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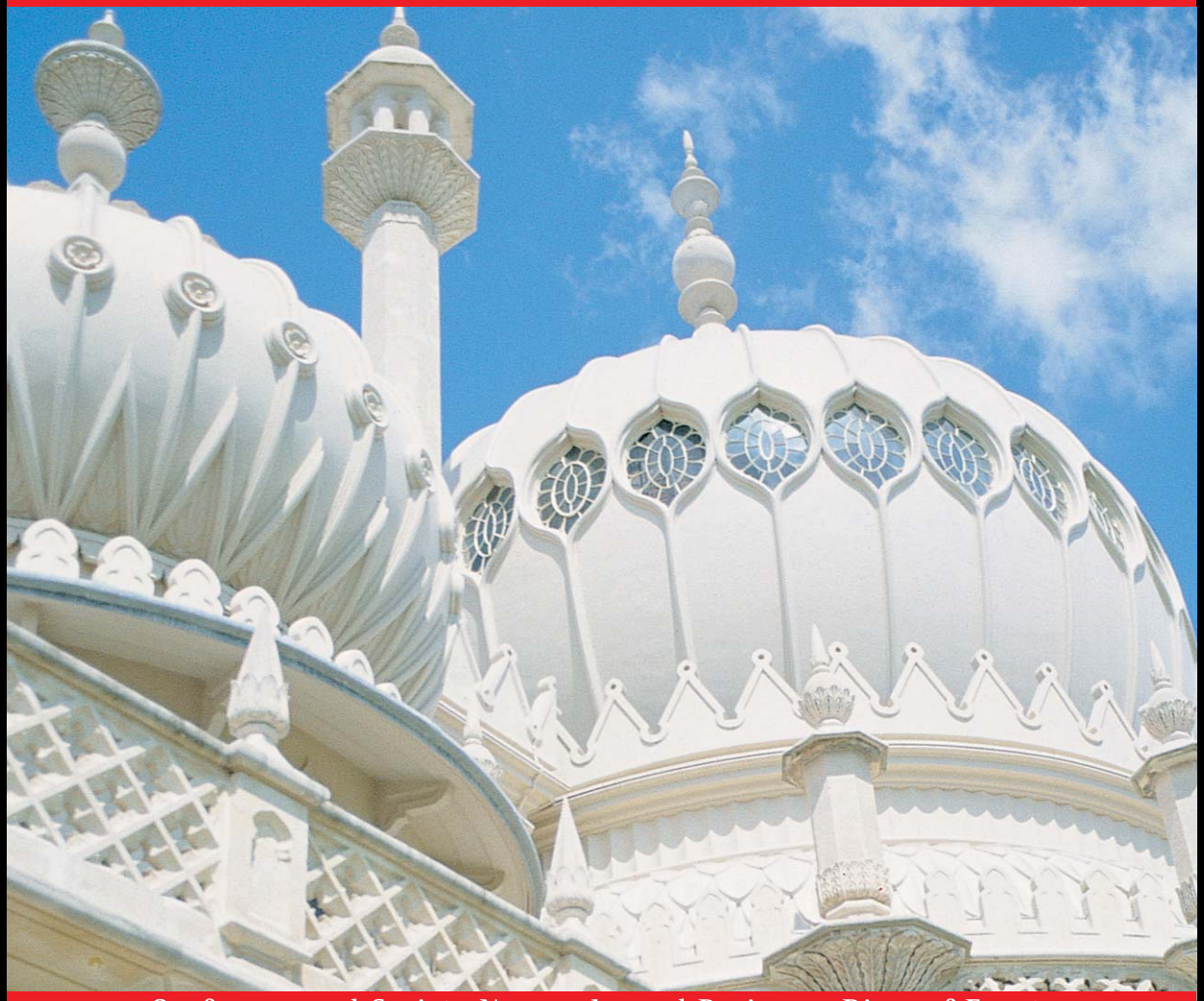

Conference and Society News • Journal Reviews • Diary of Events

Nick Gutowski, Sian Ellard
The Congenital Cranial Dysinnervation Disorders (CCDDs)

Adolfo M Bronstein
Benign Paroxysmal Positional Vertigo (BPPV): Diagnosis and Physical Treatment

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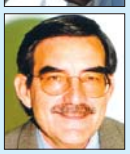

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Congenital cranial dysinnervation disorders (CCSDs) cover a range of conditions which are now starting to be understood at the gene level, and as such have been instructive in helping to put basic embryological processes into clinically relevant neurology and vice versa. It is this topic which Nick Gutowski and Sian Ellard discuss in their excellent review article, which takes us from the familiar syndromes of Duane and Mobius to a range of lesser known conditions. These authors are still actively recruiting CCDD cases, so do feel free to contact them if you encounter such cases.

In the second review article, Adolfo Bronstein treats us to a terrific account on benign paroxysmal positional vertigo (BPPV) which is distilled from his vast experience of all things neuro-otological. This common disorder accounts for 20-30% of all cases referred to specialist vestibular clinics and is readily treatable with either the Epley or Semont manoeuvre. This latter manoeuvre is easily remembered as "take your patient quickly in a big swing from the symptomatic ear down to the opposite eye down". This review is nicely illustrated with links to video websites of the procedures, and as one would expect from such an author is a great education.

The succinct account on cerebrovascular disease by Allder and Mukonoweshuro continues our neuropathology series. This review lists the common, as well as rarer causes of this disorder and again comes with clear illustrations. The discussion also includes a section on lacunar infarction, which has its neurological origins in the work of Dr CM Fisher. This great neurologist will be describing his variant of the Guillain-Barre syndrome in a future issue of ACNR.

In the neurosurgery series of articles, we remain in the realm of the cerebral vasculature, as Pawan Minhas deals with intracerebral haemorrhage. In this account the causes, presentation, medical and surgical management of this condition are laid out with great clarity, and the article includes references to several recent important trials. These include the value of early surgical intervention (the STICH trial) which concludes that this is probably not a useful manoeuvre, in contrast to the use of recombinant activated Factor VII administration. Both these studies highlight how this field is moving forward, although it is sobering to remember that patients presenting with a Glasgow Coma Score of 8 or less have "an almost universally poor outcome".

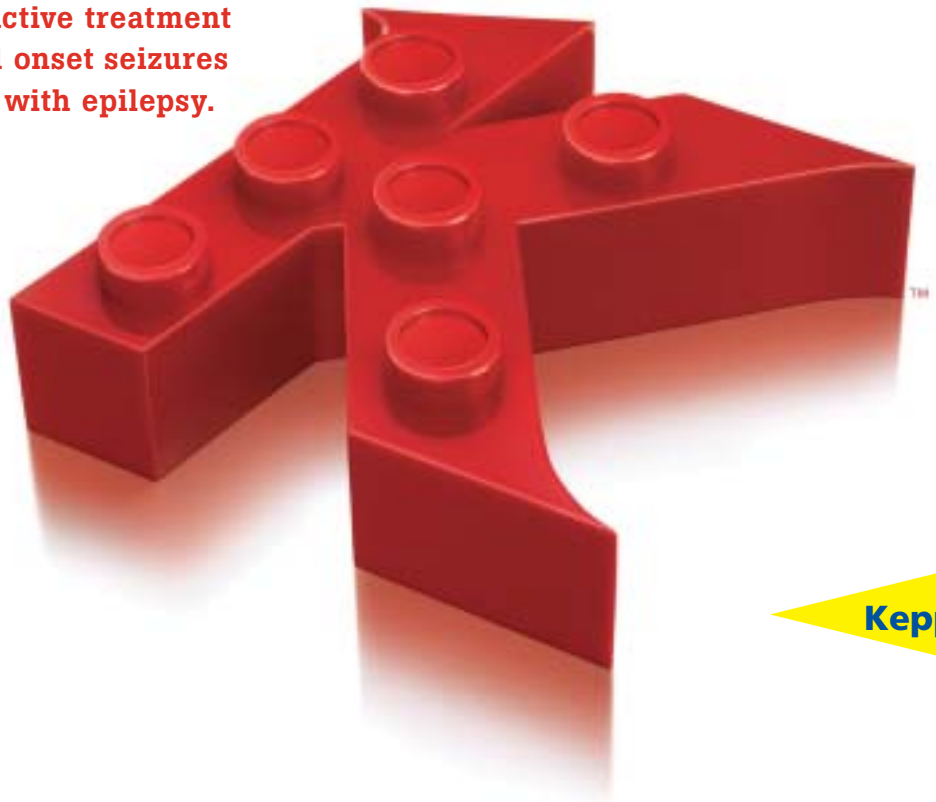
John Shneerson is well recognised as the UK expert on sleep, and in his rehabilitation article he discusses the causes of excessive daytime somnolence following brain injury. This includes a discussion on the rare (e.g. Kleine-Levine syndrome) to the more common (e.g. sedative drug side effects). This list of causes is framed by a discussion on the physiology of sleep-wake cycling in the human brain and drugs known to be of therapeutic value in its management of sleep disorders. This clear account is a wonderful summary of a complex field by a renowned expert.

Journal reviews this issue concentrate on the amygdala and novel therapeutic strategies in neurological disease, especially with respect to motorneuron disease and Alzheimer's dementia. This issue of ACNR also features an article on 'Neuromarketing' by David Lewis and Darren Bridger. This is the emerging (pseudo-)science which uses new imaging type techniques, especially fMRI, to gauge the marketing/effect/success of products. This has now evolved to the point where new fMRI facilities are being built purely for marketing research - reported at 8 in the US last year. The rationale for this approach is clearly outlined in this provocative article, and includes discussion on the paper from Neuron last year on what happens in the brain when you are given the choice between Coke and Pepsi.

Finally thanks for all your support and feedback. Do keep letting us know what you think and what you like to see in ACNR - including relevant case reports organised by Alastair Wilkins (Email: aw255@cam.ac.uk).

Roger Barker, Co-Editor,
Email: roger@acnr.co.uk

For adjunctive treatment of partial onset seizures in adults with epilepsy.



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Date of preparation: September 2004.

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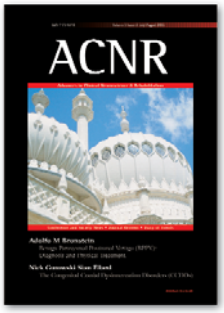

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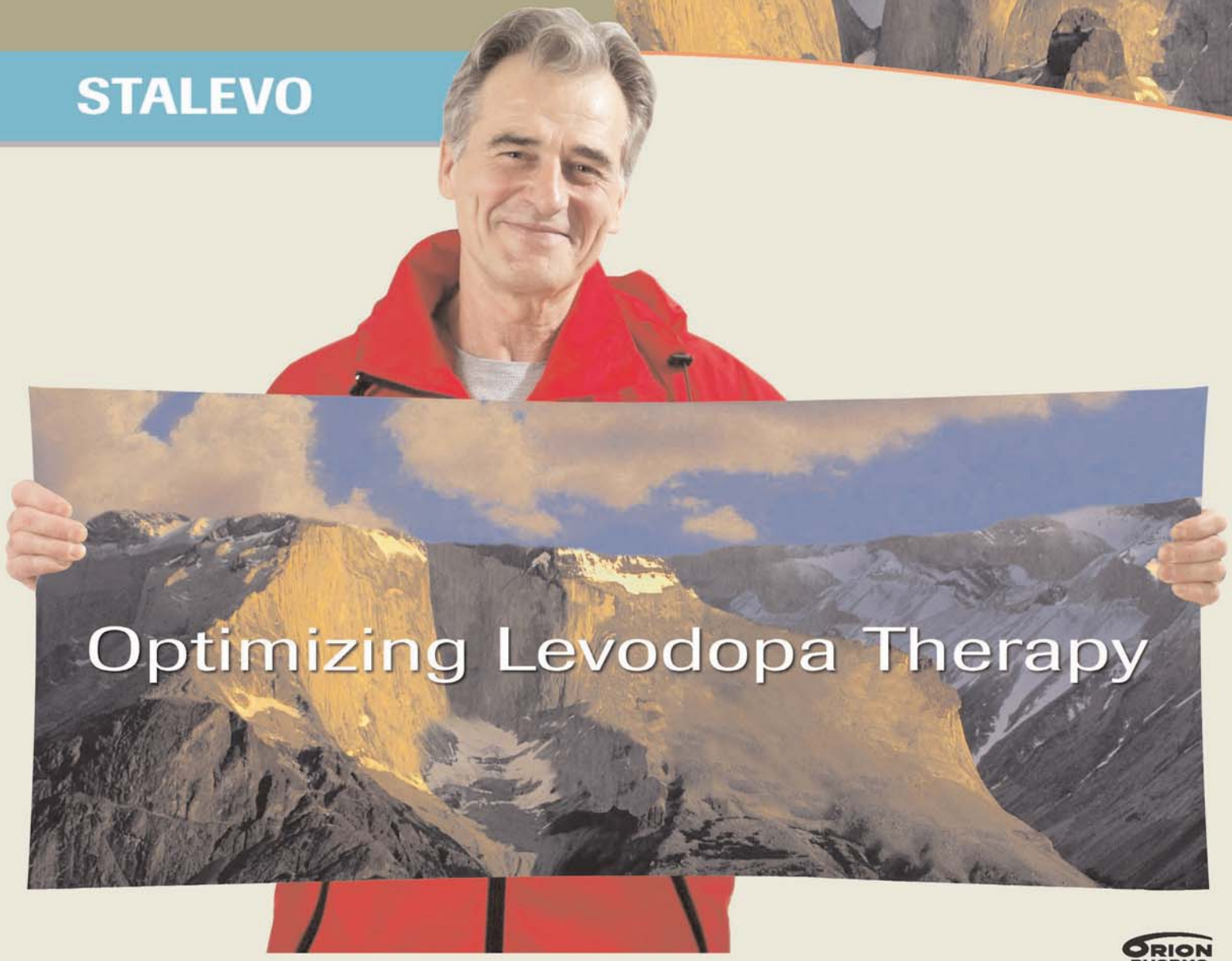

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December 2004
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The Congenital Cranial Dysinnervation Disorders (CCDDs)

The term 'congenital cranial dysinnervation disorders' or CCDDs was derived in 2002 at a European Neuromuscular Centre (ENMC) international workshop for a group of congenital neuromuscular diseases reflecting the belief that these disorders resulted from developmental errors in innervation.[1] The conditions under consideration were characterised by abnormal eye, eyelid, and/or facial movement. The group includes Duane syndrome, congenital fibrosis of the extraocular muscles (CFEOM), congenital ptosis, horizontal gaze palsy, congenital facial palsy and Möbius syndrome, but this is not an exhaustive list. The current list of clinical phenotypes, genetic loci and genes is certainly incomplete. It is envisaged that other congenital dysinnervation disorders such as Marcus Gunn Jaw winking (ptosis accompanied by elevation of the ptotic eyelid on movement of the lower jaw, due to aberrant trigeminal nerve innervation of levator palpebrae superioris) and Crocodile tears (food provokes excessive tearing, due to aberrant facial salivary fibres innervating the lacrimal gland) and disorders of afferent pathways will also be included. The purpose of this classification is to study the genes underlying the CCDDs which should enhance our understanding of human brain stem and cranial nerve development, with common functional pathways likely to emerge, as well considering potential treatments for these disorders.

The concept from muscular fibrosis to dysinnervation

Isolated strabismus is relatively common affecting 1-5% of the general population. A subset of sporadic and familial congenital, non-progressive ophthalmoplegia with restriction of globe movement was initially referred to as the "congenital fibrosis syndromes" because the primary pathologic process was thought to be in the eye muscles. Further data challenged this view. It was suggested that Duane syndrome, the most common of these disorders, may be primarily neuropathic rather than myopathic and at least five autopsy reports of Duane syndrome have documented anatomic absence of the abducens nerve. In addition, electromyography revealed paradoxical innervation of the lateral rectus by the oculomotor nerve that probably occurs in the absence of normal innervation by the abducens nerve (reviewed in reference 1). Duane syndrome also occurs in the setting of other conditions with anomalous axonal guidance.[2]

Genetic and neuropathologic studies in CFEOM also support a neurogenic cause for these disorders; an autopsy study of one affected member of a large CFEOM type 1 family showed the absence of the superior division of the oculomotor nerves bilaterally.[3] Subsequently CFEOM type 2 was shown to result from mutations in the PHOX2A gene,[4] the absence of which in mouse and zebrafish results in loss of the nuclei of the oculomotor and trochlear nerves in addition to other neuropathologic changes.

Recently familial horizontal gaze palsy with progressive scoliosis (HGPPS) has been shown to be associated with ROBO3 gene mutations. These patients also have uncrossed corticospinal and dorsal column projections due to disruption of axonal hindbrain pathway crossing.[5]

CCDDs current concepts (Figure 1)

- Congenital, non-progressive, sporadic or familial abnormalities that result from developmental abnormalities of one or more cranial nerves/nuclei with primary or secondary dysinnervation.
- Primary dysinnervation - absence of normal innervation.
- Secondary dysinnervation - aberrant innervation during development by branches of other nerves.
- Dysinnervation may be associated with secondary muscle pathology and/or other orbital and bony structural abnormalities.
- Predominantly vertical ocular motility defects result from abnormalities in development of oculomotor and trochlear nerves and/or nuclei (CFEOM variants and congenital ptosis).
- Predominantly horizontal ocular motility defects result from abnormalities in the development of the abducens nerve and/or nucleus (Duane syndrome and HGPPS).
- Predominantly facial weakness resulting from abnormal development of facial nerve and/or nucleus (congenital facial weakness, and with associated ocular motor abnormalities or Möbius syndrome).

Figure 1. CCDDs the main features

- Congenital, non-progressive
- Sporadic or familial
- Developmental abnormalities of one or more cranial nerves/nuclei
- Primary dysinnervation
  - absence of normal innervation
  - neurons do not develop or are misguided
- Secondary dysinnervation
  - aberrant innervation during development by branches of another nerve

A practical approach: genetic loci, genes and phenotypes

See Figures 2 and Table 1, a brief overview is given here.

A) Predominantly vertical disorders of ocular motility

Congenital fibrosis of the extraocular muscles (CFEOM) and congenital ptosis result from abnormalities in development of oculomotor and trochlear nerves and/or nuclei (there are several oculomotor sub-nuclei).

1. **CFEOM**. Various forms of CFEOM result from primary dysinnervation of oculomotor and/or trochlear innervated extraocular muscles. The genetic loci for CFEOM phenotypes are referred to as FEOM. Currently, three CFEOM phenotypes (mild facial weakness has been reported to occur sometimes in all phenotypes) and four FEOM loci have been defined.

   a. **KIF21A** (**FEOM1**, 12p11.2-q12)[6] The KIF21A gene encodes a kinesin motor protein, with most mutations located within the coiled-coil structure of the stalk.
   CFEOM1 phenotype. Most common CFEOM phenotype: bilateral ptosis, infraducted globes in primary position, limited supraduction, chin-up head posture and variably restricted horizontal gaze. Inheritance is autosomal dominant with full penetrance. Neuropathology shows a primary defect of the superior division of oculomotor nerve.
   CFEOM3 phenotype. See FEOM3 below, rare CFEOM3 families are due to KIF21A mutations which can be non-penetrant.

   b. **PHOX2A** (**FEOM2**, 11q13.2)[4] The PHOX2A gene (previously known as ARIX) encodes a homeodomain transcription factor protein.

Nick Gutowski is a Consultant Neurologist at the Royal Devon and Exeter Foundation Hospital and Senior Lecturer in the Peninsula Medical School. Besides his interest in the CCDDs he also maintains his scientific interest in several aspects of biochemistry, cell and molecular biology in central nervous system disorders particularly relating to astrocytes and endothelial cells.

Sian Ellard is a Consultant Clinical Scientist, Head of the Department of Molecular Genetics at the Royal Devon & Exeter NHS Foundation Trust and Senior Lecturer in the Peninsula Medical School. Her research aims to identify genetic aetiologies for a range of inherited diseases (monogenic types of diabetes and vertebral dysegmentation disorders in addition to CCDDs) in order to understand the underlying pathophysiology and provide genetic testing for affected families.

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Additional web content www.acnr.co.uk

A case on Duane's syndrome will be appearing shortly on www.acnr.co.uk

CFEOM2 phenotype. Rare form of CFEOM, bilateral ptosis and a large angle exotropia with severely limited horizontal and vertical eye movements. Inheritance is autosomal recessive. There is a primary developmental defect of both oculomotor and trochlear nuclei.

c. **FEOM3** (16q24.2-q24.3)[7]
CFEOM3 phenotype. A variable phenotype in which at least one affected family member does not meet CFEOM1 criteria. CFEOM3 results from a variable defect in the oculomotor nucleus development. Inheritance is autosomal dominant with incomplete penetrance.
CFEOM1 phenotype. See KIF21A (FEOM1) above, rarely CFEOM1 families map to the FEOM3 locus.[8]

d. **FEOM4**
CFEOM3 phenotype. See FEOM3 above. One family has been identified with a chromosomal translocation, co-inherited in an autosomal dominant pattern.[1]

2. **Isolated congenital ptosis**. Some forms of congenital ptosis may result from aberrant development of the unpaired caudal central oculomotor sub-nucleus. Two congenital ptosis loci are reported.

a. **PTOS1** (1p32-p34.1)[9]
PTOS 1 phenotype. Variable degree congenital unilateral or bilateral ptosis. Inheritance is autosomal dominant with incomplete penetrance of 90%.

b. **PTOS2** (Xp24-27.1)[10]
PTOS2 phenotype. Congenital bilateral symmetrical and severe ptosis almost impinging on the visual axis in the primary position of gaze, with chin-up head posture. Inheritance is X-linked dominant (male and females are equally affected).

