no treatment but potassium chloride may be given orally (but not in a carbohydrate-containing drink) in more severe attacks. Intravenous potassium replacement is not usually required and may be hazardous. Attacks of HypoPP are best prevented by avoiding carbohydrate-rich meals and heavy exercise but carbonic anhydrase inhibitors are often effective.

A case study on Andersen's syndrome will soon be available on our web site. See www.acnr.com for more information.

ACKNOWLEDGEMENTS
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FOOTNOTE
A national clinical and diagnostic service is available at the Centre for Neuromuscular Disease at the National Hospital for Neurology & Neurosurgery. This service is funded by the Department of Health through national specialist commissioning and any patient in the UK can be referred for this service. Further details are available from Dr MG Hanna mhanna@ion.ucl.ac.uk

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Domiciliary ventilation in neuromuscular disorders - when and how?

Dr John Shneerson is Consultant Physician and Director of the Respiratory Support and Sleep Centre at Papworth Hospital which is one of the largest units dealing with respiratory complications of neuromuscular disorders in the UK. His specialist interests are the physiology and consequences of respiratory failure in neuromuscular disorders and the development and assessment of new forms of treatment.

Introduction

Respiratory failure used to be regarded as a pre-terminal complication of neuromuscular disorders and respiratory support was usually withheld for both practical and ethical reasons. Modern developments, particularly new techniques of non invasive ventilation, have radically altered this view.

Respiratory failure develops in neurological disorders when the load on the respiratory pump exceeds its capacity. The arterial PCO2 rises as the alveolar ventilation falls and the PO2 drops in proportion. The respiratory pump fails during sleep before wakefulness[1], and this usually occurs when the vital capacity falls to around 1 litre. In non rapid eye movement (NREM) sleep the fall in respiratory drive and the increase in upper airway resistance both tend to reduce alveolar ventilation. In rapid eye movement (REM) sleep the loss of tone in all the respiratory muscles, except the diaphragm, predisposes to apnoeas, especially if the diaphragm itself is weak.

VENTILATORY TECHNIQUES

The management of neuromuscular respiratory problems has been revolutionised by the development of non invasive ventilatory support techniques, although these were initially developed for acute poliomyelitis as long ago as the 1920s. Ventilatory support is usually only required during sleep, but almost continuous support is required if the respiratory muscle weakness is severe as in high cervical spinal cord injuries, in the later stages of motor neurone disease, or Duchenne's muscular dystrophy. It is essential to fully educate the patient and the carers and to provide a home care package which is sustainable bearing in mind the current and projected disabilities of the patient.

> “Non invasive ventilation not only normalises the blood gases during the night.., but also during the day. Breathlessness, ankle swelling, daytime sleepiness and exercise ability all improve.”

1. Mask Ventilation

This is usually the treatment of choice for domiciliary ventilatory support. Both pressure and volume preset ventilators are usually effective and positive end expiratory pressure (PEEP) is only required if there are also obstructive sleep apnoeas. Supplemental oxygen should not be required unless the arterial PO2 cannot be normalised by ventilatory support alone[2]. A nasal mask (fig 1) is usually preferable to a full face mask or a mouthpiece. Complications such as nasal ulcers, mask displacement, air leaks or upper airway obstruction may arise.

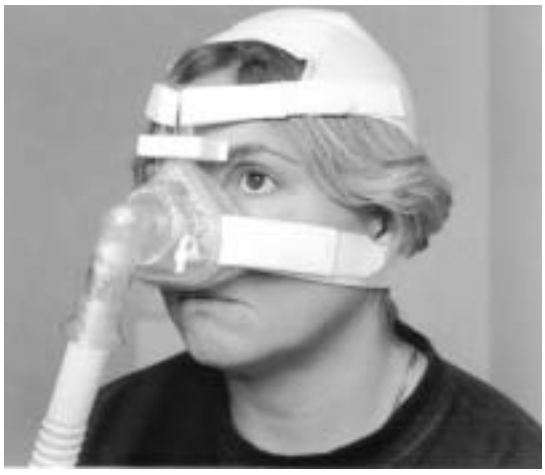

Figure 1. Nasal Mask Ventilation

2. Negative Pressure Ventilation

A cuirass or jacket (poncho) type of negative pressure ventilator (fig 2) is preferable to the much larger tank (iron lung) ventilators for long-term use[3]. Both these techniques however have the disadvantage that the subjects have to lie on their back throughout the night and have a restricted range of movements[4]. There may be difficulties in fitting a cuirass or jacket to patients with a severe scoliosis secondary to muscle weakness. Negative pressure ventilation is usually used in the controlled rather than triggered mode, so that incordination between the patient and ventilator may develop and lead to upper airway obstruction.

c. Tracheostomy Ventilation

This is required if there is upper airway obstruction, if the airway needs to be protected because of bulbar weakness, or if ventilatory support is required virtually continuously. A cuffed tube protects the airway, but the voice is lost unless the cuff can be partially or totally deflated. Tracheostomy ventilation, while effective, impairs the quality of life more than non invasive ventilation and requires a higher level of care in the home. Nevertheless it can be used successfully, particularly in those with high cervical spinal cord injuries and occasionally in motor neurone disease, although in this disorder mask ventilation is preferable whenever it can be applied successfully[5].

d. Phrenic Nerve Stimulation (Diaphragmatic Pacing)

Phrenic nerve pacing is only indicated if the phrenic nerve is intact, diaphragm muscle function is not permanently impaired and respiratory mechanics are not grossly abnormal[6]. It is most valuable with high cervical spinal cord lesions where it can significantly increase the quality of life, mobility and speech compared with conventional tracheostomy ventilation. It can also be effective when brain stem disorders cause central alveolar hypoventilation, but simpler alternatives such as mask ventilation are usually preferable. The pacemaker requires surgical implantation, preferably in the thorax rather than the neck, and there is a small risk of phrenic nerve damage either at implantation or during pacing. Phrenic nerve pacing may induce vocal cord adduction and a tracheostomy usually needs to be retained.

INDICATIONS FOR VENTILATION

The decision about when and how to initiate domiciliary ventilation requires close collaboration with a respiratory specialist experienced in ventilatory support. It is important that access to an appropriate level of care is also available during acute intercurrent illnesses, such as chest infections, and to handle any problems that may arise with domicilary ventilation.

a. Elective

The main indications for elective ventilatory support are shown in Table 1. 'Prophylactic' ventilatory support for

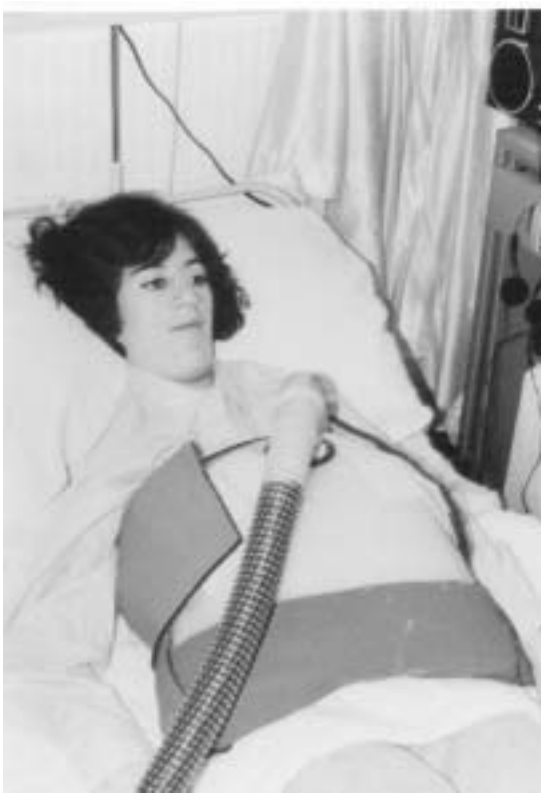

Figure 2. Cuirass Ventilation

asymptomatic patients who have not yet developed respiratory failure has been shown not to increase survival in Duchenne's muscular dystrophy, possibly because of complacency by the patient and family once ventilatory support is initiated so that help was not sought during acute infective exacerbations[7].

Occasionally patients require ventilatory support to relieve orthopnoea at night in the absence of any abnormality in the blood gases either during the day or at night due to bilateral diaphragmatic paralysis. Bilateral diaphragmatic paralysis is a feature particularly of motor neurone disease, extensive multiple sclerosis, poliomyelitis, muscular dystrophies and some myopathies such as acid maltase deficiency. It can be diagnosed by the presence of orthopnoea, paradoxical inward inspiratory abdominal movement in the supine position and a fall in vital capacity on changing from a sitting to the supine position of around 50%.

TABLE 1

Indications for Elective Ventilatory Support

- Raised arterial PCO2 during the day usually with symptoms such as sudden awakenings from sleep, irregular respiratory pattern during sleep, early morning bifrontal headaches, excessive daytime sleepiness or signs of right heart failure
- Nocturnal hypoventilation with normal waking blood gases
- Sleep disruption due to inability to lie flat even with normal night-time and waking blood gases – usually due to bilateral diaphragmatic paralysis

b. Acute

Patients with neuromuscular disorders often develop acute respiratory failure during, for instance chest infections. Ethical dilemmas may arise as to whether or not to proceed to emergency intubation and ventilation. The previous quality of life, the potential for long-term ventilatory support to improve this and the ability of the patient and the carers to cope with domiciliary ventilation all need to be taken into consideration. It is often possible to wean the subject onto a non invasive technique and to close the tracheostomy, although this may need to be retained in the long term.

OUTCOMES

Non invasive ventilation not only normalises the blood gases during the night while it is being used, but also during the day[8]. Improvement in blood gases is usually seen within a few days and can be maintained for many years, unless the neuromuscular disorder is progressive. Breathlessness, ankle swelling, daytime sleepiness and exercise ability all improve. The survival in non progressive disorders is over 80% at 5 years after starting treatment[9].

In progressive neuromuscular disorders the outcome is determined as much by the deterioration of the underlying condition, especially bulbar function as by the adequacy of ventilatory support. Nevertheless in conditions such as motor neurone disease and Duchenne's muscular dystrophy there may be considerable symptomatic benefit and improvement in the blood gases until the condition reaches its later stages. Ventilatory support should not be withheld solely because of fear of progressing from non invasive to tracheostomy ventilation or fear of becoming virtually ventilator dependent since there are various strategies to avoid these situations if they are felt to be inappropriate.

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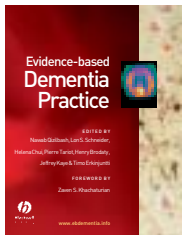
Evidence-based dementia practice



Edited by: N Qizilbash, LS Schneider, H Chui, P Tariot, H Brodaty, J Kaye, T Erkinjuntti
Publisher: Blackwell Science, 2002
Pages: 893
ISBN: 0-632-05296-1
Price: £79.50

A central tenet of medical practice today is that it should be evidence-based. A noble aim no doubt, but one that may be easier to aspire to than follow, for what is to be permitted as 'evidence', how is it to be judged or – dare one say it – spun? The evidence-based movement has fostered a systematic approach to evidence gathering and grading, with the apex of the hierarchy being randomised double-blind placebo-controlled trials and meta-analyses of such trials. What does this approach, used in this massive tome and its accompanying website (www.ebdementia.info), tell those of us (apparently) benighted enough not to have pursued such a policy in our clinical practice? All the editors of this volume are clinicians and thus much preoccupied with the practical management of individual patients.

As with any multi-author text, the outcomes are of variable quality. The opening section on evidence-based methods, authored single-handedly by Qizilbash, is very good, and that on diagnosis, edited by Helena Chui, is, to my way of thinking, outstanding. Herein the various approaches to diagnosis, particularly diagnostic criteria and investigations, are subjected to measures of sensitivity, specificity and likelihood ratios, which show that many of the investigations we so keenly arrange in fact contribute rather little to differential diagnosis.

Other sections are less compelling. In part, this may be because of the time disparities between various authors contributions: many of the literature searches which form the basis of most chapters seem to have been performed in 1999, so that more recent data are not discussed, and evidence keenly awaited by one author is reviewed by another. In other parts there is not much evidence to talk about: some of the pharmacotherapies discussed are of little more than historical interest. The section on background information seems somewhat redundant. Moreover, despite all this evidence, it is both surprising, yet reassuring, to read that the recommended way to assess the efficacy of therapeutic approaches is by asking caregivers their opinion on whether or not it has been helpful, rather than by means of some sophisticated rating scale.

It seems to me that this book aims to be the 'bible' for evidence-based dementia practice (to my knowledge, there are no competitors vying for the same niche). If so, then, like the Bible, much must be taken on faith, and there is much repetition (some wholesale, e.g. pp 675-8 and 703-5, but this may not be a problem if, as the principal editor presumes, readers are dipping into the book rather than reading all of it). If one is persuaded, as this reviewer largely is, by the systematic approach of evidence-based methods (for what is philosophy but systematic thinking?), then this is a book which has something to offer, although nothing to change ones practice at this stage. Hopefully there will be increased value in succeeding updates as more evidence accrues. It can therefore be recommended, with just a pinch of scepticism.

AJ Larner; Cognitive Function Clinic, WCNN, Liverpool

Investigating neurological disease. Epidemiology for clinical neurology

Authors: A Hofman, R Mayeux
Publisher: Cambridge University Press, 2001
Pages: 306
ISBN: 0521000092
Price: £36-95

Q.1 Write brief notes on the following:

A) Cox proportional hazards model
B) The logrank test
C) Epistasis and pleiotropy
D) Any four types of health economic evaluation.

Exactly. Me neither.

This is an unusual book. The first of its 306 pages provides a very readable and mercifully concise account of 'Quantitative methods in clinical neurology'. Nine chapters describe 'genetic epidemiology', 'gene-environment intervention', dovetailing into methodological chapters instructing us again on how to understand and assess, both at the conceptual and arithmetic level, medical publications that fill our journals and inform our practice. Common 'real' examples are used to illustrate various points with many guest appearances from the field of cerebrovascular disease, leading in helpfully from the abstract to the reality of coal-face neurology - should Mr Jones have surgery for his contralateral, asymptomatic, but horribly tight carotid stenosis or not ? This is good stuff.

The second and rather longer section comprises 12 chapters by different authors with 10-15 pages on a hotpotch of neurological diseases ranging from cerebrovascular disease, dementia (Alzheimer's and vascular), Parkinson's disease, Multiple Sclerosis, to Myasthenia Gravis, neoplastic disease, HIV infection and cerebral palsy. What no epilepsy? they cried, no headache, no chronic fatigue, no, dare I ask, (yes, I jolly well do since it constitutes about one third of my general outpatient clinics) medically unexplained symptoms?

These latter chapters follow a standardised format with an epidemiological slant as would be found in most if not all texts covering these subjects followed by a very brief offering about management. Justice cannot be done to these diseases in such a brief overview and this detracted from the quality of the first half. As a result the second part of this book was for me a disappointment.

This is a shame since a book half the length and presumably half the price would be a highly recommendable 'quickie' that would empower clinicians not already in the know (and evidence exists to the effect that we are not alone) in the planning of their own research and the critical appraisal of others.

