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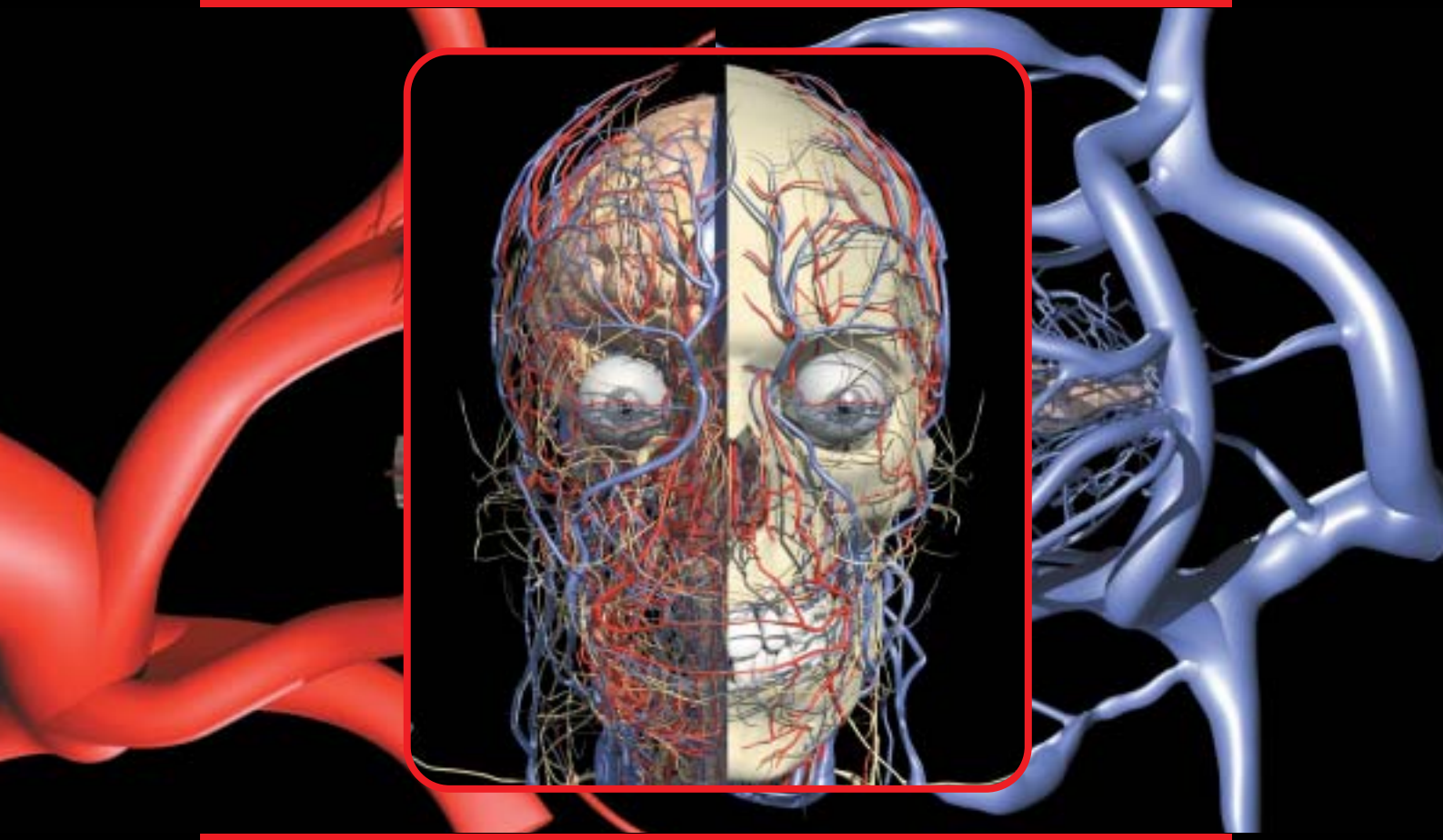

journal reviews • events • management topic • industry news • rehabilitation topic

Review Articles: Vascular Disorders of the Posterior Circulation – An Anatomico-Clinical Overview ; Involuntary Eye Movement Oscillations; Visual Hallucination and Illusion Disorders: **A Clinical Guide**

Management Topic: Dystonia

Rehabilitation Article: A Preliminary Clinical Study using RF BION®1 Microstimulators to Facilitate Upper Limb Function in Hemiplegia

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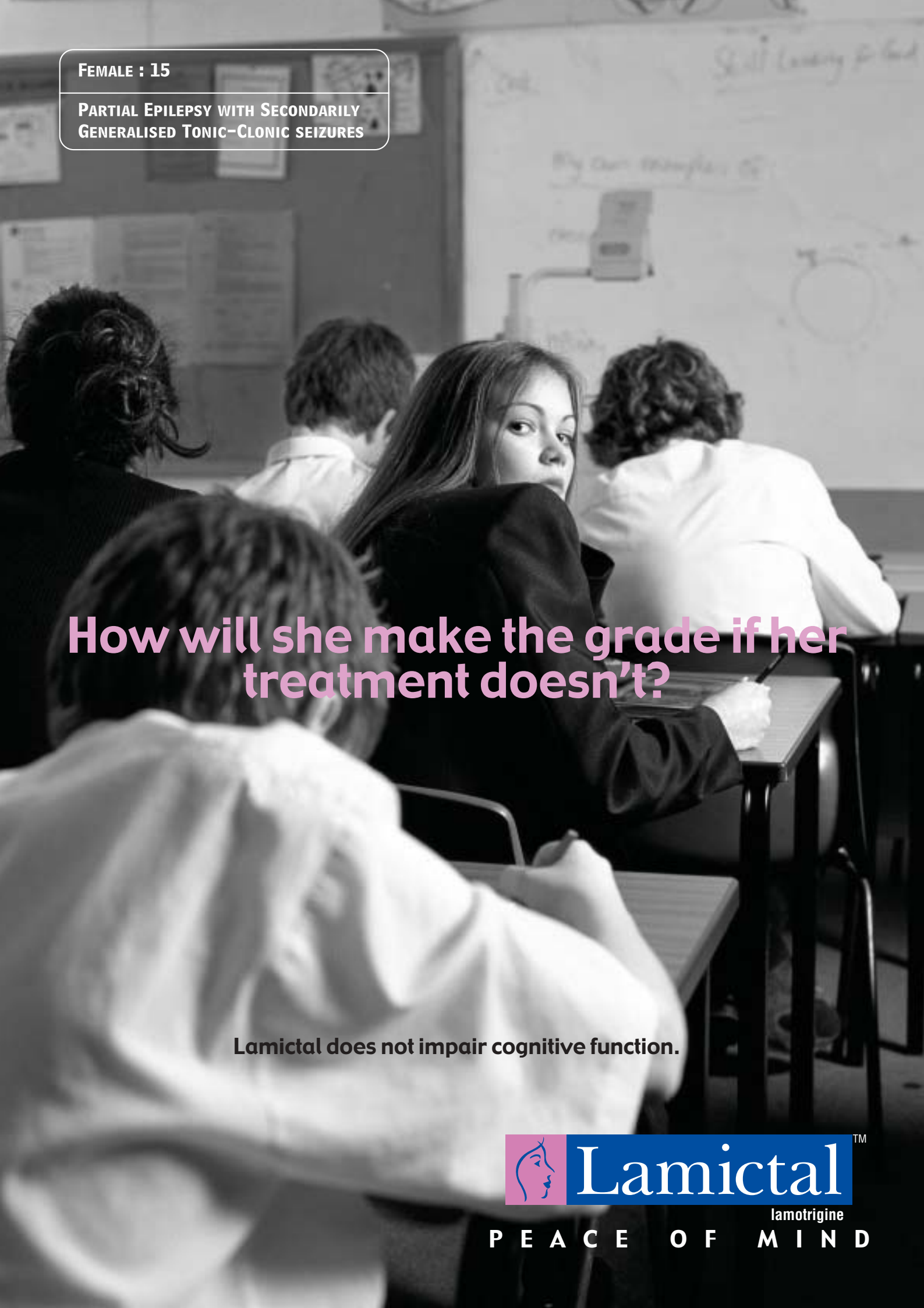
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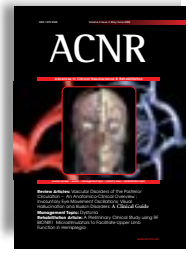

Features

Regulars

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Editorial

Welcome to another issue of ACNR, and a rather visual theme with articles on eye movements, visual hallucinations and an interview with the new chief executive of the MRC – Professor Colin Blakemore, a pioneer in the field of visual system development.

In the visual review articles, we have Dominic Ffytche taking us through the complex world's of visual hallucinations and illusion disorders, whilst the current ABN president, Chris Kennard, treats us to a learned, yet pragmatic, discussion of involuntary eye movement oscillations – primarily nystagmus.

In his article Dr Dominic Ffytche sets out to define what the patient means with these visual aberrations, before discussing how this relates to aetiological causes. This is a very interesting and rather neglected area of neuroscience, and helps delineate the neurobiological principles of how extrastriate areas relate to V1 and the evolution of visual phenomena. For the more practically minded there is also an excellent section on management.

In his article Professor Chris Kennard discusses the different types of nystagmus as well as saccadic oscillations. For those of you who have grappled with this topic and the significance of these different types of eye movement, this article is enormously helpful. Often this subject is presented in a rather complex and sterile fashion, baffling the reader with detailed neurophysiological and neuroanatomical studies, that often leave the novice more confused than when they started. However, in this article the subject is succinctly laid out with the definition, aetiology and possible therapies for each of these different abnormalities of eye movements being presented in a simple understandable way. It is an article of great clarity and I really hope that you enjoy and learn as much from it as I did.

We are also fortunate to have an excellent review of posterior circulation vascular syndrome from one of the worlds leading authorities on this, Professor Bogousslavsky along with his co-author Dr Piechowski-Jowiak. This article sets out beautifully the anatomy of this vascular system and then discusses the aetiology and clinical presentations of abnormalities within it, with clear radiographic illustrations of what is being discussed.

We also have an interview with Professor Colin Blakemore, which hopefully answers some of those questions that have been troubling you – especially given the recent government report about the MRC and their funding history and strategy. Already it seems that Professor Blakemore has made his mark, with his desire to get out and meet the scientific/clinical community and his overhaul and simplification of the MRC grant system.

The management topic on dystonia concludes our series on movement disorders and I would like to thank all those who contributed, especially David Burn in Newcastle. Our final topic is dystonia and is covered superbly by Dr Mark Edwards and Kailash Bhatia. This article, in the spirit of the series, sets out to tackle dystonia in a pragmatic fashion moving from definitions, to aetiology, investigation and ultimately treatment. This account clearly reflects a vast experience of dealing with this disorder and through Dr Kailash Bhatia we also have access to the invaluable contributions that the late David Marsden brought to this field. In the next issue our new management topic is neurosurgery for the non-neurosurgeon, with Mr Peter Whitfield providing the inspiration for these articles.

We also welcome the first of a new series of articles on cognitive neurology – to replace our previous sections on anatomy, radiology and more recently neurophysiology. In this series we will discuss how to define, assess, investigate and treat a range of cognitive disorders starting in this issue with Andrew Larner on delirium.

In addition we have an especially interesting article on the preliminary data on the clinical use of microstimulators to facilitate upper limb function in patients with hemiplegia. This is an exciting new development which shows the extent to which modern technology can be used for clinical advantage, and the way in which rehabilitation medicine is forging ahead by embracing new technological advances.

Finally there is also an excellent short paper from a member of our international editorial board, Professor Stefan, on the role of MEG in the management of epilepsy. In addition we have all our usual regular features.

So that's it for another issue, with the promise of much to come through a range of new series of articles, including neuropathology spearheaded by Professor Roy Weller. Oh yes, and don't forget the web site.

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Vascular Disorders of the Posterior Circulation – An Anatomico-Clinical Overview

INTRODUCTION

The posterior cerebral circulation consists of the vertebrobasilar system (vertebral arteries, basilar artery, posterior inferior cerebellar arteries, anterior inferior cerebellar arteries, superior cerebellar arteries, posterior cerebral arteries) (Fig. 1-3) and supplies the following anatomical structures: upper cervical spinal cord, medulla oblongata, pons, cerebellum, mesencephalon, thalami, occipital lobes, and parts of the temporal and parietal lobes (Fig. 4). Strokes in the posterior circulation comprise approximately 10% to 15% of all strokes[1] and are more common in men than in women[2]. As in supratentorial strokes, the most common etiology is ischemic (approximately 80% of cases), with the proportion of haemorrhagic strokes being similar to that seen in the anterior circulation. Although intraparenchymatous haemorrhage is slightly more frequent, while subarachnoid haemorrhage seems to be less common in the posterior territory[3].

AETIOLOGY

The risk factors for posterior circulation infarction do not differ from those for anterior circulation strokes. However, a history of prior stroke, but not transient ischaemic attacks, may be more frequently encountered in patients with posterior circulation strokes[2]. The structures most commonly affected by infarction are the brain stem (60%) and cerebellum (50%) and so are caused by lesions of basilar and/or vertebral arteries (up to 50%)[4]. The most common cause is basilar artery (BA) stenosis or occlusion (approximately 40% of patients) with the proximal and middle segments of BA being the most frequent site of occlusion[5]. Some patients may have stenosis and/or occlusion of the extracranial or intracranial part of the vertebral artery, or posterior cerebral arteries lesions. In rare instances, a dolichoectasy of basilar artery or vertebral artery may be encountered[4].

Small artery disease is a presumed cause of stroke in 15% of patients, whereas cardiac embolism (e.g. from thrombus associated with an akinetic left ventricle, atrial fibrillation, or paradoxical embolism through a PFO) is a causative factor of stroke in approximately 13% of patients. In an equal proportion of patients (i.e. 13%) there may be more than one possible cause of stroke including arterial stenosis and/or occlusion, lacunar lesions or a potential cardiogenic source of embolism, whilst in 10% of cases no potential cause of stroke can be identified.

However, there are two types of infarction in the posterior territory which are highly suggestive of a particular etiology. Isolated unilateral or bilateral brainstem infarcts (involving midbrain and/or pons) are associated with basilar stenosis, while isolated cerebellar infarctions are associated with cardioembolism[4].

Other etiologies of stroke such as for example, dissection of basilar artery or vertebral arteries (Figure 5), are rarely reported in patients with posterior circulation disorders. Cerebral venous and/or sinus thrombosis limited to the posterior circulation teritory are casuistic.

CLINICAL FEATURES

In posterior circulation infarctions severe headache and vomiting are more frequently seen than in anterior circulation strokes[2]. The common signs and symptoms include bulbar or pseudobulbar palsy, vertigo and dizziness, hemiparesis, tetraparesis, cerebellar ataxia, eye movement disorders, changes in levels of consciousness and neuropsychological dysfunction. Indeed the organisation of the brainstem relative to its vascular supply leads to a number of well-recognised syndromes. So ischemic lesions in the territory supplied by posterior inferior cerebellar artery may give the lateral medullary syndrome (Wallenberg's syndrome) [characterised by ipsilateral facial sensory disturbances, nystagmus, dysphagia, dysarthria, Horner's syndrome with contralateral hemibody dissociated sensory disturbances]. The symptoms of anterior inferior cerebellar artery occlusion are similar to those of Wallenberg's syndrome, but can additionally be differentiated by the presence of limb and trunk ataxia, tinnitus, deafness, and facial nerve involvement. Superior cerebellar artery occlusion can be distinguished by the predominance of cerebellar symptoms and a trochlear nerve palsy[6].

Basilar artery occlusion may give a large spectrum of neurological signs and symptoms of which the most

Dr Bartomiej Piechowski-Jówiak, is a Stroke fellow at the Department of Neurology, CHUV, Lausanne, Switzerland. His research interests include cerebrovascular disorders and neurosonology.

Professor Julien Boggouslavsky is Professor and Chairman of the University Department of Neurology, Lausanne, Switzerland. He is also Professor of cerebrovascular disease and Chief of the Lausanne Stroke Program, and Chief of the Neurology Service, University Hospital, Lausanne.

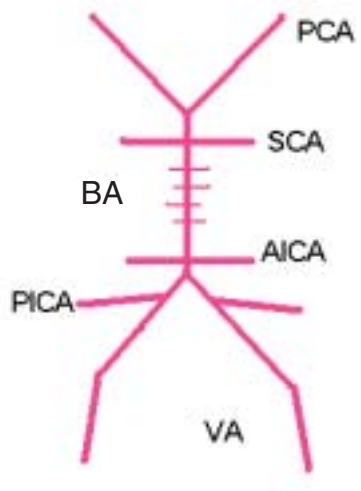

Figure 1. A schematic drawing of the posterior circulation arteries. VA: vertebral artery; PICA: posterior inferior cerebellar artery; AICA: anterior inferior cerebellar artery; BA: basilar artery; SCA: superior cerebellar artery; PCA: posterior cerebral artery.

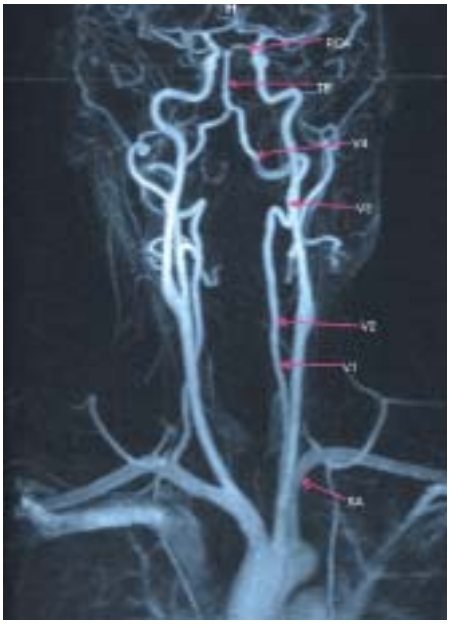

Figure 2. Magnetic resonance angiography showing normal posterior circulation arteries (abbreviation unfolded in figure 1). SA: subclavian artery; V1-V3: extracranial segments of vertebral artery; V4: intracranial segment of vertebral artery.

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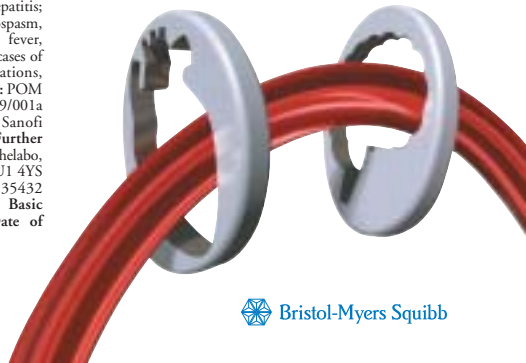

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frequent are motor deficits ranging from monoparesis to tetraplegia, and also dysarthria, vertigo, nausea and vomiting, headaches, alterations of consciousness, ataxia, and sensory disturbances[7]. Embolic occlusion of the distal part of basilar artery at the point at which it branches into two posterior cerebral arteries, gives a dramatic picture of the so called 'top-of-the-basilar syndrome'. This clinical entity is characterised by severe impairment of consciousness, usually bilateral oculomotor palsies, visual fields defects, cerebellar symptoms, and hemiplegia or tetraplegia.

Multiple infarctions in the posterior circulation are found in approximately 10% of patients with infratentorial and supratentorial infarcts being most commonly found to coexist, whilst concomitant brainstem lesions are less common. In such patients hemianopia, and cerebellar signs predominate and are due typically to vertebral and/or basilar artery steno-occlusive disease rather than cardioembolism. Multiple infratentorial strokes are less frequently seen, and are characterised by a combination of brainstem and cerebellar signs. Lacunar lesions are seen in the majority of these cases and the most uncommon scenario is multiple brainstem and posterior cerebral artery strokes[8]. However there exists a rare condition which consists of infarction in the posterior inferior cerebellar artery and the posterior cerebral artery territories, caused by occlusive disease of the intracranial vertebral artery, with bilateral occlusion of the posterior inferior cerebellar artery together with distal embolism to posterior cerebral artery. A term proximal-distal syndrome of the posterior circulation was coined to describe this clinical entity that is characterised by bilateral axial ataxia with visual field defects[9].

Overall the most common etiology of posterior cerebral artery territory infarction is cardioembolism, followed by embolism of undetermined origin, and artery-to artery embolism although in approximately 20% of cases the etiology remains unknown. Ischemic strokes in the territory supplied by posterior cerebral arteries are usually manifest as severe headaches, visual field defects (homonymous hemianopia), sensory signs, motor deficits, and cognitive deficits[10].

The occlusion of small penetrating branches of basilar artery gives rise to the lacunar lesions. There are four classical lacunar syndromes that may be linked to the posterior circulation strokes. Pure sensory stroke may be caused by the lesions confined to the pons, or thalamus. Pure motor hemiparesis may be caused by the pontine lesion. Thalamic or pontine lacunae may give symptoms of sensorimotor stroke. Ataxic hemiparesis may be caused by a pontine lacunar lesion[4].

PROGNOSIS

The outcome in patients with posterior circulation infarction is quite good, with a 30-day case fatality of <4% and less than 20% of patients being left with severe disability after one month, and approximately 30% of patients having no disability[11]. However, half of the patients with BA occlusion have a poor outcome (death or severe disability) with dysarthria, pupillary disorders, decreased levels of consciousness, bulbar symptoms, multiple posterior circulation infarcts, and cardiac embolism all being predictors of poor outcome[5,8].

Intraparenchymatous bleeding in the posterior fossa is usually a medical emergency, as pontine haemorrhages are lethal in 60% to 90% of cases, depending on the extent of haemorrhage and location (Figure 6)[12,13]. Massive pontine haemorrhages are characterised by sudden onset of coma, respiratory disturbances, tetraplegia with posturing, characteristically with pinpoint pupils, and lower cranial nerves palsies. Large cerebellar haemorrhage may present with severe headache, vomiting, hemi ataxia, nystagmus, and eventually coma. The symptoms of small thalamic hemorrhage may resemble those of lacunar infarction and may include contralateral hemisensory symptoms and usually less pronounced contralateral hemiparesis (Figure 7). In some of these cases upgaze paresis may be encountered. Large thalamic hematomas cause more complex clinical syndromes, as the affected territory is bigger and has a one-month case fatality approaching 25% - this being highest with posterolateral haemorrhages. The predictors of death are initial level of consciousness, meningeal signs, size of haemorrhage with ventricular extension, and the presence of hydrocephalus[14].