Figure 2. The main CCDDs currently recognised and subdivided

Predominantly vertical disorder of ocular motility
- Congenital fibrosis of the extraocular muscles (CFEOM)
- Congenital ptosis

Predominantly horizontal disorder of ocular motility
- Duane syndrome (DS)
- DS + radial ray (DRRS)
- Horizontal gaze palsy with progressive scoliosis (HGPPS)

Disorder of facial motility
- Congenital facial palsy

Disorder of facial motility and ocular abduction deficit
- Möbius syndrome

B) Predominantly horizontal disorders of ocular motility

These disorders include the various forms of Duane syndrome and horizontal gaze palsy and are proposed to result from primary dysinnervation abnormalities in the development of the abducens nerve and/or nucleus.

1. **Duane syndrome**. The prevalence is 1:10000 (1-4% of strabismus cases), 10% are familial.[2,11] Abducens motorneurons are reduced in number or are absent; there is aberrant innervation of lateral rectus by the oculomotor nerve (Figure 3). Congenital limitation of horizontal globe movement and some globe retraction on attempted adduction is required to make this diagnosis. The balance between the amount of aberrant innervation and the reduction/absence of abducens motor neuron function (and consequent muscle fibrosis) leads to a limitation of horizontal globe movement. Most commonly (~80%) abduction is affected with normal or minimally defective adduction, type 1 Duane syndrome (Figure 4); in type 3 Duane syndrome both abduction and adduction are limited and in type 2 adduction is limited. From case series the left eye (2:1) and females are more frequently affected although the reason for this is not known.[2,11] At least three Duane syndrome genetic loci have been defined.

a. **DURS1** (8q13)
DURS1 Phenotype. Duane syndrome is usually bilateral and may be associated with other features such as mental retardation, branchio-oto-renal syndrome and genital tract anomalies in patients with cytogenetically visible deletions. A peptidase gene, CPAH, has been highlighted as a candidate gene as it is disrupted by a balanced translocation breakpoint at 8q13 in a single patient.[12]

b. **DURS2** (2q31)[13,14]
DURS2 Phenotype. Duane syndrome is unilateral or bilateral with decreased abduction with or without decreased adduction (in bilateral cases the left eye tends to be more severely affected). There can be a variety of vertical deviations. Amblyopia is common. Inheritance is autosomal dominant.[14,15]

c. **SALL4** (DRRS, [Duane radial ray syndrome or Okihiro syndrome], 20q13).[16,17]
The SALL4 gene encodes a putative zinc finger transcription factor.
DRRS Phenotype. There is Duane syndrome (unilateral or bilateral) and radial dysplasia (unilateral or bilateral) ranging from most commonly thumb hypoplasia to most severely a phocomelic limb (similar to that seen in thalidomide cases). Other features include deafness, renal and ocular manifestations. Inheritance is autosomal dominant. Truncating mutations and SALL4 deletions have been identified in DRRS families.[16,17] No SALL4 mutations were found in 25 sporadic cases of isolated Duane syndrome.[18]

d. **Other potential Duane syndrome genetic loci**. These have been found at 22pter->22q11.2 and at 4q27-31 and are defined cytogenetically (reviewed in reference 1).

Table 1. A summary of the current CCDD classification

CRANIAL NERVE/NUCLEI	SYNDROME	GENETIC LOCUS	PHENOTYPE	GENE LOCATION	GENE
Oculomotor	*CFEOM*	*FEOM1*	*CFEOM1 (CFEOM3)*	*12p11.2-q12*	*KIF21A*
		FEOM3	*CFEOM3 (CFEOM1)*	*16q24.2-q24.3*	
		FEOM4	*CFEOM3*		
	Congenital ptosis	*PTOS1*	*PTOS1*	*1p32-p34.1*	
		PTOS2	*PTOS2*	*Xp24-27.1*	
Oculomotor & trochlear	*CFEOM2*	*FEOM2*	*CFEOM2*	*11q13.2*	*PHOX2A*
Abducens	*Duane*	*DURS1*	*Duane*	*8q13*	
		DURS2	*Duane*	*2q31*	
		Other potential loci	*Duane+*	*22pter->22q11.2*	
			Duane+	*4q27-31*	
		DRRS	*Duane with radial ray*	*20q13*	*SALL4*
	HGPPS	*HGPPS*	*HGPPS with absent long-tract crossing*	*11q23-25*	*ROBO3*
Facial	*Congenital facial palsy*	*FNP1 (MBS2)*	*FNP1*	*3q21-22*	
		FNP2 (MBS3)	*FNP2*	*10q21.3-22.1*	
Facial & abducens	*Möbius syndrome*	*MBS1*	*MBS1*	*13q12.2-13*	
		MBS4	*MBS4*	*1p22*	

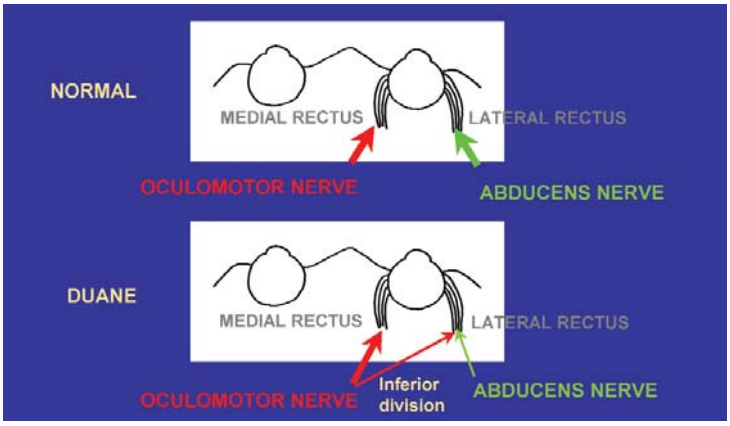

Figure 3: Pathophysiology of Duane Syndrome.

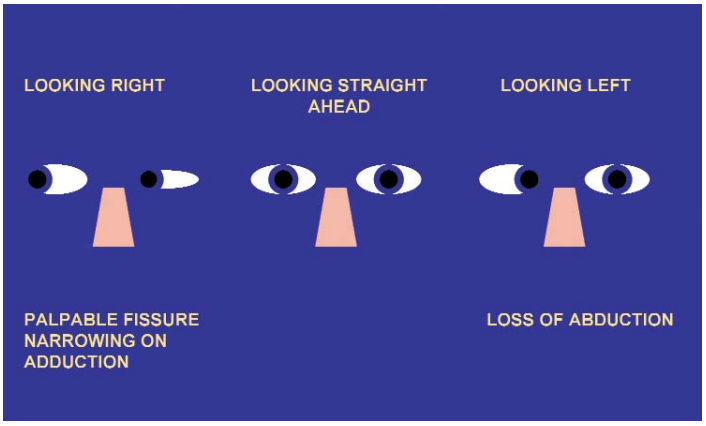

Figure 4: Left eye type 1 Duane Syndrome.

2) **Horizontal gaze palsy.** Horizontal gaze palsy is suggested to result from hypoplasia of the abducens nucleus with interneuron dysinnervation (medial longitudinal fasciculus and pontine paramedian reticular formation). It differs from the other disorders as the extraocular nerves and innervating muscles seem normal.

   a. **ROBO3** [**HGPPS** (Horizontal gaze palsy with progressive scoliosis), 11q23-25. The ROBO3 gene encodes a transmembrane receptor required for hindbrain axon midline crossing.[5]
   HGPPS phenotype. There is congenital complete absence of conjugate horizontal gaze and childhood onset progressive scoliosis. Inheritance is autosomal recessive.[5] The uncrossed corticospinal and dorsal column pathways are not associated with an obvious neurological deficit.

C) Disorders with abnormalities of facial motility

This includes congenital non-traumatic facial weakness in isolation or in association with ocular dysmotility.

1. **Facial nerve palsy (FNP)**. Isolated congenital facial weakness is usually an autosomal dominant disorder which is proposed to result from facial nuclei and/or nerve maldevelopment. Two genetic loci have been defined.

   a. **FNP1** (previously known as MBS2, 3q21-22)[19]
   FNP1 phenotype. Non-progressive, congenital isolated facial weakness, mostly bilateral, often asymmetrical. Inheritance is autosomal dominant with penetrance of 95%.

   b. **FNP2** (previously known as MBS3, 10q21.3-22.1)[20]
   FNP2 phenotype. Non-progressive, congenital isolated facial weakness, unilateral or bilateral, often asymmetrical. There can be hearing loss and rarely congenital deafness. Inheritance is autosomal dominant with penetrance of 60%.

2. Möbius syndrome. This is defined as facial weakness combined with an ocular abduction deficit. It is almost always sporadic, frequently accompanied by lingual and/or pharyngeal dysfunction at birth, craniofacial dysmorphisms, and limb malformations.[1,21] A low recurrence risk of 2% is quoted. In such cases it is thought to be due to a vascular insult in early pregnancy and misoprostol, ergotamine, cocaine and thalidomide have been implicated. Rarely cytogenetic abnormalities have been reported in association with Möbius syndrome, the phenotypes are variable but can additionally include ptosis, two loci are suggested.
   a. **MBS1** (13q12.2-13 defined cytogenetically) reviewed in reference 1.
   b. **MBS4** (1p22 defined cytogenetically) reviewed in reference 1.

Recruitment

We are still actively recruiting CCDD cases, especially Duane syndrome (both familial and sporadic), for genetics studies and would be pleased to hear of cases.

Acknowledgements
We would like to thank the European Neuromuscular Centre (ENMC), its sponsors and the participants at the workshop for their support.

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General symptomatic supportive measures may be required, along with gastric lavage, intravenous fluids and electrocardiogram monitoring. **Basic NHS Cost:** 0.088mg x 30 £10.00, 0.18mg x 30 £20.20, 0.18mg x 100 £66.67, 0.7mg x 30 £66.67, 0.7mg x 100 £212.24. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. **Marketing Authorisation Number:** Mirapexin 0.088mg x 30 tablets EU/1/97/061/001, Mirapexin 0.18mg x 30 tablets EU/1/97/061/002, Mirapexin 0.35mg x 100 tablets EU/1/97/061/004, Mirapexin 0.7mg x 30 tablets EU/1/97/061/005 Mirapexin 0.7mg x 100 tablets EU/1/97/061/006. Further information is available from: Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, Berkshire RG12 8YS. **Date of preparation:** September 2004.

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Benign Paroxysmal Positional Vertigo (BPPV): Diagnosis and Physical Treatment

Abstract

Benign paroxysmal positional vertigo (BPPV) is one of the most common causes of vertigo. It is easily diagnosed and treated. BPPV is due to the presence of otoconial debris within the semicircular canals, usually the posterior canal. The vertigo is intense but brief, usually triggered by seating, lying down and turning over in bed. The diagnosis can only be made by observing the typical nystagmus during positional manoeuvres such as the Hallpike manoeuvre or equivalent. The nystagmus occurs when the affected ear is in the side down position and is mostly torsional (rotatory) beating towards the undermost ear. On observing the typical nystagmus in a patient with a typical history one can proceed immediately to physical treatment with one of the repositioning manoeuvres. The Semont manoeuvre is described here, essentially consisting of one big swing whereby the patient is taken from one end of the couch (the ear down side) to the other (the eye down side). These manoeuvres 'reposition' the debris back to the utricle and cure patients of their current BPPV in 70-90% of cases. Links to a webpage showing videos of the diagnostic and treatment manoeuvres are provided.

Introduction

Up to 10 or 20 years ago the diagnosis of vertigo was just an academic exercise. Identification of the various causes of vertigo was largely irrelevant as all patients ended up with the same antivertiginous drugs and with little benefit. Physical therapy and rehabilitation have been at the centre of a refreshing change in dizziness treatment.

We now understand that the centre piece for the treatment of the patient with a single episode of vertigo (eg vestibular neuritis or 'labyrinthitis') and the patient with long term dizzy symptoms is rehabilitation.[1] Setting up a vestibular rehabilitation service does not require complex equipment or prolonged training. A physiotherapist, particularly a neuro-physiotherapist, or an audiologist, particularly one with an interest in vestibular disorders, can quickly acquire the necessary skills. Indeed, a recent study has shown that a GP practice nurse, with an appropriate one-day training session, can make a significant difference to the outcome of dizzy patients in primary care.[2]

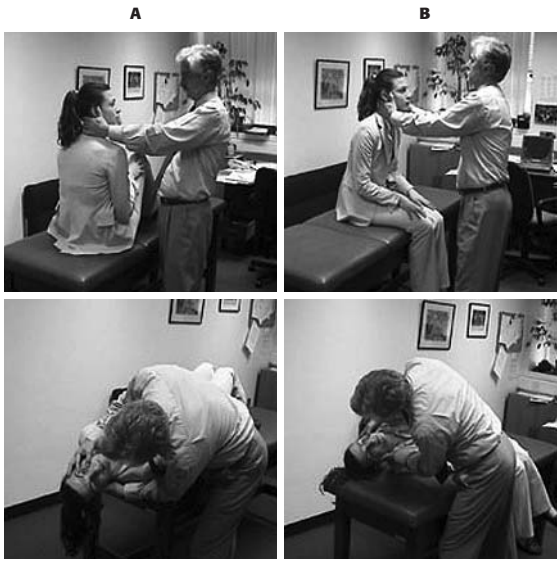


Figure 1: Two positional manoeuvres for eliciting positional vertigo and nystagmus. In this case the right ear is being investigated. Both manoeuvres are equally successful in inducing positional nystagmus and should be conducted briskly. Note how the clinician can help the patient keep the eyes open for full visibility of a positional nystagmus. A: the Hallpike manoeuvre in which the head finishes in a head hanging position. B: a trunk-sideways positional manoeuvre.

In this review, however, we will concentrate on the diagnosis and physical treatment of one specific condition, benign paroxysmal positional vertigo or BPPV. BPPV is one of the most common causes of vertigo. Both the diagnosis and treatment are straight forward and yet many patients have many drugs and expensive investigations instead of what they really need, namely a Hallpike manoeuvre for diagnosis and an Epley or Semont manoeuvre for treatment.

Symptoms

BPPV is by far the most common cause of positional vertigo, accounting for about 90% of patients. Moreover, BPPV is the number one vestibular disorder, causing 20-30% of referrals to specialised dizziness clinics.[3,4] The prevalence of BPPV increases with advancing age; women are affected almost twice as often as men. BPPV may involve each semicircular canal, with BPPV of the posterior canal being by far the most common variant. All subtypes of BPPV can be diagnosed on the basis of clinical observation during the positional manoeuvre.

Patients with BPPV complain of brief episodes (<1 min) of vertigo that appears in specific head positions, e.g. on lying down or sitting up, after turning in bed from one side to another, with head extension or bending forward. Frequently, however, the positional and brief nature of the vertigo is not recognised by the patient, even after direct questioning. Therefore, positional tests should be performed in all patients with recurrent or episodic vertigo.

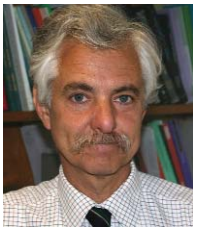
Patients are usually aware that certain head movements precipitate attacks of vertigo. They often develop strategies to avoid vertiginous attacks, e.g. sleeping upright or holding their neck stiff, which may lead to immobility and prolongation of the natural course of the disease. Indeed many BPPV patients with stiff neck and head movement-induced vertigo are often told that the problem originates in the neck – the myth of 'cervical vertigo'.[5] Another presentation is the patient with BPPV who, due to the terrifying nature of the vertigo in BPPV, develops a secondary anxiety disorder – the myth of the 'it's all in your mind' syndrome.

Each single BPPV attack lasts a few seconds but after a series of attacks, patients may complain of prolonged dizziness and imbalance lasting from hours to days. Typically, BPPV manifests itself with symptomatic episodes lasting from a few days to several months, which are interspersed by asymptomatic intervals of several months to years duration. Most cases of BPPV are idiopathic, but about 25% develop after head trauma or on the background of a pre-existing labyrinthine disorder such as vestibular neuritis or Menière´s disease. Bilateral BPPV is more common in post-traumatic patients.

Examination

Conventional clinical examination as performed by GPs, neurologists or ENT surgeons is negative in BPPV. Provocation of vertigo by positional testing and observation of typical nystagmus is the only way to make a diagnosis of BPPV. Patients must have this clearly explained to them before the positional manoeuvres. Positional vertigo is terrifying but brief - if the patient closes his/her eyes in response to the vertigo the examiner will not be able to make a diagnosis.

The most popular test for provocation and confirmation of BPPV is the Hallpike manoeuvre (Figure 1A). With this procedure the head is rotated with respect to gravity in the plane of the affected posterior canal. Alternatively, a lateral



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tilt of the trunk and head from a sitting position can be performed with the head turned 45° to the opposite side, which positions the head with the lateral aspect of the occiput onto the couch (Figure 1B). This latter manoeuvre is the only one that can be performed when the couch is placed between walls or cupboards and the patient's head cannot reach the head hanging position. In any case, with both manoeuvres, the final position of the posterior semicircular canal is identical (compare Figures 1A & B). The patient is instructed to keep their eyes open, to watch the examiner's forehead or eyes and to stay in the final position even if vertigo occurs. It is useful to help the patient keep their eyes open with your own fingers, as some patients find it difficult to keep their eyes open when the vertigo develops. Frenzel´s glasses are not necessary for observation of the nystagmus.

The nystagmus in posterior canal BPPV is mostly torsional (often called 'rotatory'), with the upper pole of the eye beating towards the undermost ear (Figure 2). In addition, there is a smaller vertical skewing upbeating nystagmus component, most prominent on the uppermost eye. Typically, nystagmus and vertigo start a few seconds after the precipitating head position is reached (latency). Nystagmus intensity increases rapidly and then decays (adaptation), usually lasting 10 to 20 seconds. On returning to the sitting position, a transient nystagmus of lesser intensity beating in the opposite direction can be observed (reversal). With repeated testing, vertigo and nystagmus decrease with repeated positioning in most cases (fatigability).

A patient with a typical history of brief rotational vertigo on lying, seating or turning over in bed and with a transient torsional nystagmus as described above does not require any further investigations. One should proceed to repositioning treatment straight away. A similar clinical history can be due to the rarer horizontal or anterior canal variants of BPPV. The former has horizontal nystagmus and the latter downbeat nystagmus with a torsional component. However, unless the clinician is conversant with positional nystagmus, an MRI is advisable to rule out cerebellar-brainstem disease whenever a positional manoeuvre induces a nystagmus atypical for posterior canal BPPV.

Pathophysiology

BPPV appears when dislodged calcium rich particles from the utricular otoconia fall into the posterior semicircular canal. These debris, due to gravitational forces, move within a semicircular canal and cause inadequate endolymph flow after changes of head position (canalolithiasis). There are five factors predisposing to BPPV, namely advanced age, head trauma, a preceding inner ear disease, migraine, and general anaesthesia. These predisposing factors act by a combination of age related or ischemic utricular degeneration and head reclination (for intubation during anesthesia).

Figure 3 shows how these otoconial debris move within the posterior canal. Once otoconia have entered the posterior canal they tend to sink to the most dependent point. When the patient is upright, they are located at the base of the cupula and do not have any effect. During the Hallpike test, the head is rotated backwards in the plane of the posterior canal, inducing movement of the particles within the canal away from the cupula and thus activation of the canal's hair cells. The nystagmus subsides after the particles have reached the most dependent point of the canal and the cupula has returned to the resting position. Agglomerates of otoconia may disperse with repeated positional manoeuvres which may explain BPPV fatigability. Although the canalolithiasis concept is supported by several histological and intraoperative findings, the most convincing proof for canalolithiasis comes from the efficacy of positioning manoeuvres, which clear the affected canal from mobile particles.

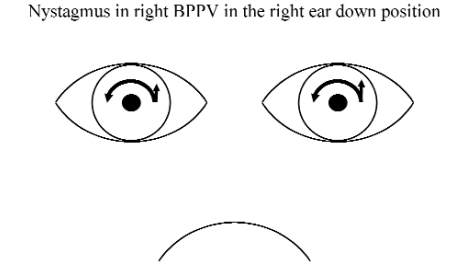

Figure 2: The nystagmus observed in a case of right sided BPPV in the right ear down position. The arrows indicate the predominant beat (fast phase) direction: torsional beating towards the right ear with a minor upbeating component. This nystagmus pattern is the result of the excitation of the right posterior semicircular canal.

Treatment

The rationale of the treatment is to redirect the otoconial particles back to the utricle where they do not cause BPPV symptoms. First of all the patient is informed about the benign course of BPPV, its mechanism and rationale for repositioning treatment. Patient cooperation is vital during the treatment as further vertigo is unavoidable during the manoeuvres. There are essentially two repositioning treatments, Epley´s and Semont´s manoeuvre. Patients should keep their eyes open for observation of nystagmus, since a positional nystagmus beating in the same direction with respect to the head indicates successive movement of the particles towards the utricle and predicts a favourable outcome to some extent. Both these therapies are highly effective in terminating an acute episode of BPPV but recurrences after several months or years are not uncommon.