John Bowen, Royal Hospital Haslar, Gosport

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Date of Preparation: February 2002

Current neurosurgical management of intractable central neuropathic pain

Introduction

Neuropathic pain arises from damaged neural tissue. It is deemed central when the neural injury is in the brain or spinal cord. Post stroke pain is one of the commonest forms of central neuropathic pain that affects about 2-8 % of patients after a stroke[1]. This pain is usually resistant to analgesic medical therapy and is extremely unpleasant. Like other forms of neuropathic pain, it is generally described as a constant burning or lacerating sensation commonly associated with painful hyperaesthesia in the same distribution[1]. Patients also complain of a crushing sensation, deep aching, allodynia and various other forms of unbearably altered sensory perception. Due to the generally intractable and incapacitating nature of this pain, various surgical management strategies have been tried over the years with varying rates of success. These include chronic deep brain stimulation (DBS), spinal cord stimulation (SCS), anterior cingulotomy, dorsal root entry zone (DREZ) lesions and in recent years, motor cortex stimulation (MCS)[2-5,7]. MCS has now become the preferred option (over DBS) in the neurosurgical management of medically intractable neuropathic pain of central origin (CNP)[2,6]. However, MCS provides satisfactory pain relief in only about 50%-75% of cases[2,6]. Our experience of managing CNP now comprises 16 patients who have been implanted with peri-ventricular gray (PVG) and / or sensory thalamic (ventroposterolateral nucleus – VPL) DBS electrodes and 6 patients with MCS. Based on this, we feel there still is a definite role for DBS in control of CNP.

Our experience with DBS for intractable central neuropathic pain

Patients and surgery

Twenty-two patients with CNP were treated between November 1995 and November 2002 at our functional neurosurgical clinic in the Radcliffe Infirmary, Oxford. Seventeen of these had post-stroke pain. All patients were referred by pain clinics as failures of drug treatment. They underwent neurological and neuropsychological assessment at our centre. Informed consent was obtained from each patient. All procedures were approved by the Local Ethics Committee, Radcliffe Hospitals NHS Trust, Oxford. Fourteen patients were stereotactically implanted with contralateral (to the side of pain) VPL DBS electrodes (Medtronic DBS 3387, Minneapolis, MN) in an area where stimulation induced paraesthesia in the area of pain and contralateral PVG DBS electrodes (Medtronic DBS 3387, Minneapolis, MN) where stimulation induced relief of pain or a sensation of warmth in the area of pain (Figure 1). One patient had only PVG and another only VPL DBS electrode implantation.

Six patients had a MCS (Resume, Medtronic, Minneapolis, MN) implanted in the parietal cortex contralateral to the painful side. They were connected to a subcutaneous pulse generator (IPG, Synergy®, Medtronic, Minneapolis, MN).

Trial stimulation, field potential recording and pain assessment

In 12 of the 14 patients with both VPL and PVG implants the DBS electrodes were externalised for a week's trial stimulation and recording of field potentials (FPs) to assess the degree of pain relief. Pain was assessed before and after surgery and during stimulation by a self-rated visual analogue scale (VAS, McGill-Melzack). FPs were recorded through the thalamic DBS leads during PVG stimulation in the ward after the patient had recovered from the operation and pain had returned to the pre-operative level.

Pulse generator

Patients who reported satisfactory relief from pain following trial PVG stimulation were then implanted with a subcutaneous pulse generator (IPG, Synergy®, Medtronic, Minneapolis, MN), placed in a pectoral pouch under general anaesthesia. The thalamic electrode was also connected but kept inactive in the initial period except in one patient who tolerated the VPL DBS better and hence that was the one used from the beginning.

Follow-up

All patients were regularly followed up to assess the degree of pain relief, adjust stimulator settings if required and to record any improvement in functional status. All the MCS cases were seen till withdrawal of treatment (range – 2 weeks to 4 years), while 14 of the DBS cases have now been seen for an average of 14 months (range - 3 to 34 months, Figure 2).

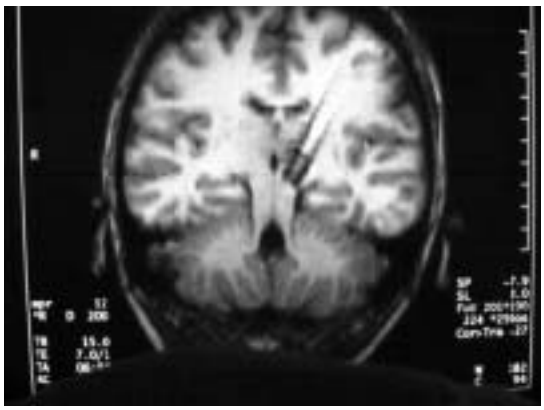

Figure 1. This figure is a MRI scan performed after implantation. It shows the two DBS electrodes placed in the left PVG and the left VPL, respectively in a patient with chronic post-stroke pain.

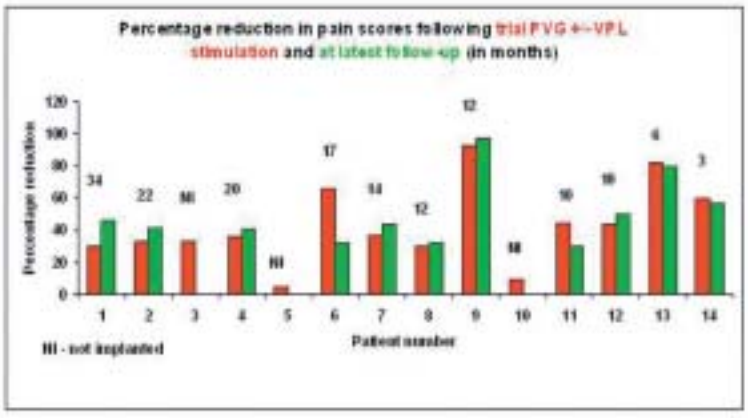

Figure 2. This figure illustrates the degree of reduction in pain scores during peri-ventricular gray (PVG) and / or sensory thalamic (VPL) stimulation. The red bars represent the reduction during the trial period while the green bars show the situation at the time of last follow-up (two patients with less than 3 months follow-up not shown). The number over each of the green bars is the length of follow-up in months.

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Professor Tipu Z Aziz studied physiology at University College London graduating in 1978. During this time he developed his keen interest in the role of the basal ganglia in movement disorders. He studied medicine at King's College London (1978-1983) and obtained his surgical fellowship in 1987 following which he pursued a career in neurosurgery. He is currently a consultant neurosurgeon at the Radcliffe Infirmary, Oxford and Charing Cross Hospital London. He is an expert in functional neurosurgery and has a special interest in the surgical treatment of movement disorders.

Results

Nine of the 12 patients who had trial PVG and VPL stimulation had satisfactory pain relief and opted to have the IPG implanted in a second procedure. Pain suppression was related to the frequency of stimulation of the PVG in all the cases of central pain. Maximum pain relief was obtained with 5 Hz – 35 Hz stimulation, while higher frequencies made the pain worse. All these patients responded better to PVG ± VPL stimulation than to VPL stimulation alone.

The FPs consisted of a very low frequency potential, of 0.2 - 0.4 Hz, in the sensory thalamus; the amplitude seemed to correlate with the intensity of pain perception. Figure 3 plots the VPL recordings from one of the patients and illustrates this point. These FPs were much stronger off stimulation and with higher frequency stimulation (≥50 Hz) when there was no pain suppression, than while stimulating the PVG at low frequencies (5 to 35 Hz) with accompanying pain relief.

Of the 6 patients who underwent MCS one was relieved of pain for four years, two had pain relief for only 2-3 weeks and three did not experience any appreciable relief.

Discussion

Eleven of the 16 patients with CNP recruited consecutively in this series had satisfactory pain suppression with PVG and / or VPL DBS. This was considerably better than our results with MCS. This also compares favourably with results reported with MCS by other groups[2,6]. As seen in Figure 2, the pain suppression obtained during trial stimulation is fairly robust and was maintained over the average follow-up period of 14 months in all but 2 patients.

Interestingly, we have found that there was correlation between the alleviation of pain sensation and the amplitude of the thalamic slow frequency FPs[4,5]. This may help the understanding of the complex nociceptive pathways.

Conclusions

Deep brain stimulation remains an important method of treatment of CNP. The most important challenge lies in selecting appropriate patients for either DBS or MCS. Both cost and potential complications are important considerations. There is a reported risk of 20% minor complications of which 4% are permanent and less than 1% risk of permanent disability or death. However, this needs to be viewed against the substantial cost of continued medical treatment, inability to work, the social and psychological toll on the patients and their families.

The future of this technique will depend on better knowledge of the neurobiology of the etiology of pain and pain pathways. It is also important to develop more objective indices to measure success in pain management and perhaps greater infrastructure to support patients with DBS implants outside the tertiary care hospital system.

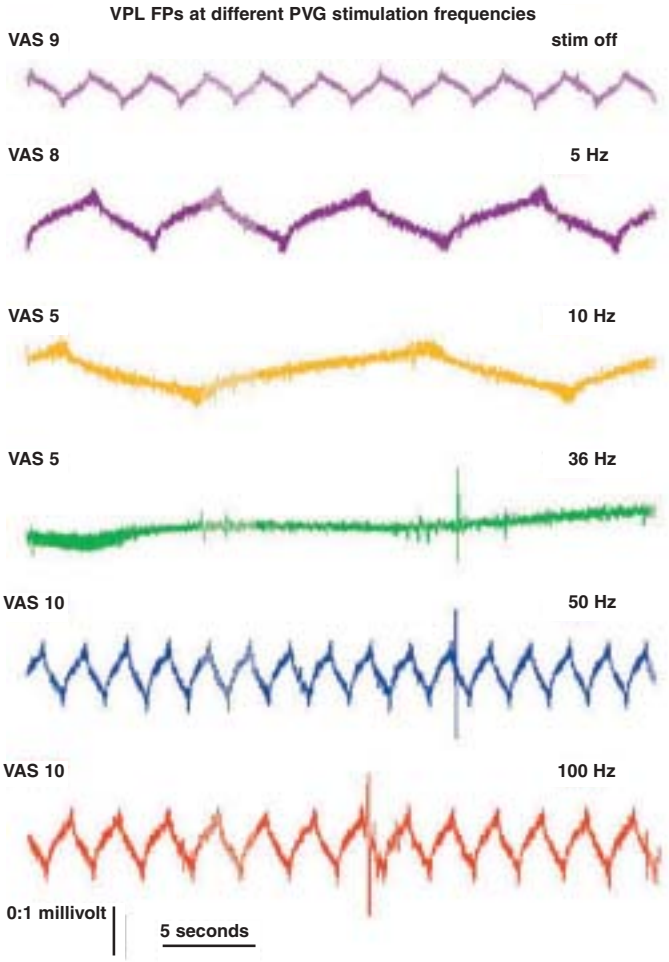

Figure 3. This figure plots the thalamic field potentials (FPs) recorded in a patient during trial stimulation of the PVG at varying frequencies. The VAS pain scores are given on the left of each trace and the frequency of stimulation on the right. It is clear from the traces that there is a decrease in the amplitude of the thalamic FPs at specific frequencies of PVG stimulation. This decrease corresponded closely with the reduction in the pain scores recorded during stimulation.

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Foot drop

Textbooks of neurology are just like cookery or gardening books. It is all so easy on paper. With a good working knowledge of neurological anatomy, it seems, almost any problem can be precisely localised. A couple of of hours yomping through a busy out patients leads to a rapid re-evaluation of that view. Foot drop, however, is a common neurological problem that is particularly amenable to an anatomical approach, so this month I will briefly outline the anatomy of peroneal nerve and discuss the clinical and neurophysiological approach to foot drop.

The common peroneal nerve is a branch of the sciatic nerve. The sciatic nerve is formed in the pelvis by fibres from the lumbosacral trunk (L4,5) and by fibres from S1,2,3. The nerve immediately leaves the pelvis through the greater sciatic notch, below the piriformis muscle. The nerve may divide immediately, or may pass either above or through the piriformis. In the gluteal region the nerve lies deep to gluteus maximus, between the greater trochanter and the ischial tuberosity. The nerve then passes down the back of the thigh to the apex of the popliteal fossa. In the thigh the nerve divides into lateral common peroneal and medial tibial divisions. The common peroneal division supplies fibres to the short head of biceps femoris.

The common peroneal nerve leaves the popliteal fossa between the tendon of biceps femoris and the lateral head of gastrocnemius. It crosses behind the head of the fibula and passes laterally around the neck of the fibula, where it is particularly vulnerable to compression or blunt trauma. The nerve gives off the sural communicating branch to the sural nerve, and the lateral cutaneous nerve of the calf. The nerve pierces the peroneus longus muscle to divide into deep and superficial branches. The deep peroneal nerve supplies the muscles of the anterior compartment - (table 1). The superficial peroneal nerve supplies the muscles in the lateral compartment (table 1) and the skin over the anterior lower leg and dorsum of the foot.

Clinical Evaluation of Foot Drop

The manner in which the common peroneal nerve snakes around the fibular head exposes it to injury and external compression and this can sometimes occur in bizarre and quite unexpected ways (table 2). Common peroneal neuropathy presents with foot drop; foot drop is due to weakness of the muscles in the anterior and lateral compartments of the leg. Since it is these compartments that work against gravity, pathology in the spinal chord, lumbar roots (L4 and L5), plexus, sciatic nerve, peroneal nerve and severe generalised neuropathies can all present in this way (Table 2). The first step in clinical evaluation is to exclude cord or other CNS pathology and examine for other peripheral nervous system involvement. In sciatic neuropathy there may also be weakness in a tibial nerve distribution also, however it is possible to have selective involvement of the common peroneal fasicles only. In L5 radiculopathy both ankle dosrsiflexion and inversion/eversion will be affected while in a pure common peroneal neuropathy inversion will be spared. There is a slight caveat however. If the foot is tested in the dropped position inversion may appear to be weak so inversion should be tested in a passively dorsiflexed position. In an isolated superficial peroneal neuropathy eversion will be weak and dorsiflexion spared while in an isolated deep peroneal neuropathy there will be weakness of dorsiflexion with sparing of eversion. In a common peroneal neuropathy sensation over the lateral foot (sural territory), sole of foot (plantar nerves) and medial calf and foot will be spared. Finally ankle jerks will be spared in a pure common peroneal neuropathy.

Neurophysiological Evaluation

The neurophysiological evaluation of foot drop nicely illustrates the old maxim that electrophsyiology is an extension of clinical assessment. The first step is to determine if the pathology is restricted to the common peroneal nerve only, so where possible it is worth studying-doing the works in both lower limbs (Bilateral peroneal and tibial motor studies, bilateral superficial peroneal and sural sensory studies). If a common peroneal mono-neuropathy is confirmed, the next objective is to determine any site of injury or compression and give an estimate of severity. This can be achieved with a combination of nerve conduction studies and EMG. Segmental conduction studies around the fibular head should be performed-focal slowing or conduction block is a sign of compression or neuropraxia and also in an isolated deep peroneal neuropathy superficical peroneal sensory studies will be normal. EMG should be performed in one L4/L5 muscle not innervated by the common peroneal nerve (tibialis posterior is often used), one deep peroneal muscle (Tibialsis anterior) and one superficial (peroneus longus). The degree of dennervation and the presence or absence of voluntary activity will give pointers as to severity of the neuropathy.