CONCLUSION

Posterior circulation strokes do not differ much from anterior circulation strokes in risk factors. However, they are distinct in their symptomatology, as different anatomical structures are involved. Different clinical symptomatology may also be explained by a more frequent arterial branch disease in the territory of the basilar artery that gives classical lacunar syndromes. Furthermore the verti-

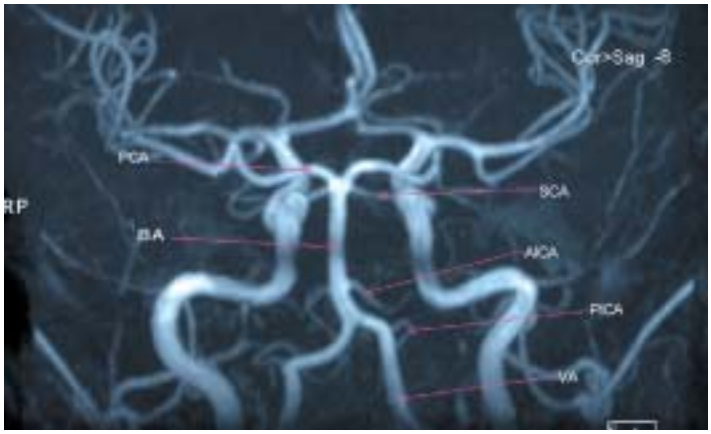

Figure 3. Magnetic resonance angiography with a detailed view of the intracranial part of posterior circulation (abbreviation unfolded in figure 1).

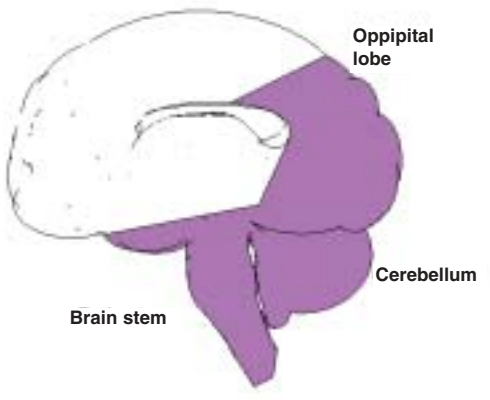

Figure 4. A schematic drawing (medial aspect of a sagittal section through the brain) of the territory suppied by posterior circlulation arteries (thalamus not shown).

cal arrangement of the posterior circulation arteries as opposed to the horizontal localisation of the anterior circulation arteries may explain the preponderance for the multiple infarcts at the different levels in the posterior circulation, while multiple infarcts in the anterior circulation are much rarer.

From a clinical point of view it is important to remember that some clinical syndromes such as basilar thrombosis, or posterior fossa haemorrhage are medical emergencies and require prompt diagnosis and treatment.

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* Supported by research grants from the International Stroke Society and World Federation of Neurology

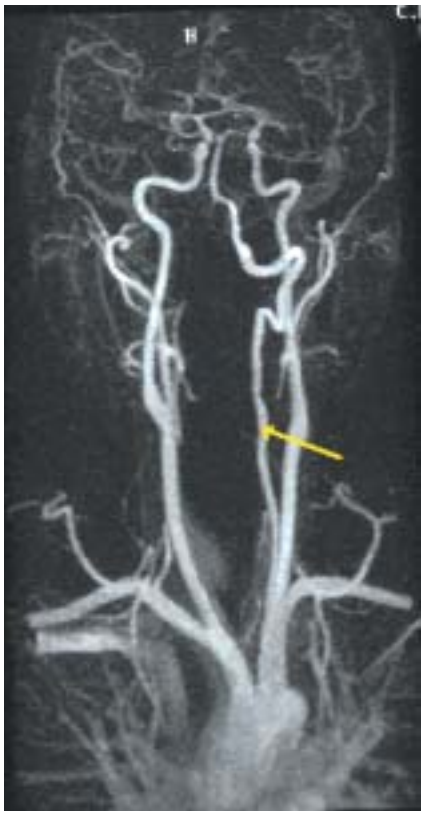
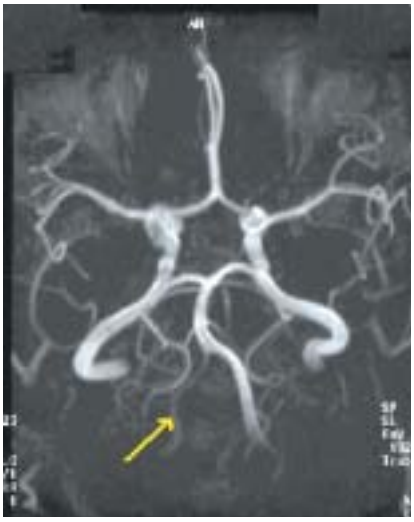


Figure 5 A. Magnetic resonance (time-of-flight) angiography of neck and intracerebral vessels showing an occlusive dissection of the right vertebral artery (segment V2-V4) (A: yellow arrow: normal vertebral artery; B: yellow arrow largely diminished flow in intracranial right vertebral artery). Magnetic resonance (Diffusion-weighted imaging) showing a right lateromedullary infarction, and bilateral small ischaemic lesions (yellow lines) in the territory of posterior inferior cerebellar artery (C).



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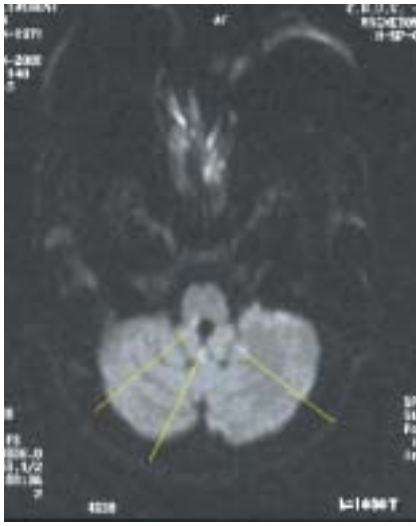

Figure 5 C.

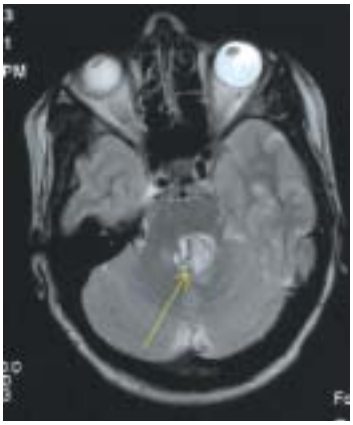

Figure 6. Acute phase magnetic resonance imaging T2 showing a secondary pontine haemorrhage (cavernoma).

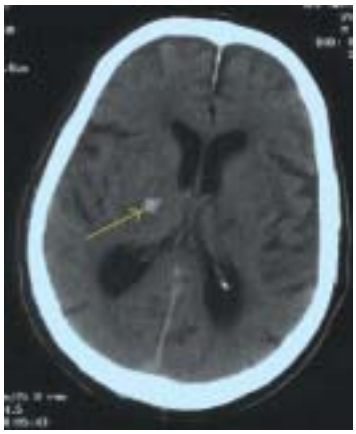

Figure 7. Acute phase cerebral computed tomography showing a hypertensive right thalamo-capsular haemorrhage.

Involuntary Eye Movement Oscillations

Rhythmic or arrhythmic involuntary sustained to and fro oscillations of the eyes are classified as either nystagmus or saccadic (rapid conjugate eye movements) oscillations. There is an important distinction between them. Saccadic oscillations are initiated by saccadic eye movements, whereas in nystagmus the oscillations are initiated by smooth eye drifts and the fast phase in jerk nystagmus is corrective and not primary (Table 1) (Figure 1). This short review will describe the commonest types of these ocular oscillations, their causation and management[1,2,3,4].

Nystagmus

Nystagmus is an oscillation initiated by a slow drift of the eye. This drift may be sinusoidal (pendular nystagmus) or be followed by a fast corrective (saccadic) eye movement (jerk nystagmus). Although the direction of the nystagmus is conventionally described by the direction of its quick phases (for example upbeat nystagmus) it is important to remember that it is the smooth eye movement imbalance which reflects the underlying disorder (Table 2). Nystagmus usually results from a disturbance in one of the three mechanisms which hold gaze still – visual fixation, vestibulo-ocular reflex and the eccentric gaze holding mechanism[5].

The commonest form of jerk nystagmus is *peripheral vestibular nystagmus*, which most frequently results from labyrinth or vestibular nerve dysfunction. Tonic vestibular input from the intact side is unopposed by input from the affected side causing drift of the eyes to that side. This type of nystagmus is usually mixed i.e. various combinations of horizontal, vertical and torsional components; it is always unidirectional, the quick phases beating away from the underactive labyrinth; its intensity increases when the eyes are turned in the direction of the quick phases; it is markedly suppressed by visual fixation (by using Frenzel goggles); it is usually accompanied by vertigo, which is of limited duration due to central compensation. If nystagmus persists for more than a few weeks, it is usually due to an abnormality of the central vestibular pathways. Treatment with diphenhydramine, promethazine, or prochlorperazine is appropriate for relief of the accompanying nausea and should be stopped as soon as possible since they can impair the normal compensatory mechanisms.

Several different types of *central vestibular nystagmus* are described, all of which show no change in intensity with the removal of visual fixation in contrast to peripheral vestibular nystagmus. *Downbeat nystagmus* may or may not be present in the primary position. It beats directly downwards and is often accentuated in lateral gaze. When present in the primary position a disturbance of the vestibulocerebellum, drug intoxication or an abnormality at the cranio-cervical junction, such as a Type 1 Chiari malformation, are usually found[6]. These causes include cerebellar degenerations, anticonvulsant drugs, lithium intoxication and intra-axial brainstem lesions. In about half of the patients with downbeat nystagmus, no cause can be found. Treatment can be attempted with clonazepam, baclofen, trihexyphenidyl or acetazolomide for the nystagmus associated with episodic ataxia type II[7,8].

Upbeat nystagmus when present in the primary position, is usually associated with focal brain-stem lesions in the tegmental gray matter, either at the pontomesencephalic junction or at the pontomedullary junction, involving the nucleus prepositus hypoglossi or the ventral tegmental pathway of the upward vestibulo-ocular reflex. Multiple sclerosis, tumour, infarction and cerebellar degeneration are the commonest causes[9]. This type of nystagmus is occasionally suppressed by clonazepam.

Torsional nystagmus is a jerk nystagmus around the anteroposterior axis. It is commonly associated with other types of nystagmus. However, when it is pure it indicates a lesion of the lateral medulla, involving the vestibular nuclei. Occasionally it may be due to a midbrain-thalamic lesion, involving the interstitial neucleus of cajal (INC.)

Gaze-evoked nystagmus is a common clinical observation with limited localising value. It is a jerk nystagmus which is absent in the primary position and is only present on eccentric gaze. It is due to abnormal functioning of the gaze-holding integrator neurons in the paramedian pontine reticular formation (PPRF) region, resulting from impaired inputs from the cerebellar flocculus. Bilateral horizontal, together with vertical, gaze-evoked nystagmus commonly occurs with structural brainstem and cerebellar lesions, diffuse metabolic disorders and drug intoxication. Treatment is not required since this type of nystagmus rarely causes severe visual problems.

Periodic alternating nystagmus (PAN) is a primary position horizontal nystagmus that changes direction in a crescendo-decrescendo manner, characteristically approximately every 90 sec. Between each directional change there is a null period of 0 to 10 sec. It is usually associated with lesions affecting the nodulus or uvula of the cerebellum. There is a congenital form[10], and acquired forms are due to Chiari malformations, multiple sclerosis, fourth ventricle tumours, spinocerebellar degenerations and anticonvulsant intoxication. Baclofen has been shown to be an effective treatment for the acquired form[11].

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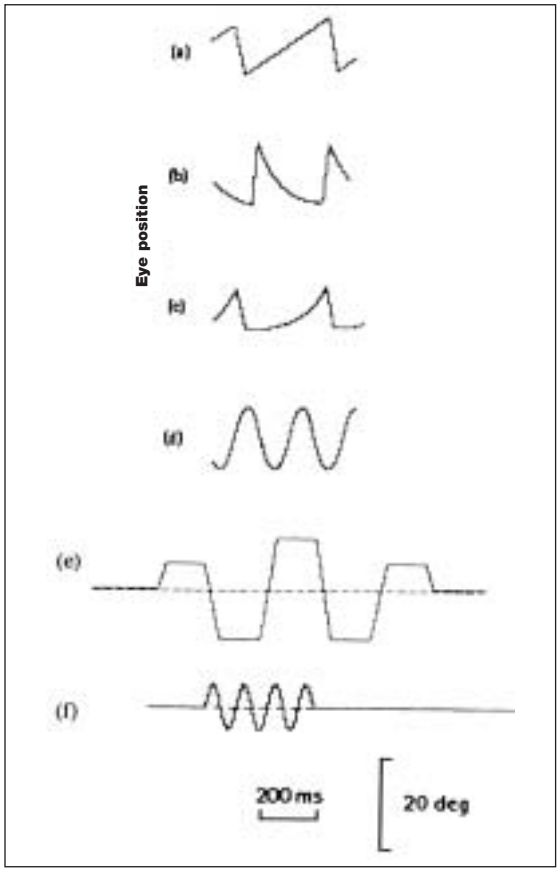

Figure 1. Wave forms and saccadic oscillations of nystagmus. (a) Constant velocity drift of the eyes. This occurs in nystagmus caused by peripheral or central vestibular disease and also with lesions of the cerebral hemispheres. The added quick phases give a sawtooth appearance. (b) Drift of the eyes back from an eccentric orbital position toward the midline (gaze-evoked nystagmus). The drift shows a negative exponential time-course with decreasing velocity. This waveform reflects an unsustained eye position signal caused by an impaired neural integrator. (c) Drift of the eyes away from the primary position with a positive exponential time-course (increasing velocity). This waveform suggests an unstable neural integrator and is encountered horizontally in congenital nystagmus and vertically in cerebellar disease. (d) Pendular nystagmus, which is encountered as a type of congenital nystagmus and with acquired disease. (e) Macrosaccadic oscillations: hypermetric saccades about the position of the target. (f) Ocular flutter: to-and-fro, back-to-back saccades without an intersaccadic interval. (Redrawn from Leigh and Zee. *The Neurology of Eye Movements. Oxford University Press, 1999*[28]).

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Pendular nystagmus is either congenital or acquired due to cerebellar and brainstem disease, usually multiple sclerosis[12]. Acquired pendular nystagmus may have both horizontal and vertical components, and the amplitude and phase relationships of the two sinewaves determine the trajectory of the eyes e.g. oblique, circular or elliptical[13]. It can affect one eye or both, equally or unequally, and is often symptomatic resulting in oscillopsia. It may be associated with oscillations of other structures such as the palate, head or limbs[14]. In some patients gabapentin or memantine may reduce the amplitude of nystagmus and relieve oscillopsia[15].

Congenital nystagmus is almost invariably a horizontal conjugate nystagmus, which is unaltered by vertical position. It is generally of jerk type with accelerating slow phases, and has an eccentric null position often leading to a head turn or occasionally a head oscillation[16]. Fixation effort enhances congenital nystagmus. Less commonly the nystagmus is of a pendular type. Reversed optokinetic nystagmus, beating in the direction of the target motion, is a feature of congenital nystagmus[17].

Latent nystagmus is a type of congenital nystagmus that is only present on monocular viewing and which then beats toward the viewing eye[18]. It is absent on binocular viewing. If the patient has amblyopia in one eye latent nystagmus is present with both eyes viewing, when it is called manifest latent nystagmus.

Saccadic oscillations

Saccadic oscillations are bursts of saccades, which may be intermittent or continuous, causing a disruption of fixation. Two main types can be identified, those with brief periods of fixation between saccades (intersaccadic interval approximately 200 msec) and those composed of back-to-back saccades (Table 3).

The oscillations with intersaccadic intervals include square wave oscillations consisting of sequences of square wave jerks (SWJ), which can occur in Alzheimer's disease and progressive supranuclear palsy. *Macrosaccadic oscillations* (up to 40 deg) straddle the intended fixation position and show a crescendo-decrescendo pattern. This type of oscillation is usually observed in acute damage to the dorsal cerebellum involving the deep cerebellar nuclei, as in demyelination, tumour or haematoma[19].

Table 1 – Definitions of types of ocular oscillation

Nystagmus – a sustained to and fro oscillation initiated by a smooth eye movement

Saccadic oscillations – sustained oscillations initiated by fast (saccadic) eye movements

Table 2 - Types of nystagmus and their mechanism

Impaired vestibulo-ocular reflex
- Peripheral vestibular
- Central vestibular – downbeat, upbeat, torsional, periodic alternating nystagmus

Impaired gaze-holding mechanism
- Gaze-evoked nystagmus

Visual fixation
- Congenital nystagmus
- See-saw nystagmus

Unknown mechanism
- Pendular nystagmus

Oscillations without any intersaccadic interval (back-to-back) include opsoclonus, ocular flutter and convergence-retraction saccadic pulses. *Opsoclonus* consists of multidirectional (including oblique and torsional) back-to-back saccades of varying amplitude. It has been suggested that the disorder arises due to disordered pause cell function in the PPRF[20]. A variety of posterior fossa disorders can give rise to the condition, including parainfectious brain stem encephalitis, metabolic-toxic states or as a paraneoplastic (non-metastatic) disorder; in children it is associated with occult neuroblastoma and in adults with small cell carcinoma of the lung and carcinoma of the breast and uterus[22,23]. Both anti-Ri and anti-Hu antibodies have been identified in paraneoplastic opsoclonus in adults. It can also occur in neonates associated with myoclonus - 'dancing eyes and dancing feet.'[24] This appears to be a maturational deficit which usually resolves over approximately 6 weeks. Treatment may be with plasmapheresis or intravenous immunoglobulins[21] and drug treatments have included corticosteroids, propanolol, verapamil, clonazepam and gabapentin. *Ocular flutter* consists of bursts of back-to-back saccades in the horizontal plane only, observed in patients with multiple sclerosis and signs of cerebellar disease[25]. It can also be observed in patients recovering from opsoclonus. A voluntary form of flutter (voluntary flutter) can be induced by about 8% of the population, usually by convergence. It consists of salvoes of horizontal back-to-back saccades. Lesions of the dorsal midbrain are often associated with upward gaze palsies and *convergence-retraction nystagmus* (Parinaud's syndrome). This is incorrectly termed a nystagmus since it actually consists of asynchronous adducting saccades and should be redesignated convergence-retraction saccadic pulses[26]. It may alternatively be due to opposed vergence movements[27].

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Table 3 – Types of saccadic oscillations

1. With an intersaccadic interval
   - Square wave oscillation
   - Macrosaccadic oscillation
   - Convergence-retraction pulses (nystagmus)
   - Ocular bobbing

2. Back-to-back saccades
   - Opsoclonus
   - Ocular flutter
   - Voluntary flutter (nystagmus)

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Visual Hallucination and Illusion Disorders: A Clinical Guide

Dominic Ffytche is a Senior Lecturer and Consultant at the Institute of Psychiatry and has recently completed a Wellcome Clinician Scientist Fellowship. He has a special interest in visual perception and its pathologies and runs a Visual Perceptual Disorders Clinic at the Maudsley Hospital.

The past century of advances in visual neurobiology and perceptual science have all but passed visual hallucinations by. Much of our assessment and management owes more to 18th century Natural Philosophy than 21st century Neuroscience. Part of the problem has been that the experiences are traditionally considered rare, of poor localising value and without associated morbidity. However, recent recognition of their true prevalence across a range of disorders[1-4] and the fact that they typically cause distress, are stigmatising, often inappropriately medicated and can precipitate institutional care, has awakened research interest. Although much has yet to be learnt, the basic and clinical science findings help formulate a structured approach to their assessment and management. What follows is a science-led guide to how one might approach a patient presenting with visual hallucinations, either occurring *de novo* without previously recognised pathology or, more typically, in the context of ongoing neurological, ophthalmological or psychiatric disease.

Defining the symptom

Rote definitions of hallucinations and illusions trip easily off the tongue, leaving the impression that the two are entirely separate entities. However, in clinical practice the difference between them is less than clear cut. Many patients who on some occasions 'see things that are not really there' will, on other occasions, 'see real things incorrectly'. Furthermore, different classes of 'incorrect seeing' (polyopia and metamorphopsic distortions, for example) seem to apply equally to hallucinated things as real things. Put another way, patients describe illusions of hallucinations - a situation which amounts to a logical impossibility. How can something not actually there, be seen incorrectly ? It all amounts to a neurophilosophical nightmare from which a pragmatic clinical escape route is to pool illusions and hallucinations into a single entity – the 'positive' disorders of visual perception – treating both as one[5]. But loosening definitions with one hand requires tightening them with the other. All reports of 'seeing things' need not indicate a positive perceptual disorder. Before diving deep into the patient's visual psyche, it is worth pausing to consider whether the symptom being described is vivid visual imagery. Visual images appear in the mind's eye and are under some degree of volitional control, as opposed to hallucinations and illusions which are externally located, unpredictable and outside volition (in the sense that one cannot choose to make a hallucination of, say, a face turn into that of a chair). Termed pseudohallucinations in the European psychopathological tradition, vivid visual images carry very different aetiological implications to those of hallucinations and illusions, imagery pointing to a diagnostic spectrum which ranges from normal phenomena to clinical anxiety syndromes. Note that, confusingly, the American psychopathological tradition uses the term pseudohallucination in a different way, referring to hallucinations that are recognised for what they are (i.e. those for which the patient has insight).

Describing the phenomenology

Although traditionally ignored as a useful clinical sign, the content of a patient's visual hallucinations may help point to the underlying diagnosis and direct future management. Time spent exploring the range of perceptual pathologies experienced pays clinical dividends. While each hallucination is, in one sense, unique – no two patients having exactly the same experience or range of experiences - take away the intricacies of detail and one is left with only two broad phenomenological syndromes, caricatured in Figure 1. In one syndrome patients will describe hallucinations from a palette which ranges from simple unformed lines, dots, colours and flashes, through more complex grid patterns and lattices to distorted faces (grotesque or gargoyle-like), unfamiliar figures in bizarre costume (often wearing elaborate hats) and extended landscape scenes. Not all the palette is experienced by every patient, some will have several types of hallucination, others just one. The experiences are typically brief, lasting seconds to minutes, silent and may be confined to a particular area within the patient's visual field. The second syndrome is derived from a different palette. Here the hallucinations range from isolated animals and figures (often familiar and without the bizarre costumes and hats of the first grouping), through extracampine hallucinations ('feeling' rather than 'seeing' an object, typically a person watching you), to multi-modality hallucinations (e.g. hearing the hallucinations talking or feeling them crawl up one's arm) and complex delusional explanations for the experiences (e.g. the neighbour's children have stolen a key to the house and wander in and out uninvited). The experiences may be brief but can last for hours or even days. Table 1 summaries key phenomenological points to help discriminate the two syndromes.