Epley has introduced the canalith repositioning procedure, in which the posterior canal is rotated backwards close to its planar orientation. The manoeuvre consists of a series of successive head positionings each of about 90° displacement and several reviews illustrate clearly how to carry it out[3,4]. My personal impression is that, unless the doctor or therapist applies this manoeuvre frequently, Epley's manoeuvre is more difficult to remember than Semont's, so the latter will be described and illustrated here.

The Semont manoeuvre involves a 180° swing of the head in the plane of the posterior canal (Figure 3). The examiner guides the manoeuvre by standing in front of the patient who is seated on a couch with the head rotated 45° away from the affected ear. Then the patient is brought with a fast movement to a lying position on the side of the provocative ear (Figure 3 - 1,2). This initial part of the manoeuvre is in fact the diagnostic phase equivalent to a Hallpike manoeuvre or, more precisely, the sideways variant Hallpike manoeuvre described under Examination and illustrated in Figure 1B. In this position vertigo is triggered and torsional nystagmus beats toward the affected (undermost) ear. After being kept in this position for approximately a minute (so all debris falls to the bottom), the patient is swung rapidly onto the opposite side of the couch (and stays there for another minute) (Figure 3 - 2,3). The manoeuvre should be executed quickly in one single movement step and so, if the patient is frail, old or overweight, an assistant can help the therapist achieve this from behind the patient. In order to memorise this manoeuvre, it is useful to think that the plane of the posterior semicircular canal lies vertically in the head at 45 degrees, midway between the sagittal and coronal planes. In order to move the head diagonally at 45

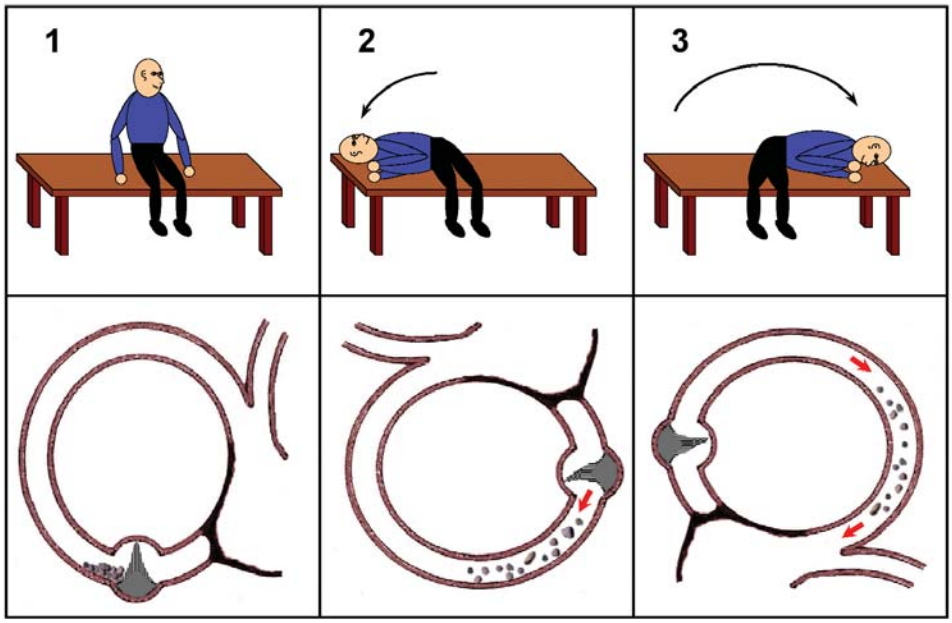

Figure 3: Pathophysiology and treatment of right sided BPPV. The cartoon illustrates canalolithiasis of the right posterior canal. On the left, the debris move down during the diagnostic positional manoeuvre (as illustrated in Figure 1B). On the right, the particles are swung out of the posterior canal back into the utricle by way of the fast head acceleration produced during the repositioning treatment (Semont manoeuvre).

degrees all you have to remember is to "go from one ear down to the opposite eye down". That is, to do a Semont manoeuvre on a patient with right BPPV (i.e. vertigo/nystagmus evoked by right ear down positional manoeuvre) swing the patient from right ear down all the way to a left eye down position (Figure 3).

Vibration of the mastoid during these repositioning treatments has been recommended but does not improve treatment outcome. Similarly, keeping upright for 48 hours after treatment has proven unnecessary. In a few patients with unusual anxiety, vertigo or nausea medication with sedatives or antiemetics before the repositioning treatment is required.

Both the Epley and Semont manoeuvres are highly effective when performed properly. After a single application complete recovery is achieved in approximately 70% of patients and 90% after a second session.[6] Randomised, controlled trials have shown that repositioning manoeuvres are clearly more effective than a sham procedure or no treatment.[7,8] For patients who do not respond to these manoeuvres or suffer from frequent recurrences, several useful procedures for self-treatment at home are available, eg Brandt-Daroff exercises or a modified Epley procedure.[9] It is advisable to visit the original publications or visit WebPages illustrating these self-treatments and prepare handouts for patients who require them.

Surgery of the posterior canal can be considered in those rare patients with longstanding BPPV who have not responded to appropriate and repeated therapeutic positionings, but this is very rarely required nowadays.

Differential diagnosis

Posterior canal BPPV must be differentiated from other forms of BPPV (horizontal and rarely anterior canal) and from central positional vertigo due to a lesion of the vestibular nuclei or caudal cerebellum. The distinction is mainly based on nystagmus features and a patient with atypical nystagmus should always be imaged. A purely vertical (either downbeat or upbeat) nystagmus strongly suggests a central positional nystagmus whereas a history of recurrences and remissions is in favour of BPPV and against a central lesion. Migrainous vertigo is often aggravated by changes of head position and may occasionally present with pure positional vertigo. The following factors help to distinguish migrainous positional vertigo from BPPV: short-duration symptomatic episodes and frequent recurrences, manifestation early in life, migrainous symptoms during episodes with positional vertigo.[10] A trial with antimigraine prophylactic agents is often required in a patient with migraine and recurrent vertigo, whether positional or not.

Conclusion

BPPV is one of the most common causes of vertigo. Diagnosis is straightforward if clinicians develop the healthy habit of doing positional manoeuvres (Hallpike or equivalent) as the single most important step in the diagnosis of patients with positional and recurrent vertigo. Treatment with repositioning procedures is effective and clinicians should get familiar with at least one of these manoeuvres (either Epley or Semont). The Semont manoeuvre is easily remembered: take your patient quickly in a big swing from the symptomatic ear down to the opposite eye down. You can see videos of these manoeuvres in www.imperial.ac.uk/medicine/dizziness

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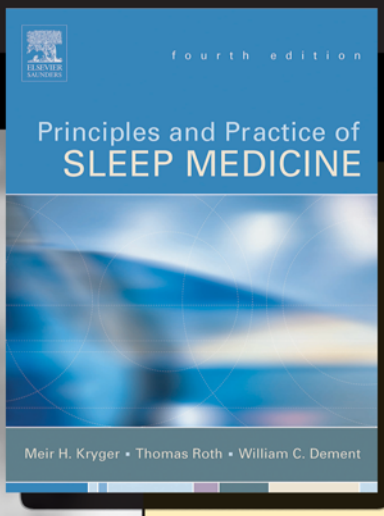

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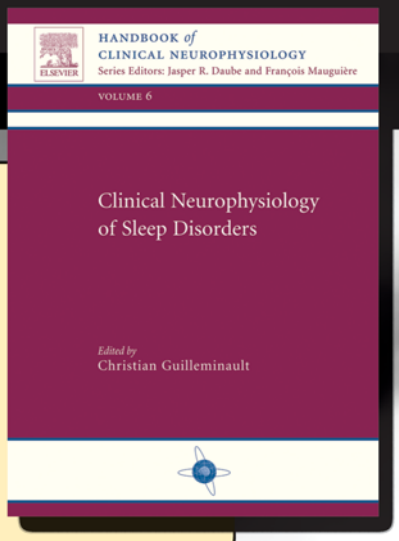

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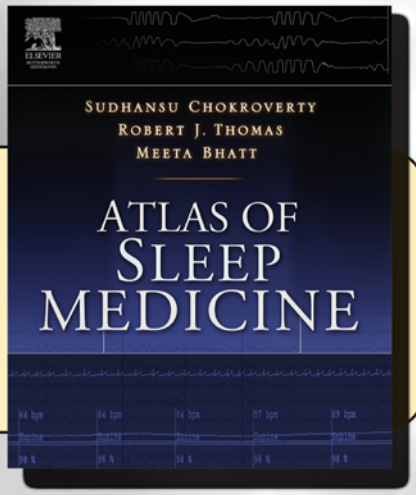

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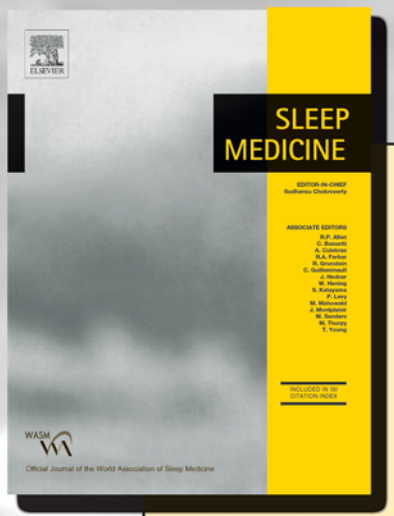

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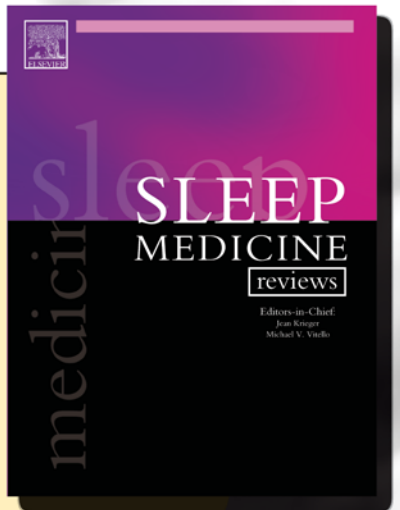

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Excessive Sleepiness after Brain Injury

Introduction

The areas controlling sleep and wakefulness in the brain are widely distributed so it is not surprising that brain injuries can disturb sleep in many ways. While many aspects of brain injury have been well researched, there is remarkably little information regarding sleep disorders, the mechanisms of changes in sleep/wake patterns or the factors that determine the prognosis of the sleep disorder.

Physiological mechanisms of sleep/wake control (Figure 1)

There are three control systems,[1] all of which can be damaged by brain injuries.

a) Homeostatic drive to sleep. The drive to enter sleep increases exponentially with the duration since the end of the previous sleep episode and declines exponentially once sleep is initiated. The most important sleep-promoting centre is the ventrolateral pre-optic nucleus (VLPO) in the anterior hypothalamus.[2] This inhibits all the main arousal systems especially those in the brain stem such as the locus coeuruleus and raphe nuclei, which form part of the ascending reticular activating system, and the tuberomammillary nuclei in the hypothalamus.

b) Circadian rhythms. These are generated in the suprachiasmatic nuclei which are responsible for the intrinsic circadian rhythm of around 24.2 hours. This entrains several important systems including sleep/wake control, temperature, feeding, motor behaviour and endocrine function to the local environmental time. Exposure to light fine tunes the circadian rhythms and is sensed, not by rods and cones, but by the retinal ganglion cells. Information from these passes especially to the suprachiasmatic nuclei which connect to the pineal gland. In the absence of light this secretes melatonin which promotes sleep.

c) Adaptive drive. This includes a variety of mechanisms that adapt sleep and wakefulness to the external environment independently of the homeostatic and circadian drives. They include behavioural responses, psychological aspects and reflex factors, including the influence of exertion and temperature on sleep and wakefulness.

Excessive daytime sleepiness after brain injuries

Excessive daytime sleepiness is a common result of brain injuries but can have several causes.

a) Post traumatic hypersomnia. This is thought to be due to widespread damage to the sleep/wake control mechanisms. The initial coma is often followed by a stage of continuous sleepiness with a reduction of REM sleep which is interrupted by increasingly frequent awakenings. Improvement in cognitive function is associated with an increase in the duration of REM sleep after the injury although there is usually poor dream recall. NREM sleep and REM sleep may be poorly differentiated which makes accurate sleep staging difficult.
The excessive daytime sleepiness may continue to improve for around a year but recovery may be incomplete. There is often a prolonged nocturnal sleep episode together with frequent and prolonged naps during the day and subalertness between these.[3] The clinical features of this post traumatic hypersomnia are similar to those of idiopathic hypersomnia apart from the history of a brain injury.

b) Sleep apnoeas. Obstructive sleep apnoeas are frequently seen after brain injuries[4,5] but there is little evidence to indicate whether they result from the brain injury or were present before the incident and only diagnosed afterwards. Secondary effects of the brain injury such as weight gain may predispose to obstructive sleep apnoeas. Central sleep apnoeas may be induced by damage to respiratory control mechanisms but little is known of their prevalence after brain injuries.

c) Narcolepsy. Narcolepsy is occasionally associated with brain injuries. Loss of consciousness at the time of the injury is usual but not invariable. Narcolepsy may follow injuries to any part of the head and usually appears immediately afterwards or within a few weeks or months.[6] The characteristic HLA type (DQB1*0602) is present in only around 50% of those with post-traumatic narcolepsy[7] whereas it is found in around 95% of Caucasians with idiopathic narcolepsy.
While post traumatic narcolepsy might be due to direct injury to the structures controlling REM sleep, it may also result from damage to the blood/brain barrier or to an inflammatory response within the pons or hypothalamus.

d) Kleine-Levin syndrome. This syndrome usually occurs in adolescence or early adult life and is more common in males than females. It is characterised by episodic daytime sleepiness which is often severe and associated with a voracious non-selective appetite (megaphagia) and, in around 25% of patients, sexual disinhibition. Psychological changes such as anxiety, depression, confusion and hallucinations are also seen. These features are probably the result of fluctuating hypothalamic inflammation which follows the brain injury.[8] The condition usually runs a fluctuating course with a tendency to gradual improvement.

e) Periodic limb movements in sleep. These have been associated with brain injuries but, like obstructive sleep apnoeas[9] they may have been present before the accident but unrecognised.

f) Circadian rhythm disorders. Brain injuries can disrupt the circadian control of sleep. A delayed sleep phase syndrome is seen after neck and also brain injuries probably due to damage to the tortuous pathway between the suprachiasmatic nuclei through the cervical spinal cord

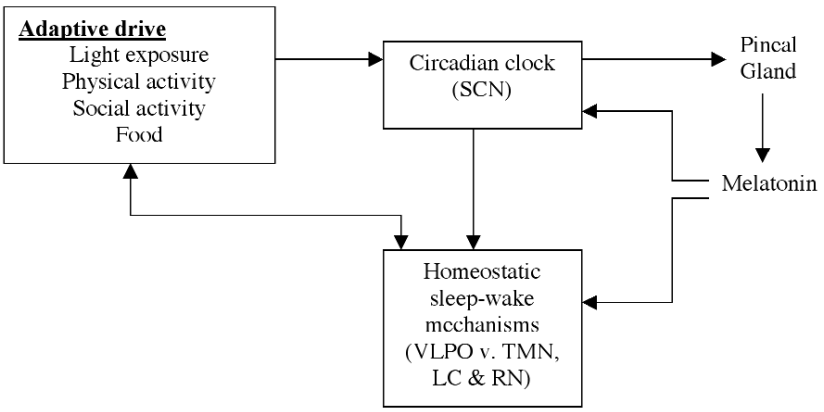

Figure 1: Mechanisms of sleep-wake control. SCN, suprachiasmatic nuclei, VLPO,ventrolateral preoptic nuclei, TMN, tuberomammillary nuclei, LC, locus coeuruleus, RN, raphe nuclei.

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to the pineal gland.[10] Impairment in vision after brain injuries frequently leads to a non-24 hour sleep/wake rhythm because of the failure of light to entrain the circadian rhythm. This becomes independent of the environment (free running) so that its relationship to the environment changes slightly each day.[11] At one point in the cycle the two may be in phase but the sleep rhythm then moves progressively forward leading initially to a delayed sleep phase and then through a period when there is insomnia at night and sleepiness during the day to an advanced sleep phase pattern before temporarily returning to synchrony with the environment again.

g) Drugs. Drugs used to treat, for instance, epilepsy or psychiatric disorders following brain injuries may cause sedation.

Treatment

a) Sleep hygiene. Maladaptive behaviour patterns are common in those with sleep disorders following brain injury. The loss of physical activity and exposure to bright light promotes subalertness during the day and impairs sleep at night. Excessive caffeine intake in the evenings and irregular sleep/wake schedules often contribute. Routines imposed in residential and nursing homes and similar institutions may also worsen sleepiness during the day and lead to insomnia at night and agitation.

b) Drugs. Treatment of excessive daytime sleepiness should be targeted at the cause of the symptoms. Periodic limb movements, for instance, may respond to a dopaminergic agent and a non 24-hour sleep/wake rhythm due to visual impairment can usually be corrected by 0.5mg melatonin at around 9pm, which entrains the circadian rhythms.

Several of the older stimulant medications such as selegiline and amantadine have been used but with little success. Amphetamines, particularly dexamphetamine, are more effective but are generalised central nervous system stimulants with important side effects.

The most effective wakefulness promoting drug is modafinil (Table 1). This is chemically unrelated to the amphetamines and is currently licensed for treatment of excessive daytime sleepiness due to chronic pathological conditions.[12] Its peak blood level is reached within 2-3 hours and it has a half life of 10-15 hours. It is metabolised in the liver and the initial dose of 100-200mg daily often needs to be increased to 400mg daily and occasionally beyond this. Around two-thirds of the dose should be given on waking and one-third in the middle of the day. It increases the activity of the histaminergic neurones in the tuberomammillary nuclei[13] which promote wakefulness, and inhibits the VLPO. Its main side-effects are headaches, nausea and dry mouth but it is usually well tolerated. Mental hyperactivity, anxiety and nervousness occur with high doses. Tolerance has not been documented and it has little potential for dependency. It can be used if necessary in combination with amphetamines and related drugs.

Table 1. Comparison of amphetamines and modafinil. Reproduced with permission[1]

	Amphetamines	*Modafinil*
Efficacy	+	+
Duration of action	*Short*	*Long*
Specificity of action	*Low*	*High*
Dependency	*Moderate risk*	*Low risk*
Withdrawal symptoms	*Common*	*Absent*
Tolerance	*30% narcoleptics*	*Unknown*
Side-effects	*Multiple, often serious*	*Few, mild*
Contraindications	*Multiple*	*Few*
Drug interactions	*Occasional*	*Rare*
Effects of overdose	*May be fatal*	*Insomnia*

Conclusions

Excessive sleepiness frequently impedes rehabilitation after brain injuries but often remains unrecognised or underestimated. It can be due to a variety of specific sleep disorders and its causes should be carefully analysed. While sleep hygiene may be of help drug therapy may need to be added to treat specific disorders such as periodic limb movements in sleep. A wakefulness promoting drug is, however, often required and modafinil has several advantages over the older central nervous system stimulants.

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Cerebrovascular Disease

Introduction

Cerebrovascular diseases (CVD) are common and serious, ranking worldwide as the third largest cause of morbidity and mortality. The outlook for patients with the recognised clinical presentations of CVD is improving. Clinical trials have delivered effective treatments for patients with acute ischaemic stroke and transient ischaemic attack.[1] Progress in CVD will continue as further research is enhancing our understanding of pathophysiology of carotid atherosclerosis,[2] lacunar infarction,[3] cerebral amyloid related haemorrhage[4] and the role of cerebrovascular disease in dementia.[5] Neuropathology is proving central to our understanding of each of these areas. In this article we review the basic pathology of cerebrovascular disease.

Cerebrovascular disease - Overview

Cerebrovascular disease encompasses two main categories; cerebral ischaemia and haemorrhage. Cerebral ischaemic injury results from the occlusion of a major cerebral artery, a small perforating cerebral artery or a venous sinus. Cerebral haemorrhage results from rupture of a cerebral artery, arterial aneurysm, arterio-venous malformation or capillaries. The clinical term 'stroke' refers to the acute clinical manifestation of any one of these processes. However, the full clinical spectrum of CVD is broad including acute behavioural disturbance, progressive cognitive impairment[6] and parkinsonism.[7]

Cerebral Ischaemia

Cerebral infarction is the endpoint of cerebral ischaemic injury wherever it occurs in the brain. Pathologically this is defined as a region of brain tissue in which all the cellular elements have undergone necrosis i.e. cell death. Infarcts can be divided into acute, subacute (2-4 days) and chronic (days to months). An infarct that has occurred 5-8 hours before death is often characterised by petechial haemorrhages in the grey matter but may be almost undetectable on gross examination in the white matter; microscopic features are usually minimal at this stage. Changes that develop within 12-36 hours include blurring of the grey/white matter interface and slight softening of the brain parenchyma. The chronic infarct shows liquefactive and cystic changes. The histology of infarcts ranges from early eosinophilic neurones (hypoxic neurones - Figure 1a) and a minimal number of neutrophils 6-12 hours after the ischaemic episode to macrophage infiltration in the subacute phase at 5 days leading to liquefactive necrosis and cyst formation with atrophy of surrounding brain in the chronic infarct (Figure 1b). The differential diagnosis for the radiological and macroscopic appearances of cerebral infarction or haemorrhage includes; primary cerebral tumours, metastatic tumours, cerebral abscess and demyelinating conditions such as acute multiple sclerosis.