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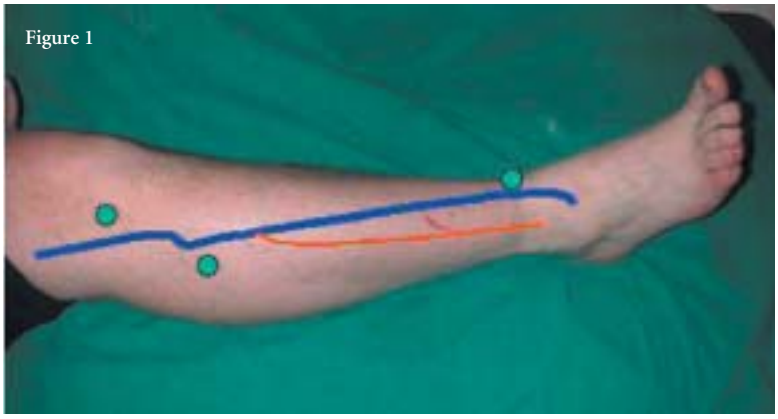

Figure 1: Course of the common, deep (blue) and superficial peroneal nerve, sites of stimulation for motor nerve conduction studies are shown by green discs.

Table 1: Muscles supplied by the two divisions of the common peroneal nerve.

Deep peroneal	Superficial Peroneal
Tibialis Anterior	Peroneus Longus
Extensor Digitorum Longus	Peroneus Brevis
Extensor Digitorum Brevis	
Peroneus Tertius	

Table 2: Some peripheral causes of foot drop	
Generalised Neuropathy	Motor Neuronopathy
	Motor Neuropathy
	Motor and Sensory Polyneuropathy
	HMSN
	Mononeuritis Multiplex
Localised Neuropathy	L4/L5 Radiculopathy
	Lumbosacral Plexopathy
	Sciatic Neuropathy eg. Buttock injection
Common Peroneal Neuropathy	Trauma at fibular head
	Forcible stretch
	External Compression eg. Casts stockings etc.
	Prolonged immobility eg. During anaesthesia
	Occupational eg. gardening
	Habitual Leg crossing
	Weight loss

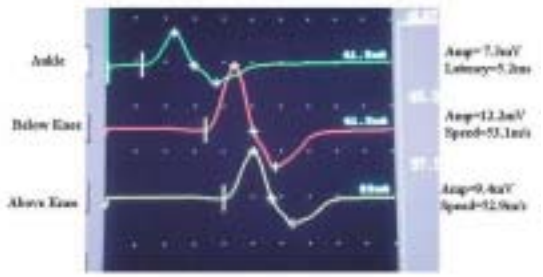

Figure 2: Normal peroneal motor study, note there is no slowing of conduction across the fibular head.

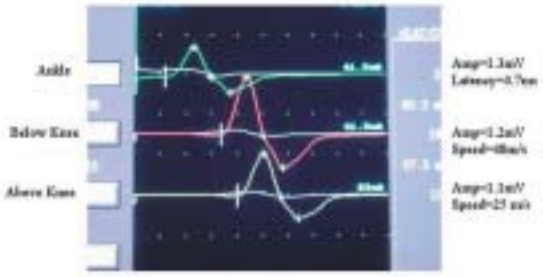

Figure 3: The same normal study superimposed on abnormal study (opposite leg). This study was taken from a patient who developed foot drop after having his leg in a plaster of Paris cast for 9 weeks, note the reduced amplitude and slowing across the fibular head.

Thomas Laycock and the romantic genesis of the cerebral reflex

Thomas Laycock (1812-1876) graduated from University College London in 1835, received his MD from Göttingen in Germany *summa cum laude* in 1839 and became the first Englishman to occupy the chair of Professor of the Practice of Medicine at the University of Edinburgh in 1855. He was the first person to apply the concept of reflex action to the brain, and was also the first to argue that the anatomical division of the central nervous system in humans is on a continuum with that found in other animals. Although he wrote on these topics fifteen years before Darwin's *The Origin of Species*, and his conclusions are compatible with currently held principles regarding the structure and function of the nervous system, he remains an obscure historical figure.

The ideological struggle over the principles that govern methodological practice in the biological sciences today occurred throughout the nineteenth century.[1,2] It would be overly simplistic to state that this struggle was a simple fight between proponents of romantic biology on one side and those of scientific reductionism on the other, however, Laycock was clearly aligned to the former camp.[3] In the first half of the nineteenth century the cerebrum was widely held to be a special part of the nervous system; the seat of the will, consciousness, and what it was to be human, it was considered to be above and beyond the laws that mediated function in the lower divisions of the nervous system. In 1833 Marshall Hall (1790-1857) published on the reflex arc in the spinal cord, arguing that reflex acts were also mediated by matter contained in the brainstem but specifically excluded the cerebrum.[4] Laycock did not agree, stating, "It will be easy to show that the excito-motor phenomena of Dr Hall, confined by him to the spinal cord, have their analogues in the cerebral hemispheres".[5] He most clearly states his hypotheses in his paper of 1845 entitled 'On the reflex function of the brain':

> Four years have elapsed since I published my opinion, supported by such arguments as I could then state, that the brain, although the organ of consciousness, was subject to the laws of reflex action, and that in this respect it did not differ from the other ganglia of the nervous system. I was led to this opinion by the general principle, that the ganglia within the cranium being a continuation of the spinal cord, must necessarily be regulated as to their reaction on external agencies by laws identical with those governing the functions of the spinal ganglia and their analogues in the lower animals.[6]

Cerebral reflexes are 'centric' in origin, patients are 'physically unable to restrain or modify' them, and conscious experience is coincident to, rather than the cause of these reflexes. Included in his examples are the blink reflex in response to visual threat and pathological laughter and crying in a patient with a cerebral tumor and secondary epilepsy. However, his favorite example is the hydrophobic gasp of the rabid patient. He notes that exposing the patient to the touch, sight, sound or even the idea of water can generate this response. He spends little time discussing animal work in his paper, but does pause to consider the influential negative experiments of Marie Jean Pierre Flourens (1794-1867), who found no evidence for the discrete cerebral localisation of brain functions in his experiments, predominantly on birds, concluding that cerebral functions were spread diffusely throughout the cerebrum.[7] Laycock notes:

> Dr Marshall Hall has relied mainly upon the experiments of Professor Flourens in support of his opinion that the brain is inexcitor, but it will be seen that these experiments consisted simply in irritating the brain by picking and tearing…Such irritations differ altogether from even the tactile sensations received by the general surface. As every nerve has its proper endowments, and requires the irritant peculiar to itself, to develop the reflex phenomena indicative of design, so the sensory gray matter in which the sensual nerves end must have its proper endowments and peculiar stimuli.

Laycock's views on the reflex sprang from his belief in both the unity of nature and its inherent purposefulness. He was part of a loosely defined movement (romantic science) which was not a self-organised club, but rather consisted of individuals who viewed biological phenomena as somehow different from the inorganic world. Although some have considered this movement a retarding force on the progress of biological science, in more recent times evidence has emerged that many of the 'great' names of the time were influenced by romantic philosophy.[1] There were many differing and contradictory shades of romantic thought at that time.[8] Lenoir argues that between the extremes of vitalism (biological forms and forces are subject to their own rules, distinct and not dependant on those governing the inorganic world) and reductionism (all biological phenomena can be explained by physical laws and forces), many scientists chose a doctrine that took the middle road, allowing for both the separation and interaction of the biological and physical worlds. These scientists worked within a philosophy of biology outlined by Immanuel Kant (1724-1804). In his *Critique of Judgement* published in 1790, Kant argues that the concept of cause and effect can and should be used when studying events that take place in the inorganic world, as consequences tend to follow one another in a linear sequence. Problems arise when applying this view to the organic world as cause and effect are linked. A tree causes leaves to grow on it yet the leaves also cause the tree to grow; in Kant's words, "An organised natural product is one in which every part is reciprocally both ends and means".[9] In order to escape this paradox, he suggests that when studying events in nature one must assume that natural phenomena have an innate purposefulness. This assumption however, must remain just that, an assumption to help guide enquiry, and one must be careful not to make the logically inconsistent leap that nature really is purposeful. For Kant the paradox of investigating biolog-

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"Cerebral reflexes are 'centric' in origin, patients are 'physically unable to restrain or modify' them …. his favorite example is the hydrophobic gasp of the rabid patient. He notes that exposing the patient to the touch, sight, sound or even the idea of water can generate this response."

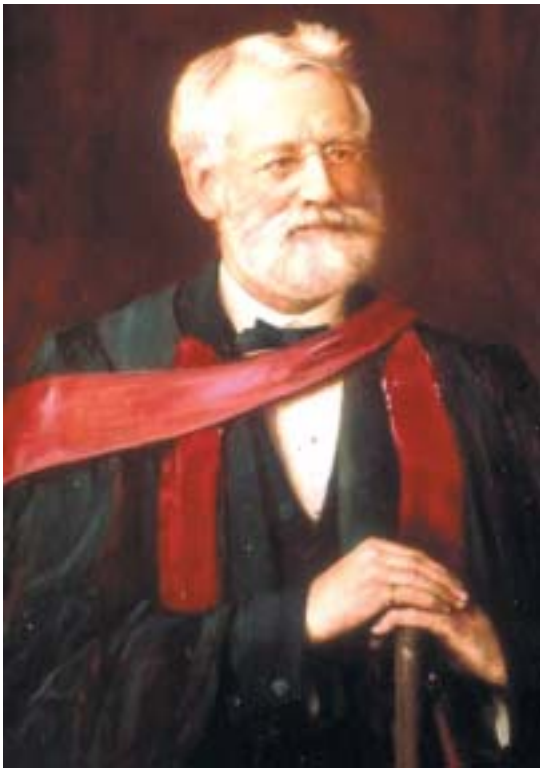
ical phenomena arises not from the phenomena themselves, but from the innate limitations in our ability to interrogate the biological world:

> In the unknown inner ground of nature, the physico-mechanical connexion of things and the organic connexion of their organic ends, may be united in one principle; we only say that our reason is unable to unite them.[10]

This teleological view of nature pervades all of Laycock's writings. For him, although the reflex is grounded in matter 'vesicular neurine', this matter is specially organised by nature to produce a function, i.e. reflex acts are directed towards some end and are thus properly defined as reflex functions. So even though he later goes on to argue that instinctive behaviours, emotional acts and some acts of intelligence (inspiration) may be due to cerebral reflexes, he does not regard himself in any way as a reductionist. The inbuilt purposefulness of the reflex lifts it above the inorganic world where events unfold without intention.

His viewpoint was out of kilter with the majority of British scientists at the time, and this served to partly camouflage his ideas. His large textbook of 1860, the title says it all, *Mind and Brain: or the Correlations of Consciousness and Organisation; with their Applications to Philosophy, Zoology, Physiology, Mental Pathology and the Practice of Medicine,* was not uniformly well received:

> Anticipating from the title, a work of much practical character we were disappointed that theory lay at the root of the whole matter. This theory is a sort of combination of the philosophy of Plato with the physiology of Stahl.[11]



Thomas Laycock (1812-1876) was the first person to apply the concept of reflex action to the brain. Picture courtesy of Royal College of Physicians of Edinburgh.

He felt that authorship of his concept of the cerebral reflex was stolen from him by William Carpenter (1813-1885) who wrote a famous and much-read textbook *Principles of human physiology.*[12] Carpenter, like Marshall Hall, argued that there was a strict cut-off at the cerebrum above which reflex action did not occur, only later changing his mind and giving himself primacy for this idea up to and including the fifth edition of his textbook published in 1855. Although he wrote to Laycock retracting this statement, the textbook passed out of his editorship and a formal corrigendum was never appended. Laycock continued to feel stung, writing articles attempting to correct this error into the year of his death.[13,14]

It was to be left to others to 'modernise' Laycock's main conclusions by re-phrasing them in more acceptable theoretical garb. John Hughlings Jackson (1835-1911) was a medical student for three years at York when Laycock taught there. Although he makes little reference to Laycock in his published works, it has been argued that Laycock was an early and important influence on Jackson who incorporated some of Laycock's views on the reflex.[15,16] Jackson recast the concept of continuity of the nervous system in animals within the acceptable paradigm of evolutionary theory, not, as Laycock did, around a belief in the unity of nature; proving that, in history as elsewhere, it is not enough to be right, you have to be right for the right reasons.

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Apomorphine treatment: A neurologist's perspective

This article is the second in our series looking at the use of apomorphine. In our first article (Vol 2, issue 5) we had the specialist nurses' perspective. In this article, Drs Steiger and Tyne comment on use of apomorphine by neurologists.

Dr Malcolm J. Steiger MD FRCP is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery, Liverpool, having trained in Neurology at the National Hospital, London. He has a particular interest in Parkinson's disease.

The Movement Disorder service at Walton offers care and management of patients with all stages of PD, including a large apomorphine programme and stereotactic surgery to suitable patients.

Dr Hilary Tyne is a Research Registrar in Neurology at the Walton Centre. Her main research interest is Parkinson's disease.

The long-term pharmacological management of patients with Parkinson's disease on dopaminergic therapy is associated with motor fluctuations, unpredictable 'off' periods and dyskinesia[1]. These can be difficult to manage despite manipulation of levodopa preparations, oral dopamine agonists, COMT inhibitors and amantadine. 'Off' periods may be unpredictable, not only causing reduced mobility, but patients suffer other distressing 'off' symptoms such as painful dystonia, depression, anxiety and fatigue[2,3,4]. An effective reliable method of relieving such 'off' periods is the use of apomorphine.

Apomorphine was first tried in patients with Parkinson's disease in l951[5], but it was noted to be potently emetic. The development of an effective peripheral dopamine receptor antagonist, that did not cross the blood brain barrier (domperidone), led Stern and Lees to review and develop the role of apomorphine in Parkinson's disease[6].

Apomorphine is a selective and potent dopamine agonist at D1 and D2 receptors. Given by subcutaneous injection it can rapidly reverse the time spent 'off'[6]. Apomorphine is given by intermittent subcutaneous injection as required, or by subcutaneous infusion over several hours per day.

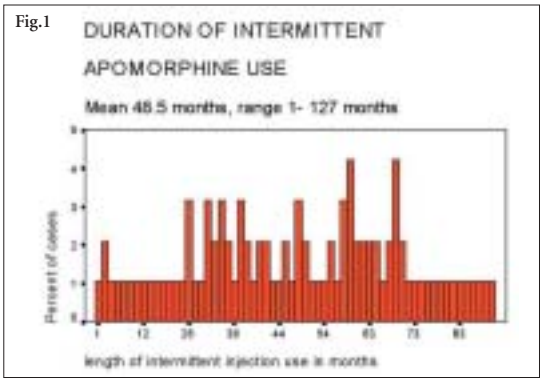
Indications

One of the major uses of apomorphine is in patients who, despite optimal oral therapy, experience sudden disabling 'off' periods. When given by intermittent subcutaneous injection the latency to onset is 10-12 minutes, with duration of effect of 20-60 minutes. For those patients experiencing frequent 'off' periods, particularly if the 'offs' are unpredictable, then apomorphine by subcutaneous infusion can be effective. Furthermore, as shown by Colzi apomorphine may reduce dyskinesias[7]. The mechanism in part relates to a reduction in oral levodopa dosage with apomorphine and also to a more physiological constant dopaminergic stimulation.

