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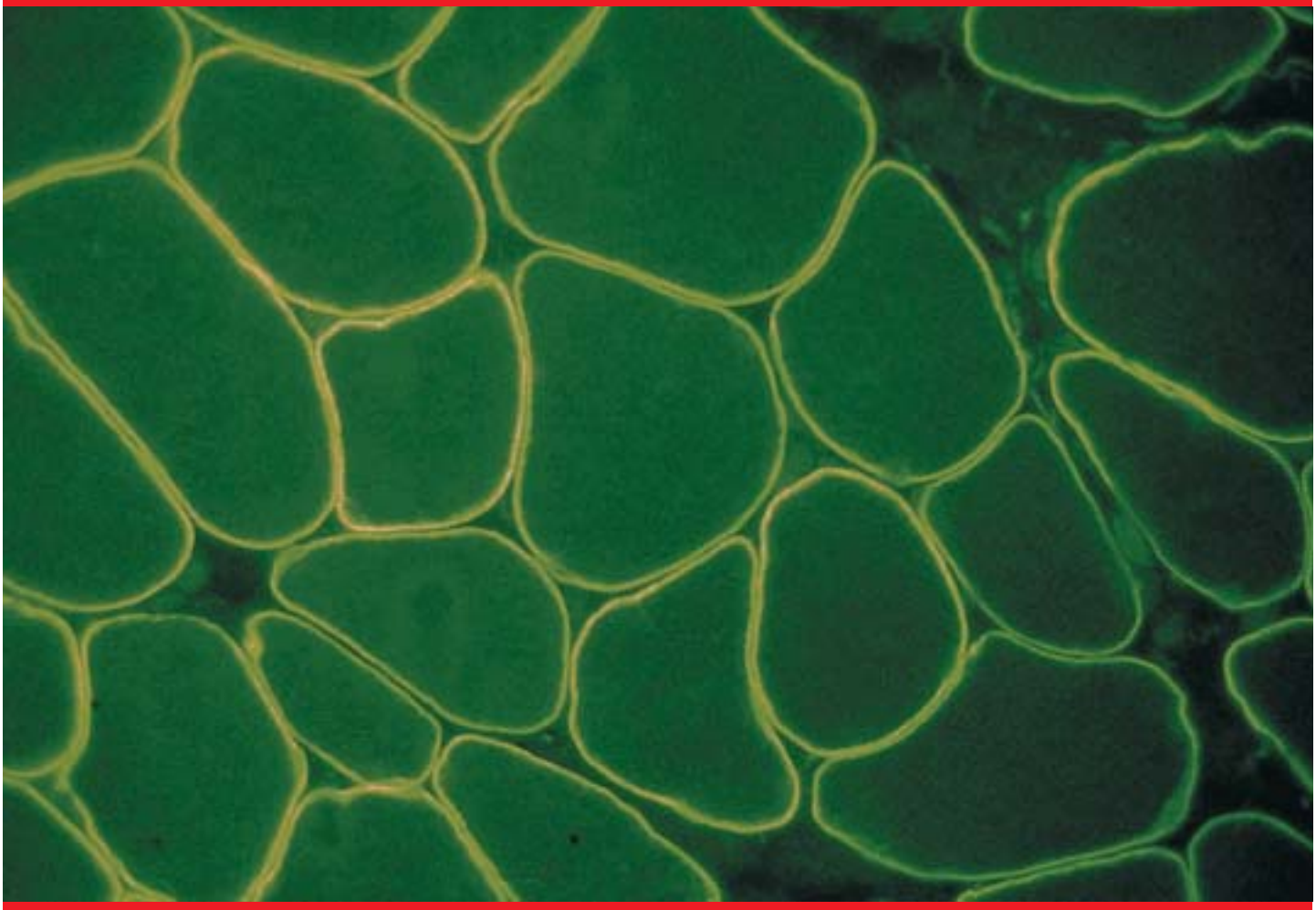
ACNR

Advances in Clinical Neuroscience & Rehabilitation



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

Review Articles: Genetic studies of Parkinson's disease; The functional organisation of the basal ganglia
Management Topic: Metabolic myopathies
Rehabilitation Article: Intrathecal Baclofen in the management of spasticity due to cerebral palsy

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Date of Preparation: August 2002.