Matching syndrome to aetiology

While the details have yet to be worked out, we know why patients with visual hallucinations fall into two broad syndromes: it is because the parts of the brain involved differ between the two. Visual hallucinations and illusions relate to transient increases in activity within visual cortex, the location of the increase defining the content of the hallucination[6,7]. Thus increased activity in face specialised cortex leads to hallucinations of faces, increased activity in colour specialised cortex, hallucinations of colour and so forth. The palette of hallucinations in a given patient thus reflects the location and extent of their susceptible cortex. The implication is that patients who experience the first syndrome have a susceptibility in different cortical regions to those with the second. Indeed, the second syndrome must extend beyond purely visual cortex to include multi-modal areas and those underlying the generation of delusions.

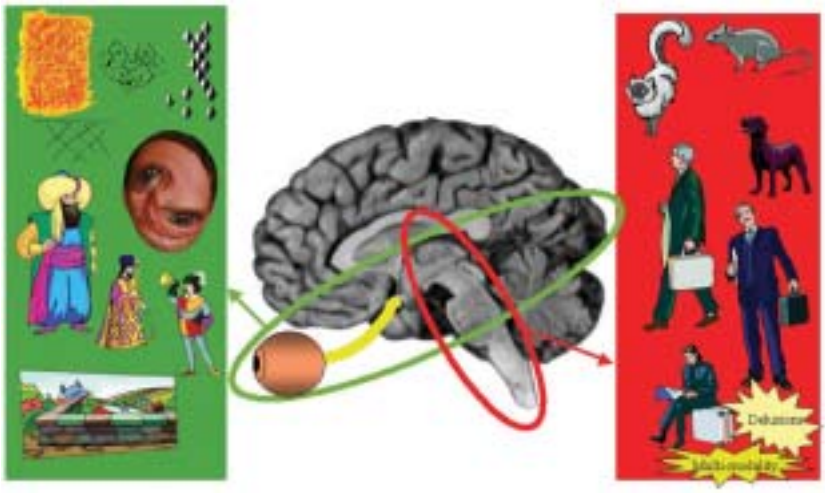

Figure 1. Visual pathway (left) and brainstem/cholinergic (right) hallucination syndromes.

The key question is what defines which cortical regions are affected in a given patient, and hence what defines which syndrome they will have. While as yet unanswered, an important clue seems to be where their primary pathology lies. Table 2 sets out the hallucination-related disorders likely to be encountered clinically, arranged into two pathophysiological groupings, one in which the primary pathology lies in the visual pathways or higher visual areas (prototypical disorder, Macular disease), the other in which it lies in the brainstem and/or cholinergic system (prototypical disorder, Parkinson's disease). The choice of terminology in the second group is not intended to diminish the possible role of other brainstem neurotransmitter systems in visual hallucinations (see[8] for review), it serves merely to emphasise that role played by the cholinergic system[9]. Of course many hallucination-related disorders fail to fit neatly into this dichotomous classification, either because their pathology is unclear (e.g. the psychoses) or because they contain elements of both. For example, visually hallucinating patients with Lewy body dementia will have both brainstem/cholinergic pathology and Lewy bodies in higher visual areas[10] while those with Parkinson's disease will have subtle visual deficits suggestive of visual pathway dysfunction[11]. However, despite its obvious shortcomings, the classification is worth pursuing as it neatly divides clinical conditions into those associated with one or other of the syndrome palettes. Thus the spectrum of visual pathway disorders outlined in Table 1 are associated with the syndrome shown on the left of Figure 1, while the spectrum of brainstem/cholinergic disorders (as well as those of mixed and unknown aetiology) are associated with those on the right of Figure 1. One might wish to refer to the visual pathway disorder palette as the Charles Bonnet syndrome, although it is important to realise that different clinical specialties use the term in different ways[5]. The hallucinations associated with visual pathway lesions and those associated with brainstem/cholinergic lesions also differ in another important respect: their prognosis. Visual pathway hallucinations tend to be self limiting and resolve without pharmacotherapy (60% of patients with hallucinations secondary to Macular disease are hallucination free at 18 months[12]). In contrast, brainstem/cholinergic hallucinations (at least those found in Parkinson's disease) tend to persist and progress[13], even acting to precipitate institutional care[14].

Management

With such a wide range of potential aetiologies and endless possibilities for clinical overlap (glaucoma in a patient with Parkinson's disease, cognitive impairment in a patient with Macular degeneration), how should a patient with visual hallucinations be managed? Clearly the answer will depend on the clinical context; however, the general principles are summarised in Figure 2. Whatever the patient's phenomenology, it is important to review their medication to minimise anti-cholinergic load and to consider whether the hallucinations/illusions may have been precipitated by concurrent infection (often a UTI in the elderly). The question of whether to investigate depends largely on the match between their hallucinations and clinical context: if the symptoms are wrong, look for another cause. Hallucinations of a familiar dog in a patient with Parkinson's disease would not warrant further investigation but hallucinations of grid patterns confined to one hemifield might prompt imaging of the visual cortex. Similarly, prolonged hallucinations of whispering figures in a patient with Macular disease might warrant referral to an old age psychiatry service whereas a brief hallucination of an Edwardian tea party would not. Two investigations deserve special mention. Sleep studies may have a place in the investigation of brainstem/cholinergic hallucinations as these have been found to relate to REM sleep behaviour disorder and daytime REM intrusions[15]. Visual evoked potentials may help characterise a visual pathway lesion but there are, as yet, no known VEP markers for susceptibility to hallucinations.

Treatment options will depend on the syndrome identified. Visual pathway disorder hallucinations may be treated with reassurance and the knowledge that the hallucinations will resolve in time, although may re-occur if the visual pathway lesion progresses. The Macular Disease Society and Royal National Institute for the Blind can provide patients with further information and, in some areas, specific hallucinator support groups. Where possible, it is worth optimising visual function as this may reduce the frequency of hallucinations[16]. For non-distressing, visual-only brainstem/cholinergic hallucinations without persistent secondary delusions, patients may be managed with reassurance, although the experiences are likely to persist and progress. For brainstem /cholinergic syndrome hallucinations that are distressing, multi-

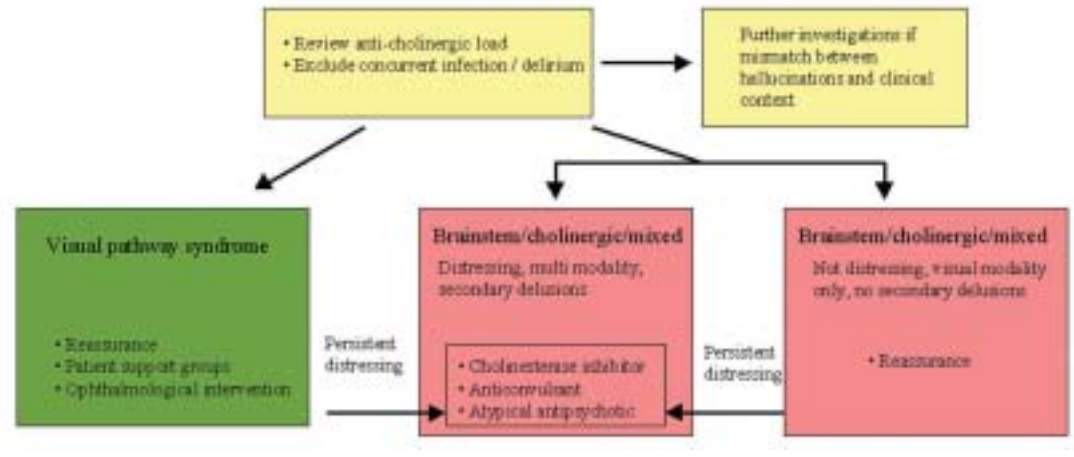

Figure 2. Management algorithm

Info on the web

Macular Disease Society
www.maculardisease.org
Tel. 0990 143 573

Royal National Institute for the Blind
www.rnib.org.uk
Tel. 0845 766 9999

Table 1. Key phenomenological features

Content checklist	Simple forms and colours Grid and lattice patterns Disembodied faces Figures: mundane/ bizarre, familiar/unfamiliar Animals Landscapes
Duration	
Other modalities	Auditory, tactile, olfactory
Delusions/Insight	

Table 2. Clinical associations

Visual pathway	Brainstem / Cholinergic	Mixed / unknown
Ocular pathology	Iatrogenic	Dementia
Macular disease	*Tricyclics*	*Lewy body*
Diabetic retinopathy	*Oxybutinin*	*Vascular*
Glaucoma	*Benztropine*	*Alzheimer's*
Infarct		
Post. cerebral artery	Parkinson's disease	Psychosis
		Schizophrenia
		Bipolar disorder
Partial seizure	Narcolepsy	Delirium
Occipital		
Migraine	Peduncular lesion	Bereavement

modality or with persistent delusions (or visual pathway syndrome hallucinations that are persistent and distressing) largely anecdotal treatment options include cholinesterase inhibitors, anti-convulsants and atypical antipsychotics[17,18]. Which class of medication to use will depend on the clinical context, with cholinesterase inhibitors a logical first choice for patients with cognitive impairment and atypical antipsychotics for those with pronounced delusions.

Future directions

While the basic science of hallucinations is beginning to inform the clinic, the converse is also true, the clinic is directing the basic science. Hallucinations and illusions that seem commonplace to the clinician pose a challenge for the basic sciences. Why should our visual systems generate spontaneous percepts of bizarrely costumed figures sporting hats ? What visual function is going wrong when we see polyopic copies of the same object, neatly arranged in rows? For the astute clinician, hallucinating patients are giving us the answers to questions that have yet to be conceived.

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I'm having difficulty concentrating at work. I feel too exhausted to play football at the weekends. I can fall asleep just waiting in traffic. I often lose track during conversations with my friends. I can no longer go to the cinema because it sends me to sleep. I've started sleeping through my lunchtimes. When I sit in front of the TV, it's all I can do to stay awake. Uncontrollable sleeping keeps me from baby-sitting for my nephews. I feel tired all the time.

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Dystonia

Introduction
Dystonia is a common movement disorder with a heterogenous clinical presentation. The fundamental clinical feature of the disorder is involuntary muscle spasm leading to the abnormal posture of the affected body part. An analysis of each patient who presents with dystonia in terms of age of onset, distribution of dystonia, and associated clinical features is invaluable in planning appropriate investigations, reaching the correct diagnosis and choosing effective treatment.

Is this dystonia?
Given the heterogenous clinical presentation of dystonia, this can sometimes be a difficult question to answer. Sustained muscle spasm leading to abnormal (but not usually fixed) posturing of the affected body part is the cardinal feature of dystonia. The spasms in dystonia are mobile, and this often leads to a slow writhing of the affected body part (athetosis). Co-contraction of agonist and antagonist muscles are the underlying reason for the abnormal posturing in dystonia, and this can be seen clinically, or more easily on simple EMG assessment of the affected body part. Tremor, often jerky and present only in particular postures, is commonly seen. Dystonia is often task or position specific, present only on writing for example, but not during other manual tasks. Patients with dystonia will often have sensory tricks or "geste antagoniste", where applying a sensory stimulus to a particular area will cause the abnormal posture to resolve.

Classifying dystonia – the essential division into primary and secondary dystonias
An outline of ways in which dystonia can be classified is given in table 1. Classifying by age at onset (below age 28, above age 28), distribution (focal, segmental, generalised) can be useful for planning investigations, and for picking out patients who present with unusual phenotypes (e.g. an adult presenting with generalised dystonia, which would be incompatible with typical primary dystonia). However, clinically the most useful division is classifying patients into those with "primary dystonia" – where dystonia is the only clinical sign (+/- tremor), and there is no neurodegeneration – and "secondary/heredodegenerative" dystonic conditions. Clinical features or "red flags" that should make one consider secondary dystonia rather than primary dystonia are listed in Table 2.

Dystonia-plus syndromes, a recent addition to the classification scheme, are idiopathic conditions where dystonia is present along with other clinical features e.g. myoclonus in myoclonus-dystonia, parkinsonism in dopa-responsive dystonia, but no neurodegeneration is evident.

Primary dystonia
In patients with primary dystonia, age at onset appears to be very important in determining the clinical phenotype. Young-onset dystonia (before the age of 28) is most commonly associated with limb onset dystonia followed by subsequent generalisation (although typically the neck is spared). About 70% of patients presenting in this way will carry the DYT1 gene mutation, a single GAG deletion in the DYT1 gene on chromosome 9. This condition has an autosomal dominant inheritance, but a very low phenotypic penetrance such that only 30-40% of gene carriers will ever develop dystonia, and in those that do, this will almost always happen before the age of 30. It is particularly important to diagnose this condition as deep brain stimulation of the internal segment of the globus pallidus (GPi, see below), appears to be a particularly effective treatment for such patients.

When dystonia appears in adult life, a focal distribution is commonly seen. These presentations, in order of frequency of occurrence include cervical dystonia (spasmodic torticollis), cranial dystonia (blepharospasm, Meige syndrome (blepharospasm and oromandibular dystonia)), writer's cramp, and other task specific dystonias. Cranio-cervical dystonia is commoner in women than men, with the opposite pattern seen in task-specific writing dystonias.

Dystonia-plus syndromes
Dopa-responsive dystonia (DRD), previously also called Segawa's disease, typically presents in childhood with limb dystonia, often with associated parkinsonism and sometimes spasticity. A diurnal fluctuation in symptom severity with a gradual worsening of symptoms throughout the day was said to be typical of the condition, but is present in only 60% of cases. This condition is usually due to mutations in the GTP cyclohydrolase 1 gene (GTPCH1), a rate limiting step in the production of dopamine from tyrosine. Although rare, it is of critical importance to the practising neurologist as it is entirely treatable by small doses of levodopa. This typically leads to complete resolution of symptoms which is sustained, without the development of long-term complications as seen in Parkinson's disease.

The condition can present with unusual phenotypes such as spastic diplegia, writer's cramp and other focal dystonias. In view of this, a trial of levodopa is strongly recommended in all those with young-onset dystonia especially as agenetic diagnosis is time consuming and not generally available. It is also important to differentiate patients with DRD from those with young-onset Parkinson's disease, many of whom will have limb dystonia in addition to Pakinsonism, and in whom the early use of levodopa is not recommended. A DAT SPECT scan (normal in DRD) can be useful in this regard. Other inherited defects of dopamine synthesis pathway, for example tyrosine hydroxylase deficiency, can also cause DRD, but usually as part of a more severe neurological syndrome.

Symptomatic dystonia
Dystonia is commonly seen following brain injury, for example perinatally (dystonic/athetoid cerebral palsy) or following stroke. In such patients a static deficit is

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Table 1: Different ways of classifying dystonia

By age at onset	By distribution	By aetiology
Young-onset dystonia) (< 28 years Adult-onset dystonia (> 28 years)	Focal Segmental Multifocal Hemidystonia Generalised	Primary (dystonia only +/- tremor; no neurodegeneration. Dystonia-plus syndromes - Dopa-responsive dystonia - Myoclonus dystonia Secondary - Symptomatic - Heredodegenerative Paroxysmal

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NB The incidence of somnolence is increased at doses higher than 1.5mg (salt)/day. *Maintenance treatment:* The individual dose should be in the range from 0.264mg base (0.375mg salt) to a maximum of 3.3mg base (4.5mg salt) per day. It is recommended that the dosage of levodopa is reduced during both the escalation and the maintenance treatment with Mirapexin, dependent upon individual response. *Treatment discontinuation:* Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.54mg of base (0.75mg of salt) per day until the daily dose has been reduced to 0.54mg of base (0.75mg of salt). Thereafter, the dose should be reduced by 0.264mg of base (0.375mg of salt) per day. *Renal impairment:* Consult the Summary of Product Characteristics for information on revised dosage schedules. *Hepatic impairment:* Dose adjustment in patients with hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications, Warnings etc.: Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings:** In patients with renal impairment a reduced dose is recommended (see above). Hallucinations are a known side-effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur. Mirapexin has been associated with somnolence and, uncommonly, sudden sleep onset. Patients who have experienced somnolence and/or an episode of sudden onset of sleep must refrain from driving or operating machines, until such recurrent episodes and somnolence have resolved. Futhermore a reduction of dosage or termination of therapy may be considered. In advanced Parkinson's disease, in combination with levodopa, dyskinesias can occur during the initial titration of Mirapexin. If they occur, the dose of levodopa should be decreased. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In cases of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. **Drug Interactions:** There is no pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules, such as cimetidine and amantadine, may interact with pramipexole resulting in reduced clearance of either or both drugs. Reduction of the pramipexole dose should be considered when these drugs are administered concomitantly with Mirapexin. While increasing the dose of Mirapexin it is recommended that the dosage of levodopa is reduced and the dosage of other anti-Parkinsonian medication is kept constant. Due to possible additive effects, caution is advised when patients are co-prescribed Mirapexin with other sedating medication or alcohol. Co-administration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** The effect on pregnancy and lactation has not been investigated in humans. Therefore, Mirapexin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Similarly, Mirapexin should not be used during breast-feeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, dizziness and peripheral oedema occurred more often than with placebo. More frequent adverse reactions in combination with levodopa were dyskinesias. These adverse events tend to decrease or disappear with continued therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin is titrated too fast. Mirapexin has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. **Overdose:** There is no clinical experience with massive overdosage. Expected adverse events include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive/emetic measures may be required. **Basic NHS Cost:** 0.088mg x 30 £10.00, 0.18mg x 30 £20.00, 0.18mg x 100 £66.67, 0.7mg x 30 £63.67, 0.7mg x 100 £212.24. **Legal Category:** POM. **Marketing Authorisation Holder:** Pharmacia Enterprises S.A., 6, Circuit de la Foire Internationale, L-1347 Luxembourg, G.D. Luxembourg. **Marketing Authorisation Number:** Mirapexin 0.088mg x 30 tablets EU/1/97/051/001; Mirapexin 0.18mg x 30 tablets EU/1/97/051/003; Mirapexin 0.18mg x 100 tablets EU/1/97/051/004; Mirapexin 0.7mg x 30 tablets EU/1/97/051/005; Mirapexin 0.7mg x 100 tablets EU/1/97/051/006. Further information is available from Pharmacia Ltd, Davy Avenue, Milton Keynes, MK5 8PH, UK. Tel: 01908 661101. **Date of preparation:** April 2003.

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commonly seen, although onset can be delayed for months or even years after injury, and late worsening of symptoms is sometimes seen.

Tardive dystonia is a common and disabling consequence of the long-term use of dopamine receptor blocking drugs. Although the newer "atypical" neuroleptic drugs appear to be safer with regard to this complication than older drugs, there are no entirely safe dopamine receptor blocking drugs (including drugs used for nausea such as metoclopramide).

Heredodegenerative dystonias – syndromic associations help guide appropriate investigation

Dystonia can be a feature of a wide range of neurodegenerative conditions, which can make selection and prioritisation of the appropriate investigations and reaching the correct diagnosis a difficult task. One aspect of such conditions that can be helpful, is that many have syndromic associations which can help guide the investigating clinician. For example peripheral neuropathy in association with dystonia would make one think of neuroacanthocytosis or metachromatic leukodystrophy as more likely diagnoses. Prominent ataxia would make one consider Wilson's disease or SCA3. Prominent bulbar involvement by dystonia would favour Neurodegeneration with Brain Iron accumulation (formerly known as Hallervorden-Spatz syndrome) or neuroacanthocytosis. A list of some of these conditions, with their associated clinical symptoms, is given in Table 3.

Investigation of dystonia

Following a careful history (in particular drug and family history) and examination, investigation of patients with dystonia should be tailored to the presentation of the patient, and in particular whether the picture is one of primary or secondary dystonia. Common clinical situations are of children/adolescents presenting with a primary focal or generalised dystonia, adults presenting with a primary focal dystonia, and the more extensive investigation of patients with presumed secondary dystonias. An outline of the investigations in these three situations is given in Table 4.

Table 2: Clinical features on history and examination suggestive of secondary dystonia

Clinical features on history and examination suggestive of secondary dystonia
Abnormal birth/perinatal history
Developmental delay
Seizures
Previous exposure to drugs e.g. dopamine receptor blockers
Continued progression of symptoms
Prominent bulbar involvement by dystonia
Unusual distribution of dystonia given age of onset (e.g. leg dystonia in an adult)
Unusual nature of dystonia (e.g. fixed dystonic postures)
Hemidystonia
Additional neurological symptoms (pyramidal signs, cerebellar signs, cognitive decline)
Other systems affected (e.g. organomegaly)

Treatment of dystonia

Drug treatment of dystonia is most appropriate in those with generalised/segmental dystonia for whom botulinum toxin (see below) would be unlikely to control the full extent of the dystonia. First line treatment is with anticholinergics such as trihexyphenydyl (Benzhexol/Artane). A slow introduction of the drug is very important to avoid side-effects, but some patients, in particular younger patients, can reach very high doses (100mg and above per day), with good effect. Clonazepam is particularly useful for the treatment of tremor, jerks and pain associated with dystonia. Other drugs which are sometimes useful include tetrabenazine, baclofen and even dopamine receptor blocking drugs. As mentioned above, all patients with young-onset dystonia should receive a trial of levodopa.

Botulinum toxin has revolutionised the treatment of patients with focal dystonia. Treatment is required every three-four months, and is expensive, but a 70-80% improvement in symptoms is common in most patients, particularly those with blepharospasm and cervical dystonia. Treatment of those with limb dystonia, in particular writer's cramp, is often more difficult and benefit can be inconsistent. Main side effects of treatment are excessive weakness of the treated muscle or spread of effect to nearby muscles (e.g. paralysis of pharyngeal muscles following sternomastoid injections). Immune-mediated resistance to botulinum toxin is seen in a small proportion of chronically treated patients, particularly those who receive high doses, "top-up" doses, or injections more frequently than every 12 weeks. An alternative toxin, botulinum toxin type B is available, but antibodies to the commonly used type A toxin can be cross-reactive with type B toxin, and in addition, a primary immune response to type B toxin can also occur. Botulinum toxin can be helpful for those with generalised dystonia where a particular functional problem can be linked to dystonia in a single or a small group of muscles.