To use apomorphine either patient and/or carer (spouse) must be able to administer the subcutaneous injection. The patient and/or carer need to clearly understand when the drug should be given.

Restrictions in the use of apomorphine are relatively few, for example age or a history of confusion should not necessarily prevent patients receiving apomorphine, since it appears to have a lower incidence of neuropsychiatric side effects compared to other dopamine agonists[8].

Fig.1



How to start apomorphine

The patient attends the day ward after commencing domperidone 20mg tds for 48 hours prior to their first dose. This reduces side effects, particularly nausea. Patients are requested to abstain from anti parkinsonian medication from the night before, so they are in a practically defined 'off' state. Subcutaneous apomorphine is given in increasing amounts to find the threshold dose needed to relieve the 'off' period. The average dose is 3mg, but can vary from 2mg to 8mg. Patients, and if possible their carer, are taught how to draw up, and administer the injections. Arrangements may be made for District Nurse support to assist in drawing up a supply of apomorphine for injection, which can be stored in the fridge.

Those requiring apomorphine by infusion are taught either as an outpatient, or in the patient's own home, with the District nurse and/or GP present to allow for their training with the infusion device. The dose is increased over the next few weeks, depending on symptoms. Oral dopaminergic medication may subsequently be reduced. The pump device also allows for bolus dosing during the infusion period if required. Patient's requirements vary, but dosage of up to 180mg, over 12 to 24 hours can be given if necessary.

Concomitant medication

Apomorphine can be used along with oral dopamine agonists. Once established on an infusion, oral agonists, as well as levodopa, may be slowly reduced if necessary.

Follow up

We recommend a close liaison between patient, Nurse Practitioner and Primary Care. Particularly after initiating apomorphine therapy, to overcome any potential problems that the patient may experience.

The majority of patient's prescriptions of apomorphine are from Primary Care.

Long term effects and benefits

Apomorphine is well tolerated, especially with domperidone cover. The majority of patients eventually stop domperidone with no increase in side effects. Confusion, hallucinations, postural hypotension, nausea, and sedation are all uncommon and haemolytic anaemia is very rare. The two most common problems may be an increase in dyskinesia on commencement; this may require a reduction in oral medication. Skin nodules can be reduced by rotating sites of injections, and ensuring that there is at least a 1:1 ratio of normal saline to apomorphine in the

KEY MESSAGES ABOUT APOMORPHINE

1. It is NOT addictive.
2. It is NOT a respiratory depressant.
3. It CAN be levodopa sparing when given by infusion, and
4. May reduce dyskinesia (Colzi *et al*).
5. May rapidly reverse rare 'off' period phenomena such as: pain, dystonia, restless legs.
6. Relatively low risk of neuropsychiatric side effects as compared to other dopamine agonists.
7. Is particularly useful in the post operative state, when oral medication may not be absorbed.
8. The pre-filled variable dose injector pen (APO-go Pen) is easy to use, especially in patients without a spouse or full-time carer. However it is expensive compared to the use of a simple insulin-type syringe.
9. It will not prevent the next dose of levodopa working.

infusion. Painful nodules respond well to massage and ultrasound therapy.

We have been using apomorphine in Parkinson's disease for 10 years; Figure 1 shows the duration of treatment for our patients on intermittent injections. Patients can be treated with apomorphine for many years without loss of efficacy.

Infusion pumps can be obtained on loan from Britannia Pharmaceuticals. The cost of apomorphine usage includes the infusion lines, needles, syringes for intermittent injections and apomorphine.

Conclusions

For many Parkinson's disease patients the usage of apomorphine has been extremely valuable in maintaining quality of independent life. The cost of apomorphine should be placed into perspective, in that it often allows patients to be independent and remain in their own home. The reliable rapid relief of distressing 'off' periods is an advantage of the subcutaneous injection. Subcutaneous infusion is usually well tolerated by patients, helping to reduce fluctuations and dyskinesias in the long-term. Apomorphine remains underused at present in our view. The success in the individual patient requires liaison and support from all those involved in the patient's care is needed, particularly the Parkinson's disease nurse specialist.

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"We would like to thank Britannia Pharmaceuticals for sponsoring this article".

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EDITOR'S CHOICE

HUNTINGTON'S DISEASE

A novel way to stopping Huntington's disease – Congo red

The genetic cause of Huntington's disease (HD) is well known, but how the mutant huntingtin (htt) causes cell dysfunction and death is not known. In this paper the authors address the role of oligomerization (and Congo red as an inhibitor of this process) in HD using cell lines and the R6/2 transgenic mouse model.

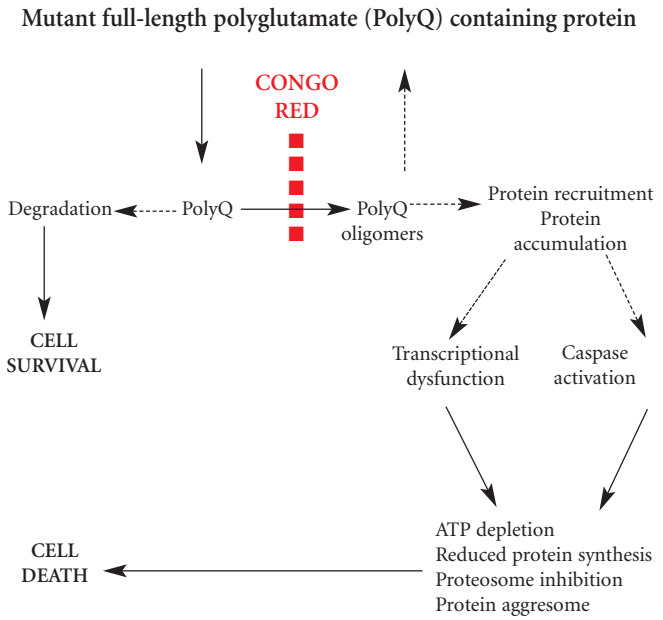
In HD the expanded polyglutamine fragments are cleaved from the full length protein and then aggregate, in some way causing cellular dysfunction and ultimately death. This aggregation can be prevented in vitro using Congo red (see figure), and this promotes cell survival, restores ATP levels and prevents the formation of markers of cell stress such as caspases. In addition by inhibiting this oligomerization, the authors also claim that protein synthesis was restored and degradation reduced without affecting basal protein turnover, although there was no effect on chaperone protein interactions with the htt.

Thus Congo red inhibits htt protein aggregation, but more than this is the finding that Congo red therapy can actually disrupt preformed polyglutamine aggregates and that this action is specific only for expanded polyglutamine and is without effect on the normal htt.

All well and good, but this has all been shown in cell lines and thus its clinical relevance remains suspect. However the authors head off this criticism by testing the compound in the R6/2 transgenic mouse model of HD – a mouse in which a truncated form of htt with 139 CAG repeats is expressed. They do this by either injecting the compound intraperitoneally or infusing it via osmotic minipumps intracerebroventricularly. This manoeuvre ameliorates some of the systemic symptoms of the mice, for example increasing survival, maintaining weight, and improving the motor deficits whilst histologically reducing the accumulation of aggregates. (Although no comment is made of brain atrophy or other histological abnormalities.)

This paper represents a tour de force of experiments and suggests that oligomerization may be a critical pathogenic event in this and other polyglutamine disorders. However, whether this proves to be the case requires further probing, as does its relevance to the clinical disease and treatment of this fatal condition. – *RAB*

Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders.
I Sanchez, C Mahlke and J Yuan.
NATURE
(2003) 421: 373-379



TRANSPLANTATION

★★★ RECOMMENDED

Don't be picky about your nose cells (when transplanting)

It is hard to imagine a time when multiple sclerosis is curable. Until then, patients and society will continue to face the huge emotional and economic costs of disability due to persistent demyelination. Remyelination is the answer, although that is easier said than done. One school of thought is that cells should be injected into the MS brain that have the capacity to migrate, divide and remyelinate– but safely, without going where they should not and without forming tumours. A cell with all these properties has yet to be identified. One candidate, being promoted by this group based at the Veterinary School in Cambridge, is the olfactory ensheathing cell. This humble cell has the great attraction –for human therapeutic purposes - that it can easily be harvested from the patient's own olfactory bulb. In animal studies, olfactory ensheathing cells clearly remyelinate and so now research is turning to the practical issues which must be faced before translating to the clinic. This paper addresses the apparently mundane question of whether it matters if the transplanted olfactory ensheathing cells are contaminated by meningeal cells during the olfactory bulb dissection. It seems that it does, but unexpectedly because a precise proportion of meningeal contamination *improves* remyelination! Not only that, but the *migration* and *proliferation* of olfactory ensheathing cells were increased. The authors can only speculate on mechanism. But, clearly, the message is do not be too fussy about purifying your olfactory ensheathing cells before transplanting…. *-AJC*

Meningeal cells enhance limited CNS remyelination by transplanted olfactory ensheathing cells.
Lakatos A, Smith PM, Barnett SC, Franklin RJ
BRAIN
2003; 126: 598-609

MULTIPLE SCLEROSIS

A cold hard look at interferon-beta treatment of multiple sclerosis

The introduction of the interferon-betas as treatments of multiple sclerosis will surely go down in medical history as an example of the triumph of spin over substance. At last a really useful independent analysis of the interferon-beta trials in relapsing-remitting multiple sclerosis has been done. Seven tri-

als, involving 1215 patients, were subjected to the Cochrane methodology. As well as humbling the extravagant claims for this class of drug, the authors also criticise the trials comprehensively. For instance, there was evidence for a treatment effect at year one, but there were insufficient data at year two to judge whether this continued. This was because of the number of drop-outs in year two and the failure of investigators to conduct an intention-to-treat analysis, even when they said they would! This was especially true of the Multiple Sclerosis Collaborative Research Group study, in which data were collected at two years on only 57% of those randomised. The authors approached this problem with a "sensitivity analysis" assuming a worst and best case scenario. If it was assumed that drop-outs had higher disease activity than those who remained in the study (which seems reasonable) then the systematic review did not find any significant effect of interferon-beta on relapse rate in year two or on the overall accumulation of disability. The only result that the authors could be certain about was a reduction in the number of people having a relapse in the first year on interferon: relative risk 0.73 (0.54-0.99). So that, in the end, is what all the fuss has been about. Not with a bang, but a whimper.

-AJC

Interferons in relapsing-remitting multiple sclerosis: a systematic review.

Filippini G, Munari L, Incorvaia B, Ebers G, Polman C, D'Amico R, Rice G.
LANCET
2003; 361: 545-52

★★★ RECOMMENDED

⁄ 4 Integrin antibodies (natalizimab) reduce multiple sclerosis relapses

To penetrate beyond the blood brain barrier into the nervous system parenchyma, pathogenic T cells and monocytes use a number of molecular mechanisms. One such molecule is ⁄ 4 integrin which is part of the ⁄ 4€ integrin (VLA-4) complex, expressed on the activated lymphocytes. Therefore blocking the interaction of ⁄ 4€ integrin and its ligand, Vascular-cell Adhesion Molecule-1 (VCAM-1), found on endothelial cells should prevent migration of pathogenic T cells into the brain. The hope would be – and to some extent this has already been demonstrated in animal experiments and pilot clinical studies – that such blockade of the VLA-4 and VCAM-1 interaction may reduce disease activity in inflammatory CNS diseases.

Miller and colleagues now provide the most substantial piece of evidence that blocking ⁄ 4 integrin modifies disease activity in multiple sclerosis. They tested a humanised antibody to a4 integrin (natalizimab or Antegren®) in a randomised double blind placebo controlled trial (n=213). This multicentre study compared two doses of natalizumab (3mg/kg or 6 mg/kg every 28 days for 6 months) with placebo injections, with follow up for 12 months after starting treatment. Patients with both relapsing-remitting and secondary progressive MS were included in the study. MRI evidence of new lesions were substantially less in the treatment groups (90% less, P<0.001). Clinical relapses were significantly diminished (50% less, P=0.02). Well-being, measured by a visual analogue test (not widely used), was improved in the treatment groups but worsened in the placebo group. A potential concern with using antibodies as a treatment is serum sickness; this occurred in 3 patients, including one from the placebo group (who did not have changes in complement levels compatible with true serum sickness)! Across the board no real difference in number of side effects could be defined between the three groups. However antibodies to natalizumab developed in 11% of those in the natalizimab groups and the emergence of these antibodies was dose dependent. These antibodies will almost certainly limit efficacy of the treatment in the long-term although this was not addressed by the authors. There was no significant difference in the changes in disability score between the groups. Although patients in this study received treatment for a limited time and follow up was limited, the effectiveness of the treatment was demonstrated by the return to placebo levels of relapse rate and new lesions on MRI in the months after treatment withdrawal.

Natalizimab is now on a fast track to licensing and is currently undergoing trials as monotherapy or in combination with Avonex, one of the interferon-betas. It is also being developed for other autoimmune conditions, such as Crohn's disease. However effective it proves to be in the short term, there is a real chance that antiglobulin responses will limit its long-term efficacy. It is no surprise that at least four pharmaceutical companies are trying to develop small molecules that have the same target but do not provoke an immune response. A drug to watch. *-TH*

A controlled trial of natalizumab for relapsing multiple sclerosis.

Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GPA, Libonati MA, Willmer-Hulme AJ, Dalton CM, Miszkiel KA, O'Conner PW, for the International Natalizumab Multiple Sclerosis Trial Group.
NEW ENGLAND JOURNAL OF MEDICINE
2003;348:15-23

⁄ 4 integrins as therapeutic targets in autoimmune disease

von Andrian UH and Engelhardt B.
NEW ENGLAND JOURNAL OF MEDICINE
2003;348:68-72

REHABILITATION

Grasping with the EEG

Developing the brain-computer interface could potentially be very helpful in patients with limited mobility. Simplicity in design and operation is the key to their success. Patient devices operated by eye movements have already proved to be applicable but have limitations in terms of portability. Typically a video camera is positioned in front of the subject, or sensors are placed directly on to the face which is cosmetically less appealing. A novel approach using the occipital alpha rhythm of the EEG has recently been improved by Heasman and colleagues using qualitative analysis (wavepacket algorithms) of this dominant rhythm. Eye closure accentuates this feature whilst eye opening usually attenuates the alpha frequency. This feature can therefore be used as a switch operated by eye closure and opening. The volitional modulation of the occipital alpha in this study, detected by a 3 electrode montage, was combined with a controller for stimulating grasp in an upper-extremity neuroprosthesis. A tetraplegic patient with a high cervical injury rapidly learnt to use the system and performed well on objective measures. Eye close initiated the grasp movement and a short delay was engineered into the system, this ensured adequate hand positioning prior to the commencement of the motor task. The speed and reliability of the system significantly improved when wavepacket analysis was incorporated (p<0.002). This relatively simple approach certainly has promise and perhaps its combination with other brain-computer interfaces could prove invaluable for re-establishing patient independence. *-JLR*

Control of a hand grasp neuroprosthesis using an electroencephalogram-triggered switch: demonstration of improvements in performance using wavepacket analysis.