It is rational to classify cerebral ischaemic injury into large and small vessel, as they are associated with different clinical syndromes, clinical outcomes and aetiologies.

Large vessel ischaemia

Large vessel infarction results from occlusion of a major cerebral artery within the carotid or vertebrobasilar circulation. They present with severe clinical strokes and are commonly fatal because of extensive brain swelling in days after stroke onset and have a poor long-term outcome.[2,8] Large vessel occlusive strokes are most commonly a result of thrombo-embolism from extracranial atheroma or cardiac emboli. Other less common large artery conditions that can cause brain infarction are listed in Table 1.

Since the description of the ischaemic penumbra identifying a region of potentially reversible ischaemic tissue within the terrority of the occluded large cerebral artery, much of the research in stroke has exploited functional imaging techniques rather than neuropathology. Neuropathological techniques have traditionally been limited in defining the penumbra, however, new pathological techniques are being developed. These techniques entail the use of animal models with a combination of imaging and pathology and they are increasing our understanding of factors involved in the development of infarction.[9] Although not entirely refined, the concept of the ischaemic penumbra has proved a very powerful stimulus to develop treatment for large vessel ischaemic injury.[10] It has recently been demonstrated that salvaging the ischaemic penumbra is how thrombolytic therapy improves clinical outcomes[11] and this should allow the time-window for therapy of strokes to

Table 1. Less common large artery conditions causing brain infarction

Premature atherosclerosis
Dissection (spontaneous or traumatic)
Inherited metabolic diseases (homocystinuria, Fabry's, pseudoxanthoma elasticum, MELAS syndrome)
Fibromuscular dysplasia
Infection (bacterial, fungal, tuberculosis, syphilis, Lyme)
Vasculitis (collagen vascular diseases - systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, polyarteritis nodosa; Takayasu's disease, Wegener's syndrome, cryoglobulinemia, sarcoidosis, inflammatory bowel disease, isolated central nervous system angiitis)
Moyamoya disease
Radiation

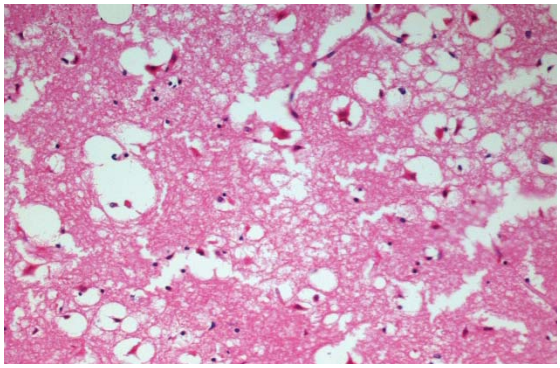

Figure 1a. Histology of an acute cerebral infarct showing neuronal eosinophilia (hypoxic/ischaemic neurones) and vacuolation of the neuropil. (Hematoxylin and eosin x20).

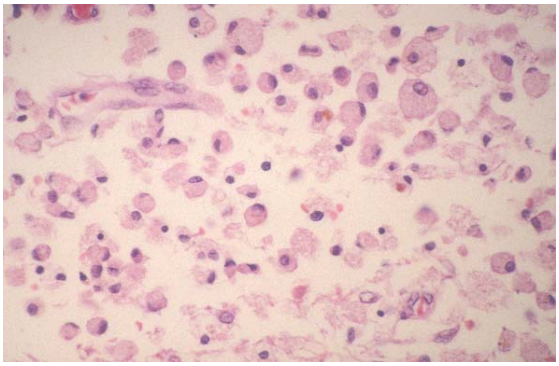

Figure 1b. Histology of a chronic cerebral infarct showing macrophages with foamy or granular cytoplasm. Some of the macrophages contain haemosiderin pigment. (Hematoxylin and eosin x20).

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be significantly increased.[12]

Atherosclerosis is the commonest cause of large vessel stroke. It is most severe at the origins of the vertebral arteries and the carotid bifurcation. Pathological study of atherosclerosis has been deemed sufficiently important that an international pathological classification has been devised. This originally comprised six types when presented in 1995. This was modified in 2000 to take in to account further developments in the field (See Table 2). This is another area where imaging and pathology are now being used in tandem to define the actual pathological processes within atheroma in vivo. Figure 2 shows the correlation between MRI finding and intraplaque haemorrhage, a hallmark of clinically symptomatic atheroma (type VI). In addition to atheromatous emboli, infarction can be caused by emboli from cardiac valve vegetations, cardiac thrombi associated with myocardial infarcts, fat, air, malignancies, parasites or material introduced during vascular surgery, interventional procedures or during angiography.

Small vessel ischaemia

The concept of small vessel stroke (lacunar infarction) was proposed by Fisher in 1965.[13] He described lesions caused by occlusion of perforating cerebral arteries secondary to lipohyalinosis within the artery walls. Research into small vessel ischaemia is undergoing a renaissance. It has recently been shown that the aetiology of clinical syndromes associated with lacunar infarction are not homogeneous and the short or long term prognoses are not benign.[14] A new proposal suggests that in most lacunar strokes, the vascular abnormality is pathologically diffuse, even if the clinical manifestations are focal and result from small vessel endothelial damage. This in turn leads to a subtle increase in blood-brain barrier permeability, and leakage of substances toxic to the brain into the perivascular tissue.[3] Support for this proposal comes from pathological and imaging data. A recently described variant of a small, microvessel-associated basal ganglia lesion with histopathological features distinct from those of classical Types I, II and III lacunes suggests a state of incomplete infarction may exists prior to infarction.[15] This has gained further support from studies using a combination of imaging with computed tomography and magnetic resonance imaging. This has allowed delineation of structures with the density or signal features consistent with an occluded (or at least abnormal) perforating artery associated with the relevant lacunar infarct.[16]

Table 2: Stary classification of Atherosclerosis

Type I	*Isolated macrophage foam cells*
Type II	*Multiple foam cells layers formed*
Type III	*Isolated extracellular lipid pools added*
Type IV	*Confluent extracellular lipid core formed*
Type V	*Fibromuscular tissue layers produced*
Type VI	*Surface defect, haematoma, thrombosis*
Type VII	*Calcification predominates*
TypeVIII	*Fibrous tissue predominates*

Cerebral haemorrhage

Intraparenchymal cerebral haemorrhage is less common than cerebral ischaemia, but has a worse prognosis. Specific treatments are still lacking for this condition although it is hoped that this will change now cerebral haemorrhage is being systemically investigated.[17] Intraparenchymal haemorrhage can be classified into subcortical and lobar haemorrhage. In many cases the underlying pathological conditions that lead to both types of haemorrhage are the same and there is significant overlap with the causes of cerebral ischaemia i.e. arteriolosclerosis and lipohyalinosis in many cases. Anticoagulation, trauma and underlying vascular abnormalities are more specific aetiological factors of cerebral haemorrhage. In young patients cerebral haemorrhage can be associated with the use of recreational drugs such as cocaine and amphetamines.

Cerebral amyloid angiopathy related haemorrhage (CAA-H) is another area where new pathological insights are emerging. CAA-H is characterised by extracellular deposition of amyloid in cortical and leptomeningeal vessels (Figure 3). It is the most common cause of lobar haemorrhage particularly in elderly normotensive individuals. Risk factors for CAA include mutations of the amyloid precursor protein (APP) gene and possession of the epsilon 4 allele of apolipoprotein E. The deposition of amyloid in blood vessel walls results in rigid and fragile blood vessels that are prone to haemorrhage. Pathological studies have highlighted an additional factor. In some patients the clinical expression of the disease relates to an associated vasculitic reaction.[4] Pathological studies also suggest that CAA may have a relevance that extends beyond cerebral haemorrhage as it may be central to how CVD and Alzheimer's pathology interact to produce dementia.[5]

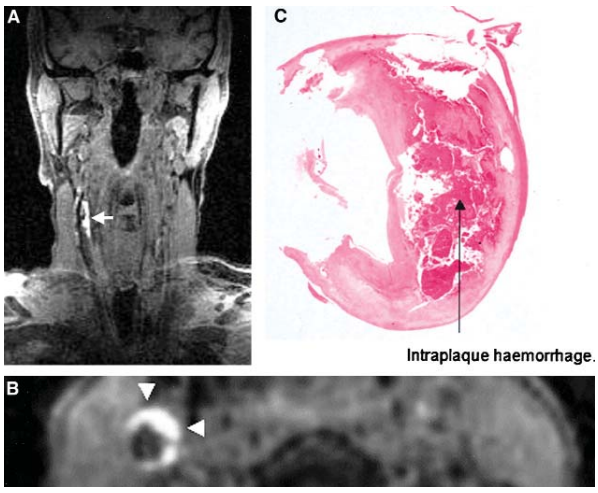

Figure 2. A and B, Extensive area of intraplaque haemorrhage is demonstrated on coronal (arrow) and axial (arrowheads) views. C, Intraplaque haemorrhage is seen on histological specimen (arrow). Moody et al - publisher LWW.

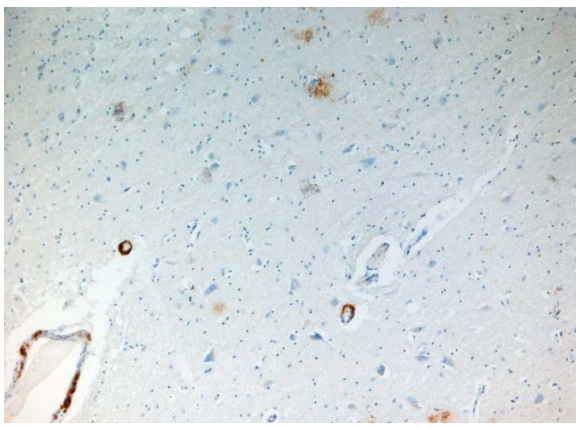

Figure 3: CAA demonstrated using an anti-Aβ antibody. Note the amyloid deposited in blood vessel walls.

Summary

The sheer size and spectrum of the clinical burden of CVD continues to evolve. This is stimulating research and clinical services for patients with CVD. Neuropathology remains central to this effort.

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Intracerebral Haemorrhage

Introduction

Spontaneous intracerebral haemorrhage carries a higher mortality and poorer functional outcome than ischaemic stroke or subarachnoid haemorrhage.[1] The mortality at one month from intracerebral haemorrhage has been observed to range from 35% – 52%. After six months, only 20% of patients can be expected to be independent. The incidence varies between different populations (15 – 35 per 100,000) but is generally twice that of subarachnoid haemorrhage. Despite the damaging impact of this condition, even the basic surgical and medical management varies widely between centres with no good evidence base for best practice. Intracerebral haemorrhage has been recently targeted as a high priority for further clinical stroke research and there have been some recent advances in understanding this condition, and towards improving outcome in the future. In particular, the results of the STICH trial (International Surgical Trial in Intra–Cerebral Haemorrhage) which randomised 1033 patients between early surgery and initial conservative therapy have recently been published;[2] and new avenues of early treatment to prevent clot expansion using activated factor VII show promise.[3]

Differential diagnosis

Table 1 outlines the different causes of intracerebral haemorrhage. The majority of intracerebral haemorrhage (70 – 80%) is termed primary in nature and results from chronic small vessel disease processes such as intraparenchymal hypertensive small vessel microaneurysms or amyloid angiopathy. Secondary intracerebral haemorrhage can be due to a structural lesion (e.g tumour, arteriovenous malformation, intracranial berry aneurysm), bleeding diathesis (e.g. warfarin, aspirin, alcohol induced coagulopathy), or a disease process causing acute and severe hypertensive changes such as abuse of sympathomimetic drugs (cocaine, ecstasy, amphetamines) or eclampsia in pregnancy (Figures 1a and 1b).

It is important to note that at a practical level, the distinction between differential causes of intracerebral haemorrhage is not always clear cut e.g: microaneurysmal small vessel changes can occur (with increasing prevalence in older patients) in the absence of clinical hypertension; an alcohol induced coagulopathy may exacerbate a bleed from other causes such as amyloid angiopathy. Secondary intracerebral haemorrhage can also occur into an ischaemic cerebral infarct. This latter entity will become more frequent with the advent of widespread use of acute thrombolysis for reperfusion in ischaemic stroke.

Table 1: Causes of Spontaneous Intracerebral Haemorrhage

Primary
Chronic hypertension
Amyloid angiopathy
Secondary to Structural abnormality
Aneurysm
Arteriovenous malformation (AVM)
Dural arteriovenous fistula
Cavernous haemangioma
Tumour
Haemorrhage into ischaemic cerebral infarct
Moya moya disease
Sagittal sinus thrombosis
Vasculitis/inflammatory vasculopathy
Secondary to coagulopathy
Iatrogenic (warfarin, aspirin, thrombolysis)
Alcohol induced coagulopathy
Blood dyscrasias e.g leukaemia, thrombocytopenia,
Hepatic failure, renal failure
Secondary to severe acute hypertension
Sympathomimetic drugs
(cocaine, ecstasy, amphetamines)
Pregnancy - eclampsia

Clinical presentation and radiological assessment

Important clinical points to note are: -

1. Any features of trauma that may confound the diagnosis of a spontaneous haemorrhage.
2. The presence of co-morbidity that may predispose to intracerebral haemorrhage (e.g. hypertension, anticoagulant history, use of illicit drugs or alcohol, and haematological disorders).
3. Any recent history of headache, focal deficit or seizures that may indicate the presence of an underlying cerebral lesion.
4. The presence of focal neurological deficit and the level of consciousness as assessed objectively with a breakdown of the Glasgow Coma Score.

Intracerebral haemorrhage classically presents with a sudden onset neurological deficit and features of raised intracranial pressure including headache, vomiting and markedly elevated blood pressure, whereas ischaemic stroke is more likely to present with a sudden onset deficit alone. Early progression of neurological symptoms including deterioration in the level of consciousness within the first few hours is more common for intracerebral haemorrhage (over 50%) than for ischaemic stroke or subarachnoid haemorrhage (5% - 20%).[1] This is thought to be due to the presence of early continued bleeding and hence clot expansion, during the evolution of an intracerebral haematoma.

These clinical features may be helpful in indicating which patients presenting with a sudden onset neurological deficit are likely to have suffered an intracerebral haemorrhage, but they cannot be reliably used to differentiate ischaemic stroke from haematoma. Hence emergent, rapid access CT scanning is essential in the diagno-

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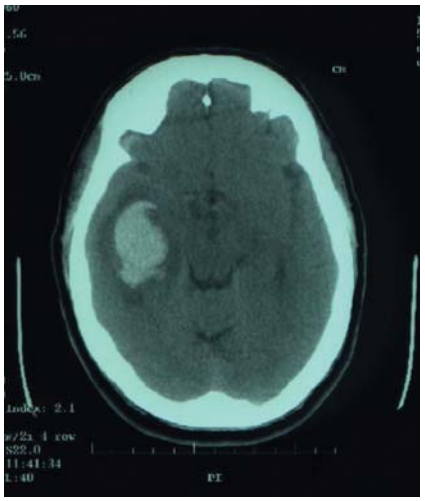

Figure 1a: Presentation CT scan of a 68 year old patient with sudden onset left/right agnosia and symptoms of raised intracranial pressure. An intracerebral haemorrhage was identified in the right temporal region causing mass effect. He improved without haematoma evacuation.

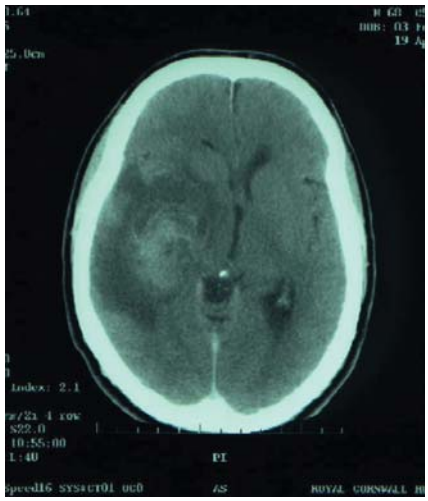

Figure 1b: Five weeks later he developed symptoms of raised intracranial pressure. A repeat CT scan revealed a space-occupying lesion, confirmed at biopsy to be a glioblastoma multiforme.

sis and subsequent management. It allows assessment of the size and location of haemorrhage along with the features of mass effect such as the degree of midline shift and effacement of the basal cisterns indicating pending tentorial herniation. The presence of intraventricular haemorrhage with resultant hydrocephalus is also important in determining surgical treatment. CT will often give information of underlying lesions causing secondary haemorrhage. Aneurysmal haemorrhage is usually associated with the presence of subarachnoid blood and typical bleed patterns extending to the Sylvian fissure (for middle cerebral artery aneurysms) or paramedian frontal lobe haemorrhage extending to the interhemispheric fissure anteriorly (for anterior communicating artery or pericallosal artery aneurysms). Arteriovenous malformations will usually show calcified vessels in association with the AVM. Tumours may be suspected where there appears to be a separate mass adjacent to the acute intracerebral haematoma (usually with contrast enhancement) or a degree of surrounding cerebral oedema in excess to that expected for an acute haematoma. Malignant melanoma is the most common metastasis to present with intracerebral haemorrhage and high-grade intrinsic gliomas can infrequently present with haemorrhage (Figures 1a and 1b). Intracerebral haemorrhage secondary to sagittal sinus thrombosis is often bilateral, paramedian in location and associated with cerebral oedema arising from cerebral venous congestion. Following intravenous contrast, the 'empty delta' sign may be evident in the superior sagittal sinus.

Lobar, peripherally located haemorrhage in the elderly is often attributed to amyloid angiopathy. More centrally located haemorrhage originating in the putamen, globus pallidus, thalamus, or internal capsule is classically assigned to chronic hypertension (as is haemorrhage in the pons and cerebellum). However these assumptions can frequently be incorrect. In a study of 102 patients[4] with intracerebral haemorrhage, 58 patients had no CT features of an underlying structural lesion (the presence of subarachnoid, Sylvian fissure or intraventricular haemorrhage, abnormal intracranial calcification, prominent vascular structures). Of these, 42 underwent delayed cerebral angiography revealing 10 unsuspected vascular lesions (8 AVM's and 2 aneurysms). More recently, the high sensitivity of an MRI or CT scan with contrast once the haemorrhage is resolving (usually 4-6 weeks after the bleed) should resolve the need for conventional invasive cerebral angiography to exclude a vascular lesion such as an AVM. Angiography can then be confined to those patients with abnormal findings indicative of an AVM or aneurysm.

Initial medical treatment

The initial medical treatment is supportive. Patients suffering from intracerebral haemorrhage frequently show respiratory or cardiovascular instability and hence airway, breathing and circulation are the first priorities, even in a patient demonstrating significant neurological decline. Ventilation will be required in patients with a Glasgow Coma Score of less than 8, if the airway or oxygenation is not being maintained, and in patients who are agitated or combative to the point that a CT scan cannot be performed. Ventilation may also be needed for patients suffering repeated or prolonged seizures. Aspiration of gastric contents whilst the airway is unprotected is a frequent risk in patients who are showing significant neurological decline.

Blood pressure management is a controversial issue.[1] Patients often have a history of chronic hypertension and will therefore require higher than normal mean arterial blood pressures to maintain adequate cerebral perfusion. In the presence of a large intracerebral haematoma, intracranial pressure may be significantly raised and hence require a higher than normal arterial blood pressure in order to maintain an adequate cerebral perfusion pressure. Yet there is evidence that those patients with abnormally elevated blood pressures are more likely to deteriorate clinically within the first few hours because of ongoing bleeding causing haematoma enlargement.[5] There is a lack of good evidence regarding the best blood pressure management strategy to employ, and it may be beneficial to individualise blood pressure targets depending on the patient's clinical circumstances. Recommendations have been made by the Stroke Council, American Heart Association[1] that patients with chronic hypertension should have mean arterial blood pressures not exceeding 130mm Hg, that if systolic arterial blood pressure falls below 90mm Hg then pressors should be given, and where intracranial pressure monitoring is used, CPP should be maintained at greater than 70mm Hg.

In patients who are warfarinised, this should be reversed immediately and fully using fresh frozen plasma and vitamin K. The risk of extension of the intracerebral haematoma remains very high whilst anticoagulation is not reversed, whereas the risk of an adverse thromboembolic event even in those patients who are most at risk (e.g. with a metal prosthetic heart valve replacement) is minimal within the first week.

A significant proportion of patients experience ongoing haemorrhage within the first few hours causing intracerebral haematoma expansion and thus clinical deterioration. A recently published randomised controlled trial has shown improved survival and functional outcome from the early administration of activated Factor VII to prevent haematoma propagation.[3] This trial is significant in being the only medical treatment to show a clinical improvement in outcome for intracerebral haematoma. Practically, there will be difficulties in the widespread institution of this type of treatment because patients must be treated very early in the evolution of their intracerebral haematoma and because of the present prohibitive cost of treatment with activated Factor VII.

Surgical treatment of intracerebral haemorrhage

Surgical treatment of intracerebral haemorrhage includes intracranial pressure monitoring for guiding subsequent intensive care management, ventricular drainage for the relief of hydrocephalus, and partial or complete evacuation of the intracerebral haematoma. The latter can be achieved by open craniotomy or by less invasive procedures such as stereotactically guided burr hole aspiration and endoscopically guided aspiration. In addition, a thrombolytic agent such as the plasminogen activator, urokinase can be instilled into the haematoma cavity to aid clearance of the clot.