Additional Web Content

For a case study on vertical gaze palsy, see www.acnr.co.uk/case%20report.htm

Table 3: Examples of some heredodegenerative causes of dystonia with associated neurological features.

Heredodegenerative Dystonias	Associated neurological features
Wilson's Disease	Kaiser-Fleischer rings, ataxia, cognitive decline
Neurodegeneration with Brain Iron accumulation (Hallervorden Spatz syndrome)	Retinal degeneration, pyramidal signs, oromandibular/ bulbar involvement
Neuroacanthocytosis	Peripheral neuropathy, oromandibular dystonia, epilepsy
Metachromatic Leukodystrophy	Peripheral neuropathy, frontal dementia
GM1/GM2 gangliosidosis	Cognitive decline
Glutaric acidemia	Cognitive decline
Huntington's disease	Cognitive decline, personality change, depression, supranuclear eye movement abnormalities
Niemann Pick type C	Vertical gaze palsy, cognitive decline
Ataxia telangectasia	Supranuclear eye movement abnormalities

Continuous control

Twenty-four hour symptom control – one dose a day

Cabaser®
CABERGOLINE
The once-daily dopamine agonist

As adjuvant therapy to levodopa

CABASER® (CABERGOLINE). Abbreviated Prescribing Information. Before prescribing see Summary of Product Characteristics. **Presentation:** Cabaser tablets: Containing 1, 2 or 4 mg cabergoline. **Uses:** The treatment of symptoms of Parkinson's disease, as adjuvant therapy to levodopa plus dopa-decarboxylase inhibitor, in patients affected by 'on-off' mobility problems with daily fluctuations in motor performance. Improvement of motor deficit has been demonstrated while permitting a substantial decrease in L-dopa dose. **Dosage and Administration:** Adults and elderly patients: The recommended therapeutic dosage is 2-6 mg/day as adjuvant therapy to levodopa, given as a single daily oral dose. Dose should be titrated slowly against efficacy and tolerability. A starting dose of 1 mg daily is recommended; the dosage of concurrent levodopa may be gradually decreased, while the dose of Cabaser is increased. In view of the long half-life of the compound, the dose may be increased in gradual weekly or bi-weekly intervals by increments of 0.5-1.0 mg, up to optimal doses. Use in Children: not recommended. **Contra-indications:** Hypersensitivity to any ergot alkaloid. Warnings: In patients with severe hepatic insufficiency the dose should be reduced accordingly. Cabaser is an ergot derivative. Fibrotic reactions have occurred after prolonged usage of ergot derivatives. Patients with a history of such disorders should not be treated with Cabaser. Renal insufficiency has not been shown to modify Cabaser kinetics. Caution is advised in patients suffering from severe cardiovascular disease, Raynaud's syndrome, peptic ulcer, gastrointestinal bleeding or a history of major psychotic illness. In cases of unexplained high ESR, or emergence of respiratory symptoms, a chest X-ray is recommended to exclude pleural effusion/fibrosis. Symptomatic hypotension can occur following administration of Cabaser: particular attention should be paid when administering Cabaser concomitantly with other drugs known to lower blood pressure. Cabaser has been associated with somnolence and, uncommonly, sudden sleep onset. Patients who have experienced somnolence and/or an episode of sudden onset of sleep must refrain from driving or operating machines, until such recurrent episodes and somnolence have resolved. Furthermore a reduction of dosage or termination of therapy may be considered. **Drug Interactions:** No pharmacokinetic interaction with levodopa or selegiline has been observed in clinical studies in Parkinsonian patients. Concomitant use of other ergot alkaloids with Cabaser is not recommended. Cabaser should not be administered concurrently with drugs which have dopamine antagonist activity since these might reduce Cabaser's efficacy. Cabaser should not be used in association with macrolide antibiotics since systemic bioavailability of Cabaser and adverse effects could increase. The effects of alcohol on overall tolerability of Cabaser are currently unknown. **Pregnancy and Lactation:** Based on limited clinical experience, cabergoline does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities. As a precautionary measure, it is recommended that women seeking pregnancy discontinue Cabaser one month before intended conception, in order to prevent possible foetal exposure to the drug. If conception occurs during therapy, treatment is to be discontinued as soon as pregnancy is confirmed. Do not use in nursing mothers as lactation may be inhibited; no information on the excretion of cabergoline in maternal milk in humans is available. **Undesirable Effects:** Events most frequently reported in clinical studies were dyskinesia, hyperkinesia, hallucinations or confusion. Other events include nausea, vomiting, dyspepsia and gastritis, as well as dizziness and hypotension. Symptomatic pleural effusion/fibrosis has been reported with a frequency <2%; in these cases discontinuation of Cabaser is expected to lead to immediate improvement of symptoms. Cabaser has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. In view of Cabaser's pharmacological class, other reported events include angina (reported in 1%), erythromelalgia (0.4%) and peripheral oedema (6%). CNS events are more common in the elderly. **Overdose:** No incidences reported in the proposed indication. Symptoms of overdose are likely to be related to dopaminergic activity. **Legal Category:** POM. **Basic NHS Cost:** 20x1mg £75.45; 20x2mg £75.45; 16x4mg £75.84 all bottles. **Product Licence Numbers:** CABASER 1mg: PL0022/0169, CABASER 2mg PL0022/0170, CABASER 4mg: PL0022/0171. **Product Licence Holder:** Pharmacia Laboratories Limited, Davy Avenue, Milton Keynes, MK5 8PH, United Kingdom. **Date of Preparation:** January 2003.

Peripheral surgical treatment of dystonia has been used in the past to treat focal dystonias (e.g. cervical ramisectomy or selective peripheral denervation for cervical dystonia), and some benefit has been reported. Regrowth of sectioned nerves is often seen over time however, and with the advent of botulinum toxin, these treatments are now typically only considered for those with botulinum toxin resistant focal dystonia.

Both thalamotomy and pallidotomy have demonstrated effectiveness in the treatment of generalised dystonia, but both carry notable surgical risks. In recent years, deep brain stimulation of the GPi has gained favour as a successful treatment for generalised, and more recently focal dystonias. The operation itself carries less risk than lesion procedures, and results over the past 5 years or so have demonstrated a worthwhile and sustained benefit in many patients. This is most clearly the case for patients (mainly with generalised dystonia) who carry the DYT1 gene. Other patients with primary generalised and focal dystonias have also been reported to gain good benefit. Patients with secondary dystonia typically show a much less favourable response to DBS, and would need careful consideration before surgery was contemplated.

Table 4: List of investigations appropriate to three typical clinical scenarios. Investigation of secondary dystonia should be guided by syndromic associations (see Table 3).

Young-onset dystonia, clinically of primary type	Adult-onset dystonia clinically of primary type	Patients with dystonia where secondary dystonia considered
Copper studies, slit lamp to exclude Wilson's disease (NB liver biopsy remains gold standard)	Copper studies and slit lamp to exclude Wilson's disease if presentation under 50 years of age.	- MRI Imaging brain/spine (structural lesions, leukodystrophies, "eye of tiger" sign in NBIA (formerly known as Hallervorden Spatz syndrome) - Nerve conduction studies (neuroacanthocytosis, metachromatic leukodystrophy) -Copper studies, slit lamp, ?liver biopsy (Wilson's)
MRI brain	Consider MRI brain	- Huntington's disease gene test
DYT1 gene test	MRI spine if fixed/painful dystonia.	- White cell enzymes (GM1, GM2, metachromatic leukodystrophy)
Trial of levodopa	Paraspinal EMG, anti-GAD antibodies if painful axial muscle spasms to exclude stiff person syndrome	- Alphafetoprotein, immunoglobulins (ataxia telangiectasia) - Lactate/pyruvate, mitochondrial mutations, muscle biopsy (mitochondrial disease) - Fresh thick blood smear for acanthocytes (neuroacanthocytosis) - Plasma amino acids, Urine for organic acids, aminoacids, oligosaccharides (Glutaric academia, GM1, GM2) - Bone marrow biopsy / axillary skin biopsy (Niemann Pick C, Kufs) - Phenylalanine loading test CSF pterins assessments (DRD) - ERG, retinal examination , PANK2 gene test (positive in some cases of neurodegeneration with brain iron accumulation (Hallervorden Spatz syndrome)).

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Brain Tumour Information For Headstrong Kids

For the thousands of children who have a brain tumour, new multi-media information is now available. For the first time, children with brain tumours and their parents have collaborated with the Brain and Spine Foundation to produce Headstrong. Involving children in this way is a new approach to providing health information on brain disorders.

Headstrong helps children find out more about their illness, cope with their treatment and therefore lessen their anxiety. The first in a planned series of information services for children, it comprises a ring-bound folder for children aged seven to nine years old, a magazine-style publication for those aged 10–12 years, CD-Rom and a website.

But what makes Headstrong so different is that children have described their own experiences, hopes and fears in order that the information reflects what children and their parents say they need. The overall style of Headstrong has also been influenced by the children's views on the text and design. It has been developed by a panel of doctors specialising in cancer in children, experts from Great Ormond Street Hospital, hospital play specialists, experts in children's welfare, children's writers and graphic designers. "Headstrong is a highly skilled resource which helps children with brain tumours understand their condition while encouraging openness with their parents and carers," said Dr David Walker, consultant paediatric oncologist at the University of Nottingham.

"It was clear from our research that children and their parents were badly in need of information about brain tumours," said Ms Maggie Alexander, director of the Brain and Spine Foundation. "Our collaboration with children to develop health information for their own age group has not been done before. We were surprised and pleased by their terrific enthusiasm to help other children with a brain tumour and their parents or carers."

Using cartoons, illustrations and scenarios based on what the children had said in discussion groups, Headstrong explains what a brain tumour is, the symptoms, what a scan is, surgery, chemotherapy and radiotherapy as well as the recovery process. The facts are brought to life with the feelings and worries that children experience. Hannah, who had a brain tumour removed when she was just seven years old, tells the reader what it is like to lose her hair, whilst Joshua, 15, shows off his scar to his sister.

Around 350 children are diagnosed with a brain tumour each year and approximately 2,500 children between seven and 12 years old are living with one. "We believe that this project will also encourage children to have their say in decisions about their treatment. Everyone is different and children should be enabled to participate in managing their illness," said Ms Alexander.

Headstrong, which has been endorsed by the Centre for Health Information Quality, is being offered to specialist centres and hospitals where children are treated. Nurses, GPs, teachers and families will also find the information useful.

For further information contact Elaine Snell, 020 7738 0424 or E.Mail: elaine.snell@which.net

Don't just prescribe Mestinon: personalise it!

Mestinon®
pyridostigmine bromide

Personalised therapy

Because every Myasthenia Gravis patient is individual

To get the most out of Mestinon, the most widely prescribed 1st-line treatment for Myasthenia Gravis (MG)[1,2,3,] **it has to be taken at frequent intervals:**

- ***A half-life of 3-4 hours means that a dose frequency of around every 4 hrs is necessary for continuous cover***
- ***Frequency may be increased to every 3 hrs when awake[4]***
- ***Dosage should be tailored to the needs of the patient***

Don't just prescribe Mestinon: personalise it. Make sure every patient gets the most out of Mestinon – 5-6 times a day!

Prescribing Information:

Presentation: Each tablet contains 62.5mg pyridostigmine bromide (equivalent to 60.0mg of the base). **Indications:** Myasthenia Gravis, paralytic ileus and post-operative urinary retention. **Dosage and Administration:** *Myasthenia Gravis – Adults* – Doses of 30 to 120mg are given at intervals throughout the day. The total daily dose is usually in the range of 5-20 tablets. *Children* – Children under 6 years old should receive an initial dose of half a tablet (30mg) of Mestinon; children 6-12 years old should receive one tablet (60mg). Dosage should be increased gradually, in increments of 15-30mg daily, until maximum improvement is obtained. Total daily requirements are usually in the range of 30-360mg. The requirement for Mestinon is usually markedly decreased after thymectomy or when additional therapy is given. When relatively large doses of Mestinon are taken by myasthenic patients, it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects. It should be noted that the slower gastro-intestinal motility caused by these drugs may affect the absorption of Mestinon. In all patients the possibility of "cholinergic crisis", due to overdose of Mestinon, and its differentiation from "myasthenic crisis" due to increased severity of the disease, must be borne in mind. *Other indications: Adults* – The usual dose is 1 to 4 tablets (60-240mg). *Children* – 15-60mg. The frequency of these doses may be varied according to the needs of the patient. *Elderly* – No specific dosage recommendations. **Contra-indications, Warnings etc:** *Contra-indications* – Gastro-intestinal or urinary obstruction, known hypersensitivity to the drug and to bromides. Extreme caution is required when administering Mestinon to patients with bronchial asthma. *Warnings* – care should also be taken in patients with bradycardia, recent coronary occlusion, hypotension, vagotonia, peptic ulcer, epilepsy or Parkinsonism. Lower doses may be required in patients with renal disease. *Use in pregnancy:* The safety of Mestinon during pregnancy or lactation has not been established. Experience with Mestinon in pregnant patients with Myasthenia Gravis has revealed no untoward effects. Negligible amounts of Mestinon are excreted in breast milk but due regard should be paid to possible effects on the breast-feeding infant. *Side effects:* These may include nausea and vomiting, increased salivation, diarrhoea and abdominal cramps. *Drug interactions* – None known. **Pharmaceutical Precautions:** *Storage* – Recommend maximum storage temperature 25ºC. Protect from light and moisture. **Legal Category:** POM. **Package Quantities:** Amber glass bottles with aluminium screw caps and desiccant, containing 200 tablets. **Basic NHS Price:** £50.15. **Product Licence Number:** PL 15142/0006. **Product Licence Holder:** ICN Pharmaceuticals Ltd, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire. RG24 8WD.

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Date of Preparation: May 2003

VP004/0304

VALEANT Pharmaceuticals International

A Preliminary Clinical Study using RF BION®[1] Microstimulators to Facilitate Upper Limb Function in Hemiplegia

Jane Burridge is a senior research fellow in neurorehabilitation at the University of Southampton. Her main area of research is into functional electrical stimulation, the effect of this on motor learning and muscle activation patterns, and working with signal processing engineers, the development of control systems for voluntary activation of stimulation. Jane is also currently leading a European clinical trial to evaluate the effect on walking of an implanted drop-foot stimulator with stroke patients and is a member of a European consortium on measurement of spasticity.

Ruth Etherington is a Research Fellow working on the BION Project at the University of Southampton. She has worked as a Senior Physiotherapist in Neurorehabilitation, specialising in stroke rehabilitation. Her research interests are in upper limb therapy in patients with stroke, especially functional electrical stimulation and its effect on neglect and motor relearning.

A brief background to Functional Electrical Stimulation

Functional Electrical Stimulation (FES) has been used to facilitate movement in people who have suffered an upper motor neuron lesion since Liberson designed the first drop-foot stimulator in 1960[1]. Since then the technique has been accepted by only a small number of clinicians and therapists. There are various reasons for this: firstly insufficient research and clinical evidence for its effectiveness - although there have been many papers published on the use of FES they have tended to be with small numbers of subjects and often employing weak methodology. Recently more convincing evidence from larger research studies has been published[2,3,4], a systematic review[5] found evidence for improved upper limb motor control with surface FES systems, and systems that allow voluntary control over the activation of stimulation, such as through the same muscle EMG signal, have been shown to result in improved motor learning[6]. The Odstock drop-foot stimulator has probably gained more clinical acceptance than any other FES device with now over 2000 patients using it in the UK. Acceptance in this case has been due not only to research evidence[7] but also to strong clinical support and education of therapists in selection of suitable patients and application of devices. Even when the stimulator is set-up effectively however, wearing an external device that requires careful donning and doffing does not appeal to all patients, regardless of whether it is functionally effective. As rehabilitationists, we are more interested in interventions that can facilitate recovery to restore rather than replace lost movement.

This project aims to address the last two issues by using an implantable microstimulator that can remain implanted even if no longer needed and developing a system to facilitate recovery by supporting voluntary movement rather than replacing it.

The BION microstimulator

The radio frequency (RF) BION (RFB) device has been developed by the Alfred Mann Foundation in the US. It is an injectable cylindrical microstimulator with a cathode electrode at one end and an anode at the other. It can be implanted through a small incision (5mm) using a canula, thus reducing the expense and risks associated with other implantable devices due to the surgical procedure and the presence of leads within the body. Once implanted, the RFB receives power and stimulation commands (data) via a 2MHz RF inductive link from an external RF coil, which is connected to the BION Control Unit. A single RF Coil and BION Control Unit can simultaneously control several individually addressed RFBs implanted near each other. Figure 1 shows the RFB and the instruments used for implantation.

Previous clinical experience

Similar devices have been used in the US in the treatment of subluxed shoulder and RFBs are currently being tested in the US in the treatment of obstructive sleep apnoea. These applications require minimal control of stimulation; in the arm rehabilitation project, developing the control system to activate the individual devices appropriately to facilitate a normal, functional movement is the major challenge.

The objectives of this project

Approximately 75% of middle cerebral artery infarcts result in a motor deficit, particularly of the upper limb[7] and 24% of patients have residual upper limb motor loss at three months post-stroke[9]. Various longitudinal studies have investigated the long-term outcome following stroke; Kwakkel in his review quotes that for 30 to 60% of patients the paretic arm remains without function[10], and Wade reported that half of all acute stroke patients starting rehabilitation will have a marked impairment of function of one arm of whom only about 14% will regain useful upper limb function[11]. Upper limb function is clearly a major problem, and because individuals are unable to perform functional repetitive movements with their hemiplegic arm, potential motor recovery is not realised. The objective of this project is to test the feasibility of using the RFB to improve motor re-learning and recovery of arm and hand function following stroke by facilitating functional arm movements. Movement will be elicited by electrical stimulation of the weak muscle groups in such a way that the phases of movement are responsive to the task .

Project plan

A minimum of six and a maximum of fifteen subjects will be enrolled in the study. They will have had a stroke at least three months prior to recruitment and have impaired arm and hand control, but retain some functional grip and have sufficient elbow flexion to bring their hand to their mouth. RFBs will be implanted into the forearm to activate extensor carpi ulnaris and radialis, extensor digitorum superficialis, extensor pollicis longus and abductor pollicis. By positioning devices either adjacent to the nerve or within the muscle itself, close to the motor point, we expect to be able to activate these muscles using four devices. In the upper arm we will use two more devices implanted into the medial and lateral heads of triceps. With this combination of implants we aim to support elbow extension, wrist extension and opening of the hand. By 'switching off' the finger and thumb devices subjects will be able to use their own remaining control of finger and thumb flexion to grasp an object; while continued stimulation to the wrist extensors will maintain a functional hand position for grasping.

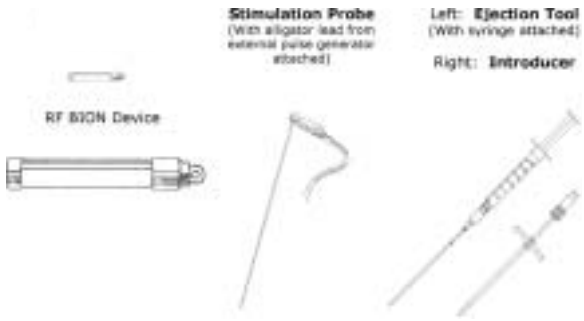


Figure 1 shows the RF Bion microstimulator and the insertion tools. A suture is attached to the eye in the end of device that enables it be withdrawn if necessary for up to two weeks following insertion.

[1]BION is a registered trademark of Advanced Bionics Corporation

The project falls into three phases. During the first and second we will be developing a control system that, in the third, will be tested using conventional outcome measures – the Action Research Arm Test and the Fugl-Meyer (upper limb section). Throughout the study the effect of stimulation on muscle force, motor control, antagonist co-activation during active flexion and extension and response to passive stretching will be assessed in a specially designed rig. Figure 2 shows the output from the tracking test in which the subject attempts to follow a tracking target, moving sinusoidally across a screen, by flexing and extending their wrist. EMG signals from the wrist flexors and extensors in this example show normal reciprocal inhibition, subjects who have poor control of movement and spasticity demonstrate less accurate tracking and more co-activation between the two muscle groups. Indices have been derived to quantify co-activation and we will be interested to see whether there is improvement after the RFBs have been used for functional exercise over a period of about six weeks.

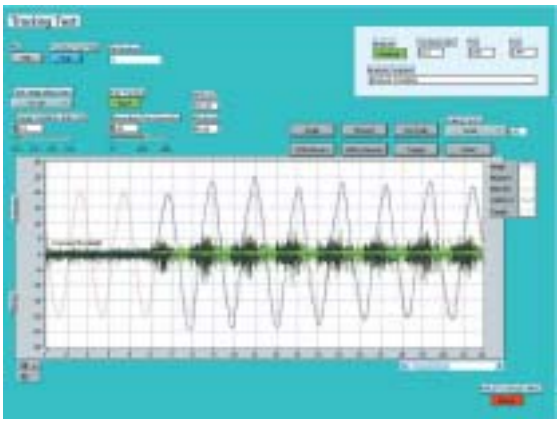
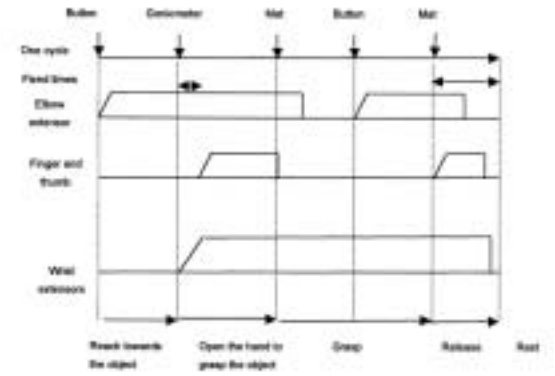


Figure 2 An example of the output from the wrist rig showing the tracking signal, the subject's attempt to follow it and the EMG signals from the wrist flexors and extensors. In this example of a normal unimpaired subject there is reciprocal inhibition between the two muscle groups and accurate tracking.

Initially, stimulation will be pre-programmed so that each RFB is active for a fixed period with a predetermined profile (amplitude, rise and fall time etc.). During the second phase we will use triggers operated either by the therapist or the patient so that stimulation periods can be varied according to the task being performed. Subjects will be able to use this system at home, while in the laboratory we will design and test ways of using signals from sensors such as accelerometers and goniometers to control the output from each device. This will enable stimulation to be controlled by the user's movement rather than by a conscious unrelated action. Figure 3 illustrates an example of how sensors may be used to trigger changes in stimulation.