Heasman JM, Scott TRD, Kirkup L *et al.*
MEDICAL & BIOLOGICAL ENGINEERING & COMPUTING
2002:40:588-593

Pilot study finds cannabis alleviates neurogenic symptoms in some patients

For many years now anecdotal reports of the benefits of cannabis have been aired in the media, but with continuing legal and social arguments against its use controlled evaluation of its effects have been along time coming. The effects on spasticity of a cannabinoid, Delta-9- tetrahydrocannacbinol (THC) has been tested in small studies but now whole plant cannabis medicinal extracts have become available for clinical research. A pilot evaluation carried out in Oxford by Wade and colleagues is reported in Clinical Rehabilitation. The purpose of the study was to determine whether cannabis medicinal extracts could alleviate neurogenic symptoms that are unresponsive to standard treatment.

Twenty-four patients were recruited, some by self-selection, to this double blind randomised, placebo controlled, cross over trial. Eighteen of the patients had multiple sclerosis, four had spinal cord injuries, one a brachial plexus lesion and one had phantom pain after a limb amputation. In the first instance tolerance to a 1:1 preparation of THC and cannabidiol (CBD) administered by a spray under the tongue was tested. Patients used the spray at home and the recommended dosing was altered according to the patients' reports of intoxication. Having achieved a suitable dosing level the patients entered an eight week double blind study phase with four two week phases so that the THC:CBD mixture, THC alone, CBD alone and placebo could each be tested for 2 weeks. A large number of symptoms were scored daily on visual analogue scales. These included pain, spasticity, bladder dysfunction and coordination. Other dimensions such as affect, energy, sleep, appetite and well-being were also scored. In addition at each two-week assessment a battery of standardised assessments was administered.

THC alone was more effective than placebo at relieving pain, muscle spasm, spasticity and loss of appetite, the combination treatment THC: CBD significantly improved muscle spasm and sleep. Intoxication with rapid initial dosing was the biggest adverse problem; because of this three patients withdrew from the initial phase of the study.

In designing this study the investigators adopted a cautious approach to check the patients ability to tolerate a cannabis derivative. This being done with open label THC:CBD before the trial may well have affected patient's blinding to the treatments. Also for 'ethical reasons' the patients were allowed to take home a supply of THC:CBD as 'rescue medication' to use while they were on the trial, though the investigators report that many of the patients did not use it. These considerations together with the heterogeneity of patients' and wide range of symptoms measured complicated the study. However it was a valuable step in assessing the way to proceed in systematic

research of the benefits of this controversial medicine. *–AJT*

A preliminary controlled study to determine whether whole plant cannabis extracts can improve intractable neurogenic symptoms.
Wade DT, Robson P, House H, Makela P, Aram J.
CLINICAL REHABILITATION
2003: 17: 21-29

PARKINSON'S DISEASE

Dairy products and Parkinson's disease

Despite the recent huge interest in genetic causes for PD, the majority of patients have late onset disease with no family history. It is important therefore that we continue to search for environmental risk factors for the disease. The greatest limitation of case control studies is the introduction of recall bias that occurs when exposure status is determined retrospectively. Information derived from large cohorts of individuals followed up prospectively therefore represents a particularly valuable resource.

This study uses information from the Health Professionals Follow up Study (HPFS) and the Nurses Health Study (NHS); in particular the dietary information recorded from food frequency questionnaires at baseline. Follow up of these cohorts has identified 210 incident cases of PD in men, and 184 in women based on self reporting with confirmation sought from medical records.

Comparison of the highest and lowest quartiles of intake of dairy products (including cream cheese, sour cream and milk) among men shows a relative risk of 1.8 (CI 1.2-2.8) for the highest intake after adjustment for covariates such as smoking, caffeine and physical activity, (p trend =0.004). This association was not seen in women, and no other food groups were associated with PD risk in either sex.

Since this study has used information collected prospectively with long follow up periods, in large numbers of patients, it would be wrong to dismiss these results as chance findings alone, although the differential effect between the sexes is puzzling. The authors discuss the potential roles of nutrients or contaminants in dairy products that may explain these findings. *–TF*

Diet and Parkinson's Disease: A potential role of dairy products in men.
Chen H. Zhang S.M. Hernan M.A. Willett W.C. Ascherio A.
ANNALS OF NEUROLOGY
2002:52:793-801

★★★ RECOMMENDED

Lewy bodies and Aggresomes: altered protein handling and Parkinson's disease?

Parkinson's disease is characterised pathologically by selective neuronal death of dopaminergic neurons in the substantia nigra pars compacta and by protein aggregates or 'Lewy bodies' occurring within the cytoplasm.

Recently, protein characterised inclusion bodies known as 'aggresomes' have been found close to the centrosome (microtubule organising centre) in various cells. Functionally, aggresomes are thought to help break down abnormal proteins and keep them away from the rest of the cell. This paper accumulates evidence that Lewy bodies act to sequester and degrade excessive abnormal proteins in an aggresome-like way to try to protect neurons from cytotoxicity.

Lewy bodies were immunoreactive for the proteins gamma-tubulin and pericentrin (both centrosome/aggresome markers) in patient brain tissue analysed post-mortem. Staining depended upon specific neurodegenerative disease neuropathology. Lewy bodies in patients were found to store proteolytic enzymes and proteosome activators e.g. ubiquitin-activating enzyme (E1), and PA700 and PA28 and HSP70, which are all recruited by aggresomes to aid protein break down. Staining patient brain tissue with specific, novel antibodies to ubiquitin protein conjugates (potential markers of proteolytic stress) revealed Lewy bodies and aggregates of ubiquitinated proteins. Furthermore, aggregates appeared to be being transported to the centrosome and to form larger Lewy body structures. The smaller aggregates of ubiquitinated proteins remained elusive when stained with usual anti-ubiquitin and anti-alpha synuclein antibodies. Finally, cultured dopamine neurones displayed aggresome/Lewy body like inclusions during proteolytic stress.

These findings link formation of Lewy bodies with aggresomes and suggest inclusions are a cellular protective response to increasing levels of abnormal proteins within neurons. Investigating abnormal protein is already prominent in neuroscientific research for neurodegenerative conditions (e.g. CJD, and Huntington's disease). This paper strengthens arguments that a similar approach be taken to explore Parkinson's disease. *-LAJ*

Aggresome-related biogenesis of Lewy bodies.
McNaught K S P, Shashidharan P, Peri D P, Jenner P, Olanow W.
EUROPEAN JOURNAL OF NEUROSCIENCE
2002: 16: 2136-2148

★★★ RECOMMENDED

GDNF and Parkinson's disease: Round 1 to sceptics

The prospect of treating neurological disorders with neurotrophic factors is not a new one, but to date has been disappointing and sadly this study adds yet another negative result to the literature.

GDNF was first identified in 1993, where it was found to have a profound effect on dopaminergic neuronal survival in the substantia nigra. Subsequently many studies have investigated this further in vitro, and in different animal models of PD using a variety of delivery systems with encouraging results. It was on this background that the current study was conceived in which 50 patients with moderately advanced PD were randomised to receive an intracerebroventricular infusion of either placebo or one of various different doses of GDNF. The patients were then followed over an 8 month period for signs of efficacy as well as side-effects, with a cohort of cases being followed for a longer 20 month period.

12 patients were in the placebo group with equal numbers distributed in the remaining 5 different dose groups. Side-effects were common and included nausea, anorexia and vomiting with weight loss in the higher dose groups with Lhermitte's phenomena being reported. None of the different doses of GDNF offered any benefit to the patients.

This negative study is clearly a disappointment but is not surprising given the post-mortem study, published already, in a patient receiving GDNF from this trial, which showed no dopaminergic cell rescue or axonal sprouting. However it has long been suspected that the diffusion of such factors from the CSF into the brain parenchyma is poor, and thus efficacy is much more likely with direct intra-parenchymal delivery of the neurotrophic factor. Indeed Steve Gill and colleagues in Bristol using such an approach are now reporting efficacy and thus whilst round 1 has been won by the sceptics of the use of GDNF in PD, round 2 may prove to be very different. Watch this space! *-RAB*

Randomised, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD.
Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws ER Jr, Lozano AM, Penn RD, Simpson RK Jr, Stacy M, Wooten GF.
NEUROLOGY
(2003) 60:69-73

BRAIN INJURY

Repeated concussion may have a cumulative effect

The severity of a concussive episode may depend upon a history of previous concussion. In this intriguing study the authors investigated this possible relationship in high school athletes. A group of athletes with no previous concussion history was compared with a group in whom there was a history of three or more previous concussive episodes. The latter group was more likely to show evidence of loss of consciousness, post traumatic amnesia (PTA) and confusion following a subsequent concussive episode, when examined on the field of play.

Careful pre-season neuropsychological testing was undertaken in high school athletes. Further evaluation was performed on the basis of rigorously-defined inclusion criteria on the field of play. A computer based analysis (ImPACT – Immediate Postconcussion Assessment and Cognitive Testing) was undertaken. Information from pre-season questionnaires facilitated comparison of the effects of a subsequent concussive episode on the known frequency of previous concussive episodes, ranging from 0 to 9. The majority of athletes in both groups were competing at American football and a variety of other sporting activities were also represented. Only 5% of athletes with no prior concussive history suffered loss of consciousness after an injury compared with 26% of athletes who had suffered three or more concussive episodes. Overall the effect in this group was that they were nine times more likely to experience 3 or 4 on-field abnormal signs of injury in a concussive episode.

Various theories are discussed to explain these findings. The athletes may have an innate vulnerability to concussion (a lowered threshold); or the previous episodes may be cumulative. Furthermore other studies cited indicate possible longer-lasting cognitive sequelae – even years after the event. This is preliminary work with particular flaws in terms of numbers of athletes studied and the possible duration of any cumulative effect. Nonetheless it does raise important questions concerning return to competition in athletes who have suffered repeated relatively minor concussive episodes as well as the more general possible cumulative effects of serial head injuries. This study should be of interest to all clinicians responsible for the initial assessment and subsequent management of patients suffering from minor head injuries. *– RMR*

Cumulative effects of concussion in high school athletes.
Collins MW, Lovell MR, Iverson GL, Cantu RC, Maroon JC, Field M
NEUROSURGERY
2002; 51 (5): 1175-1179

EPILEPSY

Save a tree in 2003

In the new eco-friendly, health conscious era, we as reviewers are duty bound to draw your attention to research that may exploit poverty stricken villagers in the rainforests, cause deforestation and global warming, damage your health and increase the cost of your household insurance. This is such a study.

Many anti-epileptic drugs are now available and I would challenge any neurologist to provide a truly rational scheme for the prescription of different drugs, especially in focal epilepsy. There are also hundreds of studies looking at the prescription of different drugs in different populations, young, old, learning disabled etc. and drawing spurious conclusions about relative efficacy. In this study two hundred patients who had received levetiracetam (LEV) were reviewed in a retrospective analysis. Sixteen patients became seizure-free and 19 had improved seizure control. They were compared with the 9 who had deterioration of their seizures. The authors found that the mean age of those that deteriorated was 27 and the mean age of those that improved was 45 ($p<0.05$) and of those who became seizure-free was 51 ($p<0.05$). TLE did well whereas other focal epilepsy did not. What about the other 156 patients (78%) who seem to have been mysteriously lost from the study? Presumably their seizures were unchanged. What were their demographic and clinical characteristics? There were 38 statistical comparisons in this study, making the true test of significance $p< 0.013$. At best this paper poses a question, which needs to be answered in a proper research study.

I don't mean to single out this paper, it is symptomatic of a wider malaise. If you are engaged in this kind of research, please stop now. If you are an editor, think of the trees! *-MRAM*

Levetiracetam may be more effective for late onset partial epilepsy.
CW Bazil, Rose A, Resor S, Yapicular B, Hirsch LJ.
ARCHIVES OF NEUROLOGY
2002; 59:1905-1908.

Cerebral venous thrombosis- seizures and fatality

These two articles describe cohorts of patients, one from Portugal, the other from Germany, with cerebral venous thrombosis.

In the Portuguese series of 91 patients there was a 34% rate of early symptomatic seizures (n=31). Two patients died as a result of seizures. These patients presented earlier and had other features of cortical venous thrombosis (focal signs, parenchymal change on neuroimaging). Eight patients had late seizures (2-10 months) and were more likely to have had acute symptomatic seizures and haemorrhagic venous infarction. The presence of seizures however was not found to relate to functional outcome at one year.

The German series comprised 79 patients, all treated with iv heparin, and sought factors which predicted fatal outcomes. Overall mortality was 10% and was associated with stupor or coma at the start of therapy, older age, and slower cerebral transit estimated from intra-arterial angiography. Patients who died also tended to have haemorrhagic infarcts but this probably reflected more extensive thrombosis and was not in itself an adverse risk.

What should we do differently in light of these findings? For patients with early symptomatic seizures it seems reasonable to treat with anticonvulsants for a year after the acute event. One should be vigilant in aggressively managing early symptomatic seizures as they can lead directly to death. The authors raise the question of prophylactic anticonvulsants for patients with haemorrhage (without early symptomatic seizures) but I do not think they have come close to proving the case for so doing. If a patient with venous thrombosis has a significantly impaired conscious level at the start of anticoagulation therapy they are more likely to have extensive thrombosis probably also involving the deep cerebral veins. Their outlook is worse than more alert patients and maybe one should be more aggressive in moving on to local thrombolysis unless there is early clinical improvement with intravenous heparin. *-PJM*

Seizures in cerebral vein and dural sinus thrombosis.
Ferro JM, Correia M, Rosas MJ, Pinto AN, Neves G.
CEREBROVASCULAR DISEASE
2003;15:78-83

Heparin treatment in cerebral sinus and venous thrombosis: patients at risk of fatal outcome.
Mehraein S, Schmidtke K, Villringer A, Valdueza JM, Masuhr F.
CEREBROVASCULAR DISEASE
2003;15:17-21

ALZHEIMER'S DISEASE

★★★ RECOMMENDED

Why vaccination for AD did not work

The possible use of A€ vaccination for the treatment of Alzheimer's disease (AD) has attracted much attention following the demonstration in transgenic mice of its efficacy in reducing brain amyloid burden and protecting against some deficits in learning and memory. This was thought to result from anti-A€ antibodies triggering microglial A€ clearance through Fc-receptor mediated phagocytosis. However, phase I/II clinical studies with vaccine AN-1792 had to be halted when some patients developed CNS inflammation (meningoencephalitis). This experimental paper suggests a possible explanation for this outcome.

Female C57BL/6 mice, 6-8 weeks old, were immunised with 100µg A€1-42 (A€) with or without 500 ng pertussis toxin (PT) iv x2 (day 0, 2). In this context, pertusiss was used as an "adjuvant" to boost T-cell immune responses and overcome the immune system's natural reluctance to generate autoimmunity (BCG or "Freund's adjuvant" are often used for the same reason). All the A€ + PT animals developed symptoms and signs of CNS inflammation 13-20 days post-immunisation, which lasted up to day 75, whereas A€ animals did not. Neuropathology in the A€ + PT animals showed perivenular aggregates of T-cells and macrophages in leptomeninges and parenchyma. In draining lymph nodes, there was an increased percentage of A€-specific CD4+ T-cells producing interferon-*y*, indicating a T-cell response against A€ of Th1-type. In serum, anti-A€ IgG antibodies were predominantly IgG2a rather than IgG1.