The rationale for haematoma evacuation is potentially twofold. Firstly it is effective in relief of raised intracranial pressure when there is significant mass effect. This may improve outcome by preventing brainstem compression and subsequent coning, improving global cerebral perfusion to prevent ongoing ischaemia to the brain, or indirectly by allowing control of intracranial pressure so that patients can be more rapidly weaned on the intensive care unit and hence be less susceptible to medical complications such as ventilator associated pneumonia. Secondly haematoma evacuation may be beneficial in minimising the surrounding brain oedema and secondary neurotoxic injury that occurs as a delayed reaction within the penumbra surrounding the intracerebral blood clot.[6] The early retraction of blood clot, the presence of thrombin and activation of the coagulation cascade, and the presence of haemoglobin breakdown products is believed to be key in the development of cerebral oedema and secondary neurotoxicity. Balanced against these potential benefits is the added cerebral trauma of surgical evacuation. Evacuation is often only partial and this may not be sufficient to prevent secondary neurotoxicity. Evacuation is more likely to be incomplete (or even leave significant residual haematoma causing mass effect) when less surgically invasive procedures such as endoscopic or stereotactic aspiration are employed. The majority of large intracerebral haemorrhages destroy the internal capsule and hence patients are likely to remain densely hemiplegic. Surgical evacuation of a haematoma large enough to cause significant mass effect may therefore achieve little more than to convert patients who would not survive into patients who will be left severely disabled.

McKissock *et al.* published the first randomised controlled trial for the surgical treatment of intracerebral haemorrhage in 1961,[7] showing that outcome was worse in surgically as opposed to conservatively treated patients. Subsequent trials have generally shown conflicting results with insufficient power. To progress from this, the STICH trial[2] recruited 1033 patients who were randomised to early surgery or initial conservative therapy. Patients were eligible if they presented within 72 hours of a supratentorial, non aneurysmal, non AVM bleed, if the treating neurosurgeon was uncertain which treatment was better for the patient (the clinical uncertainty principle) and if surgical treatment was intended within 24 hours. This was a trial for early surgery and so patients in the medical arm could undergo haematoma evacuation at a later date (about a

quarter of patients did require this). Outcome and mortality did not differ significantly between the two groups. Predefined subgroup analysis showed benefit in early surgery when the haematoma was less than 1cm from the cortical surface, suggesting that surgery might be better when less surgical trauma is caused in reaching the haematoma, a possibility which has previously been raised from the benefit conferred in outcome from endoscopic evacuation of intracerebral haematoma in an earlier trial.[8] One very important finding of STICH was that patients presenting with a Glasgow Coma Score of eight or less had an almost universally poor outcome.

Summary

Intracerebral haemorrhage remains a frequent and devastating condition within the central nervous system. The evidence base for considering optimal treatment is lacking but recent trials are beginning to rectify this. Progress in improving outcome for the future will require widespread availability of good quality neurointensive care facilities and early referral systems for acute stroke in general. In addition a better understanding of the factors that produce early clinical deterioration by haematoma enlargement (and particularly how this can be controlled haematologically and with blood pressure management), and delayed deterioration by secondary neurotoxic processes will be important. Any future trials of surgery are likely to need to consider techniques that minimise trauma to the brain, yet achieve consistently good haematoma evacuation.

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Neurology 4th Edition

Mark Mumenthaler,
Heinrich Mattle with Ethan Taub
Published by: Thieme
Price: EUR 39,95
ISBN: 3135239047

This newly published fourth edition of the English version of the classic German neurology textbook aims, in the authors' own words, to be a comprehensive text of neurology for practising physicians, but also not to be too unwieldy, and readable for both study and reference. The book is an unusual size. It is too big for most people's white coat pockets, but not big enough to intimidate or inspire on the shelf; it may have been designed for the briefcase. Overall we thought it was a little (or medium sized) gem, we highly recommend it, and any minor gripes are a reflection of how much we have used it rather than any real concerns about content.

We read through the book and then delved into it to look up current problems on the ward. We then had to decide where it would live: the bin, the hospital library, the desktop, or the briefcase.

It is subdivided into 15 sections covering a broad range of neurological subjects in both adult and paediatric neurology. On the whole, it achieves its aim of being comprehensive, and readers looking for more detailed material can consult the reference list provided.

The read through was fun; the 438 illustrations and 210 tables make for quick and easy reference and there are many excellent neuroimaging studies of various modalities. The chapter on dementing disorders and neuropsychology, and the chapter on disturbances of cerebral perfusion were superb with a helpful mix of microscopic and telescopic perspectives. We were impressed by the space given to syncope and other disorders which mimic epileptic seizures. Epilepsy and anti epileptic drugs are classified in useful tables although the discussion about teratogenicity is very short and does not appear in the otherwise helpful list of ten principles for the treatment of patients with epilepsy. Perhaps a subsection should be added dealing with the particular problems of epilepsy in women. Having the references available on line makes for a much more concise book and the scales and genetics in the appendix are a useful reference tool. At times the formatting of the text could be easier on the eye (if the formatting of the British National Formulary can make drug information readable, anything is possible) but that may be an inevitable problem in a book of this size. There are a few errors, for example on page 9, in diagram g, 'coccygeal' is spelt 'kokzygeal', and on page 76, fig.2.13 a/b the labels remain in German. On page 35, table 2.5, the phrase 'feeble mindedness' may be more appropriately replaced by 'learning disability', and on page 41 it is stated that a large head in a neonate often reflects familial 'microcephaly', which should surely be 'macrocephaly'.

Specific problems we looked up included the diagnosis and treatment of autonomic dysreflexia in patients with spinal cord injury, Lambert Eaton Myaesthenic syndrome (LEMS), and the anatomy of the cerebral venous sinuses. Autonomic dysreflexia is not mentioned by name but paroxysmal hypertension is described in ten lines and the management is not discussed. As this is one of the common life threatening problems after spinal cord injury this was a surprise. LEMS is described well and the description of the anatomy of the venous sinuses was just what we wanted. Two out of three; not bad.

It's in the briefcase.

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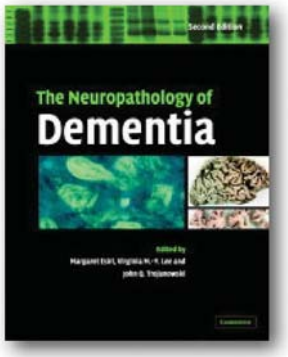
University Hospital of Wales, Cardiff & Vale NHS Trust.

The Neuropathology of Dementia



M Esiri, VMY Lee,
JQ Trojanowski (eds.)
Published by: Cambridge University Press 2004 (2nd edition)
Price: £195.00
ISBN: 0-521-81915-6

Everything about this second edition is bigger than the first (of 1997): editors (3 vs. 2); chapters (24 vs. 19); pages (578 vs. 440; cf. blurb: "this new edition is almost twice the size of its predecessor"; might possibly refer to word count?); contributors (45 vs. 19); and price (£195 vs. £75): hence the greatest proportionate increase, regrettably, is in the latter.

The opening chapters deal with general issues such as the definition of dementia, brain anatomy, safety precautions, and the practical approach to neuropathological diagnosis. The latter is especially good in tackling thorny diagnostic issues such as mixed pathology, mild pathology appropriate to age, no pathology to account for a clinical diagnosis of dementia, and pathology typical of a dementia syndrome in the absence of a clinical diagnosis. Chapters devoted to the molecular diagnosis of dementia and to neuroimaging in Alzheimer's disease may surprise (could one imagine neuropathology chapters in textbooks devoted to the neurogenetics or neuroimaging of dementia?) but reflect the inclusiveness of the approach to information gathering taken by neuropathologists which should sit well with clinicians.

Of the fifteen chapters dealing with specific clinicopathological entities, appropriately the longest is devoted to Alzheimer's disease, approximately one third of which reviews the pathogenesis of this most prevalent dementia syndrome (the final chapter on transgenic mouse models of neurodegenerative disease also addresses this concern with pathogenesis). However, as clinicians we were disappointed to find little on the neuropathological heterogeneity associated with presenilin mutations (for example, there is no mention of cotton wool plaques), a situation which contrasts with the chapter discussing the hereditary tauopathies.

It is difficult to think of particular omissions: vascular dementia, prion disease, Parkinson's disease and dementia with Lewy bodies, frontotemporal dementias, Huntington's disease, multiple sclerosis, head injury, alcohol-related cognitive decline are amongst the topics covered, though from a clinical perspective there is no specific discussion of primary progressive aphasia and semantic dementia. If you are seeking an account of progressive subcortical gliosis of Neumann the index will not help you (try 261; also 168). There are few references dated later than 2002 which presumably reflects a long gestation period. Hence, the E46K α-synuclein mutation is not mentioned (Zarranz et al., Ann. Neurol 2004; 55: 164-73).

Verdict: obviously a must for neuropathologists with an interest in dementia; highly desirable (if budgets allow) for clinicians with an interest; and a possible for the departmental library.

AJ Larner, M Doran,
Cognitive Function Clinic, WCNN, Liverpool.

To list your event in this diary, e-mail brief details to: Rachael@acnr.co.uk

2005

July

MS Professional Network
7 July, 2005; Bristol, UK
E. CBray@mssociety.org.uk

Society for Research in Rehabilitation
7-8 July, 2005; Southampton, UK
E. angela.webster@manchester.ac.uk

Conference on Neuropsychological Rehabilitation
11-12 July, 2005; Galway, Ireland
www.conference.ie/Conferences/index.asp?Conference=14

Multidisciplinary Care in Parkinson's Disease: from science to practice
12 July, 2005; London, UK
E. info@mepltd.co.uk, www.mepltd.co.uk

4th Congress of the International Society for Autonomic Neuroscience
12-16 July, 2005; Marseille, France
www.atout-org.com/isan2005/

PSIGE Conference 2005
13-15 July, 2005; Chester, UK
E. PSIGE2005@bps.org.uk
Tel. 0116 252 9555, Fax. 0116 252 7123

12th Meeting of the Neurosonology Research Group of the World Federation of Neurology
13-15 July, 2005; Osaka, Japan
www.congre.co.jp/nsrg/

Bioscience 2005
17-21 July, 2005; Glasgow, UK
www.BioScience2005.org

Venice Epilepsy Summer School – International School of Neurological Sciences of Venice International Course: Bridging Basic with Clinical Science-2
18-27 July 2005; Venice, Italy
E. epilepsysummercourse@univiu.org

Prognosis & Life Expectancy in Complex Neurological Disabilities
19 July, 2005; London, UK
Tel. 0208 780 4500, x 5140,
E. institute@rhn.org.uk

6th ASNA Biennial Convention
21-23 July, 2005; Jakarta, Indonesia
http://asna.perdossi.or.id/

COGSCI 2005: 27th Annual Meeting
21-24 July, 2005; Stresa, Italy
www.cognitivesciencesociety.org/cogsci.html

Introduction to Neuropsychological Rehabilitation
22 July, 2005; Ely, Cambridge
E. alison.gamble@ozc.nhs.uk

August

Clinical Neuropsychology of Social Cognition
19 August, 2005; Ely, UK
Tel. 01353 652173

14th National Neurotrauma Conference
19-21 August, 2005; Kolkata, India
Contact: Dr GK Prusty
Tel. 913 324 654 994 , Fax. 913 324 567 880,
E. drgk@prusty.com

International Society for Neurochemistry
August 21-26, 2005; Innsbruck, Austria
E. isn2005@congress-innsbruck.at or alois.saria@uibk.ac.at

World Congress on Pain
21-25 August, 2005; Sydney, Australia
E. iaspdesk@juno.com

European Conference on Visual Perception
22-26 August, 2005; A Coruña, Spain
http://ecvp2005.neuralcorrelate.com/
E. mariamuniz@congrega.es

8th Workshop on the Neurobiology of Epilepsy
24-26 August, 2005; France
E. wonoep2005@ibdm.univ-mrs.fr

26th International Epilepsy Congress
28 August-1st September, 2005; Paris, France
Tel. +353 1 409 7796,
E. paris@epilepsycongress.org

Measuring Behaviour 2005
30 August - 2 September, 2005; Wageningen, The Netherlands
E. mb2005@noldus.nl,
www.noldus.com/mb2005

September

Changing Gear: Working with Behaviour - a road map for progress
1-2 September, 2005; London, UK
E.proactive_therapy@btinternet.com,
Tel. 020 8748 1965

British Aphasiology Society (BAS) International Conference
4-7 September, 2005; University of Essex, UK
www.bas.org.uk/symposia.htm

The Construction of the Social Brain. A seminar with Professor Jordan Grafman
5 September, 2005; Cardiff, UK
E. Halliganpw@cardiff.ac.uk

Biomechanics of the Lower Limb in Health, Disease and Rehabilitation
5-7 September, 2005; Manchester, UK
E. j.fletcher@salford.ac.uk

Encephalitis Explored: Assessment, Rehabilitation and Therapies
6-7 September, 2005; York, UK
Tel. 01653 692583, E. mail@encephalitis.info,
www.encephalitis.info

Event Processing by the Human Prefrontal Cortex. A seminar with Professor Jordan Grafman
7 September, 2005; Cardiff, UK
E. Halliganpw@cardiff.ac.uk

Joint ABN/SBNS meeting
7 - 9 September, 2005; Torquay, UK
Tel. 020 7405 4060, E. info@theabn.org

Symposium: Genetics in Modern Medicine
9 September, 2005; Edinburgh, UK
E. h.olaez@rcpe.ac.uk, Tel. 0131 225 7324.

The Neurorehabilitation of Children and Young Adults
9 September, 2005; Ely, UK
www.easternrehabgroup.org.uk,
E.marlena.judd@addenbrookes.nhs.uk/
lloyd.bradley@addenbrookes.nhs.uk

European Paediatric Neurology Society
14-17 September, 2005; Goteborg, Sweden
Tel. +46-31-708 60 00, Fax. +46-31-708 60 25,
E. epns2005@gbg.congrex.se

Behavioural Experiments in the rehabilitation of Acquired Brain Injury
16 September, 2005; Ely, UK
E. alison.gamble@ozc.nhs.uk

8th Congress of the European Federation of Neurological Societies
17-20 September, 2005; Athens, Greece
Tel. 0041 22 908 0488, Fax. 0041 22 732 2850,
E. efns05@kenes.com, www.efns.org/efns2005

World Congress on Huntington's Disease
10-13 September, 2005; Manchester, UK
E. david.craufurd@man.ac.uk,
Fax. 0161 276 6145,
www.hda.org.uk/congress/index.html

33rd Annual Meeting of the International Society for Pediatric Neurosurgery
11-15 September, 2005; Vancouver, BC, Canada
www.venuewest.com/2005/ispn/

Methods in Mind, BPPS Meeting
12-16th September, 2005; Aston University, UK
www.hop.man.ac.uk/bpps/,
E. events@acnr.co.uk

fMRI experience VII
15-16 September, 2005 Birmingham, UK
www.fmrixp.com/7

Behaviour Experiments in the Neuro Rehabilitation of Acquired Brain Injury
16 September, 2005; Ely, UK
Tel. 01353 652173

9th Congress of the European Federation of Neurological Societies (EFNS)
17-20 September, 2005; Athens, Greece
E. efns05@kenes.com

Attention - Advanced Cognitive Rehabilitation Workshop
17 September, 2005; Gatwick, UK
Tel. 01276 472369,
E. enquiries@braintreetraining.co.uk

Treatment of neurological diseases-an evidence-based approach. Cochrane Neurological Network workshop
18 September, 2005; Athens, Greece
E. cochrane.neuronet@unimi.it

An International Educational Course: Pharmacological Treatment of Epilepsy
18-25 September, 2005; Eilat, Israel
E. eilatedu@targetconf.com,
Fax. 97-235-175-155

International Psychogeriatric Association Annual Meeting
20-24 September, 2005; Stockholm, Sweden
E. stockholm2005@ipa-online.org

78th Congress of the German Neurological Society
21-23 September, 2005; Wiesbaden, Germany
Fax. +49 7621 78714
E. info@akmcongress.com

European Brain & Behaviour Society (EBBS) 37th Meeting
24-28 September, 2005; Dublin, Ireland
E. info@EBBS2005.com, www.ebbs-science.org

The second IBRO/FENS Summer School "Development and Plasticity of the Human Cerebral Cortex"
24 September-1 October, 2005; Croatia
E. school@hiim.hr,
http://www.hiim.hr/english/index.html

Scientific Symposium of the Multiple Sclerosis International Federation (MSIF) and 7th Greek Conference
25-27 September, 2005; Thessaloniki, Greece
E. ms@artion.com.gr , Tel. 302 310 250 927.

6th Meeting of the International Society for NeuroImmunoModulation
25-28 September, 2005; Athens, Greece
Tel. +30 210 7257693, E. info@erasmus.gr

130th Annual Meeting of the American Neurological Association
25-28 September, 2005; San Diego, US
www.aneuroa.org/index.html,
E. tanyahess@llmsi.com

10th International Congress of the World Muscle Society
28 September-1 October, 2005; Iguassu Falls, Brazil
www.wms2005.com/

34th Annual Meeting of the Child Neurology Society
28 September-1 October, 2005; Los Angeles, US
www.childneurologysociety.org/events/evt_001.asp

ECTRIMS-ACTRIMS 2005
28 September-1 October, 2005; Thessaloniki, Greece
www.akm.ch/ectrims2005

The Conversation: MS Professional Network Conference in Scotland
30 September, Stirling, UK
E. h.maunder@msscoietyscotland.org.uk, or
Tel. 0131 335 4050

October

British Geriatric Society Autumn Meeting
4-7 October, 2005; Harrogate, UK
Tel. 020 7608 1369

1st Annual Meeting of the International Spine Society
6-8 October, 2005; London, UK
www.spineinternational.org/iss-meetings.html,
E. contact@spineinternational.org,
Fax. 32 38 214 532.

British Society of Neuroradiologists Annual Meeting
7-8 October, 2005; Edinburgh, UK
E. john@bsnr.co.uk

Congress of Neurological Surgeons Annual Meeting
7-12 October, 2005; Boston, US
Tel. 001 630 323 5144, Fax. 001 630 323 6989,
E. info@1CNS.org

The 6th Euroyapmeet - conference for Younger People with Parkinson's
7–9 October, 2005; Ireland
E. Lizzie@epda.eu.com

BNA National Meeting

3-6 April, 2005; Brighton, UK

This year's national BNA meeting was held over four days at the beginning of April, in the sunny seaside town of Brighton. Events took place within the Brighton Centre and adjacent Belgrave Hotel, and were as eclectic and exciting as promised. With the large number and wide range of plenary lectures, symposia, posters and exhibition stands, there was barely time to sample the local fish and chips or take a stroll along the famous pier. The conference was well attended as always, and filled with the faces of those familiar and those yet to be acquainted. It was also noticeable that a number of delegates had previously attended the BNA Post-Graduate Symposium in Manchester last September, and were now meeting again in Brighton; a measurable success of that particular symposium that its attendees were already crossing paths and networking less than a year down the line.

The BNA Committee.

The meeting was opened on the afternoon of Sunday 3rd April by the President of the BNA, Richard Fracowiak, and the drinks reception in the Brighton Centre that followed later that evening ensured that all delegates felt very welcome. The scientific programme of events also began on Sunday, with The Wolstencroft Lecture delivered by Pierre Magistretti from Lausanne. Entitled 'Cellular Bases of Neurometabolic Coupling and its Relevance for Functional Brain Imaging', his presentation focused on developments in our understanding of the coupling between neuronal activity and glucose utilisation by the brain, with particular reference to the 'astrocyte-neuron lactate shuttle' model.

The theme of neuroimaging remained strong throughout the meeting and continued on the second day, with a symposium exploring advances in magnetic resonance (MR) methodology. Speakers in this session gave an informative overview of the progress being made in our understanding and utilisation of MR imaging. David Thomas from the Wellcome Trust High Field MR Research Lab at UCL described advances in neuroimaging involving scanning at magnetic fields as high as 4.7 Tesla (conventional MR scanners typically operate at 1.5 or 3.0 Tesla). His talk explored the pros and cons of high field imaging, and the techniques being developed to improve spatial resolution with impressive results. The use of array coil imaging, discussed by Dr Thomas, was also examined in detail by the second speaker in this session. Joseph Hajnal from Imperial College gave a comprehensive explanation of the advantages of using arrays of receiver coils and partially parallel imaging, which make use of more localised sensitivity and can improve acquisition time and distortion artefacts during imaging. He also offered a valuable insight into how these methods might be developed in the future. The next talk was from Fernando Calamante of ICH, who described developments in the specific field of diffusion MR imaging. Diffusion MR, which relies on the diffusion properties of water molecules within different structures, is a relatively novel technique that allows the visualisation and investigation of fibre tracts within the brain. Also from ICH, Mark Lythgoe then spoke about other ways in which our knowledge and use of MR methods are progressing, with a discussion covering a number of topics including the use of high-throughput high resolution imaging in animal model systems and its applications. Finally, Raman Saggu from the University of Oxford gave a specific insight into her work examining the effects of interleukin-1β on cerebral energetics, using MR spectroscopy in a model of low-flow ischaemia in the rat.