The rationale that underpins this approach is that if the stimulation is responsive to the user's needs, enabling them to successfully achieve a variety of simple tasks, then motor-learning will be enhanced. A novel idea for controlling stimulation that we will test is a force sensitive mat; the user reaches to grasp an object resting on the mat, when the object is touched the small movement is recognised by the sensors embedded in the mat and the resulting signal is used to switch off finger and thumb extensor/abductor RFBs to allow the object to be grasped. When the object is replaced on the mat the signal becomes a command to switch on the finger and thumb



RFBs allowing the object to be released. Other ideas are an accelerometer worn as a ring on the finger that detects movement of the hand and a goniometer worn across the elbow to control the triceps RFBs.

Figure 3. Shows a possible set-up for phase 3 of the project in which stimulation is controlled by body-worn sensors and a force sensitive mat. The sequence illustrates activation of triceps to reach for and replace the target object. Activation of wrist and finger extensors opens the hand and, when the object is touched a signal from the pressure sensitive mat triggers stimulation to the finger extensors to be switched while stimulation to the wrist extensors is maintained, allowing the object to be grasped. After the object has been 'used', a signal from the pressure sensitive mat detects when the object is replaced on the mat triggering the fingers to be re-activated to release the object.

Future work

This is an ambitious project that we expect to take about 30 months. At the end, if we have a system that works and sufficient evidence for its effectiveness in improving arm and hand function, then we shall design and perform a clinical trial. The research is funded by the Alfred Mann Foundation (Valencia, CA, USA), who have been designing and testing a series of BION devices. Future generations of devices are currently being developed and these include battery-powered devices that will require a body worn coil and sensing devices that will be able to 'talk' to stimulating devices, thus removing the need for external sensors. The possibilities are very exciting and this project marks an important milestone in the evolution of FES.

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Delirium: Diagnosis, Aetiopathogenesis and Treatment

Delirium is a richly varied syndrome of cognitive and behavioural features which may co-exist with other somatic and mental disorders. As there is currently no diagnostic test and no reliable biomarkers have yet been identified, delirium remains a clinical diagnosis. A high index of clinical suspicion may be required in order to make the diagnosis, which should probably be considered in any patient labelled as confused (a term frequently used but with variable meaning[1]), vague, uncooperative, rambling, agitated, or unable to give a coherent history.

Diagnosis and differential diagnosis

Both the Diagnostic and Statistical Manual (DSM) and the International Classification of Diseases (ICD) have diagnostic criteria for delirium.

DSM-IV-TR recognises four diagnostic categories:

- Delirium due to a medical condition
- Substance-induced delirium: due to intoxication or withdrawal
- Delirium due to multiple aetiologies
- Delirium not otherwise specified

Three common diagnostic criteria are required:

- Disturbance of consciousness:
  This may encompass both quantitative and qualitative aspects of consciousness, hence "level"(= arousal, alertness, vigilance) and "intensity" (= selective attention) of consciousness; reduced clarity of awareness of environment; reduced ability to focus, sustain, or shift attention. Disordered attention may be evident clinically as increased distractibility.
- Change in cognition:
  This may manifest as disorientation, language disorder, memory deficit, perceptual disturbance (illusions, hallucinations). These features should not be better accounted for by dementia.
- Development/Course:
  Onset over a short period of time (hours, days) with fluctuation during the course of the day. Disturbance of sleep/wake cycles is typical, often with worsening of symptoms at night ("sundowning").

In addition there may be diagnostic criteria by category, based on evidence from the clinical history, examination, or investigations, of a general medical condition; substance intoxication, medication use related to disturbance; more than one aetiology; or insufficient evidence for any of the above.

In ICD-10, the requirements for diagnosis are similar, and include:

- Impairment of consciousness and attention
- Global disturbance of cognition
- Psychomotor disturbance
- Disturbance of sleep-wake cycle
- Emotional disturbances

A brief consideration of these diagnostic criteria will indicate the potential clinical heterogeneity of delirium. However, two principal subtypes of delirium are described. The less common, but more easily recognised, is characterised by agitation or hyperactivity. The more common, but insidious, "quiet" variant, characterised by hypoactivity, withdrawal, and apathy, may be easily overlooked and/or misdiagnosed as depression. Not surprisingly, it is the latter form of delirium which has a poorer outcome.

Rating scales have been developed which may be helpful in screening for the diagnosis, such as the Delirium Rating Scale (DRS), the Confusion Assessment Method (CAM), and the Neecham Confusion Scale (NCS); or for measuring the severity of delirium, such as the Confusional State Evaluation (CSE) and the Delirium Severity Scale (DSS).

The differential diagnosis of delirium includes:

- Dementia
- Aphasia (especially Wernicke's aphasia)
- Psychiatric disorders:
  schizophrenia
  depression/mania
  attention deficit disorder

Many texts include tables which list the factors differentiating delirium from dementia, for example in terms of onset (acute *vs.* insidious), course (fluctuating *vs.* stable), and duration (hours/days vs. months/years). However, it is of crucial importance to recognise that the two conditions show significant overlap, dementia being an important predisposing factor for the development of delirium, and delirium sometimes being the presenting feature of dementia.[2,3] In any elderly person developing delirium, the possibility of an underlying diagnosis of dementia must be considered. However, meaningful assessment of cognitive functions to confirm or refute a diagnosis of dementia cannot be undertaken whilst delirium persists, because of the impairments of consciousness and attention.

Epidemiology, aetiology, pathogenesis, investigation

Delirium is common, more so in hospital in-patients (the subjects of the majority of studies) than in the community. In medical in-patients, prevalence of delirium may be 10-20%, and incidence 5-10%. In surgical patients, the incidence may be up to 30%. Certain types of surgery seem particularly associated with delirium, especially cardiac and orthopaedic (especially hip fracture surgery).

Studies have identified a number of factors which may contribute to the aetiology of delirium. These may be conveniently classified as predisposing and precipitating.

Predisposing factors include:

- Age: frailty, physiological age, rather than chronological age *per se*;
- Sex: men > women;
- Neurological illness: dementia;
- Burden of co-morbidity; dehydration;
- Drugs: especially anticholinergics;
- Visual, hearing impairment.

Precipitating factors include:

- Medications: benzodiazepines, opiates
- Intercurrent illness:
  Infection: systemic, focal (CNS)
  Metabolic: hypoglycaemia, hypoxia
  CNS disorders: head injury, epilepsy, inflammatory
- Iatrogenic events: surgery

A multifactorial model of pathogenesis suggests an inverse relation between pre-existing vulnerability (predisposing factors) and the severity of insult (precipitating factors) required to initiate delirium.

The pathophysiology of delirium is an area of much research. It is believed that diverse aetiologies may

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Box 1: Suggested investigations in delirium

Bloods:	FBC, ESR, film; U+Es, glucose, LFTs, thyroid function, Ca^{2+} + Po_4; blood cultures; arterial blood gases; +/- toxicology
Urinalysis	
Imaging:	CXR CT brain
CSF:	cell count, glucose, protein, Gram stain; +/- Ziehl-Neelsen stain, culture, oligoclonal bands
Neurophysiology:	EEG: degree of slowing correlates with clinical state

converge on a "final common neural pathway", involving in particular the prefrontal, parietal, and fusiform (especially right), cortices. The factors implicated include excessive stress response, mediated by the hypothalamo-pituitary-adrenal axis; imbalance of neurotransmitters, most particularly reduced acetylcholine and increased dopamine; and immunological factors such as cytokines (increased TNF-alpha, reduced IGF-1, somatostatin)[4].

The aetiological formulation into precipitating and predisposing factors guides the approach to investigation. The aim should be to identify any possible precipitating factors, such as an underlying medical disorder (Box 1, above).

Treatment and prognosis

Specific treatment may be instituted if delirium is diagnosed early and an underlying aetiology or precipitating cause is identified, such as a medical condition (infection, metabolic disturbance), substance misuse, iatrogenesis (use of certain medications).

More general measures must not be overlooked, such as maintenance of fluid intake and nutrition. If spectacles and/or hearing aids are normally worn they should be provided, after ensuring that they are in working order, to minimise sensory deprivation and the potential for misinterpretation of sensory stimuli. Environmental modulation, to avoid under- or over-stimulation, is recommended[5], but is often impractical on general medical and surgical wards. Relatives and friends may visit regularly, to encourage orientation. Sleep should not be disturbed if possible.

Drug therapy is not mandatory, with the possible exception of hyperactive patients who are deemed at risk of harm to themselves or others. There is currently little trial data to guide drug use. The options include neuroleptics, either traditional D2 receptor antagonists, such as haloperidol, or newer atypical antipsychotics; or benzodiazepines, such as lorazepam. The neuroleptics appear to be superior, and early regular low dose therapy may be the most appropriate usage. It has been suggested that cholinesterase inhibitors, licensed for the treatment of Alzheimer's disease, may have a role but the available data are currently anecdotal.

The prognosis of delirium is generally good if the condition is recognised and treated appropriately. However, long term complications such as functional decline, institutionalisation, and increased mortality are recognised. Prognosis is worse if no underlying cause is found. The possibility that underlying dementia may "emerge", having been "unmasked" by the delirium, must be borne in mind.

Following the adage that prevention is better than cure, an intervention trial in hospital in-patients at high-risk for delirium showed that a strategy of repeated reassurance and patient orientation, early mobilisation, provision of hearing aids and glasses, avoidance of dehydration and non-pharmacological sleep promotion, reduced the incidence and duration of delirium[6]. This has rightly been hailed as a landmark trial. Furthermore, in light of these findings, it has been argued that the incidence of delirium is a marker of the quality of hospital care[7].

Further Reading

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Professor Colin Blakemore: An interview with the new chief executive of the MRC

Professor Colin Blakemore took over as the new Chief executive of the MRC in October last year. Professor Blakemore is well known to most neuroscientists throughout the world with an impressive list of prizes and awards for his research over the years, including his pioneering work during the 1970s and 1980s on the visual system and its development. He has been the Waynfleete Professor of Physiology in Oxford since 1979 and is a great communicator and advocate of the public understanding of science, achieved through regular appearances on the television and radio. In this interview Professor Blakemore answers some of the questions we posed about research in the UK and how it relates to clinical training and medicine. We look forward to seeing how well these will be realised through the MRC in the next few years.

1) Do you think there is enough investment in British science?

As the Chief Executive of a research council, how could I say "Yes"? I would be lynched by the substantial number of researchers whose applications have been turned down by the Medical Research Council over the past three years despite being rated Alpha-A (world-class research). The fact that all the research councils have difficultly in funding even their internationally competitive applications is surely a signal that more investment is needed. Britain still continues to "punch above its weight", and, in most areas of science, is second only to the United States in its international impact. But present performance reflects investment 20 years ago or more. I really worry about the standing of British science 10 years from now if the science budget doesn't keep up with demand.

2) Do you think that the government fully supports animal research in the UK? Are there ways this could be better supported by the government?

Over the past 4 years, the Government has been increasingly robust in its support for essential research involving animals. This is a big change from the position of new Labour before the 1997 election. Although the Government did not set up a Royal Commission on the use of animals in research, which they had suggested in a pre-manifesto statement, their attitude initially seemed quite hostile. Introduction of a new tier of local ethical review, and increased bureaucracy in the Home Office, led to unacceptably long delays in the approval of project licenses. The discontent of the research community and protests from the pharmaceutical and biotech industry, as well as the rise of extreme animal rights activism, led the Government to reassess its position. The strong support of the Science Minister, Lord Sainsbury, was crucial in this change of stance. The campaign against Huntingdon Life Sciences, involving secondary terrorism and threats against shareholders, banks, insurance companies and stock dealers, finally persuaded the government to go very public in its support for animal research and its determination not to allow a tiny group of terrorists to damage research and the economy. It has been vindicated in this policy by the steady shift in public opinion. The latest polls show that fully 90% of the population now support the use of animals in research, as long as there is no alternative and suffering is minimised.

This is not to say that the problem is solved. The recent decision of Cambridge University not to go ahead with the long-delayed construction of a major new centre for primate neuroscience, because of escalating costs and threats from activists, has put new pressure on the Government to act against undemocratic extremism. I believe that the Government is determined not to allow the terrorist fringe to win but is still uncertain about how to achieve this. Personally, I have become convinced that industry's proposal for a focused, separate piece of legislation, along the line of that directed against football hooliganism is the right way forward. Also, in my opinion, the operation of the 1986 Animal Act needs to be further reviewed, with the intention of easing the unjustified bureaucratic burden on UK researchers.

3) Do you believe that "clinical science" is a distinct form of research? Is it sufficiently encouraged and funded?

There isn't a sharp boundary between basic biomedical research and clinical research, but there is certainly a range and style of research, with a direct mission to tackle problems of human health, which is appropriately called "clinical". I am thinking of the latter stages of proof-of-concept, clinical trials, epidemiological research, health service research and public health research. In my opinion, this important area of science needs and deserves more encouragement and funding. We have had 50 years of fantastic basic biomedical research, which has delivered extraordinary advances in our understanding of genetics, molecular mechanisms and cell biology. It is right that we should now shift the emphasis a little, to nurture research aimed at translating this basic knowledge into the improvement of human health, as recommended in a recent report from the Academy of Medical Sciences. However, to achieve this will require substantial new funds, and will also need cooperation and action by many organisations, including the Medical Royal Colleges, the General Medical Council and the Health Departments. The MRC stands ready to play its part, but cannot do the job alone.

4) Have the Calman reforms of medical training been helpful or not in promoting clinical science?

"Calmanisation", as it is commonly referred to, was aimed principally at streamlining conventional clinical training, and answering the demand for more doctors. It has done a good job of helping to fulfil that remit. But it has created problems for clinical research. The system of training numbers and training records has constrained the freedom of young clinicians and has discouraged them from taking time out for proper research training. This problem is very widely recognised (although it must be said that all developed countries are experiencing similar problems in attracting and training first-class clinical researchers). We, the biomedical funders, need to work with the GMC, the Medical Royal Colleges, the Academy of Medical Sciences and other interested parties to argue for modification of the present training regime and of the

professional structure of medicine, so as to make it easier for young doctors to train in research and to establish their own research laboratories.

5) What do you think will be the major research areas in the next 10 years?
In the biomedical sciences, much of the research in the coming decade will be devoted to translation of genomic information into greater understanding of normal organic function and of genetic contributions to disease. This will involve a rebirth of systems biology, extending genetic information from the cellular level to the whole organism. Genetic manipulation will be an essential tool, as will increasingly sophisticated techniques for visualising and selectively modifying genetic expression *in vivo*. The knowledge derived from massive epidemiological studies, including the UK's Biobank, will provide information about interactions between genes and environment in health and disease, and this will lead to the growth of "personalised medicine". Chemistry will be crucial for the future of the biological sciences, especially in the area of nanobioscience and in the design of compounds to interact with identified endogenous molecules in organisms. This approach will be important in genomic and proteomic manipulation, providing new tools for basic research and medical application. As for other fields of science, I guess that research on sustainable and/or more efficient energy production will be important. There will be ever more sophisticated battery design, new, more efficient solar power devices, and perhaps, energy for nuclear fusion. Optical computing will forge ahead, as will nanotechnology of all kinds.

6) How could the MRC grant system be improved?
I hope that it has been! At the time of writing, the MRC has just announced a raft of changes in its committee structures, its methods of strategic development, the empowerment of its research boards, and the introduction of new funding schemes. These changes have been based on the wide consultation that I have carried out over the past 4 months, through "roadshow" visits to 17 universities and a large number of meetings with unit and institute directors, MRC Board members, the MRC Advisory Board, the Council, and other stakeholders. The philosophy behind the changes in grant schemes is a desire to simplify the system and to introduce much greater flexibility. 12 grant schemes have been replaced by 5, including a single form of "Research Grant" to replace programme grants, pilot grants, discipline-hopping awards, etc, and to cover needs met in the past by 3-year project grants. The principle of the new Research Grants is that applicants will simply apply for what they need to accomplish the research proposed, specifying not only the level of support but also the preferred duration – from 2 years to 5 or more. The Cooperative Group Grant scheme, which was not popular, will be replaced by new, simpler Collaboration Grants, held as supplements to Research Grants. Linked to these schemes are other fundamental changes in the MRC. Research Boards will have their own budgets and will be responsible for developing a "portfolio" of activity in their area of science – from training to institute support. Strategy will be developed "bottom-up" by means of new committee structures and new mechanisms for consulting the research community. The refereeing system will be altered, with more targeted reviewing, using "Colleges of Experts", associated with each research Board, as well as overseas referees. Numerical scoring systems will be introduced, and referees and Boards will be asked to put somewhat more emphasis on track records than on the minute details of future proposals for research, when judging applications from established researchers. I don't want the MRC to fall into what one might call the NIH trap – encouraging applicants to describe in detail their present research as if it were what they intend to do in the future! We are also piloting a new form of support for younger investigators ("New Investigator Awards"), which, if successful, will be part of a revised set of forms of support for young researchers that I hope to introduce early next year.

7) How do you feel the MRC is perceived by researchers?
There is no doubt that the image of the MRC was somewhat tarnished because of the dramatic fall in funds available for response-mode funding over the past 5 years. I am convinced that this decline was not due to financial mismanagement at the MRC, as suggested by the House of Commons Science & Technology Select Committee in its report on the MRC last year. Rather it was caused by unfulfilled expectation of substantial increased income from government in the first Comprehensive Spending Review, coupled with an inability to carry forward more that 5% of the annual budget. We now have much more sophisticated financial modelling and a 10% carry-forward limit, which will, I am sure, enable us to avoid such disheartening fluctuations in grant funding in future years. I hope that the modest increase in response-mode funds available this year and next, together with the MRC's commitment to transparency and consultation, will raise the confidence of researchers in the organisation.

8) Do you feel there is sufficient public understanding in science? How would you encourage more?
It all depends on what one means by "understanding". There is, contrary to received wisdom, remarkably strong enthusiasm for science amongst the general public, and considerable confidence in scientists. In a recent opinion poll, three-quarters of the population said they were "ama zed" by the achievements of science. Another poll found that people admired Einstein more than David Beckham! And an annual Mori poll shows an unchanging two-thirds of the public who say that they trust scientists to tell the truth. On the other hand, the near-hysteria about such topics as GM foods and MMR vaccination and autism reveals that the public are not well informed about the processes of science. Understanding of risk and how to assess it is poor. The public expect infallible pronouncements from scientists and are confused when they hear researchers expressing differences of opinion in areas of genuine uncertainty. In my opinion, we, the researchers who benefit from public funds, have a responsibility to keep the people informed about how we spend their money. Even more important, we must trust the public to guide us in areas of ethical concern. But if we are to have confidence in the public's rightful role in determining how far science can go, they must understand how science and scientists work. Of course, busy researchers will ask why they should bother to give their precious time to public communication, when there is no professional recognition for that effort. I think that the universities, the research councils and other funders, and the organisers of the RAE should acknowledge that public communication is a legitimate professional activity. I am thinking about ways in which the MRC could offer small incentives for this kind of work.

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by June 6th, 2004. A bumper version of events is available on our website at www.acnr.co.uk

2004

May

Occupational Therapy for the Physical Rehabilitation of Neurological Disorders
May, 2004; London, UK
E. ACNRevents@aol.com

Ireland MS Week
1-8 May, 2004; Ireland
www.ms-society.ie

Seventh Eilat Conference on New Antiepileptic Drugs
9-13 May, 2004; Sardinia, Italy
Fax. 00 972 2 5175155,
E. eilatvii@targetconf.com

Research Skills for Health Professionals
10-14 May, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

14th European Congress of Physical & Rehabilitation Medicine
12-15 May, 2004; Vienna, Austria
Tel. +43 1 405 13 83 22,
E. ecprm2004@medacad.org,
www.ecprm2004.org

13th European Stroke Conference
12-15 May, 2004; Mannheim, Germany
E. hennerici@eurostroke.org

Alzheimer's Disease: Update on Research, Treatment, and Care (CME conference)
13-14 May, 2004; San Diego, US
E. sjohnson@ucsd.edu

3rd Regional International Society of Psychoneuroendocrinology (ISPNE) Congress for Central & Eastern Europe
13-15 May, 2004; Cappadocia, Turkey
Fax. 00 903 124 677 062,
E. ccosanoz@serenas.com.tr

Changes in neuronal gene expression and CNS drug responses
13-16 May, 2004; Avignon, France
www.ISNConference.org

Neuropathic Pain: Changing Paradigms and Treatment
13-16 May, 2004; Madrid, Spain
Fax. 00 41 22 732 2850,
E. ncohen@kenes.com

The EFNS Academy for Young Neurologists
14-17 May, 2004; Stare Splavy, Czech Republic
Tel/Fax. 00 420 2 6716 3563,
E. efns@fnkv.cz

2nd ALS Research Workshop and Young Investigator's Meeting
14-16 May, 2004; Nice, France
E. f.whitton@iop.kcl.ac.uk

3rd International Neuro-Oncology Update
17 May, 2004; Memphis, US
www.memphisbraintumor.org

The Acquire Conference on Behaviour After Acquired Brain Injury
17 May, 2004; Birmingham, UK
Tel. 01869 343449,
E. info@acquire.org.uk

Research Skills for Health Professionals
17-21 May, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Systematic Reviews
19 May, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

14th Alzheimer Europe Meeting
20-23 May, 2004; Prague, Czech Republic
Tel. 0042 0 239 041 661,
Fax. 0042 0 239 041 663,
E. info@alzheimer-conference.org

Systematic Reviews
21/24/26/28 May, 2004; Oxford, UK
Tel. 01865 286942, Fax. 01865 286934,
E. cpdhealth@conted.ox.ac.uk

Inaugural Meeting of the AEP Section on Neuroimaging
27-28 May, 2004; London, UK
Tel. 0115 969 2016

June

46th Annual Scientific Meeting of the American Headache Society
1-4 June, Philadelphia, US
Fax. 001 856 423 0082,
E. ahshq@talley.com

American Association on Mental Retardation 128th Annual Meeting
1-5 June, Philadelphia, US
Fax. 001 202 387 2193

11th Asian & Oceanian Congress of Neurology
3-6 June, 2004; Singapore
E. claire_lee@ttsh.cm.sg

3rd Research Forum of the European Association for Palliative Care - Methodology for Palliative Care Research
3-6 June, 2004; Stresa, Italy
Fax. 00 39 02 380 06761,
E. mariagrazia.tacconi@effetti.it