This study illustrates the difficulties of manipulating the immune system for therapeutic purposes. The desired effect of the vaccine is a "Th2" response, producing an antibody that clears A€ aggregates. And yet a little non-specific stimulus, in the form of an adjuvant, drives a perivenular inflammatory encephalomyelitis associated with Th1-like A€-specific T-cells, B-cells producing complement fixing anti-A€ antibodies, and macrophages. Thus despite encouraging laboratory findings in patients treated with AN-1792 (ACNR 2002; 2(6): 29), the challenge remains to the hypothetical basis for vaccination treatment of AD. *-AJL*

Vaccination with amyloid-b peptide induces autoimmune encephalomyelitis in C57/BL6 mice.
Furlan R, Brambilla E, Sanvito F, Roccatagliata L, Olivieri S, Bergami A, Pluchino S, Uccelli A, Comi G, Martino G.
BRAIN
2003;126(2):285-291

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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

Current Opinion in Neurology
Lippincott Williams & Wilkins, 241 Borough High Street, London, SE1 1GB. Tel 0207 940 7564, Fax 0207 940 7530
Email. rmclachl@lww.co.uk, www.Lww.co.uk

Epilepsia
Blackwell Publishing, Commerce Place, 350 Main Street, Malden, MA 02148-5018, USA. Tel. 888 661 5800, Fax. 781 388 8270,
www.blackwellscience.com/epi

Events Diary

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 April 7th, 2003.

2003

March

Faculty of Old Age Psychiatry Residential Meeting
6-7 March, 2003; London, UK
Tel. 0207 2352 351 x 142, Fax. 0207 2596 507, E. pcornell@rcpsych.ac.uk

Goal Planning in Acute and Community Settings
7 March, 2003; Ely, UK
Alison Gamble, Tel. 01353 652173, Fax. 01353 652164, E-Mail. alison.gamble@pow.lifespan-tr.anglox.nhs.uk

Preventive Pharmacotherapy of Headache Disorders
7-9 March, 2003; Copenhagen, Denmark
Hanne Aggergaard, Tel. +45 43 233 291, Fax. 45 43 233 926, E. hagn@glostruphosp.kbhant.dk

Heart & Brain, 6th International Stroke Conference and 3rd Conference of the Mediterranean Stroke Society
12-15 March, 2003; Monte Carlo, Monaco
Tel. +972 3 5140018/9, Fax. +972 3 5172484, E. Stroke6@kenes.com

Innovative Therapies in Autoimmune Disease Conference
13-16 March, 2003; Washington, US
Tel. 001 404 633 3777, E. acr@rheumatology.org

Transcranial Magnetic Stimulation in Movement Disorders Santa Margherita Ligure, Genova
14-15 March, 2003
Tel. +39 010 583 224, Fax. +39 010 553 1, E.aristea@aristea.com

3rd Advanced Prosthetic and Amputee Rehabilitation Course
17-19 March, 2003; London, UK
Mrs Sandy Weatherhead, BSRM, Tel. 01992 638865, E-Mail. admin@bsrm.co.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
21 March, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

Living with Epilepsy
27 March, 2003; Lingfield, UK
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338, E. klaird@ncype.org.uk, www.ncype.org.uk

American Academy of Neurology 55th Annual Meeting
29 March-5 April, 2003; Honolulu, Hawaii
Tel. 001 651 695 1940, Fax. 001 651 695 2791

Neurological Aspects of Sleep
31 March, 2003; London, UK
Tel. 020 7290 3941, E. sleep.disorders@rsm.ac.uk

April

British Society for Rheumatology 20th AGM
1 April, 2003; Manchester, UK
Tel. Caroline Pembroke, 0207 242 3313, Fax. 0207 242 3277, E-mail. caroline@rheumatology.org.uk

IPA European Regional Meeting
1-4 April, 2003; Geneva, Switzerland
E. ipa@ipa-online.org

36th Annual Scientific Meeting of The Pain Society
1-4 April, 2003; Glasgow, UK
Tel. 0207 6318 870, Fax. 0207 323 2015, E. meetings@painsociety.org

See the Bigger Picture - Learning Difficulties, ADHD, DAMP, Dyslexia
2-3 April, 2003; Edinburgh, Scotland
Tel. 0046 31 818 200, Fax. 0046 31 818 226, E. congrex@gbg.congrex.se

ABN Spring Scientific Meeting
2-4 April, 2003; Cardiff, UK
E. abn@abnoffice.demon.co.uk

Annual Meeting of the American Academy of Neurology
5-12 April, 2003; Nashville, US
Tel. +1 651 695 1940

Cannabis
7 April, 2003; London, UK
RSM, Tel. 020 7290 2984, E. cns@rsm.ac.uk

Neurology for Neuroscientists IX
7-8 April, 2003; Oxford, UK
Prof. J B Clark, E. nneurosc@ion.ucl.ac.uk, www.ionlucl.ac.uk/neurochemistry/N4N/programme.html

The Multidisciplinary Approach to Epilepsy
10 April, 2003; Lingfield, UK
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338, E. klaird@ncype.org.uk, www.ncype.org.uk

British Geriatric Society Spring Meeting
10-12 April, 2003; Aberdeen, UK
BHM Ltd. Tel. 01825 768 902, Fax. 01825 768 902, E. contact@bhm.co.uk

1st European Workshop on Evolutionary Computation & Bioinformatics
14-16 April, 2003; Essex, UK
Dave Corne, Tel. 0118 931 8983, E. d.w.corne@reading.ac.uk

2nd Emirates Neuroscience Conference
12-17 April, 2003; Dubai, United Arab Emirates
Dr Javaid Iqbal, Tel. 0097 142 666 416/0097 142 711 221, Fax. 0097 142 711 221, E. jiqbal49@emirates.net.ae

17th National Meeting of the British Neuroscience Association
13-16 April, 2003; Harrogate, UK
Tel. 0151 794 5449, E. harrogate2003@bna.org.uk

Approaches to the Lumbar & Thoracic Spine
14-16 April, 2003
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329, E. neurosurgery@rcseng.ac.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
18 April, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

Annual Meeting of the American Association of Neurological Surgeons
26 April-1 May, 2003; San Diego, US
www.neurosurgery.org

One Day Conference on Neurological Sight Problems
30 April, 2003; Merseyside, UK
Emily Thompson, Tel. 0151 298 2999.

May

Quantitative Motion Analysis Short Course
May 2003; Birmingham, UK
Tel. 0121 414 4906, E. p.k.chahal@bham.ac.uk

Pain
1 May, 2003; London, UK
RSM, Tel. 020 7290 2984, E. cns@rsm.ac.uk

6th International Conference AD/PD
8-12 May, 2003; Seville, Spain
Kenes International, 17 Rue du cendrier, PO ox 1726, CH-1211 Geneva, Switzerland.
Tel. +41 22 908 -488, Fax. +41 22 7322850, E. adpd@kenes.com

EFNS Academy for Young Neurologists
9-14 May, 2003; Stare Splavy, Czech Republic
Ing. Magda Dohnalova, Tel/Fax. +420 2 6716 3563, E. efns@fnkv.cz

Psychosocial Aspects of Epilepsy
15 May, 2003; Lingfield, UK
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338, E. klaird@ncype.org.uk, www.ncype.org.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
16 May, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

The Society of Neurological Surgeons 2003 Annual Meeting
18-20 May, 2003; Cincinnati, US
David G Peipgras, Tel. 001 507 284 2254, Fax. 001 507 284 5206, E. piepgras.david@mayo.edu

2nd World Congress of Physical & Rehabilitation Medicine - ISPRM
18-22 May, 2003; Prague, Czech Republic
Congress Secretariat Tel. +972 3 9727500, Fax. +972 3 9727555, E. physical@kenes.com

European Conference on Shaken Baby Syndrome
19-20 May, 2003; Edinburgh, UK
Tel. Marilyn Sandberg, 001 801 627 3399, E. msandberg@mindspring.com

4th Parkinson's Disease Nurse Specialist Association National Conference
19-20 May, 2003; Birmingham, UK
www.pdnsa.org.uk or E. stella.smith@stgeorges.nhs.uk

Basic Neurophysiology
19 May, 2003; London, UK
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329, E. neurosurgery@rcseng.ac.uk

Clinical Neurophysiology
20 May, 2003; London, UK
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329, E. neurosurgery@rcseng.ac.uk

MS Trust Study Days
21 May, 2003, London, UK
Tel. Catherine Thornley on Tel. 01462 476704.

Neuropathology
21-22 May, 2003; London, UK
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329, E. neurosurgery@rcseng.ac.uk

8th Euroacademia Multidisciplinaria Neurotraumatologica
21-24 May, 2003; Graz, Austria
E. hans.tritthart@klinikum-graz.at

8th Annual Meeting of Rehabilitation in MS
22-25 May, 2003; Montana, Switzerland
Tel. +41 27 485 62 28, E. quadrimed.ch@freesurf.ch

Neurology for Neurosurgeons
22-23 May, 2003; London, UK
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329, E. neurosurgery@rcseng.ac.uk

5th World Congress on Brain Injury
23-26 May 2003; Stockholm, Sweden
E. info@internationalbrain.org. or Tel. 001 703 683 8400 ext 101

The Spectrum of Multiple Sclerosis Care
28 May - 1 June, 2003; San Diego, US
Tel. 001 201 837 0727 x 120, E. info@mscare.org

10th European Federation of Endocrine Societies Postgraduate Clinical Endocrinology Course
29-31 May, 2003; Riga, Latvia
Tel 37 17 085 014, Fax. 37 17 820 020, E. endocrinology@latviatours.lv

June

Advances in Molecular Mechanisms of Neurological Disorders
1-4 June, 2003; Warsaw, Poland
Prof Katarzyna A Nalecz, Tel. +48 226 686 216, Fax. +48 226 686 544, E. knal@nencki.gov.pl

Biennial Symposium of the International Evoked Response Audiometry Study Group
8-12 June, 2003; Tenerife, Canary Islands
Tel. +34 922 670 181, Fax. +34 922 670 191, E. congresos@viajesmencey.es

Balance 2003
9-11 June, 2003, UK
Tel. Jane Burgneay 02380 592288, E. jbb@isvr.soton.ac.uk

6th Meeting of the European Neuro-Ophthalmology Society
15-18 June, 2003; Goteborg, Sweden
Bertil Lindblom, Tel. +46 313 433 253, Fax. +46 313 412 904, E. bertil.lindblom@neuro.gu.se

13th Meeting of the European Neurological Society
14-18 June, 2003; Istanbul, Turkey
AKM Congress Service, Clarastrasse 57, PO Box CH 4005, Basel, Switzerland. Tel. +41 616 867 711, Fax. +41 616 867 788, E. info@akm.ch

79th Annual Meeting of the American Association of Neuropathologists
18-23 June, 2003; Orlando, US
Dr Joseph Parisi, Tel. 001 507 284 3394, Fax. 001 507 284 1599, E. aanp@mayo.edu

North West Nurses Epilepsy Forum (Learning Disabilities)
20 June, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

12th European Conference on Clinical Hemorheology
22-26 June, 2003; Varna, Bulgaria
Fax. +3592 707498, www.12ECCH.primasoft.bg, E. biorheo@imbm.bas.bg

MS Trust Study Days
25 June, 2003, Llandudno, UK
Tel. Catherine Thornley on 01462 476704.

International League Against Epilepsy Annual Scientific Meeting
26-28 June, 2003; Manchester, UK
Tel. 01691 650290, Fax. 01691 670302, E.denise@conference2k.com

Brain 03 & BrainPET 03
29 June-3 July, 2003; Calgary, Canada
Tel. 001 403 210 9397, Fax. 001 403 220 7054, E. brain03@brain03.org

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

July

FEBS 2003 meeting on Signal Transduction
4-8 July, 2003; Brussels, Belgium
Professor J E Dumont, Tel. +32 2 555 41 35, Fax. +32 2 555 46 55, E. cleclere@ulb.ac.be

ISAN 2002: Advancing Autonomic Neuroscience after the Genome
4-8 July, 2003; Calgary, Canada
Dr Joseph Davison, E. jdavison@ucalgary.ca, Fax. 001 403 283 328.

CNS 2003: The Annual Computational Neuroscience Meeting
6-10 July, 2003; Alicante, Spain
Chris Ploegaert, E. cp@bbf.uia.ac.be, www.neuroinf.org/CNS/cns2003

BSRM/AFRM Spring Meeting
10-11 July, Cambridge, UK
Tel. 01992 638865, E. admin@bsrm.co.uk

6th IBRO World Congress of Neuroscience
10-15 July, 2003; Prague, Czech Republic
Tel. 00420 224 21 06 50, Fax. 00420 224 21 21 03, E. ibro2003@biomed.cas.cz

4th International Conference on Acoustic Neuroma and other CPA Tumours
13-17 July, 2003; Cambridge, UK
Barbara Ashworth, Tel. 01223 847 464, Fax. 01223 847 465

BGS PD Special Interest Group - Multidisciplinary Care in Parkinson's Disease & Parkinsonism from Science to Practice
15 July, 2003; London, UK
Tel. 020 7561 5400, E. info@mepltd.co.uk

The Role of EEG in Childhood Epilepsy
17 July, 2003; Lingfield, UK
Katie Laird, NCYPE, Tel. 01442 831 337, Fax. 01342 831 338, E. klaird@ncype.org.uk, www.ncype.org.uk

North West Nurses Epilepsy Forum (Learning Disabilities)
18 July, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

17th Mexican Congress on Neurological Surgery
19-25 July, 2003; Monterrey, Mexico
Dagoberto Tamez, Tel. 55 55 430 013, Fax. 55 55 430 013, E. smcirneu@dsi.com.mx

Oxford Summer School on Connectionist Modelling
20 July-1 August, 2003; Oxford, UK
Tel. 01865b 271 353, E. susan.king@psy.ox.ac.uk

August

North West Nurses Epilepsy Forum (Learning Disabilities)
15 August, 2003; Widnes, UK
Sam Loughran, Sam_loughran@hotmail.com, Tel. 0151 420 7619

11th International Congress of the IPA
17-22 August, 2003; Chicago, US
Tel. 001 847 784 1701, Fax. 001 847 784 1705, E. chicago2003@ipa-online.org

12th International Symposium on Intracranial Pressure & Brain Monitoring (ICP2003)
24-28 August, 2003; Hong Kong
Tel. +852 2632 2951, Fax. +852 2647 3074, E. icp2003@cuhk.edu.hk, www.surgery.cuhk.edu.hk/icp2003

1st Congress of the International Society for Vascular Behavioural & Cognitive Disorders
28-31 August, 2003; Goteborg, Sweden
Tel. +46 31 708 60 00, E. vas-cog2003@gbg.congrex.se, www.congrex.se/vas-cog2003

7th Congress of the European Federation of Neurological Societies
30 August - 3 Sept, 2003; Helsinki, Finland Tel. +43 1 880 00 270, Fax. +43 1 88 92 581, E. Headoffice@efns.org

September

PD Academy - A Masterclass in the Management of Parkinson's Disease
September 2003; Cornwall, UK
E. events.redpublishing@btopenworld.com

IPCAT 2003; Workshop on Information Processing in Cells & Tissues
8-11 September, 2003; Lausanne, Switzerland
Christof Teuscher, Tel. 0041 21 693 66 30, Fax. 0041 21 693 37 05

MS Trust Study Days
10 September, 2003, Penrith, UK
Tel. Catherine Thornley on 01462 476704.