Other symposia on this day covered topics that included progress in stem cell biology, sensory integration for cognition and action, and the role of microglia in brain injury. In the afternoon, there was also a symposium tackling the important issue of human neuropathology for neuroscience research, with speakers from the CJD Surveillance Unit at the University of Edinburgh (James Ironside), the Institute of Neurology in London (Janice Holton), the UK Multiple Sclerosis Tissue Bank (Richard Reynolds) and the University of Nottingham (James Lowe). These valuable talks highlighted the importance of effective and open communication with the public with regard to the use of human tissue for research purposes, and explored the crucial matter of new regulations following The Human Tissue Act of 2004. There were also two plenary lectures on this second day of the meeting. In the morning, Peter Seeburg (Heidelberg) discussed the critical properties of AMPA receptors, and their role in olfaction and spatial memory, with reference to mouse models. Mechanisms of endocannibinoid signalling were introduced in the second plenary lecture, which was given by Tamas Freund. In his lecture he presented work from his group in Budapest, investigating the importance of CB receptors and exploring potential therapeutic targets for the treatment of anxiety.

There were a number of special events on the second day of the meeting. The first of these was a BNA Discussion Group debating current issues in the teaching of neuroscience. There were also a series of short presentations about the Foresight 'Brain Science, Addiction and Drugs' Project. This Foresight Project, as part of the Government's Office of Science and Technology, has been set up to provide an evidence-based review of how science and technology may impact our understanding of addiction and the use of psychoactive substances. The project involves Government science advisors, the Home Office, the Police, drugs charities, the pharmaceutical industry and medical research organisations, with the aim that the ethical, legal and economic issues associated with its findings will be considered (see the Foresight Project website www.foresight.gov.uk).

On Monday evening, there was another BNA Discussion Group, this time tackling the ever-important issue of Public Awareness of Science. Speakers for this event included BBC Science Radio Correspondent Pallab Ghosh, Huseyin Mehmet from Imperial College, Science Communicator Myc Riggulsford and Elaine Snell, Science Communicator and Executive Officer for the European Dana Alliance for the Brain (EDAB; www.edab.net). The event was organised in collaboration with EDAB, an organisation designed to promote brain research and one which has a very good relationship with the BNA (indeed EDAB was recently presented with an Award for Public Service by the BNA). Following the event, Elaine confirmed that the workshop had been a real success, and that this success was made measurable by the fact that several of the speakers were approached by delegates on separate occasions to discuss the issues raised. It appears that science communication remains a critical issue for scientists and the media alike. Similarly, an example of another much encouraged collaboration, that between science and the arts, was evident in the fascinating images on display in the foyer exhibition 'Thinking Science - Making Art', a collection provided by Lizzie Burns and the Medical Reseach Council, and Catherine Draycott and The Wellcome Photographic Library.

A brisk walk along the sea-front on Tuesday morning was an ideal way to start the third day of the meeting. Symposia on this day again covered a broad range of issues, from stem cell plasticity, to information coding in auditory cortex and neuroinflammation. One of the afternoon sessions was focused on promoting recovery

after stroke, and chaired by Cathy Price from UCL. Speakers in this session included Richard Wise from the MRC Clinical Science Centre at the Hammersmith Hospital, who described functional neuroimaging research demonstrating the converging pathways involved in language processing in both healthy individuals and aphasic stroke patients. The implications concerning targeted behavioural and drug therapies to rehabilitate patients were discussed. In the same session, Argye Hillis from Baltimore also discussed mechanisms and stages of language recovery after stroke. Professor Paul Matthews from the University of Oxford Centre for fMRI of the Brain explored evidence that common mechanisms exist in the healthy and injured brain, with regard to motor learning and control. He too made the point that future therapies may be specifically targeted and manipulated, based on strong biological rationale and informative neuroimaging methods. The session ended with a presentation from Jean-Claude Baron from the University of Cambridge, who gave a complementary overview of research mapping motor recovery after stroke.

The plenary lecture on the third day of the meeting was delivered by James McCulloch from the University of Edinburgh, who spoke about the concern that although a significant insight into the mechanisms of ischaemic cell death had been gained in recent years, this success was yet to be translated into new drug treatments. He discussed the obvious importance of research efforts to meet this challenge. On Tuesday afternoon, there was also the Trends in Neurosciences Lecture, given by Trevor Robbins from The University of Cambridge, and entitled 'Chemistry of the Adaptive Mind'. Professor Robbins gave an overview of research, in both experimental animals and humans, into the action of drugs that affect the prefrontal cortex via ascending neuromodulatory systems, and explored the implications for our understanding and treatment of neuropsychiatric disorders. Special events of note on Tuesday were the BNA Annual General Meeting held at lunchtime, and of course the 'legendary' BNA Conference Banquet and Party in the evening.

Another fairly early start saw the fourth and final day begin with the penultimate plenary lecture. Hugh Perry (University of Southampton) described work from his group using mouse models of prion disease. He presented findings about the interactions between brain inflammation and systemic inflammation, which may contribute to the progression of chronic neurodegeneration. The final plenary lecture of the meeting, concerning axonal regeneration in the CNS, was delivered by Marie Filbin from New York. She presented research from her lab, which shows that elevation of cAMP can promote spinal axon regeneration in an otherwise inhibitory environment; an effect that is transcription-dependent and requires the activation of the transcription factor CREB.

Throughout the meeting in Brighton there were a variety of themed poster sessions, which should also be mentioned. On the final day, for example, investigators displayed their work on topics including genes and behaviour, behavioural pharmacology, tumours, pain, cerebrovascular disease, trauma, infection, inflammation, gene therapy, neural networks and neuroimaging, to name but a few. It is obviously impossible to mention them all, but fair to say that each poster session reflected the high standard and scope of research presented throughout the meeting, which was brought to a close on Wednesday afternoon leaving enough time for a visit to the Royal Pavilion before a reflective journey home.

The BNA National Meeting 2005 was supported by GlaxoSmithKline, Eli Lilly, Nature Reviews Neuroscience, the Trends Journals, the European Dana Alliance for the Brain, the Association of British Neurologists, the British Neuropathology Society, the Physiological Society and the OST Foresight Project.

Helen L Jamison (DPhil Student),
Dept. Experimental Psychology & Centre for fMRI of the Brain (FMRIB),
The University of Oxford.

See ACNR 3:5 for an interview with Professor Richard Frackowiak, and ACNR 4:3 for a review article on The Impact of Systemic Inflammation on Brain Inflammation by Professor Hugh Perry

CONFERENCE PREVIEW: 2nd National United in Care Conference

23rd November, 2005; Royal College of Physicians, Regent's Park, London.

The second national United in Care conference is to be held at the Royal College of Physicians on Wednesday 23rd of November 2005, organised by Medical Education Partnership (MEP) Ltd in association with the British Geriatrics Society (BGS).

The practice of geriatric medicine involves healthcare professionals from many different disciplines and the BGS is committed to promoting multidisciplinary approaches in the field. The United in Care series of conferences aim to identify ways in which interdisciplinary collaboration can be improved among healthcare professionals who are providing care for older people. A highly successful inaugural conference was held in London in December 2004.

United in Care 2005 focuses on two important themes – **End-of-life care** and **Mental health issues of medically unwell older people**. Speakers include experts who work in these emotive areas and the programme includes:

- The needs of patients and patient safety – Mary Baker MBE, President of the European Federation of Neurological Associations and the European Parkinson's Disease Association.
- The meaning of futility: a clinical perspective – Dr Edmund Dunstan, Consultant Geriatrician and Honorary Clinical Lecturer, University of Birmingham.
- Resuscitation in old age: what it means for patients, their families and healthcare staff – Dr Kevin Stewart, Consultant Physician and Medical Director, Winchester and Eastleigh Healthcare NHS Trust.
- The role of hospital clinical ethics committees – Dr Jim Eccles, Consultant Geriatrician and Chair of the Clinical Ethics Committee, Leeds Teaching Hospitals.
- End-of-life decisions in care homes – Dr Katherine Froggatt, Senior Lecturer, Palliative and End-of-Life Care Research Group, School of Nursing & Midwifery, University of Sheffield.
- Flu immunisation for patients and staff – Professor Margot Gosney, Professor of Elderly Care Medicine, Reading University.
- Community matrons: holistic care for the 21st century – Aileen Fraser, Consultant Nurse, Bristol University Hospitals.
- Mobility, rehabilitation and cognitive impairment – Professor Val Pomeroy, Professor of Rehabilitation of Older People, St. George's Hospital Medicine School, London.
- Recognition and management of delirium in acute hospitals — Dr Duncan Forsyth, Consultant Physician, Addenbrooke's Hospital, Cambridge.
- Who develops delirium and why – Dr David Anderson, Consultant Old Age Psychiatrist, Mossley Hill Hospital, Liverpool.
- What makes clinical guidelines work in the clinical setting? – Professor Martin Eccles, Professor of Clinical Effectiveness and The William Leach Professor of Primary Care Research, University of Newcastle upon Tyne.
- How specialist mental health nursing can help in general hospital wards – Clare Wai, Liaison Mental Health Nurse, Cambridge and Peterborough Mental Health Partnership NHS Trust.

A report on the new British Geriatrics Society guidelines for the recognition and management of delirium in acute hospitals will also be given by Dr Jim George, Consultant Physician and Clinical Director, Cumberland Infirmary, Carlisle.

Abstracts relevant to the interdisciplinary care of older people are also invited for poster presentation. Preliminary results and audit are welcome.

The programme has been devised to encourage debate and full participation of all members of the interdisciplinary team who are involved in the management and care of older people.

For further information contact: MEP Ltd,
53 Hargrave Road, London N19 5SH
Tel: 020 7561 5400
Email: info@mepltd.co.uk
Web: www.mepltd.co.uk

XVIIIth World Congress of Neurology

5-11 November 2005 Sydney Australia

is without a doubt one of the most beautiful cities in the world.

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HOSTS

WFN

The World Federation of Neurology (WFN)

The Australian Association of Neurologists (AAN)

Sydney, the host city for the World Congress of Neurology 2005, is without doubt one of the most beautiful cities in the world with a reputation for friendly people, a cosmopolitan lifestyle, wonderful shopping and world-class entertainment. The magnificent harbour, renowned Opera House and sunny beaches combine to make Sydney a unique destination.

The Congress Program will feature:

- A topical scientific program covering (along with other subjects of interest) the following main themes:
  - Epilepsy
  - Stroke
  - Multiple Sclerosis
  - Headache/ Pain
  - Dementia/ Movement Disorders, Neurological Infections
- Frontiers of Neuroscience Lectures presented by: Professor Salvatore DiMauro • Professor Peter Doherty • Professor Colin Masters • Professor Yoshikuni Mizuno • Professor Bert Sakmann
- Education Program – Comprehensive and affordable teaching courses designed to complement the main scientific themes
- Bursaries will be provided to support young neurologists wishing to attend the Congress. For criteria and the application process please visit the Congress website www.wcn2005.com

Want to know more?

To register please visit the Congress website or contact:

WCN 2005 Congress Secretariat
GPO Box 2609
Sydney NSW 2001 Australia

Telephone: +61 2 9241 1478
Facsimile: +61 2 9251 3552
Email: info@wcn2005.com

Key dates

Abstract submission deadline	**1 May 2005**
Notification of acceptance of abstracts	**July 2005**
End of early rate registration fee	**5 August 2005**
Accommodation booking deadline	**23 September 2005**
World Congress of Neurology 2005	**5-11 November 2005**

World Congress of Neurology
5-11 November 2005 Sydney Australia

www.wcn2005.com

British Psychophysiology Society

Methods in Mind

The 7th 'fMRI Experience' and Annual Conference of the BPPS

12-16 September, 2005; Aston University

This five day meeting is free for all delegates and consists of a number of symposia including: Social Neuroscience, Cognitive Neuropsychiatry, Imaging: Visualisation of Brain Imaging Data as well as Innovations in Mapping the Mind. The symposia will be lead by world leaders in cognitive neuroscience.

In addition there will be a number of masterclasses where delegates can learn to collect and analyse data from MEG (VSM Medtech CTF) and fMRI (AFNI) technologies.

Delegates can participate in masterclasses or attend demonstrations in dense array EEGs (EGI) and multimodal EEG/MRI imaging techniques (Neuroscan Compumedics and Advanced Medical Equipment Ltd).

www.fmriexp.com/7/

WORLD CONGRESS ON HUNTINGTON'S DISEASE

Midland Hotel, Manchester, UK
10th - 13th September 2005

www.hda.org.uk/congress

The World Congress on Huntington's Disease is a joint meeting of the World Federation of Neurology Research Group on Huntington's Disease and the International Huntington Association. The scientific programme covers the topics of genetics and genetic counselling, drug discovery and development, pathogenesis, clinical neurology, neuropsychology, neuropsychiatry, therapeutics, clinical trials, public policy and education.

Invited speakers include: **Elizabeth Aylward, Gill Bates, Elena Cattaneo, Steve Dunnett, James Gusella, Sir Peter Harper, Michael Hayden, Karl Kiebutz, Martha Nance, Hank Paulson, Anne Rosser, David Rubinsztein, Sheila Simpson, Leslie Thompson, Aad Tibben, Erich Wanker and Anne Young.**

The congress will be of interest to all researchers and health professionals interested in Huntington's Disease.

CDP approval has been granted by the Royal College of Physicians (17 points) and the Eurpoean Accreditation Council for CME (15 points).

For further information and registration please visit: www.hda.org.uk

Contact Details
www.hda.org.uk/congress
congress@hda.org.uk
Tel: +44 (0) 20 7223 7000

MOTOR NEURONE DISEASE ASSOCIATION

Dublin 2005

16th INTERNATIONAL SYMPOSIUM ON ALS/MND

8 - 10 December 2005
Dublin, Republic of Ireland

A unique annual event which brings together leading international researchers and health and social care professionals to present and debate key innovations in their respective fields.

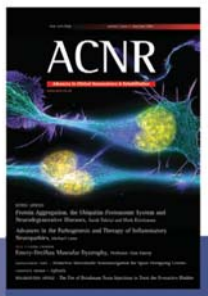
For a programme and booking form, contact the Conference Team at the MND Association, PO Box 246, Northampton NN1 2PR, or email symposium@mndassociation.org.

Conference Reports

Would you like to contribute a conference report to ACNR? Over the coming months, we will be reporting from the following events:

- 15th Meeting of the European Neurological Society
- ABN Autumn Meeting
- Gamma Knife radiosurgery meeting
- 130th Annual Meeting of the American Neurological Association
- International Psychogeriatric Association meeting
- 9th Congress of the European Federation of Neurological Societies
- 12th Congress of the International Headache Society
- 4th International Congress on Vascular Dementia
- World Congress of Neurology
- 16th International Symposium on Amyotrophic Lateral Sclerosis / MND

If you are attending any of these events and would like to write a report for a future issue, please contact our Conference Report Co-ordinator Dr Andrew Michell on Email: awm13@cam.ac.uk



EDITOR'S CHOICE

PPARγ agonists for Alzheimer's Disease?

It is well-recognised from epidemiological studies that NSAIDs reduce the risk of developing Alzheimer's disease (AD). The mechanism of this effect is uncertain; the possibility that it is mediated via cyclo-oxygenases (COX) must be weighed against the ineffectiveness of selective COX2 inhibitors in treating established disease. Activation of the nuclear receptor peroxisome proliferation-activated receptor-γ (PPARγ), leading to inhibition of pro-inflammatory gene expression, is another possibility, examined in this paper. APPV717I transgenic mice, which develop amyloid deposits and glia-mediated inflammatory responses typical of AD around 10 months of age, were fed with rodent chow supplemented with ibuprofen (62.5mg/kg/day) or pioglitazone (40mg/kg/day) for 7 days before sacrifice. The latter is a thiazolidinedione, a highly specific PPARγ agonist, used in the treatment of type 2 diabetes (although it had no effect on blood glucose levels in these animals). Treated animals showed:

- reduced number of activated microglia and reactive astrocytes in brain cortex and hippocampus;
- reduced expression of proinflammatory enzymes (COX2 in microglia, iNOS in astrocytes);
- reduced expression at both mRNA and protein level of BACE1, a key enzyme in the APP processing pathway;
- reduced Aβ1-42-immunopositive plaque area and staining intensity;
- reduced soluble Aβ1-42 peptide (pioglitazone only).

These findings suggest that brief oral treatment with these agents acts rapidly to inhibit inflammatory responses in brain, so modulating amyloidogenesis. The authors suggest that PPARγ agonists might be explored in the treatment of AD. Obviously, however, given the clinical experience with NSAIDs in AD, there must be misgivings about the efficacy of PPARγ agonists in clinical practice. - ***AJL***

Heneka MT, Sastre M, Dumitrescu-Ozimek L, Hanke A, Dewachter I, Kuiperi C, O'Banion K, Klockgether T, Van Leuven F, Landreth GE.
Acute treatment with the PPARγ agonist pioglitazone and ibuprofen reduces glial inflammation and Aβ1-42 levels in APPV717I transgenic mice.
BRAIN
2005;128(6):1442-53.

HEAD INJURY: Roids no good

Sometimes it takes a huge effort to answer a simple question, in this case does early treatment with corticosteroids improve the outcome of head injury? The answer is no. In fact they may make things worse…. Top marks for the trial acronym, CRASH, which stands for corticosteroid randomisation after significant head injury! In this MRC trial 10,008 adults with head injury and a Glasgow Coma Scale score of 14 or less, within 8 hours of injury, were randomised to a 48-h infusion of corticosteroid (methylprednisolone) or placebo. The follow-up was impressive: at six months they had data from 9,673 (96·7%) patients. The risk of severe disability and/or death was higher in the corticosteroid groups by statistically significant, but rather small, differences. For those who like these things, the stats were: risk of death higher in the corticosteroid group (1,248 [25·7%] vs 1,075 [22·3%]; relative risk 1·15, 95% CI 1·07–1·24; p=0·0001); and the risk death or severe disability (1,828 [38·1%] vs 1,728 [36·3%] dead or severely disabled; 1·05, 0·99–1·10; p=0·079). Subgroup analysis by injury severity or time since injury did not reveal any useful differences. This is a very useful trial. I wonder if it will have any influence on the use of corticosteroids for spinal cord injury, which seems to be prevalent. Or are we going to have to randomise 10,000 people with that condition in the CRASS trial?!? - ***AJC***

CRASH trial collaborators.
Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months.
LANCET
2005;365(9475):1957-9.

MOTOR NEURON DISEASE: Interfering with silencers

★★★ RECOMMENDED

The identification of genetic causes of neurodegenerative disorders of the CNS has led to the development of therapeutic approaches which attempt to silence the disease causing gene product. This has perhaps been most studied using small interfering RNA (siRNA), that promote specific endonucleolytic cleavage of the mRNA targets of the mutant gene/protein. Adopting this strategy has proven successful in vitro, although it has proved difficult to completely silence the relevant element. Nevertheless the problem in vivo is even more problematic, in that there are issues of delivery – how do you get siRNA into all relevant cells with long term silencing? One approach around this has been to use viral vectors, which have a long history in the experimental delivery of therapeutic agents (especially growth factors) for CNS disorders. The favoured viral vector has changed over time, but of late much interest has focused on lentiviruses, because of the efficiency with which these viruses can infect neural cells. In this paper, Patrick Aebischer and colleagues explore this approach in vitro and then in vivo with the $SOD1^{G93A}$ transgenic mouse model of familial motor neuron disease/amyotrophic lateral sclerosis (ALS). Mutations in Cu/Zn superoxide dismutase (SOD) have been known for over 10 years to cause rare familial forms of ALS, through a proposed toxic gain of function. Transgenic mice containing the mutant form of this gene develop a progressive ALS like illness over about a 6 month period. Using these mice, Aebischer et al show that intraspinal lumbar injection of a lentiviral delivery system for siRNA to SOD1, slows down the onset of disease and its progression in hindlimb muscles and related behaviours. This is an exciting study and comes hot on the heels of a study last year using a similar approach with transgenic SCA mice (see Caplan NJ (2004) Nature Medicine 10:775-776), which gives weight to the validity of this approach. There are though still a number of unresolved issues, including the most appropriate target of the siRNA as many neurogenetic diseases have multiple causative mutations. In addition, issues of delivery are still very real. In this study only lumbar regions were injected, although in the case of ALS one could argue for targeted delivery as there are clearly some motorneuronal pools that are more important than others (such as those innervating the bulbar/respiratory musculature). Nevertheless this work once more shows how far we have come in the treatment of neurological disorders through studies of rare genetic causes of common neurodegenerative diseases of the CNS - ***RAB.***

Raoul C, Abbas-Terki T, Bensadoun JC, Guillot S, Haase G, Szulc J, Henderson CE, Aebischer P.
Lentiviral-mediated silencing of SOD1 through RNA interference retards disease onset and progression in a mouse model of ALS.
NATURE MEDICINE
2005;11:423-8.