Intensive Summer Course in Otology and Neuro-Otology
6 - 8 June 2004; Sunny Beach, Bulgaria
E Pr Pavel Dimov,
E. pdimov@uni-sz.bg

American Society of Neuroradiology - 42nd Annual Meeting
5-11 June, 2004; Washington, US
Fax. 001 630 574 0661,
E. meetings@asnr.org

College of Occupational Therapists 28th Annual Conference & Exhibition 'Occupation Matters'
8-11 June, 2004; Harrogate, UK
Tel. 020 8977 0011

Meeting of the Canadian Congress of Neurological Sciences
8-12 June, 2004; Calgary, Canada
Fax. 00 403 229 1661,
E. brains@ccns.org

SRR Summer Meeting
8-9 June, 2004; Glasgow, UK
Ann Hughes, Tel: 0115 9249924

EPTA Continuing Professional Development Conference
9-11 June, 2004; Lincoln, UK
E. nigel.hudson@phnt.swest.nhs.uk

EULAR 2004: European Congress of Rheumatology
9-12 June, 2004; Berlin, Germany
E. eular@bluewin.ch

Conference on MND for Health and Social Care Professionals
10 June, 2004; Birmingham, UK
Tel. 01604 611845 or
E. pam.aston@mndassociation.org

46th Annual Scientific Meeting of the American Headache Society
10-14 June, 2004; Vancouver, Canada
Fax. 001 856 423 0082,
E. ahshq@talley.com

8th International Symposium on Mucopolysaccharide and Related Diseases
10-13 June, 2004; Mainz, Germany
Tel. 0049 6 214 106 137,
E. daniela.ruckriegel@mcon-mannheim.de

3rd Brain Stem Society Meeting
11-12 June, 2004; 2004
Fax. 39-0 55 570 227,
E. m.daliana@oic.it

Hydrotherapy in Neurology
12-13 June, 2004; Rippon, UK
Tel. 01765 604700

The Movement Disorder Society's 8th International Congress of Parkinson's Disease & Movement Disorders
13-17 June, 2004; Rome
Fax. 414 276 3349,
E. congress@movementdisorders.org

8th European Congress of Research in Rehabilitation
13-17 June, 2004; Ljubljana, Slovenia
Tel. ++386 1 437 66 00,
E. crt.marincek@mail.ir-rs.si

12th World Congress of the International Association for the Scientific Study of Intellectual Disabilities
14-19 June, 2004; Montpellier, France
Fax. 020 610 812, E. felce@cardiff.ac.uk

7th Headache Congress - European Headache Federation
16-20 June, 2004; Rotterdam, The Netherlands
Fax. 00 41 227 322 850,
E. headache@kenes.com

Advances in Neuroblastoma Research
16-19 June, 2004; Genoa, Italy
Fax. 00 39 0 103 762 322,
E. ANR2004Genoa@neuroblastoma.org

Neurovascular Update: Intracranial Aneurysms
17-18 June, Boston, US
Fax. 617-384-8686,
E. hms-cme@hms.harvard.edu

2nd International Meeting on Multiple System Atrophy
17-18 June, 2004; Rome, Italy
Tel. 0039 0 670 384 513,
E. eva.appelgren@serono.com

BSCN Scientific Meeting
18 June, 2004; Cardiff, UK
E. bscn@secretariat.freeserve.co.uk

ENABLE: Can Technology Help People with Dementia?
21-23 June, 2004; Oslo, Norway
Fax. 00 47 33 33 21 53,
E. post@nordemens.no

Rethinking Rehabilitation
21-24 June, 2004; Oslo, Norway
Tel. +47 24 10 24 00
E. grete.hjermstad@ri-norway.no

Muscular Dystrophies: Advances in diagnosis and management
23 June, 2004; Leeds, UK
Tel. 0113 3055086,
E. adele.archer@nhs.net

5th World Stroke Congress
23-26 June, 2004
Tel. 00972 3 5140000,
E. stroke2004@kenes.com

International Symposium on Coma and Impaired Consciousness (satellite to ASSC8)
24 June, 2004; Antwerp, Belgium
www.ruca.ua.ac.be/assc8/satellite.html

Standardised Assessment in OT - special emphais on neurology, part 2
24-25 June, 2004; London, UK
E. ACNRevents@aol.com

8th Annual Meeting of the Association for the Scientific Study of Consciousness
25-28 June, 2004; Antwerp, Belgium
www.ruca.ua.ac.be/assc8

14th Meeting of the European Neurological Society
26-30 June, 2004; Barcelona, Spain
E. gerard.said@bct.ap-hop-paris.fr

A right to die gracefully - defining brain death
30 June, 2004; London, UK
www.bna.org.uk

July

Motor Disabilities: Assessment, Rehabilitation And Neurophysiological Support
1-10 July, 2004; Marseille, France
Prof A Delarque, Service de Rééducation, CHU La Timone, 92 rue Auguste Blanqui, 13005 Marseille, France

Latin American Congress on Epilepsy
2-5 July, 2004; Mexico City, Mexico
www.epilepsiamexico2004.org

Neurogenetics Symposium
6 July, 2004; Cardiff, UK
E. jacqui.carrington@suht.swest.nhs.uk

Australian Society for the Study of Brain Impairment (ASSBI) & International Neuropsychological Society (INS) Annual Meeting
7-10 July, 2004; Brisbane, Australia
Fax. 00 61 292 480 894,
E. neuropsych@tourhosts.com.au

FENS 2004 Satellite meeting of the European Chapter of the Molecular & Cellular Cognition Society
8-9 July, 2004; Lisbon, Portugal
www.molcellcog.org

4th Forum of European Neuroscience
10-14 July, 2004: Lisbon, Portugal
http://fensforum.neurosciences.asso.fr/

Techniques and Applications of Molecular Biology: A course for medical practitioners
12-15 July, 2004; Warwick, UK
Tel. 024 7652 3540,
E. charlotte.moonan@warwick.ac.uk

9th International Conference on Alzheimer's Disease & Related Disorders
17-22 July, 2004; Philadelphia, US
Tel. 001 312 335 5813,
Fax 001 866 699 1235,
E.internationalconference@alz.org

XV meeting of the International Neuro-Opthalmology Society
18-22 July, 2004; Geneva, Switzerland
Fax. 00 41 22 839 8484,
E. info@symporg.ch

6th World Congress on Myofascial Pain and Fibromyalgia
18-22 July, 2004; Munich, Germany
Fax. 001 210 567 6964,
E. duncan@uthscsa.edu

BioScience2004 - from molecules to organisms
18-22 July, Glasgow, UK
www.BioScience2004.org,
E. erica.hammond@portlandpress.com

Assessment and Management of Children with Physical Disabilities
19-21 July, 2004; Institute of Child Health, London, UK. Tel. 020 78298692
E. courses@ich.ucl.ac.uk

August

International Society for Developmental Neuroscience
4-7 August, 2004; Edinburgh. UK
Tel. 001 604 822 2673,
E. steeves@icord.org

Rehabilitation International Assembly and World Congress
9-14 August, 2004; Oslo, Norway
E. grete@ri-norway.no

The Neurochemical Monitoring System
16 August, 2004; Hong Kong
Fax. 00 852 2647-3074,
E. icp2003@cuhk.edu.hk

128th American Neurological Association Annual Meeting

18-22 October, 2003; San Francisco , USA

Since attending my first ANA annual meeting in 2001 this meeting continues to get my vote as the most rewarding of the large annual general neurology meetings to attend. The ANA tends to focus on clinically relevant developments in the basic sciences. Other advantages of the meeting include its relatively small size. It is less commercialised than the other large international meetings and it has a simple programme with no parallel sessions.

The main plenary session of the 2003 meeting was a public policy symposium dominated, not unexpectedly, by emerging infections and the threat of bioterrorism. Richard Johnson, from John Hopkins, gave a masterly talk on the new threat facing the international community from naturally emerging infections. Although his talk was relatively broad, he focused his attention on the recent epidemics of West Nile virus in the US, the international SARS epidemic and the recent Hanta and Nipah viruses outbreaks. An alarming and sobering statistic was the new epidemiological data, which emerged from the SARS outbreak, of how rapidly a new infection is likely to spread. International air travel and the number of air travellers make it likely that any new, highly infectious agent has the potential to spread to all four quadrants of the globe within a 24-48 hour period. The implications for the international community are considerable and as a result new international surveillance systems will need to be put in place in an attempt to counteract this threat. He emphasised that practising neurologists should have a high index of suspicion with regard to new and emerging infections, e.g. meningoencephalitic syndromes in patients with a significant travel history. Sadly, the threat of bioterrorism has made the ideal of eradicating certain infectious diseases, e.g. smallpox and polio, an unrealistic goal. National health systems will have to be forever prepared to deal with the deliberate reintroduction of these infections by terrorist organisations.

In the symposium on animal models Dennis Choi from the Merck Research Laboratories gave an enlightened talk on the failure of animal stroke models to deliver a successful therapeutic agent. He presented modelling data on the effects of passive diffusion of therapeutic agents into the infarct zone, which is likely to contribute substantially to the therapeutic effect of agents in animals with small brains compared to us humans with brains that are several orders of magnitude larger. In the same session Dale Schenk from Elan Pharmaceuticals presented an update of the A-beta immunisation strategy in the APP transgenic mouse model of Alzheimer's disease. It was reassuring to hear that despite the recently aborted clinical trial this strategy still has potential; possibly by using humanised anti-A-beta monoclonal antibodies. After receiving the Raymond Adams Lectureship, Stephen Hauser ended the session with a talk on new experimental models for multiple sclerosis. He reminded us that despite intensive efforts we have yet to exclude an environmental cause for the disease.

The highlight of the session on sleep physiology and sleep disorders was the eloquent talk by Emmanuel Mignot about how he and his colleagues uncovered the genetic cause for narcolepsy in dogs and how this subsequently led them to discover that in the majority of humans with narcolepsy there is an acquired deficiency of hypocretin 1, presumably as a result of autoimmune destruction of the group of hypothalamic neurones in the suprachiasmatic nucleus that produce the peptide.

The session on episodic disorders was a powerful reminder of how far we have come in uncovering the genetic causes of some rare but very instructive disorders, which have become known as the channelopathies. Specific examples discussed included defective potassium channel Kir2.1 functioning in the oral-facial-digital or the Andersen-Tawil (type 7 long QT) syndrome and the role for ankyrin-B, a non-ion channel protein, in type 4 long QT syndrome. In the latter syndrome calcium signalling is altered, as well as the functions of several channels and pumps that normally interact with wild-type ankyrin-B as a result of the presence of mutant ankyrin-B. Michael Moskowitz, from the Massachusetts General Hospital, who was awarded the prestigious Soriano Lectureship by the Academy, presented his unifying, but slightly confusing model to explain migraine headache. Samuel Berkovic concluded the session with an update on the epilepsy channelopathies. His talk demonstrated the molecular complexity which underlies the seizure disorders along with the future benefits that molecular medicine will bring to neurology.

In addition to the plenary sessions there were many excellent poster sessions and stimulating platform presentations affirming that academic neurology is alive and well, and benefiting fully from the molecular revolution that is sweeping modern medicine. In conclusion, if I was asked to choose one meeting to attend each year it would be the annual ANA meeting.

Dr Gavin Giovannoni
Institute of Neurology, Queen Square, London

The Role of MEG in Epilepsy Diagnosis and Treatment

Electrophysiological techniques (MEG/EEG) record activity generated by neuronal currents and provide specific information concerning epileptic activity. Their high temporal resolution permits assessment of fractions of milliseconds with magnetic fields being less distorted by different conductivities of tissues (scalp, skull, cerebrospinal fluid, meninges and brain parenchyma) than electric ones. Thus MEG is a reference–free method whilst EEG records tangential and radial components[1]. Whereas MEG selectively detects tangential components of source currents, in clinical practice this does not seem to detract from the utility of MEG because most epileptic spikes have both tangential and radial components. In fact simultaneous EEG and MEG recordings have demonstrated superior sensitivity of MEG especially in neocortical epilepsy[2]. The development of MEG-systems with up to 200–300 channels now permits non invasive, contactless and fast recordings from the whole cortex within one session[3].

The presurgical evaluation of patients with neocortical epilepsy is difficult because of the large extent of the cortex[4], of which the frontal lobe alone comprises 40%. Fast propagation of epileptiform discharges and so-called "silent" areas of the cortex add to the difficulties of the evaluation of these patients[5]. Patients with nonlesional neocortical epilepsies who comprise 20–30% of referrals for presurgical evaluation, pose major problems in the surgical treatment of epilepsies because invasive recordings are always required and even then may not provide sufficient localising evidence to offer patients surgery[6]. It is in these patients where MEG may be able to provide unique localising information[7-10], which may in turn lead to the identification of previously unrecognised MRI lesions[11]. MEG can also be used to optimise the placement of intracranial electrodes as well as define the extent of resection in some of these patients[10].

Indeed MEG helps to define the relationship between the lesion and the epileptogenic cortex such that it can help in the decision as to whether lesionectomy alone can be performed without invasive recordings. On the other hand MEG may reveal extra-lesional cortical involvement and guide invasive electrode placement and the extent of tailored resection, and in some cases it can show extensive abnormalities which preclude invasive monitoring or surgical treatment[10]. In this respect there is a particular difficulty in interpreting scalp-EEG and in performing invasive recording in patients who have undergone previous surgery or cranial trauma, and the non-invasive data provided by MEG may be especially helpful in these circumstances[12]. Cortical dysplasia is increasingly recognised as a cause of neocortical epilepsy, especially in children and the extent of the demonstrated radiological abnormality and the epileptogenic zone are not always concordant, either one may be larger or smaller than the other. MEG has proved helpful in optimising the resection in these cases[13,14] whilst in patients with mesial temporal lobe epilepsy with noncongruent findings from standard presurgical procedures, MEG can again provide useful information for their further management[15,16].

The localisation of sensorimotor cortex and other eloquent cortical areas are required to design neurosurgical strategies and MEG has exquisite sensitivity and reliability for localisation of functional cortex and is used routinely for this purpose[17-19]. The accuracy of these MEG results makes it ideally suited for preoperative planning as well as in intraoperative neuronavigation[18], especially as structural imaging can fail to identify functionally significant areas which may be displaced not only by tumours or edema, but also shifted due to brain plasticity[20].

MEG is a promising new technique with particular applications to the care of patients of all ages with epilepsy. MEG offers unsurpassed temporal and excellent spatial resolution of neurophysiologic data and so provides data that previously could only be obtained by invasive intracranial EEG monitoring.

Prof. Dr. Hermann Stefan,
Erlangen, Germany

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Consensus Paper on the International Workshop on MEG held on May 2nd – 3rd, 2003 at the University of Erlangen-Nuernberg, Department of Neurology

Organisers: Prof. Dr. Hermann Stefan, Erlangen, Germany
Prof. Dr. Christoph Baumgartner, Vienna, Austria

Professor Hermann Stefan trained in neurology, psychiatry, neuropathology, and epileptology at the University Bonn. He is Professor of Neurology/Epileptology in the Department of Neurology, University Erlangen-Nürnberg, and specialises in the treatment of epilepsies, especially difficult to treat types of epilepsy and presurgical evaluation, including Magnetic source imaging (MEG/EEG) and MR-Spectroscopy.

Participants IWOMEG 2003 (in alphabetical order)
Jean-Michel Badier, France
Gregory L. Barkley, USA
Christoph Baumgartner, Austria
Scott Buchanan , USA
Michael Buchfelder, Germany
Manuel Campos, Chile
Patrick Chauvel, France
Kathrin Druschky, Germany
John Ebersole, USA
Dawn Eliashiv, California, USA
Rudolf Fahlbusch, Germany
Yegang Feng, China
Michael Fischer, Germany
Michael Funke, USA
Oliver Ganslandt, Germany
Martine Gavaret, France
Alexandra Genow, Germany
Ruth Gessner, Germany
Peter Grummich, Germany
Gordon Haid, Canada
Hans Holthausen, Germany
Rüdiger Hopfengärtner, Germany
Erika Kirveskari , Finland
Prof. Knowlton, UK
Pal Larsson, Norway
Christian Maihöfner, Germany
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Hannes Nowak, Germany
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Christina-Elena Valaki, Spain
Terry Vanderkruyk, Canada
Klaus Wassmuth, Germany
Heinz-Gregor Wieser, Switzerland
Joyce Wu, China

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

Handbook of Neurological Rehabilitation

Edited by: Richard Greenwood, Michael Barnes, Thomas McMillan & Chris Ward
ISBN: 0863777570
Publisher: Psychology Press
Price: £120

This book is not a handbook in the Oxford pocket style, but a comprehensive reference book of 730 pages. The first edition, from a different publisher and under a slightly different name, became the standard British general neurorehabilitation text. The new edition retains the main sections on principles of practice, assessment and treatment of functional deficits, and then management of specific disorders. The 70 authors are almost all from the UK, so the treatments recommended may be more practical here than some in North American books.

There is a good description of how a multidisciplinary team can work together effectively: this process does not happen without considerable effort and commitment. The section on mechanisms of recovery discusses cellular damage and repair, plasticity, tissue transplantation and learning. The section on mobility deficits includes descriptions of physical consequences of neurological disablement, biomechanics, rehabilitation engineering, assistive technology and functional neurostimulation, which clearly shows the difference of emphasis in neurology and rehabilitation text books. The management of bladder, sexual, respiratory, swallowing, pain, visual complications of neurological disability, chronic fatigue and dysarthtria are explained, and the treatment, rather than just identification and measurement, of cognitive impairments is described. The management of disabled school leavers, and the transition to adult services is discussed, in the context of cerebral palsy, spina bifida and hydrocephalus.

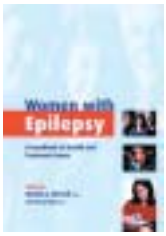
The text is easy to read and up to date, with some references from as recently as 2000, and the index is much more comprehensive than in the last edition. However, there is no discussion of how to identify patients who will respond well to shunting following following intracranial bleeding and decompressive craniectomy, which is a common problem in acute rehabilitation units.

Pictures are rather sparse and some look very dated, particularly those of pieces of equipment: the Lightwriter looks more like an early prototype than the "executive toy" described in the text. The next edition would benefit from many new photographs and website addresses of manufacturers, patient support groups and local contacts for provision of environmental control units.

All doctors actively managing chronic disabling neurological disease should become familiar with this book. In many cases, it will also be a more useful first reference for therapists and nurses than a neurology or neurosurgery textbook.

Stephen GB Kirker, Cambridge

Women with epilepsy. A handbook of Health and Treatment Issues.



Edited by: Müller-Forrell WS (editor) with contributions by Boltshauser E, Kollias S, Lieb W, Martin E, Müller-Forrell WS, Pitz S, Schwarz U & Wichmann W
Publisher: Springer-Verlag, 448 pages, 1368 illustrations (66 in colour)
ISBN: 3-540-63302-2
Price: £139.50

The authors describe this book as being for patients, their families, friends and clinicians. It tries to straddle the divide between being educational for clinicians and informative for patients but it is really a book for lay people, even though there are references with each chapter. They will find it a good source of information on many aspects of epilepsy and there are some very interesting chapters. There are clearly biological and social issues that affect women and not men and vice-versa, but in a world of women presidents and chief executives and house-husbands, a gender specific text feels frankly retrogressive in parts. Lisa Lindahl, a successful business woman presents an insightful case as a vociferous advocate for epilepsy services for women. However, I felt that although she is airing her own historically important personal grievances, the tone and portrayal of male doctors as the bad guys is very "late twentieth century". No doubt she would argue that I just felt my Y chromosome was threatened by her approach. The real stars of the book are Joan Kessner Austin (mother) and Janet Austin Tooze (daughter) who co-wrote a chapter called "Parenting the daughter with epilepsy". This chapter is both moving and practical for parents navigating the fine line between sufficient care and over-protection, with clear advice about exploring the emotional issues surrounding epilepsy. It is preceded by another excellent chapter discussing epilepsy and relationships with many of the issues equally applicable for men and women.

Some predictable areas are covered, the menstrual cycle, the menopause, family planning, osteoporosis and psychiatric complications. As a book written for lay people, the background is well presented but for the clinician, the meat of the specific clinical issues in relation to epilepsy is often a little thin. For example the key question of teratogenicity is covered in only 7 pages and the view expressed, that many abnormalities occur with similar frequency whichever of the older antiepileptic drugs is used is not one that I share. Similarly, the following chapter on neurocognitive outcome of children born to mothers with epilepsy does not mention the deleterious effect claimed for valproate in a couple of recent studies.

So if you want an entré into women's issues in epilepsy, this book does it very well, and the highlights are the personal insights. If you need to solve any more detailed clinical problems, you will be left wanting.

Mark Manford, Cambridge

Neurological rehabilitation of Parkinson's disease

Edited by: Martha Morrell and Kerry Flynn.
Publisher: Cambridge University Press. 2003.
ISBN: 0-521 65541 2 (paperback) 0 521 65224 3 (hard-back)
Price: £19.95/£55

This book is the first in a new series from Queen Square, aiming to "deliver the essentials of neurological rehabilitation in a concise and user-friendly fashion". It is a neat volume of 130 pages which would fit into a large pocket. Use of tables, key points in shaded boxes, and indexing is good, and each chapter includes helpful references.

Reading this book from cover to cover would take you through pharmacological management; psychosocial impact, mainly depression and its treatment; a comprehensive, critical review of non-pharmacological therapy; service delivery; outcome measures; and future directions, like neural grafts. I suspect clinicians seeing a lot of people with Parkinson's disease would need more detail but this book offers a good introduction to rehabilitation in Parkinson's disease.

CA Young, WCNN, Liverpool

EDITOR'S CHOICE

Multiple sclerosis: Have we got it all wrong?

A paper in the *Annals of Neurology* has to be pretty special to get reported in The Economist, as this was. The findings of this study of one lesion from one case with multiple sclerosis are certainly remarkable. Whether they are extraordinary enough to completely rewrite the textbooks is another matter. But any study of multiple sclerosis pathology from John Prineas has to be taken very seriously.

The patient is an unusual one: a 14 year old girl dying of neurogenic pulmonary oedema 17 hours after the symptomatic onset of a brainstem plaque. The autopsy was 13 hours later. It is very rare for such early stages of the multiple sclerosis lesion to be examined pathologically. Contrary to all expectations, the first abnormality seen was oligodendrocyte death, by a process similar to apoptosis (with nuclear condensation but without activation of caspase 3). There is microglial activation but neither T cell infiltration nor myelin phagocytosis. The authors examine the brains of 11 other patients with multiple sclerosis and find, amongst many plaques, 9 lesions in 6 other cases with similar apoptosis of oligodendrocytes.