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

Joint Meeting of the British Neuropathological Society and the Société Française de Neuropathologie

18-20 December 2002.
University of Southampton, UK.

It was a fresh frosty sunny December day that welcomed delegates from all parts of Britain and France, from other European countries and from North America to the initial symposium of this conference, 'The Role of Neuropathology in the Post-Genomic Era'. Sebastian Brandner (London) showed how transgenic and knock-out mice are used as models for the study of CNS development and neoplasia, and Dominique Figarella-Branger (Marseille) discussed how progress in the post-genomic era will lead to greater understanding and how one single genetic defect, or even an identical mutation in one gene can lead to different muscle disease phenotypes. Charles Duyckaerts (Paris) gave an erudite account of the development of ideas in neurodegenerative diseases. James Nicoll (Southampton) discussed the results of studies showing that the @4 allele of the apolipoprotein E gene is associated with poor outcome after several different types of acute brain injury including that due to trauma and intracerebral haemorrhage. The granular osmiophilic deposits surrounding vascular smooth muscle cells that are the pathological hallmarks of CADASIL were described by Marie Magdeleine Ruchoux (Lille). This inherited angiopathy is caused by mutations in the *Notch3* gene in humans and in animal models. David Ellison (Newcastle) grasped the key challenges in tumour biology, by defining how genetic abnormalities affecting the phenotype of tumour cells can be used to devise novel therapies.

Following the symposium, James Lowe (Nottingham) gave his Alfred Meyer memorial lecture, 'Genetic Influences on Regulation of Protein Degradation in the Brain'. He described how intracellular mechanisms involving ubiquitin and the proteasome system were disturbed in dementias such as Alzheimer's disease and Lewy body dementia. He outlined subtle changes in protein expression that give rise to neurofibrillary tangles in Alzheimer's disease and Lewy bodies in Parkinson's disease.

Over the next two days, delegates were treated to a wide array of platform presentations and posters covering advances in many branches of neuropathology and neuroscience. Four contributions were of particular interest.

James Nicoll (Southampton) reported the first neuropathological findings in the brain of a patient from the clinical trial of amyloid €-peptide (A€) immunotherapy for Alzheimer's disease (AN-1792; Elan Pharmaceuticals). The pathology strongly resembles that in mice treated with A€ immunotherapy, with patchy loss of A€ plaques and some evidence of phagocytosis of A€ by microglia. Also present, but not seen in the mouse studies, was a T lymphocyte meningoencephalitis, likely to correspond to the side effect seen in some other patients who received AN-1792. Such observations suggest that immunotherapy can prevent or reverse abnormal accumulation of protein in the human brain and may be relevant to other neurodegenerative disorders (*e.g.* CJ disease, Huntington's disease) in which proteins accumulate in brain tissue. This highlights a significant role for Neuropathology in assessing the effects of such therapy on the underlying pathological processes.

Gray *et al* (Paris) discussed the pathology of healed 'burnt out' Varicella- zoster- virus (VZV) encephalitis in a 46 year old patient with AIDS treated by Highly Active AntiRetroviral Therapy (HAART). MRI showed multiple necrotic lesions and VZV PCR was positive in the CSF. Following HAART and high doses of Acyclovir, CD4 cell levels increased, viral load decreased and VZV PCR became negative in CSF. However, he died from bronchopneumonia. Neuropathology showed characteristic 'target-like' lesions of VZV leukoencephalopathy and ventriculitis. But, histologically, the lesions consisted only of necrosis and macrophages with no virus. This case suggests that opportunistic infections for which effective treatment is available may be definitively cured with immunorestoration, and in those patients who die from another cause 'burnt out' pathology may be found.

Professor Nicholas Kopp, President of the Société Française de Neuroradiologie.

Foote, Chari, and Blakemore (Cambridge) described repopulation of demyelinated areas of spinal cord tissue by oligodendrocyte progenitor cells (OPCs) even in the presence of astrocytosis. They studied the *taiep* rat which is a long-lived myelin mutant with chronic progressive demyelination, associated with astrocytosis. Thoracic spinal cord was exposed to 40Gy X-irradiation in adult *taiep* rats, to deplete the tissue of OPCs. Repopulation by OPCs was examined at 3 and 28 days, using riboprobes to platelet derived growth factor receptor alpha (PDGFR/), a marker for OPCs. Results showed that the rate of repopulation of OPC-depleted tissue in *taiep* rats was not significantly different from control animals, suggesting that astrocytosis does not affect repopulation of progenitor depleted tissue by OPCs. These findings present a potential therapy for remyelination of areas of demyelination in MS by transplantation of OPCs even in chronic MS lesions with extensive astrocytosis.

Professor Roy Weller (President of the British Neuropathological Society) presenting James Lowe with the impressive Alfred Meyer medal at the end of the memorial lecture.

Dr. Tibor Hortobagyi, invited by the BNS as a young investigator from Hungary, showed that inhibition of the nitric oxide synthase-poly (ADP-ribose) polymerase activation cascade is neuroprotective in traumatic brain injury and enhances protgenitor cell graft survival.

The Conference Banquet took place in the 17th century school building in Winchester College. This gave the opportunity for the more erudite members of the French Society to translate the Latin inscriptions on the walls. Professor Christopher Thompson, Head of the Southampton School of Medicine replied on behalf of the guests and emphasised the key role played by Neuroscience in a modern Medical School.

The meeting was superbly organised by Mrs.Stephanie Birkbeck-Garfield whose fluent French added both charm and utility to the meeting.

● *The next meeting of the British Neuropathological Society is in Glasgow 3-5 July 2003 and that of the Société Française de Neuropathologie in Rouen in June 2003.*

Professor Roy Weller,
Neuropathology University of Southampton, UK.

BNA 17th National Meeting

13-16 April, 2003; Harrogate, UK

'Harrogate 2003' offers a series of plenary lectures, symposia, poster sessions, workshops, debates and discussions to celebrate recent achievements in neuroscience. "This will be the largest gathering of neuroscientists ever seen at our national meeting as registrations have already topped 800 – no wonder when you see the quality of the science on display", commented Dr Yvonne Allen, BNA Executive Secretary. There is still plenty of time to register (registrations continue on-site too!) if you are interested in participating in this major neuroscience event, set in the delightful spa town of Harrogate, right in the heart of spectacular Yorkshire countryside, offering legendary Yorkshire hospitality!

To follow is a summary of the scientific programme and important dates to remember. The full scheduling of the scientific programme, peripheral events and social gatherings is available on the BNA's website at www.bna.org.uk

Plenary Lectures will be given by Albert Aguayo (Canada); Monique Dubois-Dalcq (France); Tim Griffiths (UK); Mike Hutton (USA); Barry Keverne (UK); Trevor Smart (UK); Clifford Woolf (USA).

Symposia include

- Advances in clinical neuroscience
- Neural cells, stem cells and the repair of CNS lesions
- New insights into neuronal rhythms
- Viral transfection of neurones: probing function and repair of dysfunction
- New approaches to understanding stress and anxiety
- Injury to the developing brain
- Subunit-selective modulators of receptors and ion channels: dissecting normal and treating abnormal brain function
- Corticosteroids and cognition
- Ageing and dementia: recent advances
- Development of the cortex
- Mechanisms of neuromuscular synaptic development, maintenance and repair
- Dopamine and the neurobiology of reward
- Cellular and molecular approaches to plasticity
- Peripheral nerve injury and regeneration
- Stress signalling in the brain
- Glial cell interactions with the extracellular matrix in health and disease
- Neuroinformatics and neuroimaging

There will also be a series of three symposia sponsored by The Biochemical Society that will explore the latest ion channel research, particularly the assembly and targeting of GABA, NMDA, AMPA and nicotinic cholinergic receptors.

An exhibition displaying the latest books, equipment and technology for neuroscience research will be open to all delegates, as well as a full range of social events.

Teaching of Neuroscience Group

A special workshop on 14th April to discuss the provision of neuroscience teaching in schools will consider in particular whether there should be a Neuroscience A/S level or A level, as recently proposed. There will be specialist talks concerning the teaching of 'brain science' in the national curriculum.

Public Awareness of Science Group

A special workshop on 14th April to discuss 'Communicating science to the public' will be addressed by Lord Robert Winston and Professors Nancy Rothwell and Colin Blakemore, all of whom have a wealth of experience to share concerning this challenging and important skill. Elaine Snell will also describe 'Brain Awareness Week' in the UK, coordinated by the European Dana Alliance for the Brain, an important initiative to enhance public awareness of progress in brain research.

E-Mail: harrogate2003@bna.org.uk if you would like further information.

Venue: Harrogate International Conference Centre, Harrogate

BNA Awards 2002

The BNA have awarded Majorie Wallace with an 'Award for Public Service', and Richard Morris with an award for 'Contribution to British Neuroscience'. The awards were made at the BNA's Christmas Symposium in London.

Majorie Wallace has contributed extensively to television, radio and newspapers, and is an active campaigner. **Richard Morris** received the award for his inspiring work on synaptic plasticity and long term potentiation.

For more information, see the forthcoming BNA newsletter.

Stimulator provides simple, flexible answer for neuroscientists

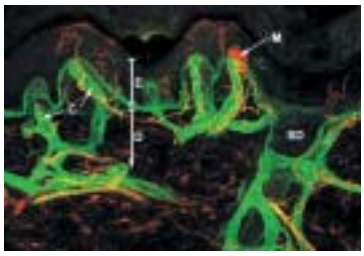
According to the company, The DS8000 Multichannel Stimulator from World Precision Instruments represents a quantum leap in the performance of the research stimulator. Using a powerful single board computer, DS8000 is the most advanced stimulator on the market. With a built-in computer, all of the waveform is generated digitally with precision timing. It can generate more complex stimulating wave patterns than any other instrument on the market, and the use of a LCD touch screen display/input makes it simple to use without a manual. A built in digital oscilloscope will also allow the user to check the waveform instantly on the screen. The instrument can be rack mounted with all of the frequently used connectors on the front panel. An Ethernet connection allows the user to transfer custom waveforms and upgrade the software using TCP/IP protocol via remote Ethernet access.

The DS8000 has 8 analogue outputs, 8 TTL outputs and 8 combined analogue or TTL outputs. Each combined output can be comprised of a combination of any 1 to 8 channels. Three independent internal timers and three independent external triggers are offered. The output waveforms offered include unipolar pulse, bipolar pulse, rectangular pulse, step, sine and ramp. In addition, researchers can design their own waveforms. An external trigger, internal analogue channel, internal TTL channel, or any of the three built-in timers can be used to control each output channel.

For further information contact World Precision Instruments on Tel. 01438 880025, Fax. 01438 880026, E.Mail. DS8000@wpi-europe.com, or see them on stand 13 at the BNA.

Secondary antibodies and proteins from Stratech

Stratech's portfolio offers secondary antibodies and proteins of the highest purity and specificity from Jackson ImmunoResearch. The range of 4000 products includes whole IgG and (Fab')2 affinity purified antibodies conjugated to AMCA, FITC Cyanine dyes, TRITC, Rhodamine Red X, Texas Red, HRP and Alkaline Phophatase. Visit us at stand 17 at the British Neuroscience Association Meeting-A Jackson catalogue is a must!



Pic caption:
Confocal image of human skin innervation. A skin biopsy of finger, immunostained for pan-neuronal marker, protein gene product 9.5, localised with Cy3 (red and yellow) and basement membrane marker, type IV collagen, with Cy2 green. Epidermal nerve fibres arise from the nerve bundles comprising the subepidermal neural plexus. A Meisner's corpuscle M is present in papillary dermis. Basement membrane labelling delineates the boundary between epidermis E and dermis D, capillaries C and sweat gland duct SD.

For more information E-Mail info@stratech.co.uk, Tel. 01353 722500, or Fax. 01353 727755.

Digitimer at the BNA

Digitimer are manufacturers and distributors of scientific instrumentation for the research environment. As well as promoting the popular modular NeuroLog electrophysiological system they also manufacture a wide range of stimulators for every situation.

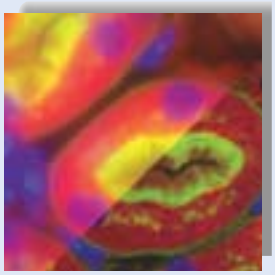
Digitimer represents a number of companies into the UK with complimentary equipment, some of which are as follows:

Harvard/Medical Systems: Microincubators and temperature controllers, Iontophoresis and pressure injectors; Heka Electronic: Patch Clamp amplifiers with acquisition and analysis; Instrutech: Data Acquisition Hardware, Data Storage VCR Adaptors; AutoMate Scientific: Drug Perfusion systems; Quest Scientific: "Hum Bug" 50Hz Noise reduction system; Narishige: Micromanipulation systems; Alpha Omega: Multi-Spike detection, Multi-Channel Acquisition and software; TMC: Anti-vibration tables and Faraday cages.

For more information contact Digitimer Ltd, 37 Hydeway, Welwyn Garden City, Hertfordshire, AL7 3BE. Tel. 01707 328347, Fax. 01707 373153, E-Mail. sales@digitimer.com, Website: www.digitimer.com or visit their stand at the BNA meeting in Harrogate.

ApoTome – A minor revolution in fluorescence microscopy

Imaging Associates are pleased to announce the launch of ApoTome from Carl Zeiss. The classical challenges in displaying optical sections in 2D and 3D fluorescence imaging are now a thing of the past. ApoTome provides unmatched contrast and image quality without stray light from other focal planes, time-consuming reconstructions, long calculations and post-processing.



ApoTome offers superb image quality with the thickness of an optical section of one Airy unit and exceptional resolution in 3D imaging. Fast, and affordable de-blurred images are now possible - even with thick specimens.

Using ApoTome a grid is inserted into the plane of the field diaphragm of the reflected beam path of the fluorescence microscope. In this position, the grid pattern is projected into the specimen plane and is clearly visible through the eyepiece and via the imaging system. In the second step, a finely adjusted scanning mechanism moves the grid pattern in defined steps in the specimen plane. In the third step, images are made at each grid position and a single image is calculated using a fast mathematical algorithm. The result is a precise optical section through the specimen. With this technique, it is possible to image the entire 3D information of a specimen and to display it in 3D with increased resolution and heightened contrast and with no blurring.

For more information contact Dr Kay Jones at Imaging Associates Ltd, 6 Avonbury Business Park, Howes Lane, Bicester, OX26 2UA. Tel. 01869 356242/ 07799 412062, Fax. 01869 356241, or see us on stand 14 at the BNA.

New cross sectional imaging suite at William Harvey Hospital

Damien Green, MP for Ashford recently performed the official opening ceremony at the Cross sectional Imaging Suite of the William Harvey Hospital in East Kent.