THE TEMPORAL LOBE: Musical Offering

This paper in Brain takes as its topic the basis of scary music. This is an interesting topic as all film goers will testify…after all if you watch the predatory giant shark in Jaws about to attack without the music (as was once shown on Nationwide several decades ago!!), then the dramatic impact is greatly diminished. So how does music do this - where in the brain could music mediate such an effect? One obvious target would be the amygdala, given its close association with fearful stimuli – both experimentally in animals and in the clinic. In this study, 16 right handed patients with either a right OR left medial temporal lobectomy were studied using an emotional recognition task involving instrumental music. The patients had all had surgery for intractable temporal lobe epilepsy, of non-tumour origin. This music was categorised into fearful, peaceful, happy or sad and the subjects had to score these emotional impressions out of 10 – similar in many ways to the facial grading tests of emotion. Each subject was tested with 56 stimuli and careful attention was paid to ensure that any deficits were specific for the emotional content of the music. Interestingly, the study showed a relatively selective deficit in the recognition of scary music, with the other musical emotions being unaffected, irrespective of whether the patient had had a right or left temporal lobe resection. The authors therefore conclude that "These findings suggest that the anteromedial temporal lobe (including the amygdala) plays a role in the recognition of danger in a musical context". Although no evidence can be provided that the amygdala really is the source of this aspect of musical emotional processing, it would nevertheless seem the most likely candidate given its known role in the processing of fearful stimuli through other sensory modalities. Thus once more emphasising that structures involved in these forms of high level sensory processing, do so for a specific emotion but independently of the exact mode of sensory stimulation….Now who has turned the sound down on my television and what is all the fuss about that man stabbing at the shower curtain. - ***RAB***

Gosselin N, Peretz I, Noulhiane M, Hasboun D, Beckett C, Baulac M, Samson S.
Impaired recognition of scary music following unilateral temporal lobe resection.
BRAIN
2005;128: 628-640.

AMYGDALA: Look into my eyes… and be fearful

★★★ RECOMMENDED

SM, a 38-year-old woman, has selective lesions of the amygdala bilaterally. She had previously been shown to lack normal fear responses and her interpersonal conduct is indiscriminately trusting and friendly. The experimental paradigm here consisted of a remarkable 3000 presentations of faces expressing either happiness or fear. However, only a small area (a random 'bubble') of any face was visible at each presentation, the remainder being obscured. In comparison with controls, SM required more bubbles to identify facial expressions reliably. Regression analysis of bubble locations contributing to fear recognition showed, in controls, the eye region to be most critical. By contrast, only bubbles around the mouth region seemed to influence SM's responses. Gaze monitoring, furthermore, found that SM consistently failed to fixate on the eyes of presented faces. Curiously, on the control task of deciding the sex of presented faces, not only did SM perform within the normal range but her visual scanning of the presented images was also normal. The implication is that perception links into emotional processes and ordinary object recognition in different ways. Most strikingly, when SM was instructed specifically to look at the eyes of the presented faces she attained normal fear recognition. This elegant case study therefore suggests that the amygdala engages in emotion recognition by influencing visual fixation and perception. The theory is both novel and intuitively plausible, given the proximity of the amygdala to multimodal sensory association cortices in the anterior temporal lobe and the increasing appreciation that perceptual processes merge seamlessly with other neural functions as disparate as memory and movement. Although the single instruction to SM that she should 'look at the eyes' failed to resolve permanently her impaired emotion recognition, the possibility is raised of rehabilitating patients with similar behavioural problems. As well as occasional patients with focal lesions, this might include patients with neurodegenerative disease and those with autistic-spectrum disorders. - ***RD***

Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR.
A mechanism for impaired fear recognition after amygdala damage.
NATURE
2005;433(7021):68-72.

NEURODEGENERATION: antibiotics are the answer

Unlocking the full potential of existing pharmaceutical agents, given the enormous expense of developing new compounds, seems an ever more attractive proposition. Such endeavors encompass drugs for which years of investment and favourable initial safety studies ended with disappointing efficacy trials, as well as drugs listed in current formularies perhaps with unsuspected virtues. This paper describes a series of experiments whereby beta-lactam antibiotics show promise in the context of glutamate excitotoxicity, a pathogenetic mechanism implicated in several neurological diseases, including motor neuron disease. The foundation of the study was a screen of over 1000 currently licensed drugs that involved immunoblotting GLT1 (the receptor responsible for glutamate reuptake) on rat spinal cord slices exposed to one of the myriad drugs. Beta-lactam agents as a group were found to increase expression of GLT1 and this led to further experiments focusing specifically on ceftriaxone. In doses similar to those achieved during treatment of infectious diseases, ceftriaxone activated the human GLT1 promoter in cell culture and, in vivo, induced long-lasting increases in rat brain GLT1 expression. Neuroprotective properties were shown both in cultured neurons and in neural tissue preparations. Crucially, administration of ceftriaxone in a mouse model of motor neuron disease delayed the onset of clinical signs and prolonged survival. The initiative of Rothstein and colleagues is especially welcome given the various factors that conspire to limit pharmaceutical investment in neurodegenerative diseases generally. It is to be hoped that their specific findings will be substantiated by further work. – ***RD***

Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Dykes Hoberg M, Vidensky S, Chung DS, Toan SV, Bruijn LI, Su ZZ, Gupta P, Fisher PB.
Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression.
NATURE
2005;433(7021):73-7.

DEMENTIA: Painkillers kill neurons

★★★ RECOMMENDED

Traditional pain medication has been associated with protection from Alzheimer's disease. However, a recent study by Kukar and colleagues, published in Nature Medicine, suggests that non-steroidal anti-inflammatory drugs (NSAIDs) may in fact be detrimental to Alzheimer's disease. Several lines of evidence have indicated that NSAIDs would be useful in treating Alzheimer's disease. First, epidemiological studies suggest that long-term NSAID therapy reduces the risk of developing Alzheimer's disease. Second, inflammatory processes are activated in Alzheimer's disease. Third, Kukar has previously shown that NSAIDs are able to lower Aβ42 production. Aβ42 is a neurotoxic peptide that readily aggregates into fibrils and deposits as plaques in Alzheimer's disease brain. It is believed to be the initiating molecule in the pathogenesis of Alzheimer's disease. The initial aim of this cell-based screen was to identify NSAID-like compounds that reduced Aβ42 production but had little effect on the COX enzymes. COX enzymes are the targets of NSAIDs, which convert arachidonic acid to prostaglandin H2 in the first step of prostanoid production. There are two classes, COX-1, which is constitutively expressed and COX-2, which is expressed only during inflammation and is responsible for the production of pro-inflammatory prostanoids. Due to its constitutive expression, inhibitors of the COX-1 enzyme are associated with detrimental side-effects. The results of Kukar's screen of hundreds of NSAIDS and their analogues were both surprising and disappointing. Just a single compound was identified that lowered Aβ42 production and lacked COX activity. Numerous compounds, principally the COX-2 selective NSAIDs, were found to promote Aβ42 production in vitro and in vivo. Three-day oral treatment of mice with the COX-2 inhibitor, celecoxib, raised Aβ42 production 2-fold. Alzheimer's disease-causing mutations in presenilin-1 and presenilin-2 and in amyloid precursor protein (APP) only increase Aβ42 production by 30-100%. Despite the curious association between COX-2 selectivity of NSAIDs and propensity for Aβ42-raising, the effect was independent of COX-2 binding. Like the Aβ42-lowering NSAIDs, these compounds were shown to target the γ-secretase complex, which cleaves APP to generate Aβ42. It is proposed that these compounds alter APP cleavage via allosteric modulation of the enzyme complex. The authors are wary of extrapolating their findings to humans because the concentrations of the Aβ42-raising compounds in vitro were higher than those found in humans. The concentrations in mice were more similar to those found in humans but pharmacokinetic differences between the species must be taken into account. The main implication of the study is that exogenous com-

pounds or even alterations of endogenous isoprenoids could increase Aβ42 production and in this way represent a novel risk factor for Alzheimer's disease development. Greater understanding of the mode of action of these γ-secretase modulators may aid in the design of new inhibitors of Aβ42 production and improve Alzheimer's disease therapy. It still remains unclear if the beneficial effects of NSAIDs on inflammation in Alzheimer's disease outweigh the harmful effects. - ***LMS & SJT***

Kukar T, Murphy MP, Eriksen JL, Sagi SA, Weggen S, Smith TE, Ladd T, Khan MA, Kache R, Beard J, Dodson M, Merit S, Ozols VV, Anastasiadis, Das P, Fauq A, Koo EH, Golde TE.

Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Aβ42 production.

NATURE MEDICINE

2005;11(5):545-50.

PAIN: rTMS can provide long lasting relief from neuropathic pain

Electrical stimulation of motor cortex using surgically implanted electrodes provides pain relief for some but not all people with medication resistant neurogenic pain. The implantation surgery is expensive and there has been no way of determining which patients could benefit from the treatment. Recently a non-invasive method of cortical stimulation using rapid rate Transcranial Magnetic stimulation (rTMS) has been shown to provide transient pain relief in some patients suffering from neurogenic pain. Now a paper in JNNP reports that a course of rTMS over five days can result in prolonged and significant pain relief. This raises the possibility that response to treatment with rTMS could be a useful and inexpensive predictor of the effectiveness of direct motor cortex stimulation. In a randomised controlled trial of 48 patients Khedr et al compared rTMS treatment with sham rTMS. Twenty-four of the patients had trigeminal neuralgia and 24 had post stroke pain mostly affecting face upper limb and trunk. Fourteen patients with each diagnosis were treated with 10 minutes of real TMS over the hand area of motor cortex (20 Hz, 10 x 10s trains with stimulator intensity at 80% of motor threshold). The stimulation was given every day for five consecutive days. The control group received sham stimulation of the same duration. Pain was assessed with the Leeds Assessment of Neuropathic Symptoms and Signs and by Visual Analogue Scale. Compared with the sham treated group, the group treated with real rTMS showed a statistically significant and clinically meaningful reduction in pain. The effect appeared to be cumulative over the first four days and lasted at least until the final assessment at two weeks after the last treatment session. Distributions of rating scores among the patients showed that not all patients with either diagnosis responded to the real rTMS. In addition to the promise of rTMS as a predictor of which patients might benefit from implanted electrodes, the results of this study show that stimulating over the hand area of motor cortex can reduce pain in the face as well as the upper limb; presumably because of spread of the effects to adjacent cortical representations. Since it is easy to determine the stimulation intensity needed from the motor threshold of small hand muscles, this means that in future patients on the waiting list for motor cortex implanted electrodes and those who do not want to undergo surgery could be offered courses of rTMS in the clinic. - ***AJT***

Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC.

Long lasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain.

JOURNAL NEUROLOGY, NEUROSURGERY & PSYCHIATRY

2005;76:833-8.

MULTIPLE SCLEROSIS: Bad things may happen when rescuers are turned back at the gates

★★★ RECOMMENDED

So, at last, we have some published data on the much-discussed complication of progressive multifocal leucoencephalopathy (PML) with the new drug, natalizumab (Antegren or Tysabri). Amazingly, and surely wrongly, this drug was licensed as a treatment for relapsing remitting MS on the basis of an interim analysis of two phase III trials, which have yet to be published: AFFIRM (natalizumab alone) and SENTINEL (natalizumab in combination with interferon-beta-1a). Natalizumab is a monoclonal antibody that binds to the α4-integrins on lymphocytes and prevents their entry to gut and brain. Press releases from the manufacturers of natalizumab, Biogen, had claimed that, in the recent two-year results from the AFFIRM trial, natalizumab reduced relapse rate by 67% and reduced progression of disability by 42% compared to placebo over two years. These results represent a very significant improvement on the currently available disease modifying therapies for multiple sclerosis, which offer at best a third reduction in relapse rate.

However, in early March 2005, Biogen stopped distributing natalizumab. A fatal case of PML was diagnosed in a patient treated with the drug in combination with interferon-beta-1a. The pathology of this case has now been published. After three years of seemingly characteristic (if oligoclonal band negative) multiple sclerosis, and two years' treatment with interferon-beta-1a, she was entered into the SENTINEL study. Thirty months later she had developed new neurology, including a "decreased fund of information" (how ever did that nonsense get past the editors?) Three months later she was dead, after a clinical typical course for PML. For some reason, a MRI scan done seven months before the first PML symptoms was "not available" and the report was insufficiently clear to tell if there were pre-symptomatic PML lesions. The pathology of her case is scary: nearly every tissue section from both cerebral hemispheres had either macroscopic or microscopic PML lesions!

The second multiple sclerosis patient is the most instructive. He developed the first symptoms of PML 25 months after starting natalizumab. But, actually, a MRI scan the preceding month showed an odd lesion that - in retrospect - was the first sign of PML. The reason this is important is that there is a hint in this report that PML may not have the awful prognosis we all assume. The patient continued to deteriorate for three months after natalizumab was stopped. However, after that point, JC virus was no longer detectable in his blood. And his MRI lesions became enhancing, suggesting an inflammatory response (similar to the "immune reconstitution syndrome" seen in HIV patients with PML). This is not always a good thing: patients can deteriorate during this phase of the illness. However it does mean the blood-brain-barrier is breached and this can allow access to the brain for cytarabine. This is the only drug which kills JC virus in vitro, unlike cidofovir which is sometimes used in this condition. At all events, this patient received cytarabine and his condition improved somewhat. He remains very disabled... but he is alive and has survived PML which is no mean feat.

News of these two cases came to the attention of a Belgian group, who had looked after a man with Crohn's disease who had taken part in a trial of natalizumab for inflammatory bowel disease. 16 months after starting natalizumab, he presented to hospital with confusion and several large non-enhancing white matter lesions on a MRI scan. He deteriorated and died. At the time, he was thought to have an astrocytoma. But, when his pathology was re-examined, it was more compatible with PML. Furthermore, his serum contained measured JC virus DNA from 12 months onwards after treatment. An important point is that PML had not appeared at any time during his previous treatment with azathioprine or infliximab.

So what have we learnt about PML, the demyelinating central nervous system infection by the "JC virus"? 50-80% of the population are seropositive for JC. It is believed that the virus itself remains latent in the kidneys and the lymphoid organs. We associate its reactivation normally with devastating immune damage, particularly HIV infection. We now know that this need not be the case: natalizumab has - until all of this - seemed a rather benign drug, certainly no less toxic than azathioprine or infliximab. It seems that we are all poised to get PML.. and only prevented from it by the quiet continuous trafficking of T lymphocytes through the brain. As the NEJM editorial puts it: "bad things may happen when rescuers are turned back at the gates".

And is this the end of natalizumab treatment of multiple sclerosis? The data, such as we have, suggests that it may be more efficacious than the current licensed drugs. First we need to know the risk of PML after natalizumab. Biogen are currently re-examining and imaging all 3000 pts who have received natalizumab for any condition. Then we need to ask if that risk is worth the benefit? Difficult decisions. - ***AJC***

Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P.

Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn's Disease.

NEW ENGLAND JOURNAL OF MEDICINE

2005;Jun 9; [Epub ahead of print].

Kleinschmidt-Demasters BK, Tyler KL.

Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis.

NEW ENGLAND JOURNAL OF MEDICINE

2005;Jun 9; [Epub ahead of print].

Langer-Gould A, Atlas SW, Bollen AW, Pelletier D.

Progressive Multifocal Leukoencephalopathy in a Patient Treated with Natalizumab.
NEW ENGLAND JOURNAL OF MEDICINE
2005;Jun 9; [Epub ahead of print].

EPILEPSY: Neuropsychiatric porphyria in patients with refractory epilepsy: report of three cases

"Would I have thought of it?" is the question that I always ask myself when I see reports like this. The first patient was a twenty year-old woman who developed tonic clonic seizures at the age of 12. She then developed recurrent bouts of abdominal pain and vomiting – phew, a smart handle I could probably spot! Epilepsy deteriorated with drop attacks and she developed disturbed sleep, weight loss and constipation and was found to have elevated urinary δ-aminolaevulinic acid and a metabolic defect in the hydroxymethylbilane synthase gene. She was treated with haem arginate and antiepileptic drugs were changed to gabapentin and clonazepam on which she has one seizure per year. The second patient was 40 with a 3 year history of refractory epilepsy and hyponatraemia around 119 mmol/L (I didn't know that). She had an episode of limb shaking during an EEG thought to be non-epileptic (oh dear, I'm in trouble!). She suffered with recurrent low back and left inguinal pain and constipation (no, I still wouldn't have got it). She had nocturia with dark, foul smelling urine and paraesthesiae in both hands and mentioned that she was sensitive to sunlight with occasional rashes (at last, perhaps the penny would have dropped, but I guess these were sought rather than volunteered). Urinary δ-aminolaevulinic acid was raised along with total faecal porphobilinogens and a mutation of protoporphyrinogen oxidase oxidase was found confirming a diagnosis of variegate porphyria. Phenytoin was changed to lamotrigine and seizures reduced to 2 per year, along with improvements in her biochemistry. The third case was a 27 year-old woman with an 18 year history of refractory epilepsy. She had had 3 tonic-clonic seizures at the onset but subsequent attacks were of shooting of pins and needles through her body, sometimes with shaking or weakness of the right side for a few seconds without loss of consciousness (this is looking tricky!). Telemetry showed epileptiform discharges during the attacks (that's better). She then developed tonic falls thought to be non-epileptic (Oh no, not again!). A wide variety of AED's was tried and finally she was started on topiramate with her carbamazepine. Four months later she was found collapsed on the ground and required intensive care. Standard investigations yielded no cause but her EEG showed a metabolic encephalopathy and then urine was noted to be dark (Bingo, but too late!). She had elevated urinary δ-aminolaevulinic acid and faecal protoporphyrin with a mutation in the protoporphyrinogen synthase gene. She was treated with haem arginate and medication was changed to gabapentin plus clobabzam and then her seizures declined but she was left with a severe spastic quadriparesis, and dysarthria with preserved cognition. So, the important lessons are that refractory epilepsy can be the presentation and other features may only emerge years later. Seizures can be odd and may be mistaken for non-epileptic attacks. Severe constipation and hyponatraemia as well as abdominal pain should ring alarm bells and the colour of the urine needs to be asked for. How much porphyria are we missing? I confess I have never diagnosed a case. - ***MRAM***

Winkler AS, Peters TJ and Elwes RDC.
Neuropsychiatric porphyria in patients with refractory epilepsy: report of three cases.
JNNP
2005;76:380-3.

EPILEPSY: Removal of epileptogenic sequences from video material. The role of colour

565 children had a fit whilst watching Pokémon on Japanese TV in one showing in the 1990's. Personally, having endured my son watching Pokémon videos and swapping Pokémon cards, I can understand this as a valid critical response. However, the Japanese medical community felt it was pathological and worthy of investigation. The authors of this paper assessed whether specific components of the broadcast could be modified to alter the EEG response to transmission rather than my favoured but less scientific approach of chucking a brick at the telly. (Fuddy-duddies of the world unite!) In this transmission, a particular property of colour modulation, especially flicker transitions between red and blue were critical in generating seizures, a property termed chromatosensitivity. The authors took 25 patients with clear photosensitive epilepsy and measured the range of frequencies of flash to which they were photosensitive. The most epileptogenic sequence was embedded in 12 seconds of cartoon. Different colours were altered separately to reduce the colour modulation, with as little effect on the cartoon content as possible. Because the sequence was digitised at 25Hz, only a flicker frequency of 12.5Hz was assessed in the experiments. The cartoon was then played back on 50Hz and 100Hz televisions. and the maximal epileptogenic properties of the sequence, involving alternating red-blue flicker were suppressed. Twenty-three patients were sensitive to the Pokémon video and one of the others was colour-blind (deuteranope). One man taking valproate was not sensitive to standard flashes did show EEG changes to Pokémon. The responses of the 23 patients sensitive to the original cartoon were compared to the responses to the modified cartoon. The number of grade 4 photoparoxysmal responses (the worst grade) was 56% on the 50Hz TV and 41% on the 100Hz TV, reducing to 17% on the 50Hz and 4% on the 100Hz TV. A 100Hz TV may reduce the epileptogenic properties of mains flicker but will not protect against the epileptogenic effects of the most potent colour switching components of a cartoon. Cartoonists may need to take the colour composition into account in planning their cartoons but nothing works better than a brick. – ***MM***

Parra J, Kalitzin SN, Stroink H, Dekker E, de Wit C, Lopes da Silva FH.
Removal of epileptogenic sequences from video material. The role of colour.
NEUROLOGY
2005;64:787-91.

EPILEPSY: Neuropsychological effects of exposure to anticonvulsant medication in utero

The authors contacted 547 women attending epilepsy clinics, of whom 219 agreed to participate in the study and 163 women had 256 children between the ages of 6 and 16. Of these, 249 underwent neuropsychometric assessment. Factors associated with a lower IQ were maternal IQ, exposure to valproate and more than 5 maternal seizures during pregnancy. Valproate was the only drug to show differences compared to children of women not exposed to AED. Verbal IQ of the 41 children born to mothers taking valproate was 84(77-89) compared to 94(90-99) for the 52 children born to women taking carbamazepine. Of valproate children 22% had VIQ<69 compared to 4-6% in the other groups. Polytherapy had no effect in this study, unless it included valproate, which differs from other studies. The results add to the authors' previous findings in a younger cohort also with a selective verbal IQ deficit attributable to valproate - making this trend increasingly worrying to those of us who regularly find that valproate is the only drug that works for some women. Apparently testosterone has selective effects on right and left hemisphere development; enhancing right and inhibiting the left. Valproate-induced rises in testosterone levels could in theory cause differential developmental effects through this mechanism. - ***MRAM***

Vinten J, Adnab N, Kini U, Gorry J, Gregg J, Baker GA for the Liverpool and Manchester Neurodevelopment Study Group.
Neuropsychological effects of exposure to anticonvulsant medication in utero.
NEUROLOGY
2005;64:949-54.

EPILEPSY: More tea vicar?