The authors conclude that the primary event in multiple sclerosis is the programmed death of oligodendrocytes, of unknown cause, and that demyelination and infiltration of inflammatory cells are all secondary. Dogma has it that apoptosis does not induce inflammation, so that needs explaining.

This is not a completely novel suggestion. The landmark series of papers from Claudia Luchinetti and Hans Lassmann describe a rare subset of multiple sclerosis lesions without much inflammation and a primary oligodendropathy as their key feature: the "Type III" lesion. However Barnett & Prineas are claiming this is the universal mechanism for multiple sclerosis plaque formation.

This is provocative stuff and, of course, seriously bad news for anti-inflammatory treatment strategies. - ***AJC***

Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion.

Barnett M & Prineas J.
ANNALS OF NERUOLOGY
2004; 55: 458-468

REHABILITATION: Training doctors with disabilities

Having recently learnt that a young third year medical student, who lost his hand at wrist level during a summer job, is soon due in our prosthetic clinic, this article caught my eye. Though focused on the North American medical school system and US legislation, it does offer an interesting insight into how we in the medical profession view how people with disabilities can or should be facilitated to qualify and practice as a doctor.

Similar to legislation in the UK, Ireland and most European countries, the Americans with their Disabilities Act outlaws discrimination based solely on disability including admission to educational institutions. It specifies that applicants must be able to perform the "essential functions" of the educational program but in turn the institution must provide "reasonable accommodations". The authors discuss the Association of American Medical Colleges 1979 report and how it tried to define the essentials of an "undifferentiated" medical graduate as one who possesses all of the technical skills required to enter any speciality of medicine. This report identified five categories of abilities and skill deemed necessary for a graduate to posses: observation; communication; motor; conceptual, integrative, and quantitative; and behavioural and social. Thus the questionnaire was based on this construct.

Though 2,930 people associated with the Northwestern University School of Medicine were sent a questionnaire, no firm conclusions can be drawn from this survey given the poor response rate from only 523 (18%). The questionnaire consisted of three multiple choice questions, 27 questions in five-point Likert-scale format, five demographic questions and a space for comments along with a cover letter. The group surveyed included most "levels" of the medical profession: attending physicians, house staff in residency programmes and third year medical students. Perhaps not surprisingly Physical Medicine & Rehabilitation had the highest response rate (26.9%) of the specialities compared to 14.9% for other medical specialities and 11.1% for surgical ones (though the authors didn't offer that this may have been due to their contacts in the department).

The majority of responders (69.8%) disagreed with the above interpretation of "undifferentiated" graduates and this held true regardless of disability status or level of training. Technical skills used in interpretation and observation (such as auscultation and palpation/percussion) were more important to respondents than those skills that are purely procedural (such as suturing and performing CPR). One comment noted that physicians rarely work in isolation so that they needn't be expected to perform all skills. On the opposite end of the spectrum was "would you fly with a blind pilot, if the pilot's assistant reads the instruments?" In the past couple of years there has been greater awareness of the issue of people with disability entering and working in the medical field (see BMJ Oct 18). However, more research like this survey is warranted on this side of the Atlantic. I wonder what lies in store for my third year medical student who (already!) is interested in cardiology? - *JJMACF*

Technical Standards for the Education of Physicians with Physical Disabilities: Perspectives of medical students, residents, and attending physicians.

VanMatre RM, Nampiaparampil DE, Curry RH, Kirschner KL
AM J PHYS MED REHAIL
2004;83:54-60

EPILEPSY: My memory is awful

Memory disturbances in epilepsy are widely recognised and frequently complained of by patients. There are clearly many potential mechanisms, which may contribute, including the aetiology of the epilepsy; the epilepsy syndrome; seizure frequency; interictal electrical disturbances; medication and social consequences. This study tries to tease out some of the factors implicated. 121 children with epilepsy aged 7-12 years were included if they had moderately frequent interictal EEG changes, no evidence of a malignant epilepsy syndrome but some evidence of cognitive problems or fluctuations in cognitive performance. Activity of epilepsy was assessed in the period before and during a variety of cognitive tests. These included baseline measures of knowledge base such as vocabulary and transient measures of cognition, including short-term memory attentional tests and speed of information processing.

Reading and arithmetic showed no significant delay in children with generalised epilepsy but a mean of over 1 year delay in children with focal epilepsy, both cryptogenic and symptomatic. Generalised seizures were associated with a delay in reading by 10 months and partial seizures by 21 months. This effect was much greater than any effect of frequency of epileptic EEG activity on these measures. Reaction time scores were not affected by type of epilepsy but were adversely affected if patients had frequent epileptic discharges. Memory testing for word recognition, figure recognition or Corsi memory span were worse in patients with epilepsy than in controls. Word recognition was significantly more severely affected in patients with symptomatic epilepsy than in the other groups. Not surprisingly, seizures during testing had an adverse affect on memory tests.

So what does all this mean? Firstly, aspects of cognition affected will depend on the type of epilepsy and the activity of epilepsy. Focal epilepsy associated with structural abnormalities give problems akin to developmental delay, presumably due to the structural damage and not directly related to the epilepsy. Frequent seizures affect processing speed as do frequent "subclinical" EEG discharges but the effect of the latter is mild and limited to transient cognitive processes. When assessing patients with epilepsy and memory complaints, we need to clarify the nature of the complaint, ideally with psychometric testing and relate it to the epilepsy and seizure types as well as EEG findings, before deciding on how to change drug treatment. -*MM*

The relative influence of epileptic EEG discharges, short non-convulsive seizures and type of epilepsy on cognitive function.

Aldenkramp A, Arends J
EPILEPSIA
2004;45:54-63

★★★ RECOMMENDED

DEMENTIA: Driving and dementia

Drivers suffering from dementia are two to five times more likely to be involved in road accidents than age-matched controls (no comparisons with adolescent males available!). Conversely, advising patients not to drive can have serious practical repercussions, can dent self-esteem and undermine doctor-patient relationships. Reger and colleagues contribute a meta-analysis of 27 primary studies that evaluate neuropsychological tests in the prediction of driving ability.

Numerous standard neuropsychological tests are included, subdivided into six domains according to the primary function tested (attention, visuo-spatial skills, memory, executive functions, language and 'general' cognition). The primary studies compare test performance to three more-or-less direct measures of driving ability – on-road tests, non-road tests (e.g. driving simulators) and caregiver reports; official accident records proved too heterogeneous to include. An effort is made to restrict the analysis to subjects diagnosed with Alzheimer-type dementia and to standardise 'effect size' across the myriads of primary studies. Correlations excluding controls are rightly given

prominence: incorporating controls into such analyses would overestimate predictive value.

In the analyses that exclude control subjects, no significant association is found between general tests (mainly MMSE) and on-road assessments. The effect sizes for correlations with driving scores are 'small' in each of the cognitive domains except for visuo-spatial function, where the effect size is 'moderate'. Whilst this might have been expected, it is surprising that tests of attention (also conventionally regarded as crucial to driving) appear to have less predictive value.

The message is that neuropsychological tests do not add greatly to evaluations of driving ability. In difficult cases, specialist driving assessments using simulators and on-road testing seem warranted. *-RD*

The relationship between neuropsychological functioning and driving ability in dementia: a meta-analysis.

M.A. Reger, R.K. Welsh, G.S. Watson, B. Chorleton, L.D. Baker and S. Craft.
NEUROPSYCHOLOGY
2004, 18: 85-93.

COGNITION: Emotions in Urbach-Wiethe disease

No, not the garbled name of an unusual myoclonic epilepsy syndrome but another autosomal recessive condition, extremely rare and associated with bilateral calcification of the amygdala. Urbach-Wiethe disease is associated with deposition of hyaline-like material in the skin, mucous membrane and other organs; it has been associated with learning difficulties and with seizures, although neither point is emphasised here.

The main contribution of the paper is in drawing attention to a disease, which despite its rarity, may prove to be a very instructive natural experiment. The authors have found cases, mainly in South Africa, that compare favourably to matched controls in most areas of cognition but have deficits in emotional processing. There are particular difficulties with recognising 'complex' emotions (surprise and disgust, as compared to fear) and some impairment on an association task involving olfaction. Very much as expected, memory for emotionally arousing material was severely impaired.

It is to be hoped that the rather limited imaging data-set (CT, SPECT and one PET) is an indication of more to come. *-RD*

Amygdala, affect and cognition; evidence from 10 patients with Urbach-Wiethe disease.

M. Siebert, H.J. Markowitsch and P. Bartel
BRAIN
2003, 126: 2627-2637.

MEMORY: Caudate contributions to working memory: an fMRI study.

Common cognitive problems displayed in neuro-rehabilitation settings are deficits in executive function and patients often display specific difficulties on tests of planning and working memory. Converging neuroscience sources show frontal regions of the brain like the frontal cortex being important to working memory. Recent clinical evidence from close analysis of Parkinson's patients however suggests that subcortical brain structures also have an important role.

This fMRI study targeted subcortical structures such as the caudate nucleus to see how activation here relates to specific aspects of working memory. Crucially attempts have been made to isolate component cognitive contributors to working memory by designing the experimental paradigm to assess "maintenance, retrieval and manipulation" independently. During an originally designed verbal memory test, ten healthy participants were scanned using event related functional Magnetic Resonance Imaging. Alongside the neuroimaging process parallel behavioural measures relating to performance were recorded. By combining design with techniques different aspects of the task could be correlated with activation in specific regions of interest. This was in order to illuminate brain function during particular aspects of working memory.

Signal increases were evident in the "frontostriatal network" during the task. Bilateral caudate nuclei activation seemed to be relatively increased when manipulating information over and above maintaining and retrieving it. This interesting finding is consistent with other recent research suggesting that Parkinson's disease patients (who characteristically show neurodegenerative signs of dopaminergic loss in the caudate nuclei) display difficulties in executive function and in manipulation aspects of working memory. Perhaps this research will lead to tests for cognitively relevant pharmacological/ therapeutic interventions targeting subcortical function. *-LAJ*

Striatal contributions to working memory: a functional magnetic resonance imaging study in humans.

Lewis S.J.G, Dove A, Robbins T.W., Barker R.A. and Owen A.M.
EUROPEAN JOURNAL OF NEUROSCIENCE
2004: 19: 755-760

NEUROINFLAMMATION and degeneration

The role of inflammation (including activated microglia) in neurodegenerative disease and regeneration following acute lesions is complex. Whether or not activated microglia are beneficial or detrimental to regeneration, repair and neurogenesis, is unresolved. Lindvall *et al* found that activated microglia, as induced by lipopolysaccharide (LPS) infusion, reduced survival of new born neurones and postulated this as a mechanism for poor regeneration post injury despite robust initial neurogenesis.

In the first experiment, infusion cannulae were implanted into the right cortex of rats, and LPS from E. Coli was infused. The numbers of activated microglia (as determined by immunohistochemical staining for ED1) were quantified 6 and 28 days later, and were very much higher in LPS treated rats compared to vehicle. The numbers of ED1 positive cells were significantly negatively correlated with BrdU/ NeuN double-labelled cells. BrdU is a nucleoside analogue, which incorporates into dividing cells, and when colabelled with neuronal markers indicate new neuronal formation. That is, the more activated microglia, the less neurogenesis (in the subgranular layer, an area of basal neurogenesis).

Rats were implanted with a stimulating/recording electrode (right hippocampus) and status epilepticus was induced, interrupted by intraperitoneal phenobarbitone. The numbers of activated microglia were much greater in generalised status. As expected, partial status induced a robust neurogenic response (measured by double labelled BrdU/NeuN cells), but this was attenuated in generalised status (although still higher than the basal rate of neurogenesis). This was seen at 28 days (double labelled cells then indicating those which had survived from the initial labelling injections on day 1). Markers for proliferation (Ki67) were not different between partial and generalised status, indicating that there is an effect on cell survival as opposed to formation. The degree of new neuronal survival in partial status was reduced to levels seen in generalised status by infusion of LPS into animals that had undergone partial status. Infusion of LPS increases levels of activated microglia without inducing further tissue damage. Thus this effect seems to be specific to microglial activation rather than tissue damage. Finally, the authors showed that the attenuation of new neuronal survival seen in generalised status could be ameliorated by intraperitoneal injections of minocycline. Minocycline is a specific inhibitor of activated microglia, and readily crosses the blood-brain barrier.

So microglial activation in this model inhibits neurogenesis; it is not yet known whether this effect is reproducible in other acute lesions, or in neurodegeneration. The role of activated microglia is likely to be complex and involve different effects (supportive versus toxic) depending on timing and location of injury, morphological state of the microglia, surrounding environment, and so on. *-WP*

Inflammation is detrimental for neurogenesis in adult brain.

Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O.
Proc Natl Acad Sci U S A. 2003 Nov 11;100(23):13632-7.
Epub 2003 Oct 27.

TECHNIQUES: A new agent to measure neurogenesis

The concept of adult neurogenesis is an exciting one, having profound implications for our understanding of memory and learning, plasticity and repair. Unfortunately, it has been difficult to measure and the most widely accepted method is beset with difficulties and inaccuracies. Bromodeoxyuridine (BrdU) is a thymidine analogue, which incorporates into DNA during the S phase of replication and thus labels dividing (proliferating) cells. Neurogenesis has been measured by counting cells, which label for both neuronal markers and BrdU (thus indicating that the neurones have recently proliferated). This method has problems, which will be described below.

Doublecortin (DCX) is a microtubule associated phosphoprotein required for neuronal migration and differentiation, and is expressed in immature neurones. Doublecortin immunoreactivity has sometimes been used as a marker for neurogenesis but it has not been systematically validated until now. Rao and Shetty compared immunoreactivity for BrdU, DCX and both in the adult rat dentate gyrus. Proliferating cells were labelled with a 100 mg/kg intraperitoneal injection of BrdU per day for 12 consecutive days. They showed that 90% of all DCX positive cells in the dentate gyrus are also BrdU positive. The remaining 10% may not be labelled because either they were generated before the 12 day injection regime, after injection but before sacrifice or in between the daily injections. 76% of all BrdU positive cells were also DCX positive therefore most differentiate to neurones. 95% of DCX positive cells expressed TuJ1 (an immature neuronal marker), none expressed nestin (which indicates an undifferentiated state) or glial markers, demonstrating its sensitivity and specificity. No DCX cells were positive for TUNEL staining (a measure of apoptosis) despite many reports that around 50% newly generated neurones die by 4 weeks. Neurones could lose their DCX immunoreactivity as they become apoptotic; they could be dying via another mechanism other than DNA fragmentation (which is what TUNEL mea-

sures); or simply, apoptosis may be occurring in temporal clusters, missed when the rats are sacrificed. In addition to measuring neurogenesis, in thicker brain slices DCX accurately demonstrates dentrites and can be used to quantify dendritic outgrowth.

The validation of DCX to measure neurogenesis is a very exciting development because it overcomes many of the problems encountered when using BrdU:

- No injections are required with DCX
- It is less stressful for the animal
- There are no problems with under- or overestimating labelled cells
- There are no concerns about killing cells as with high dose BrdU regimes
- Some neuronal markers are not very specific, and one must rely on neuronal markers when using BrdU
- Importantly, DCX can be used in human PM tissue where BrdU clearly cannot.

More work needs to be done, however, to validate DCX in different species, different brain regions and in lesioned or diseased brains. *-WAT*

Efficacy of doublecortin as a marker to analyse the absolute number and dendritic growth of newly generated neurones in the adult dentate gyrus.
Rao MS, Shetty AK
EUROPEAN JOURNAL OF NEUROSCIENCE
2004 (19) 234-246

★★★ RECOMMENDED

CELL THERAPY: Regenerative capacity of the human brain called into question

Cell therapy is a potential neuroreparative strategy to combat neurodegenerative disease. One approach is to transplant cells directly into the diseased brain, but the two well publicised randomised controlled trials in Parkinson's disease have produced mixed results despite promising preclinical rodent and primate data. Alternatively, it might be possible to stimulate stem cells in the adult human to repair the brain from within, much like the regeneration seen in some non-mammalian vertebrates. It is known, for example, that precursor cells exist in the adult human brain in the subventricular (subependymal) zone around the lateral ventricles and the dentate gyrus of the hippocampus.

A recent study by Sanai *et al* has cast new light on these issues. They studied 65 neurosurgical brain specimens and 45 from autopsy, and revealed two key findings. Firstly, stem cells were found in a subventricular band around the lateral ventricles. Staining with Ki-67 (a nuclear protein associated with DNA synthesis and cell division) revealed that 0.77±0.29% of these cells were in division, but none expressed markers of immature neurons, suggesting a lack of endogenous neurogenesis in this area. When removed and grown in culture these cells differentiated to neurons, astrocytes and oligodendrocytes, suggesting that the stem cells retained potency but were restrained by their environment in vivo.

Secondly they failed to demonstrate the rostral migratory stream - a band of neuroblasts seen migrating from their origin in the subventricular zone towards the olfactory bulb in adult rodents. Thus there are fundamental differences between the human brain and the brains of other mammals commonly used to model neurodegenerative disease. This would suggest that we exercise caution in interpreting data from animal models of disease, and restrain from rushing prematurely into clinical trials. *-AWM*

Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration.
Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S,Lawton MT, McDermott MW, Parsa AT, Manuel-Garcia Verdugo J, Berger MS,Alvarez-Buylla A.
NATURE
2004; 427 740-744

NEUROPSYHOLOGY: Out of body experiences

This fascinating article reviews the literature pertaining to out of body experiences (OBE) and related phenomena, and reports extensive data from 6 patients. The authors point out that while related perceptual disturbances such as phantom limb have a neuroscientific correlate, this is not the case for OBE, which has remained partially in the domain of mythology and mysticism.

Three autoscopic phenomena (AP) are described according to visuospatial perspectives: autoscopy (AS), he-autoscopy and OBE. Patients who experience AS see a parasomatic body from their own visuospacial perspective, while patients with OBE see themselves from the perspective of their parasomatic body, and he-autoscopy is between these two states (with alternating, but not simultaneous perspectives). Whereas all AP are characterised by a disintegration of personal space, OBE also represents disintegration between personal and extrapersonal space. AP have been reported in psychiatric, neurological and 'normal' cases (prevalence of around 10%, 1-2 per lifetime).

6 patients were employed for this study and underwent detailed questioning pertaining to the phenomenology of the experience, clinical examination, surface EEG, MRI (T1, T2, FLAIR), PET, and SPECT. Results of neuroimaging were superimposed onto 3D MRI to visualise the exact lesion location. 5 of 6 patients had frequent complex partial epilepsy without generalisation, and the other had presumptive TIA from complicated migraine. One epileptic patient had OBE while undergoing cortical stimulation (as part of the epilepsy surgical workup). One patient experienced AS; three he-autoscopy; and three OBE.

A variety of emotions were reported during AP: three experienced fear; two felt the experience was surprising and intriguing and one felt joy. AP (particularly OBE) tended to be very vivid - indeed there have been reports of patients jostling with and talking to their parasomatic bodies. The parasomatic bodies are recognised as 'self' despite some patients seeing only parts, from behind, wearing different clothes/ being of a different age etc., suggesting that self-recognition is only partially visual.

While memory was relatively spared (in contrast to medial temporal lobe epilepsy), language and praxic deficits and agnosias predominated, localising dysfunction to the posterior temporal-parietal region. EEG and imaging studies localised dysfunction primarily to the temporoparietal junction (TPJ). During AP, patients underwent brief or partial impairments of consciousness except in the patient who experienced OBE during cortical stimulation.

The authors remind us that continually updated integration of sensory (proprioceptive, tactile, visual) with vestibular information (including discarding of inconsistent information) is required for our central representation and relation to extrapersonal space. They speculate that failure of such integration, by the TPJ, may lead to the experience of seeing one's body in a position which does not concur with where it is felt; thus generating AP. Lesions of the TPJ can lead to visuo-spatial neglect, is activated during egocentric perspective shifts in normal subjects, and physiologically, is important in processing and integrating sensory inputs. The authors hypothesise that vestibular disintegration is also required for AP. Vestibular function is more disturbed in OBE as opposed to AS, and this could give rise to the sensation of the parasomatic body floating upwards from the real one. With AS, other types of sensory information may be dysfunctional e.g. body part illusions were experienced, sometimes only part of the parasomatic body was seen, and the position of the experient's body dictated that of the parasomatic. OBE tended to occur when the patient was supine, and AS when sitting or standing.

In summary, the authors have provided a detailed study of six patients with this rare but intriguing condition and proposed a neurological basis for it; the paper is well worth reading, particularly the patient's descriptions (including pictorial) of their experiences. *-WAT*

Out-of-body experience and autoscopy of neurological origin.
Blanke O, Landis T, Spinelli L, Seeck M. BRAIN
2004; 127: 243-258

For reasons of space, you can find the following additional reviews on our web site at www.acnr.co.uk/contents.html, under journal reviews

RECOMMENDED - MOTOR NEURON DISEASE: Dysfunctional Glutamate Receptors in Sporadic ALS - LMS, SJT
RNA editing and death of motor neurons: Kawahara Y, Ito K, Sun H, Aizawa H, Kanazawa I, Kwak S. NATURE
RECOMMENDED - EPILEPSY: Buzzing the Pleasure Centre -MM
Ictal pleasant sensations: cerebral localization and lateralization.
Stefan H, Schulze-Bonhage A, Pauli E, Platsch G, Quiske A, Buchfelder M and Romstöck J. EPILEPSIA
Drugs for idiopathic epilepsy. - MRAM
The relationship between treatment with valproate, lamotrigine, and topiramate in the generalised epilepsies: Nicholson A, Appleton RE, Chadwick DW and Smith DF. JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY
Epilepsy and hormones - MRAM
Interictal EEG discharges, reproductive hormones, and menstrual disorders in epilepsy: Herzog AG, Coleman AE, Jacobs AR, Klein P, Friedman MN, Drislane FW, Ransil BJ, Schomer DL. ANNALS OF NEUROLOGY
CREUTZFELDT-JAKOB DISEASE: Diagnosis of sporadic Disease. - AJL
Prion deposition in olfactory biopsy of sporadic Creutzfeldt-Jakob disease: Tabaton M, Monaco S, Cordone MP, Colucci M, Giaccone G, Tagliavini F, Zanusso G. ANNALS OF NEUROLOGY
REHABILITATION: Eyes closed for better balance after stroke - AJT
Reliance on visual information after stroke. Part II: Effectiveness of a balance rehabilitation program with visual cue deprivation after stroke: a randomised controlled trial: Bonan IV, Yelnik AP, Colle FM, Michaud C, Normand E, Panigot B, Roth P, Guichard JP, Vicaut E. ARCHIVES PHYSICAL MEDICINE AND REHABILITATION
PAIN: Integrins are integrally involved in mediating pain states - LMS, SJT
Integrin signalling in inflammatory and neuropathic pain in the rat: Dina OA, Parada CA, Yeh J, Chen X, McCarter GC, Levine JD. EUROPEAN JOURNAL OF NEUROSCIENCE
NEURODEGENERATION: keeping active is good for the brain - RAB
Environmental Enrichment Rescues Protein Deficits in a mouse model of Huntington's disease indicating a possible disease mechanism: Tara Spires et al. JOURNAL OF NEUROSCIENCE

NEURODEGENERATION: Keeping active is good for the brain

Mouse models of Huntington's disease have been used as a way of testing novel treatments to see if the natural history and progression of the disease can be modified. In this study a different approach is undertaken which examines how environmental enrichment delays disease progress in mouse models of disease. Over the last three to four years it has been shown that if you place mouse transegenic for the Huntington's disease gene into environments in which they are stimulated both from a motoric and cognitive point of view there is slowing of disease progression in terms of pathology as well as as behavioural deficits. The origin of this is not known but in this recent paper it is hypothesised and demonstrated that it may relate to the secretion of BDNF. In particular this group have shown by Western blot that BDNF levels in two specific areas namely the hippocampus and striatum are reduced in the R6/1 transgenic HD mice, and that this can be restored using environmental enrichment. However, other areas of the brain do not show any changes in BDNF suggesting that it is relatively region specific, and in addition other trophic factors (i.e.NGF) are unaffected so showing that it is specific for this trophic factor as well.