This new suite provides state of the art cross sectional imaging in both CT and MR for the hospital and also other surrounding hospitals. The unit was purpose built and is equipped with a Siemens SOMATOM Multislice CT providing high resolution multislice imaging at low patient doses, and a Siemens MAGNETOM Symphony MRI scanner with world class Quantum gradients allowing a wide spectrum of applications.

Steve Griffiths, the Radiology Manager, is delighted with the installation and service support that has resulted in an enhanced range of investigations and increased throughput for the local area.

Steve said that the Syngo platform supporting both the CT and MR scanners aids the development of all staff to multi-skill, which is in line with their policy of staff development and role extension.

For more information contact Mike Bell on Tel. 01344 396317.

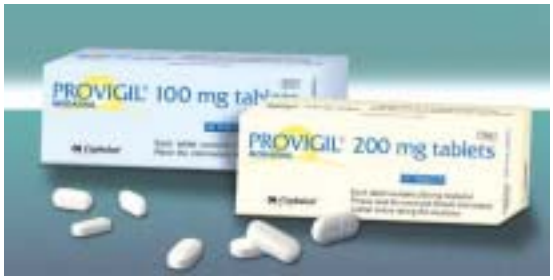
Pictured around the SOMATOM CT scanner are (L to R), Seonaid Floyd, Senior Radiographer, Meryl Davenport, Siemens, Sharon Smith, Senior Radiographer, James Coombes, Senior Radiographer, Alan Steward, Siemens, Debbie Mallon, Cross Sectional Imaging Superintendent and Dr David Rand, Lead Consultant Radiologist.

Video for Physiotherapists in PD

'Common mobility problems in Parkinson's disease and how to address them' is a video by Mariella Graziano, physiotherapist, made with the support of The Association of Physiotherapists in Parkinson's disease Europe (APPDE). The video shows simple and effective ways to overcome some of the movement difficulties associated with Parkinson's disease. It gives useful ideas on how to manage freezing, getting out of a chair, walking and doing two things at once. It will be of great help to people with Parkinson's disease, their carers and also an excellent resource for the multidisciplinary-team.

The video includes a license so that you can show it to patients. It is available for 35 euros and can be purchased on line from: www.parkinsoninfo.dk/www-uk/shop.htm

Treatment for excessive daytime sleepiness



The recent British Thoracic Society Conference saw the launch of a new treatment for the excessive daytime sleepiness (EDS) associated with obstructive sleep apnoea/hypopnea syndrome (OSAHS).

Provigil® (modafinil), an established treatment for narcolepsy, has received a licence extension for the treatment of EDS associated with OSAHS. Provigil helps restore a normal pattern of daytime alertness and is said to be a major new development in the treatment of OSAHS, an under-recognised and under-diagnosed disorder.

Around 700,000 Britons suffer from OSAHS. During sleep, the upper airway collapses, causing an apnoea, in which the person stops breathing for up to 60 seconds. In response to the resulting low and dangerous oxygen levels,

The brain wakes the sufferer so that breathing can resume. The disturbances to sleep resulting from apnoeas can lead to excessive daytime sleepiness - the symptom that Provigil is now licensed to treat.

For medical enquiries on Provigil, please call Cephalon's Medical Information Department on 0800 783 4869.

VNS Therapy Web Site

The Vagus Nerve Stimulation (VNS) Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalisation) or generalised seizures, which are refractory to antiepileptic medication.

There are now over 17,000 patients worldwide implanted with VNS. Cyberonics have continued to develop their website to support the increasing number of professionals, patients and families looking for current information and guidance on VNS therapy. The site, which contains up to date newsletters, information leaflets and contact details for all Cyberonics UK staff, can be accessed through www.vnstherapy.com/international

Healthcare professionals may register on the site to receive regular updates via the eNewsletter system, this provides summaries and abstracts of the most up to date clinical data on VNS therapy for both Adult and Paediatrics. Professionals, patients and families may also use the site to download information in PDF format or alternatively a full information pack can be requested and posted to a named address.

Autonomic Failure - A Textbook of Clinical Disorders of the Autonomic Nervous System

Fourth edition: C J Mathias & R Bannister - ISBN 0-19-262850-X

This fourth edition of Autonomic Failure covers the many recent advances made in our understanding of the autonomic nervous system. There are 20 new chapters and extensive revisions of all other contributions. It explains how to distinguish autonomic disorders from underlying primary disorders, and thus how to improve investigation, diagnosis and clinical management. It also gives practical information on physiological, pharmacological, neurochemical and neurohistological investigative techniques.

"... a book that no neurologist or indeed anyone with an interest in the autonomic nervous system can afford to be without ... strongly recommended." British Journal of Hospital Medicine.

SPECIAL PRICE FOR READERS OF ACNR! £55 (normal price £75). To order telephone 01536 741727 and quote code ABACNR03. *For more information and full contents see the website at www.oup.com/uk/isbn/0-19-262850-X*

Portable telemetry system

Micromed are pleased to announce the first truly portable telemetry system, which enables the user to record over 24-hours of video EEG. This is in keeping with Micromed's reputation of providing real features that offer the user real benefits.

Can I record Video EEG on the ward? = YES
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Can I record Video EEG at our satellite site? = YES
Can I see the product today? = YES
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For further information, please contact Micromed at 11, Drakes Way, Mayford, Woking, Surrey. GU22 0NX. Tel. 01483 728822 Fax. - 01483 755663, E-Mail. mmeduk@aol.com

micromed

Advanced Medical Equipment Ltd becomes Neuroscan distributor in the UK and Ireland

Neuroscan (www.neuro.com), the leading provider of computer software and supportive hardware for the advanced study of EEG, has found a new home in the UK and Ireland. Advanced Medical Equipment Ltd has been appointed as the new distributor in these two territories. Neuroscan is known around the globe as the provider of technologies for high-density EEG/EP recording and analysis, dipole source localisation, multi-modal neuroimaging and EEG/EP-fMRI integration. "We are very excited of course about becoming Neuroscan distributors in these two important territories", says Miguel Rodriguez, Managing Director of AME. "This is an exciting time to be linked with Neuroscan. They are currently undergoing a period of change, and these changes include a return to their old primary focus to research". Neuroscan recently announced their acquisition by Compumedics (www.compumedics.com) a leading manufacturer of diagnostic equipment for sleep research and neurophysiology based in Melbourne, Australia.

It was also announced that AME sister companies Intelimed Ibérica SL, based in Madrid and Intelimed SA de CV based in Mexico City are the new Neuroscan distributors for Spain and Latin America respectively.

For further information please contact AME on 01403 260156 or visit www.advancedmedicalequipment.com

advanced MEDICAL equipment ltd

Neurological Therapeutics: Principles and Practice

"Diagnose and dismiss". This was the often-cited summary of the role of the neurologist. Few predicted the rapid evolution of the field of neurological therapeutics and therefore a comprehensive textbook focused primarily on therapeutics has become essential.

Martin Dunitz is therefore delighted to announce the publication of Neurological Therapeutics: *Principles and Practice*. This two-volume reference-text and companion volume provide a source that is both authoritative and accessible for daily use. Including thirteen major subspecialty groupings of neurological diseases and disorders, with comprehensive summary tables and informative figures, and supporting recommendations, it guides treatment decisions for effective and efficient patient management in the busy clinic setting.

More than 270 major topics are covered by 345 internationally-renowned contributors in more than 3000 pages. The companion volume contains many of the 600 illustrations for quick and easy reference.

A must-buy for every neurologist. Order before 31st July at the 15% discounted price of £225! Tel: 020 7842 2000.

MD Martin Dunitz Taylor & Francis Group

April 2003 • 8 _ x 11 • 3,120 pp • £275 • 1-85317-623-0 • 240 line drawings • 302 halftones • 37 full-colour images • 2 volume set with companion volume

Web Browser

Web Address	Details
PRODUCT INFORMATION	
ambion.com	**Ambion (Europe) Ltd**: The RNA resource from the RNA company. Information, research papers, developments, technologies, protocols, products, and manuals for RNA manipulations.
camb-labs.com	**Cambridge Laboratories**: Information on our range of neurology products and useful backgrounders on various neurological disorders. Links to key neurological organisations and patient associations are provided.
vnstherapy.com/international	**Cyberonics Europe**:Up to date information on Vagus Nerve Stimulation Therapy - the effective and tolerable treatment for refractory epilepsy, includes clinician and patient resources plus contact details for Cyberonics.
PUBLISHERS	
dunitz.co.uk	**Martin Dunitz Ltd:** Part of the Taylor & Francis Group, Martin Dunitz publishes top quality, high level medical books in areas such as cardiology, neurology, psychiatry, oncology and urology.
acnr.co.uk	**ACNR magazine:** Download free PDF's of articles past and present and link to other sites of interest.
CONFERENCES	
epdaconferences.org	**European Parkinson's Disease Association**: 5th European PD Association meeting.
bnpa.fsnet.co.uk	
dcn.ed.ac.uk/ectmc	

To list your web site in the Web Browser call Rachael on 0131 477 2335.

New for 2003!

We are delighted to announce the launch of ACNR's web site

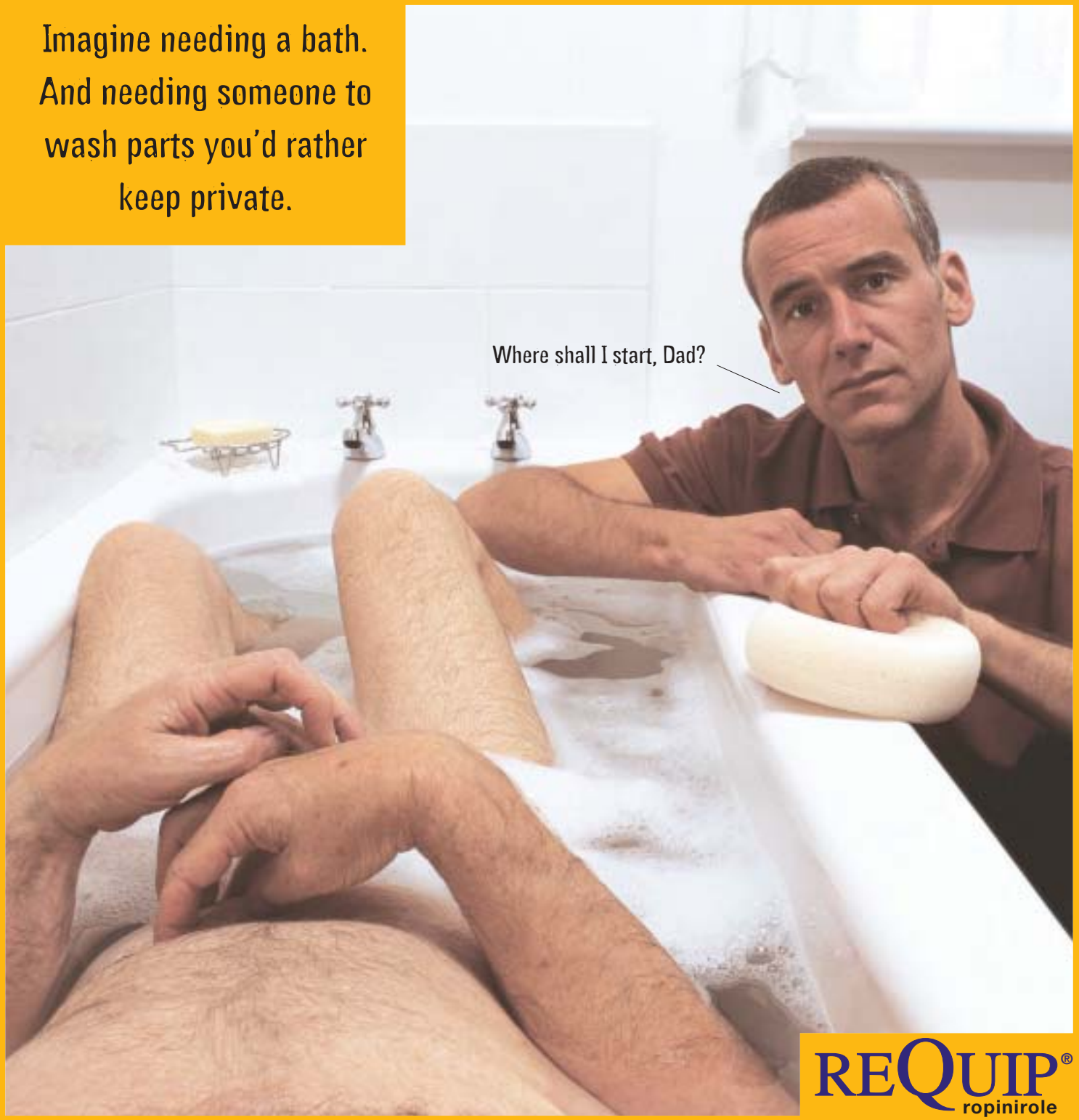
www.acnr.co.uk

- Download free PDFs of current/previous issues, as well as individual articles.
- Join our e-mail newsletter list, to receive site update information
- Send us your comments and suggestions

"For those of you who struggle with the concept of paper, you can now go back to your computer!"

Roger Barker, Co-editor

Imagine needing a bath. And needing someone to wash parts you'd rather keep private.



REQUIP® ropinirole

FIGHTS PARKINSON'S. DEFENDS DIGNITY.

REQUIP (ropinirole) Prescribing Information
Presentation 'Requip' Tablets, PL 10592/0085-0089, each containing ropinirole hydrochloride equivalent to either 0.25, 0.5, 1, 2 or 5 mg ropinirole. Starter Pack (105 tablets), £43.12. Follow On Pack (147 tablets), £80.00; 1 mg tablets – 84 tablets, £46.20; 2 mg tablets – 84 tablets, £92.40; 5 mg tablets – 84 tablets, £184.80. **Indications** Treatment of idiopathic Parkinson's disease. May be used alone (without L-dopa) or in addition to L-dopa to control "on-off" fluctuations and permit a reduction in the L-dopa dose. **Dosage** Adults: Three times a day, with meals. Titrate dose against efficacy and tolerability. Initial dose for 1st week should be 0.25 mg t.i.d., 2nd week 0.5 mg t.i.d., 3rd week 0.75 mg t.i.d., 4th week 1 mg t.i.d. After initial titration, dose may be increased in weekly increments of up to 3mg/day until acceptable therapeutic response established. If using Follow On Pack, the dose for 5th week is 1.5mg t.i.d., 6th week 2.0mg t.i.d., 7th week 2.5mg t.i.d., 8th week 3.0mg t.i.d. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually by around 20%. When switching from another dopamine agonist follow manufacturer's guidance on discontinuation. Discontinue ropinirole by reducing doses over one week. Renal or hepatic impairment: No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. Elderly: Titrate dose in normal manner. Children: Parkinson's disease does not occur in children – do not give to children. **Contra-indications** Hypersensitivity to ropinirole, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Ropinirole has been associated with somnolence and episodes of sudden sleep onset. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction seen with other Parkinson's disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Adverse reactions** In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo, however, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see 'Precautions' and 'Effects on ability to drive and use machines'). **Effects on ability to drive and use machines** Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Overdosage** No incidences reported. Symptoms of overdose likely to be related to dopaminergic activity.

POM

Marketing Authorisation Holder SmithKline Beecham plc t/a GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT.
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