Ginseng contains a variety of ginsenosides, in the leaves, stems and roots. The proportion of the different types varies between plants; American ginseng (Panax quiquefolius) has a lower Rg1/Rb1 ratio than Asian ginseng (Panax ginseng). Rg1 is said to have excitatory properties and Rb1 inhibitory properties so in theory American ginseng is more likely to have antiepileptic effects. A variety of concentrated ginsenosides, with differing concentrations of key components such as an extract of Rb1, were given to rats before having seizures induced by pilocarpine, kainic acid or pentylenetetrazole (PTZ). The Rb1 extract was given in different doses. The latency to seizure onset was prolonged and seizure duration shortened in PTZ preparations by Rb1 in a dose-dependent manner. Mortality of the animals was reduced from around 30% to zero at higher doses of Rb1 and other ginsenosides also had a beneficial effect. Dose dependent changes were also seen with Rb1 in kainate preparations. In the pilocarpine animals Rb preparations improved various parameters. There was a dramatic reduction in heat-shock protein expression in treated animals, a measure of brain stress. Mortality was increased by unselected extracts of roots or leaves from American ginseng, when compared with control untreated animals. These have a lower proportion of Rb ginsenoside. So when the vicar comes to tea, find out what sort of epilepsy he has before you offer the ginseng. - ***MRAM***

Xiao-Yuan Lian, Zhi-Zhen Zhang and Janet L Stringer.
Anticonvulsant activity of ginseng in seizures induced by chemical convulsants.
EPILEPSIA
2005;46:15-22.

Market Researchers make Increasing use of Brain Imaging

Although it is now more than thirty years since EEG was first used to evaluate viewer responses to television commercials[1] and a decade since the introduction of fMRI, it is only in the past eighteen months or so that one has started to hear the unmistakeable rumble of an approaching band wagon! The name of that bandwagon is Neuromarketing.

Hailed by some leading market researchers as the most important advance in their industry for a century it has also been dismissed by sceptical neuroscientists as verging on a pseudo-scientific scam. A recent editorial in *Nature Neuroscience*, for example, suggested that many cognitive scientists who had watched colleagues in molecular science grow rich were now 'jumping on the commercial bandwagon,' adding that, "According to this view, neuromarketing is little more than a new fad, exploited by scientists and marketing consultants to blind corporate clients with science." *

That interest in Neuromarketing is growing rapidly is beyond doubt. A recent edition of the trade publication Admap (May 2005) gave over almost an entire issue to the subject, the Market Research Society's conference earlier in the year devoted a substantial section to the topic while the ESOMAR Congress, a world association of research professionals, due to be held in Cannes this September, is presenting several key-note papers on the subject. It has been reported that eight new fMRI facilities, intended for Neuromarketing rather than medical purposes, have opened over the past twelve months in the United States.

While the first use of fMRI as a marketing tool was reported by Gerry Zaltman of Harvard towards the end of the 1990's[2] the term 'Neuromarketing' was only coined by Professor Ale Smidts in 2002 and it was not until 2004 that the first ever Neuromarketing conference was held at Baylor College of Medicine in Houston.

Of the three brain-imaging techniques currently used in Neuromarketing - fMRI (Functional magnetic resonance imaging), QEEG (Quantitative electroencephalography) and MEG (magnetoencephalography) - it is fMRI which has captured the greatest interest among market researchers and enjoyed the widest publicity in the general and marketing trade press.

The piece of research most frequently cited in this context concerns the use of fMRI to investigate the impact of brand perception on consumer taste preferences conducted at the above mentioned Baylor College of Medicine. In this study researchers repeated the famous Pepsi/Coca-Cola blind taste test challenge while scanning the brains of volunteers. When ignorant of which beverage they were sampling, the subjects favoured Pepsi with their scans revealing activation of the ventromedial prefrontal cortex (a reward centre). When aware of which brand they tasted, however, the scans revealed activity in the hippocampus, midbrain and dorsolateral prefrontal cortex - areas associated with memory, emotions and emotional information processing. This led the researchers to conclude that a preference for Coke is more influenced by the brand image than by the taste itself.[3]

Other studies have used brain-imaging to evaluate video clips and TV advertisements, study decision making among shoppers and even to investigate the likely impact of political advertising during the recent presidential election. An unpublished study at the University of California, Los Angeles, for example reported differences in the neural responses of Democrats and Republicans to commercials depicting the 9/11 terrorist attacks.

MEG has also been used for Neuromarketing purposes, albeit to a far lesser extent. In one study, it was used to measure decision making among consumers in a 'virtual' supermarket. The authors reported that the right parietal cortex became active only when faced with a preferred brand and concluded that this region was involved in making conscious decisions about shopping choices, and, perhaps, for "more important life choices too."[4]

When it comes to QEEG, we must declare an interest since we are both directors of Neuroco, a newly formed company specialising in the application of this technology for commercial purposes. Among the numerous projects for which we have used QEEG over the past twelve months were; analysing the responses of viewers to television commercials and other forms of advertising, exploring the effects of looking at happy or sad facial expressions, exploring the mental states of motorists dri-

David Lewis, BSc(Hons) D.Phil has been working in the field of QEEG since the late 80's, following an interest which began when he was in the Department of Experimental Psychology at the University of Sussex. He is currently research and development director of Neuroco, a recently established Neuromarketing research consultancy. He is co-author (with Darren Bridger) of The Soul of the New Consumer: Authenticity – What We Buy and Why in the New Economy.

Darren Bridger BSc(Hon) is associate director of Neuromarketing at Neuroco.

* Brain Scam? *Nature Neuroscience* Vol.7. No. 7. July 2004, page 683.

Subject wired and carrying a Track-it ambulatory EEG in Lakeside shopping centre, Essex.

Subject wearing electro-cap behind the wheel of her car during a study of brain activity and driver stress.

ving against a deadline and examining how people react to an unexpected 'freebie'.

We believe that QEEG rather than fMRI or MEG is most likely to emerge as the technology of choice in Neuromarketing, since it is simpler and less expensive to use and enables recordings to be made in a wide range of natural environments.

Although spatial resolution is poor, it is capable of producing a continuous record of ongoing neuronal activity. Furthermore it is backed by more than 2,500 research papers published in peer reviewed journals going back more than two decades.[5,6,7,8]

Clearly there are many pitfalls awaiting those who fail fully to appreciate the inevitable limitations of all brain imaging technologies when used for market research rather than medical diagnosis. Tempted by unscrupulous 'specialists' who dangle before them the tantalising prospect of being able to 'read' the mind of consumers, even cynical advertising and marketing executives may be persuaded to part with large sums of money to little or no great purpose. This seems especially likely to happen where fMRI is used since, in our experience, non-professionals tend to be overly impressed by the images it produces and all too likely to confuse correlation with causation.

In our view QEEG, when used in conjunction with other qualitative research methods, can provide insights into consumer choices which would not otherwise come to light. In some instances it may be that these cannot be articulated, no matter how skilled the interviewer or how co-operative the subject, because they operate below the level of conscious awareness. In other cases the very act of acquiring information may interfere with the cognitions researchers are attempting to measure. This happens when, for example, people are instructed to move a so called 'interest' lever to indicate which parts of the screen has caught their attention while watching TV commercials.

The use of brain-imaging will never enable marketing professionals to discover that Holy Grail of market research, a 'buy button' - some mythical region of the brain which need only be stimulated to compel consumers to purchase a product whether or not they actually want to do so! It will never be found because, of course, it does not exist!

More realistically, we believe, Neuromarketing offers the prospect of gaining a better understanding of how the brain responds in a wide variety of everyday situations. In addition to proving of great commercial value such research offers the possibility of increasing our knowledge of brain function among a non-clinical population as it extends powerful medical technologies into a new and challenging area of research.

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News Review: Once daily treatment for Parkinson's disease

Azilect 1mg (rasagiline) has been launched in the UK by Teva and Lundbeck for use as monotherapy in early Parkinson's disease (PD) and as adjunctive therapy in moderate to advanced disease. British and German doctors are the first in Europe to be able to prescribe Azilect, a potent, second-generation, highly selective, reversible inhibitor of monoamine oxidase-B (MAO-B).

In patients with early PD, Azilect alone significantly improves the cardinal symptoms of tremor and bradykinesia, and demonstrated significant quality of life benefits when compared to placebo.

Results from a 26-week, randomised, double-blind multi-centre Early Monotherapy for Parkinson's disease Outpatients (TEMPO) study, involving 404 patients, showed that patients taking Azilect maintained their baseline total Unified Parkinson Disease Rating Scale (UPDRS) score, while patients taking placebo experienced a 4.2 UPDRS decline in score. Furthermore, patients taking Azilect in the TEMPO study benefited from a 2.91 point PD-QUALIF (Parkinson's Disease QUAlity of LIFe) score advantage over patients taking placebo.

When used as adjunctive therapy for patients with moderate to severe PD, who are optimised on levodopa and other PD treatments such as dopamine agonists and entacapone, Azilect provides significant additional therapeutic benefits by reducing 'off' and increasing 'on' time with most of the 'on' time without troublesome dyskinesias.

In another 26-week, randomised, double-blind placebo-controlled trial, involving 472 patients with more advanced disease, Azilect decreased 'off' time significantly: by 1.85 hours daily in patients treated with Azilect 1mg and by 1.41 hours in patients taking a daily 0.5mg dose. Patients enrolled in the PRESTO study (Parkinson's Rasagiline: Efficacy & Safety in the Treatment of Off) were already optimised on levodopa and other concomitant anti-parkinsonian medications, but were nevertheless experiencing at least 2.5 hours of daily 'off' time.

The second of the adjunct studies, LARGO, compared Azilect 1mg and the catechol-O-methyl transferase (COMT) inhibitor entacapone (200 mg with every levodopa dose) with placebo. The results demonstrated that once-daily Azilect 1mg is as effective as multi-dose entacapone in reducing total daily 'off' time. The 687-outpatient LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily) study showed that Azilect and entacapone reduced mean 'off' time by 1.18 and 1.2 hours respectively compared with placebo.

Additional benefits of Azilect include its once-daily dosing, lack of titration and tolerability in patients of all ages. In particular, Azilect is associated with a low incidence of side-effects such as hallucinations, oedema, somnolence and orthostatic hypotension that often limit treatment with agents such as dopamine agonists.

For more information, contact Teva Pharmaceuticals Medical Information on 01296 719768 or use ACNR's reader enquiry service.

A Sideways Look at Life

Carl Zeiss is bringing a novel microscope system to the marketplace that will provide researchers with a fascinating new insight into imaging living organisms. The company has signed a licensing deal with EMBLEM Technology Transfer GmbH, the commercial entity of the European Molecular Biology Laboratory (EMBL) to commercialise a new technology called SPIM (Selective Plane Illumination Microscopy).

SPIM produces detailed three-dimensional films of the inner workings of living organisms by eliminating a traditional microscopy problem – vertical resolution along the lightpath. In SPIM, the specimen is passed through a thin sheet of light originating from the side of the instrument and images captured layer-by-layer. The specimen may be rotated and viewed along different planes, eliminating the fuzzy and unwanted light that has prevented scientists from looking deep into tissues.

SPIM allows specimens to be imaged within a liquid-filled chamber. This means that specimens can be kept alive and enables researchers to track changes during developmental processes, such as organ formation in zebrafish or other model organisms. The imaging process is very rapid and post-processing software assembles one or more stacks of images into a high-resolution movie file.

For more information Tel: 01707 871233.

Somatom Sensation 40 reports initial results

The world's first Somatom® Sensation 40 computed tomography (CT) scanner was recently installed at the radiology department of Alamance Regional Medical Centre (ARMC), U.S. Siemens z-Sharp™ technology is said to deliver, in the clinical routine, unprecedented image quality and the industry's highest isotropic resolution of below 0.4 millimetre voxel size for the 40 slices per rotation.

The proprietary z-Sharp technology utilises an accurately and rapidly deflected electron beam creating two alternating and overlapping X-ray projections reaching each detector element that doubles scan information without a corresponding increase in dose. The result is a substantially enhanced spatial resolution and image quality, establishing z-Sharp technology as a new benchmark for diagnostic excellence, as proven by the 250 installations of the SOMATOM Sensation 64 systems.

For more information Tel: 01344 396317.

New initiatives for better access to life-saving thrombolysis

At the recent European Stroke Congress, stroke specialists were introduced to new initiatives such as telemedicine and the ACT NOW 'Stroke Lysis Box' which are allowing an increasing number of acute stroke victims to receive life-saving thrombolysis treatment.

Only 30% of patients with acute ischaemic stroke arrive at hospital within the first three hours. However, studies have shown that thrombolysis with a clot-busting drug (rtPA - alteplase), administered within three hours of the onset of symptoms of ischaemic stroke, significantly improves clinical outcome at three months.

Telemedicine involves an expert stroke physician in a specialist stroke centre, linked to non-specialist centres in a telemedicine network. The expert physician can support the caring physician in diagnosing a stroke and assessing acute stroke victims for treatment. Remote patient interviewing, data transmission and videoconferencing are available 24 hours a day to all hospitals in the telemedicine network.

The 'Stroke Lysis Box' helps in another way. It enables hospital emergency departments to provide rapid clot-busting treatment to appropriate acute stroke victims and is extending the availability of thrombolytic treatment to trained physicians in a wider range of hospitals than stroke centres.

For more information contact the ACT NOW secretariat on 020 7309 1029.

Neuroscience antibodies from Abcam

Abcam's neuroscience antibody range includes over 1500 reagents covering: neuronal markers, neurodegeneration, neurotransmission, growth & development, sensory pathways and more.

Online neuroscience resources

Abcam's Neuroscience 'abwire' (www.abcam.com/neuroscience) has been developed to help customers browse the entire antibody range. The 'abwire' is regularly updated with new neuroscience protocols, exclusive articles, conference information and improved data. You are also invited to explore Abcam's Neuroscience antibody locator to track down the synaptic, neuronal or neuronal environment products on offer.

Recent focus – new IHC data for key antibodies

Abcam's Neuroscience team have been hard at work testing many of their best selling neuronal marker antibodies in IHC. These reagents are now known to work well in a wide range of applications. For new images, revised working dilutions and the recommended protocols for many neuronal marker products go to the 'abwire' (www.abcam.com/neuroscience) for the IHC Galleries.

For more information contact Dr Rhian Hayward, Abcam Ltd, 332 Cambridge Science Park, Cambridge CB4 0FW, Tel: 01223 472030, Email: rhian.hayward@abcam.com

Instrumentation & equipment for life sciences research

Bilaney Consultants are based in the UK and Germany and supply quality pre-clinical research equipment and software to life scientists and biomedical researchers in Europe.

Coulbourn Instruments: Habitest modular animal behaviour test systems and Graphic State control and data acquisition software. Animal Startle, Tru Scan Photo Beam Activity Monitoring, Modular systems for Psychophysiology and Human Startle.

Actimetrics: Video based behaviour acquisition/analysis systems - FreezeFrame, WaterMaze, LimeLight, and Big Brother. ClockLab circadian biology acquisition/analysis system.

Plastics One: Pre-clinical research components. Standard and custom made cannula and electrode systems.

Kopf Instruments: Stereotaxic systems and Pipette pullers.

ISI ResearchSoft Bibliographic Software: EndNote, Reference Manager and ProCite.

For more information, contact Bilaney Consultants Ltd, St Julians, Sevenoaks, TN15 0RX. Tel: 01732 450002, Email: info@bilaney.co.uk, www.bilaney.com

First dynamic examinations of the cervical spine

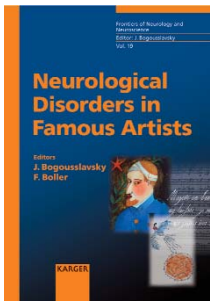
NeuroSwing is the new positioning and movement system for dynamic magnetic resonance (MR) imaging examinations of the cervical spine. The system was developed by Hightech Electronic GmbH in cooperation with Siemens Medical Solutions. The continuously variable, smooth movements of the NeuroSwing enables, for the first time, dynamic MR acquisitions of the cervical spine to be performed in anteflexion, retroflexion, lateral flexion and rotation, either separately or in combination.

Approximately 30% of all MR examinations are neurological and orthopaedic acquisitions of the cervical spine. Acquisitions of the cervical spine in motion and functional examinations were difficult to perform. Study results have shown that 50% of all lesions can only be displayed correctly in dynamic examinations, during motion or in multiple, varied positions. One of every ten static examinations produces no results.

NeuroSwing provides the ability to perform dynamic imaging of the cervical spine in daily routine diagnostics. All cervical spine movements relevant to the examination can be realised with a single device, without retrofitting or repositioning the patient. As a result, lesions or functional limitations near the cervical spine can be detected quickly and easily.

For more information, visit www.siemens.co.uk/medical

Fascinating insights into the relationship between brain disease and creativity



Neurological Disorders in Famous Artists: Frontiers of Neurology and Neuroscience, Vol. 19 has been published by Karger.

The study of how a neurological disorder can change the artistic activity and behaviour of creative people is a largely unexplored field. This publication looks closer at famous painters, writers, composers and philosophers of the 18th to the 20th centuries who suffered from neurological diseases such as stroke, epilepsy, brain trauma and dementia. The diseases of Van Gogh, Ravel, Poe, Kant, Haydn and many more are diagnosed in retrospect and treatment options according to modern medical technologies are discussed.

Presenting fascinating insights into the relationship between brain disease and creativity in famous minds, this publication is highly recommended to neurologists, psychiatrists, physicians as well as to everybody interested in art, music and literature.

Editors: J. Bogousslavsky; F. Boller; ISBN 3-8055-7914-4, CHF 109.50/EUR 78/USD 99.75

For more information Email: a.gasser@karger.ch or see www.karger.com

Flexible dosing with Lyrica® is effective in relieving chronic peripheral neuropathic pain

Tailoring of Lyrica® dosage to suit patients' individual needs may help to achieve an optimal efficacy/tolerability balance. Flexible dosing with Lyrica® (pregabalin) is as effective as fixed dosing in reducing the pain experienced by patients with painful diabetic peripheral neuropathy (PDN) and post-herpetic neuralgia (PHN), according to research published in Pain.

Results from the patients' pain scores demonstrated that the mixed group of PDN and PHN patients responded well to both fixed and flexible dosing regimens. Approximately 50% of patients experienced a ≥50% pain score reduction on either treatment regimen, a clinically significant improvement, compared with 24% of the placebo group. The study also demonstrated that both the fixed and flexible dose regimens were significantly superior to placebo in improving sleep-interference.

Dr Barbara Hoggart, a Consultant in Pain Management at the Heart of England NHS Foundation Trust, commented, "As demonstrated by this study, not all patients need high doses of pregabalin to achieve meaningful improvement in their pain. With tailored, flexible dosing the incidence of adverse events and discontinuation of therapy may decrease."

For more information contact Pfizer Ltd on Tel: 01737 331264.

Consensus statement backs the use of Abilify in treating schizophrenia

The atypical antipsychotic, Abilify® (aripiprazole) is efficacious and well tolerated in the treatment of schizophrenia, according to new guidelines on best practice prescribing.

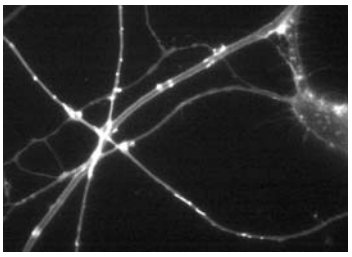
The guidelines, published in the International Journal of Clinical Practice, were drawn up by a number of leading UK psychiatrists. Lead author Dr Mike Travis from the Institute of Psychiatry in London said, "Abilify was launched in the UK last June. These guidelines provide practical guidance on how to optimise outcomes in patients using Abilify and recommend its use in clinical practice, particularly as a choice for patients for whom potential side effects such as weight gain may be barriers to long-term treatment and for patients or clinicians who are dissatisfied with current treatment."

Abilify is the first available antipsychotic of a new generation. It is effective in long-term treatment of both positive, negative and cognitive symptoms of schizophrenia.

The new guidelines, drawn up by the Schizophrenia Innovation Working Group, provide a summary of the efficacy and tolerability of Abilify as seen in clinical trials and a naturalistic study.

For more information contact Bristol Myers Squibb Pharmaceuticals on 020 8754 3519.

Seeing living cells in a whole new light



Nikon have launched three new illumination options for the TE2000 inverted microscope. TIRF2, W-TIRF and PA-GFP attachments create scope to undertake an even wider range of research level fluorescence applications - including the unique Surface Reflection Interface Contrast (SRIC) to study the surface condition of a specimen.

Unifying the TIRF and epi-fluorescence systems in a single layer, TIRF2 provides more flexibility for combination with other equipment such as optical tweezers. TIRF2 widens the range of application bases for the TE2000 from simple epi-fluorescence to intricate observation of living cells at the molecular level. Single molecular activity in contact with the surface of the coverglass can easily be captured.

Researchers using W-TIRF can achieve high performance epi-fluorescence using the TIRF illumination technique more affordably than ever. Utilising mercury, xenon, metal halide or high intensity halogen, illumination costs can be kept to a minimum without compromising quality, thanks to the superior quality of Nikon's optics.

For more information Email: discover@nikon.co.uk

DR. ALOIS ALZHEIMER

Aricept Significantly Improves Behavioural Symptoms[1-3]

Compared to untreated AD patients

Aricept® donepezil hydrochloride

BEFORE HIM,
THE DISEASE DIDN'T HAVE A NAME

BEFORE ARICEPT,
IT DIDN'T HAVE A REALISTIC TREATMENT

Aricept® donepezil hydrochloride

CONTINUING COMMITMENT TO ALZHEIMER'S

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

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