This is an interesting study because the effect of enrichment to date is not known. Our own group is interested in knowing whether the effects of enrichment relate in some way to neural stem cell proliferation given that this is a known proliferative stimulus to the adult neural precursor cell. This study, however, has taken a different tack and demonstrates changes in trophic factor which are influenced by environmental stimulation.

Whether this translates into clinical benefit is not known but it does clearly raise the important issue that physical and mental activity at least in animal models governs the trophic factor secretion and therefore neuronal support within the adult CNS. In the diseased state this may be important in promoting or at least maximising the potential of neurons which are either borne through neural precursor cells or dependent on trophic factors for their persistent survival. Thus whilst it is not clear whether this has a clinical correlate it once more lends weight to the notion that it is good for patients with diseases of the brain to be physically and mentally active. *-RAB*

Environmental Enrichment Rescues Protein Deficits in a mouse model of Huntington's disease indicating a possible disease mechanism.
Spires TL, Grote HE, Varshney NK, Cordery PM, van Dellen A, Blakemore C, Hannan AJ.
JOURNAL OF NEUROSCIENCE
2004 24 2270 – 2276

REHABILITATION: Eyes closed for better balance after stroke

Methods for rehabilitation of balance after stroke are poorly developed. Therapists typically follow one of two strategies. They might try to get patients to react to perturbation by pushing them or by sitting on a ball or standing on a wobble board, or they may try to encourage activity of postural muscles in anticipation of a task such as reaching. There has been little examination of the use of sensory information in balance to guide therapy. An investigation of the use of sensory information in chronic stroke led a French research group to think that patients are too reliant on visual information in maintaining balance. They subsequently tested the effects of balance retraining with visual cue deprivation (eyes closed) in a small randomised controlled trial. The trial and the preceding investigation of the effects of sensory information and the trial are published in two parts in the February edition of Archives Physical Medicine and Rehabilitation.

Twenty patients over one year post stroke who were able to walk without assistance were recruited to a four week balance training course of 5 one hour sessions a week. Patients without joint position sense in the affected leg were excluded. The patients were randomly allocated to train with visual deprivation (blind folded) or to train with vision (control group). Balance was assessed before and after the training course using a clever posturographic evaluation. The patient stood barefoot on a platform and sway angle of the centre of gravity was measured under conditions in which the platform and the surroundings could be stable or could be moving. Gait velocity, ease of gait and stair climbing time were also assessed. After the training program balance, gait velocity and self assessment of gait improved significantly in all patients. Balance improved more in the vision deprived group.

Depriving patients of vision probably forces patients to increase their use of somatosensory and vestibular information. Of course this method needs testing further to confirm the results and to see if they apply to more acute patients; however the method is promising and would be very easy to use in clinical practice. *-AJT*

Reliance on visual information after stroke. Part II: Effectiveness of a balance rehabilitation program with visual cue deprivation after stroke: a randomised controlled trial.
Bonan IV, Yelnik AP, Colle FM, Michaud C, Normand E, Panigot B, Roth P, Guichard JP, Vicaut E.
ARCHIVES PHYSICAL MEDICINE AND REHABILITATION
2004; 85: 274-8.

PAIN: Integrins are integrally involved in mediating pain states

Chronic pain is a common neurological problem that is largely intractable to current therapies, despite improvements in the understanding of mechanisms contributing to pain following tissue and nerve injury. This study investigates a role for integrins in mediating such pain.

Integrins are adhesion molecules that bind extracellular matrix (ECM) proteins, including laminin and fibronectin. They are transmembrane heterodimers (comprised of _ and _ subunits) that mediate signalling in both directions across the membrane. They are present on primary afferent nociceptors and are thus optimally located to sense changes in the ECM environment, which accompany inflammation and injury.

In this study, several strategies were used to disrupt integrin signalling, which concomitantly inhibited the development of hyperalgesia in rat models. Peptide fragments of laminin or monoclonal antibodies against the _1 and _3 integrin subunits (involved in laminin binding) blocked the hyperalgesia triggered by the injection of prostaglandin E2 (PGE2), and carageenan (a longer-lasting model of inflammatory pain), but not by adrenaline. Fibronectin peptides and antibodies against the _5 subunit of integrin (involved in fibronectin binding) blocked hyperalgesia induced by adrenaline, but not by PGE2 or carageenan. The _1 subunit is involved in both laminin and fibronectin binding. Monoclonal antibodies and antisense deoxynucleotides against this subunit prevented hyperalgesia induced by all the above triggers. The _1 subunit antisense molecules also inhibited taxol-mediated hyperalgesia, which is a model of neuropathic pain. Thus, it appears that integrins in fact mediate pain through several pathways.

This demonstration that integrins play a significant role in cell signalling pathways mediating sensitisation of nociceptors, not only adds to our knowledge of chronic pain mechanisms, but also offers hope for the development of better therapies for those suffering from inflammatory and neuropathic pain. *-LMS, SJT.*

Integrin signaling in inflammatory and neuropathic pain in the rat.
Dina OA, Parada CA, Yeh J, Chen X, McCarter GC, Levine JD
EUROPEAN JOURNAL OF NEUROSCIENCE
2004: 19: 634-42

★★★ RECOMMENDED

MOTOR NEURON DISEASE: Dysfunctional Glutamate Receptors in Sporadic ALS

Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurodegenerative disorder resulting from selective loss of motor neurons in the brain and spinal cord. 90% of cases are sporadic and of unknown aetiology. This report from Kawahara *et al*, describes defective editing of messenger RNA (mRNA) encoding the GluR2 subunit of the glutamatergic AMPA receptor in ALS patients. RNA editing of the GluR2 subunit leads to the exchange of a glutamine for an arginine residue in the second of its membrane-spanning domains. This GluR2 RNA editing is not only essential for the correct functioning of the AMPA receptor but is also crucial for neuronal survival. Thus Kawahara proposes that the mechanism underlying motor neuron death in ALS may be the failure to edit the GluR2 Q/R site.

The GluR2 editing efficiency in various neurons from several neurodegenerative diseases was assessed by studying the enzymatic digestion of GluR2 mRNA; a process which occurs only in the edited version of the subunit. Cerebellar Purkinje and motor cortical cells of ALS patients, as well as DRPLA and normal control cells, displayed complete GluR2 Q/R site editing. However, motor neurons dissected from ALS patients showed very variable editing efficiency at this site; 56% of the motor neurons being incompletely edited. This indicates a defect specific to ALS spinal motor neurons. The toxicity of the unedited form of the GluR2 subunit is thought to relate to its ability to promote transport of the AMPA receptor to the membrane and to enhance the permeability of the AMPA receptor to calcium ions.

Further investigation of the mechanism underlying reduced RNA editing at the GluR2 Q/R site should identify rational therapeutic targets specific for ALS. *-LMS, SJT*

RNA editing and death of motor neurons.
Kawahara Y, Ito K, Sun H, Aizawa H, Kanazawa I, Kwak S
NATURE
2004: 427; 801

EPILEPSY: When nocturnal seizures wake up

Seizures whilst you are asleep are bad enough but if they evolve into waking attacks the social consequences may be much greater. So what is the risk? In this study children with benign rolandic epilepsy or any patients with frontal lobe epilepsy which are known to be nocturnal syndromes, were excluded. This left 161 consecutive patients with pure nocturnal attacks, aged 11-83 with two thirds male. Duration of epilepsy ranged from 1-514 months. Focal

seizures affected 15% and GTCS 85%. Sixteen patients had generalised EEG abnormalities and 31 had focal changes. Seizures were mild (<1/yr) in 37%, moderate (1-6/yr) in 54% and severe (>6/yr) in 9%. Follow-up was 24-72 months during which time 14 were lost to follow up and 5 patients died. Those lost to follow-up had been observed for a mean for 25 months before they were lost to the study. Retention was 149 at 2 years, 107 at 3 years, 79 at 4 years and 42 at 5 years. Seventy-eight percent became seizure-free for at least 2 years.

All patients who developed daytime seizures did so within 55 months of follow-up. Eighteen patients (11%) developed seizures whilst awake, about two thirds of these within the first two years of follow-up. By far the strongest identifiable risk factor for conversion to waking seizures was sudden withdrawal of treatment, which was voluntary in all cases. Phased withdrawal did not carry an excess risk. The other significant identified factor was a high seizure frequency at inclusion. Patients can be reassured that it is uncommon for waking seizures to develop on a long background of nocturnal epilepsy, especially if their epilepsy is mild and they do not stop treatment suddenly. *- MM*

Risk of seizures while awake in pure sleep epilepsies. A prospective study
D'Alessandro R, Guarino M, Greco G, Bassein L for the Emiglia Romana study group on clinical and epidemiological problems in neurology.
NEUROLOGY
2004;62:254-7.

CREUTZFELDT-JAKOB DISEASE: Diagnosis of sporadic disease

The clinical diagnosis of sporadic Creutzfeldt-Jakob (sCJD) disease may be difficult. Peripheral biomarkers which may support the diagnosis include CSF 14-3-3 protein and EEG periodic complexes, but neither has perfect sensitivity or specificity. This paper suggests another possible biomarker: deposition of pathological prion protein (PrPRes) in olfactory epithelium.

In sCJD, PrPRes is found exclusively in the CNS, unlike the situation in vCJD where it may be found in reticuloendothelial tissues (hence the utility of tonsil biopsy in the diagnosis of vCJD). Having demonstrated that PrPRes may be shown in olfactory epithelium of sCJD cases post mortem but not in AD or other neurodegenerative diseases (N Engl J Med 2003; 348: 711-9), the authors undertook olfactory biopsy in a patient with suspected sCJD 45 days after disease onset. PrP immunostaining of cilia and basal cells of olfactory epithelium was found. At postmortem, pathological confirmation of sCJD was made.

The findings relate to only one patient and hence need to be confirmed in larger studies. However, if deposition of PrPRes in olfactory epithelium is proved to be an early event in sCJD, this may have implications for early diagnosis and, possibly, for early therapeutic intervention. *-AJL*

Prion deposition in olfactory biopsy of sporadic Creutzfeldt-Jakob disease.
Tabaton M, Monaco S, Cordone MP, Colucci M, Giaccone G, Tagliavini F, Zanusso G.
ANNALS OF NEUROLOGY
2004;55(2):294-296

★★★ RECOMMENDED

EPILEPSY: Buzzing the pleasure centre

Those of us who treat many epileptic patients will remember the occasional one who admits that their epileptic aura is really quite pleasant. If you ask them how pleasant, you get a coy look and an admission that it is really embarrassingly pleasant. Not surprisingly, non-compliance with treatment is reported to be quite high in this group. The current paper explores the localisation of pleasurable sensation in 11 patients undergoing presurgical evaluation. Seven patients were male, which differs from most previous reports in which females predominate and 7 had right-sided abnormalities. Most patients described a very visceral sensation of pleasure, 3 describing a feeling akin to orgasm. All three had temporal lobe discharges, two on the right and one on the left. Previous series have ascribed this sensation to the right hemisphere. All except one of the other patients also had temporal lobe abnormalities on investigation, in 8 pointing to the basal temporal lobe. The other patient experienced a feeling of euphoria – perhaps a more emotional and less visceral sensation. She had biparietal atrophy on MRI and discharges, assessed by intracranial electrodes started in the right basal temporal region and rapidly spread to the parietal cortex. Lesions were hippocampal sclerosis in 3 cases and a variety of foreign tissue lesions in the remainder, including astrocytomas and cavernomas.

If intracranial stimulators can help Parkinson's disease, how many more people would benefit from having their pleasure centre buzzed? I can see a lucrative, if not entirely ethical private practice for an entrepreneurial neurosurgeon. However, the down side is that 6 of the 11 experienced interictal depression. *-MM*

Ictal pleasant sensations: cerebral localization and lateralization.
Stefan H, Schulze-Bonhage A, Pauli E, Platsch G, Quiske A, Buchfelder M and Romstöck J.
EPILEPSIA
2004;45:35-40

New Biotène For Dry Mouth Sufferers

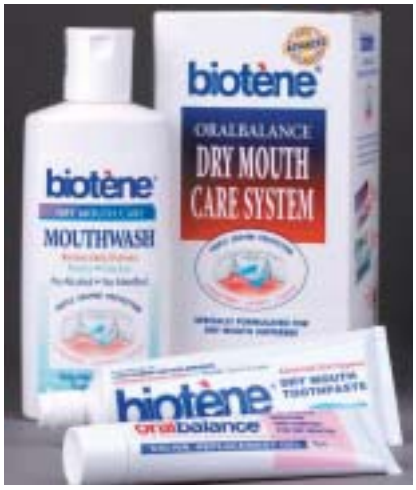
XEROSTOMIA (dry mouth) affects an estimated 10 million people in the UK. The most common cause is medication and over 400 commonly prescribed drugs cause dry mouth as a side effect, which can have adverse effects on patient compliance.

The Biotène range is said to be the first of its kind in the UK to offer long lasting relief from dry mouth. It works by boosting the levels of the protective enzymes found naturally in saliva to help maintain a healthy balance in the mouth - reducing harmful bacteria and sustaining the beneficial bacteria. The products also contain no menthol, alcohol or sodium lauryl sulphate.

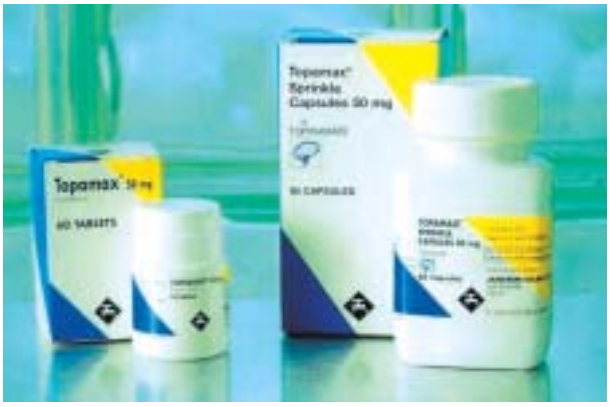
In severe cases of dry mouth, patients may experience difficulty swallowing, eating and in some cases speaking. Milder symptoms include a dry or burning sensation in the mouth, cracked lips, bad breath, mouth sores and bleeding gums.

Biotène Oralbalance Gel provides dry mouth relief for up to 8 hours. The Biotène Oralbalance Dry Mouth Care System contains Biotène Oralbalance Gel (50g) Toothpaste (75ml) and Mouthwash. The complete range is also available from pharmacies.

For surgery information and sample pack telephone Anglian Pharma on 01438 743 070 or visit www.drymouth.org.uk



The Scottish Medicines Consortium (SMC) Delivers Its Recommendation for the Use of Topamax® Monotherapy in Epilepsy in Scotland



THE Scottish Medicines Consortium (SMC) has completed its assessment of Janssen-Cilag's anti-epileptic Topiramate (Topamax®) and, following a full submission, has advised that:

"Topiramate is accepted for restricted use within NHS Scotland for its extended (monotherapy) indication. It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy.

"Topiramate should be used principally in patients who have not benefited from treatment with an older anti-convulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contraindications, interactions or poor tolerance.

"Its use for second-line therapy in epilepsy is unaffected by this recommendation."

Topamax® is a broad spectrum anti-epileptic drug, which can offer advantages for patients with generalised seizures, partial seizures and for those patients whose epilepsy cannot be definitively classified. A recent study concluded that Topamax® was at least as effective as therapeutic doses of carbamazepine and sodium valproate. In addition, the low risk of weight gain with Topamax® singled it out as a particularly effective option in patients where weight gain may create or aggravate existing health problems.

For more information contact Janssen-Cilag on Tel. 01494 567567.

ILAE UK Chapter 2004

THE 3-day 2004 International League Against Epilepsy UK Chapter (ILAE) meeting is being held in Cardiff in the City Hall, 23-25th June 2004. There is a wide-ranging programme, covering topics from the changing structure of epilepsy care (NICE, GP contract, specialist nursing), epilepsy surgery (cognitive and visual field outcomes), basic science ("what's hot and what's not"), learning disability (clinician and carer perspectives) and epilepsy in children (syndromes, febrile seizures and predicaments). There will be a controversial debate entitled "people with epilepsy should be informed about SUDEP at their first specialist consultation". There will also be a practical and interactive session (push button voting) on "Difficult epilepsy consultations".

There will be platform and poster presentations, and presentations by the prizewinning Gowers' essayists. For many, however, the highlight will be Alan Richens receiving the ILAE UK Chapter Certificate of Excellence in Epilepsy Award; Alan will then describe his passion for vintage cars in a talk entitled "Therapeutic Motoring". The meeting will be closed by honoring the late Sheila Wallace, in a touchingly personal symposium on childhood epilepsy, arranged and presented by several of her close professional friends.

The Gala dinner will be at the Angel Hotel. The Cowbridge Male Voice Choir will sing before the meal, and there will be a chance to dance afterwards. There will also be TV coverage of live European Cup football for those for whom football is as important as epilepsy.

The meeting is being generously sponsored, keeping the costs affordable. Download the registration form from the ACNR web site (www.acnr.co.uk), or e-mail denise@conference2k.com for more information.

Survey Highlights Unnecessary Burden of Peripheral Neuropathy and Neuropathic Pain

RESULTS from a survey of over 600 patients presented at the Pain Society's Annual Scientific Meeting reveal that peripheral neuropathy (PN), a neurological condition that may affect up to 8% of the population, has a much greater impact on quality of life than previously thought.

Data from this survey, conducted by the Neuropathy Trust, highlights neuropathic pain (NeP) as being one of the principal symptoms associated with neuropathy. However, the data also suggest that the impact on the patient extends far beyond pain: over a quarter suffer depression as a result of PN and NeP, and one in two experience sleep disturbance.

PN is a common condition that is often distressing, and sometimes disabling or even fatal. The population prevalence is about 2.4%, rising with age to 8% and this prevalence is likely to increase in the future due to the rising burden of diabetes (a cause of PN).

The Neuropathy Trust believes that the extent of suffering that patients experience is unnecessary. Even a modest increase in the awareness of PN and NeP amongst healthcare professionals and the general public could go a long way towards alleviating the burden of these diseases. The Survey data highlight that the extent to which patients are satisfied with their treatment correlates strongly with early diagnosis, thus indicating the need for fast-track referral.

For more information contact Sophie Goswell, Tel. 020 8233 2939, E-Mail. press@neurocentre.com

Going solo

A double-blind, randomised trial has shown that Topamax 100 mg is as effective in various seizure types:

– as carbamazepine when it is predominantly selected for partial-onset seizures[1]

– as valproate when it is predominantly selected for generalised seizures.[1‡]

TOPAMAX®
TOPIRAMATE

BECAUSE LIFE WITHOUT SEIZURES IS SO MUCH BETTER*

*In a double-blind trial in newly diagnosed epilepsy, 49% of patients taking topiramate 100 mg and 63% of children on topiramate were seizure free for the last 6 months of the study[1,2] ‡Topamax is indicated as monotherapy in adults and children aged six years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. Uses: Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. Dosage and Administration: Oral: Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3 – 6 mg/kg/day (two divided doses). Initiate at 0.5 – 1 mg/kg nightly with weekly or fortnightly increments of 0.5 – 1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5 - 9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1 – 3 mg/kg. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. Contra-indications: Hypersensitivity to any component. Precautions and Warnings: Withdraw gradually. Renal impairment delays achievement of steady-state. Caution with hepatic impairment. May cause sedation; so caution if driving or operating machinery. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and requires discontinuation of Topamax and treatment of symptoms. Increased risk of renal stones. Adequate hydration is very important. Food supplement may be required. Interactions: Possible with phenytoin, carbamazepine, digoxin, oral contraceptives and metformin. Decrease in serum bicarbonate levels. Pregnancy: If benefits outweigh risks. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). Lactation: Avoid. Side Effects: Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diplopia, headache, hypoaesthesia, fatigue, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis and suicidal ideation or attempts reported rarely. Bullous skin and mucosal reactions reported very rarely. Pharmaceutical Precautions: Tablets and Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed. Legal Category: POM Package Quantities and Prices: Bottles of 60 tablets. 25 mg (PL0242/0301) = £20.02; 50 mg (PL0242/0302) = £36.17; 100 mg (PL0242/0303) = £64.80; 200 mg (PL0242/0304) = £125.83. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.88, 25 mg (PL0242/0349) = £25.32, 50 mg (PL0242/0350) = £41.60. Product licence holder: Janssen-Cilag Limited, Saunderton, High Wycombe, Buckinghamshire HP14 4HJ, UK. Date of text revision: February 2004. APIVER250204.

References: 1. Privitera MD et al. Acta Neurol Scand 2003; 107: 165-175.
2. Wheless J, Wang S et al. Epilepsia 2001; 42(Suppl 7): (Abstract1.179).

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