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contents

september/october 2002

Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing.
Voltaire (1694 - 1778)

Perhaps more than in any other field of medicine, clinical neurology both depends upon and informs the basic sciences. This edition of ACNR provides plenty of illustrations. John Hardy and Melissa Hanson (Laboratory of Neurogenetics, National Institute on Aging, US) give an authoritative description of the current understanding of the genetics of Parkinson's disease: a research area that has blossomed with the advent of molecular genetics but which in turn is asking questions of the movement scientists. And Roger Barker, editor of the ACNR, summarises the current understanding of the circuitry of the basal ganglia, which builds upon observations from patients with movement disorders, as well as providing a rational framework for their treatment. Dipankar Nandi and Tipu Aziz (Oxford Movement Disorder Group) describe their experience of operating on four patients with multiple sclerosis for tremor, which may depend for its success on accurate pre-surgery tremor evaluation and local field potential recording from deep brain nuclei close to the deep brain stimulation electrode. Wojtek Rakowicz (former fellow of the Neuromuscular Diseases Center, Washington) continues our series on muscle disorders where Gillian Hall left off (to take up her maternity leave, for which many congratulations!). He describes the clinical features that differentiate biochemical disorders of muscle. The anatomy section describes the foramen magnum, where our understanding of the anatomy remains inadequate to explain clinical observations made over sixty years ago. And Michael Vloeberghs (Nottingham) illustrates the pragmatic end of clinical science as he describes the issues around setting up a state-of-the-art service for treating children with spasticity. Finally, in our review of the recent clinical neuroscience literature, we highlight a paper on "limbic touch": a provocative study of a patient with a unique neurological disorder that allows basic issues around sensation and perception to be explored.

The mutual dependence of clinical neurology and neuroscience underlies our decision to add 1600 full members of the British Neuroscience Association to our mailing list, which will bring our total circulation to 4,800 in the UK. Welcome to our new readers! Please tell us what you would like to see in the journal; if you have any advice on potential topics or authors, please let us know.

Alasdair Coles,
co-editor

Features

Cover picture courtesy of Manson Publishing - see book review on page 36

Regulars

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Date of preparation: August 2002.

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

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Genetic studies of Parkinson's disease

Parkinson's disease is a neurodegenerative disorder characterised by bradykinesia, resting tremor, rigidity, and postural instability. The disorder results from degeneration of neurons within the substantia nigra, creating a deficiency in dopamine-mediated movement.[1] About 50-60% of the substantia nigral neurons can be lost without obvious clinical consequence.[2] It was previously thought that Parkinson's disease had little or no genetic component, however, in the last several years there has been a large focus on genetic approaches to identify loci and genes involved in Parkinson's disease. Genetic studies involving familial parkinsonism have advanced our molecular understanding of selective degeneration of dopaminergic neurons in the midbrain. Thus far, eight loci have been identified from family linkage studies for parkinsonism; these include:

- Park 1 (alpha synuclein; 4q21-23)
- Park 2 (parkin; 6q25.2-27)
- Park 3 (2p13)
- Park 4 (4p14-16.3)
- Park 5 (UCH-L1; 4p14)
- Park 6 (1p35-p36)
- Park 7 (1p36)
- Park 8 (12p11.2-q13p.1)

The A53T mutation of the alpha synuclein gene is rare and originally described in an Italian kindred (the Contursi kindred) but has been found in other kindreds originating from Greece.[3,4] PD in these families phenotypically includes rigidity, hypokinesia, postural instability and resting tremor with a positive response to levodopa therapy and may be associated with cognitive decline, severe central hypoventialation, orthostatic hypotension, myoclonus and urinary incontinence.[2,5] Another mutation in the alpha synuclein gene, A30P was identified in one German family in a highly conserved genomic region with clinical features including all four cardinal PD signs (resting tremor, bradykinesia, postural instability, and rigidity).[5] Genetic studies have failed to find many families with the A53T or A30P mutations. More generally, alpha synuclein has been found to be the major component of Lewy bodies in more common sporadic PD; and has been shown to be one of the principal components of glial and neuronal cytoplasmic inclusions and the Lewy body like inclusions in synucleinopathies.[7]

Parkin (Park 2) has become an important gene for further research. This gene includes 12 exons and encodes for an E3 ubiquitin protein ligase involved in the ubiquitin proteasomal degredation pathway. Parkin mutations are prevalent; 50% of early onset, familial European PD cases and as many as 18% of sporadic, early onset PD cases are attributed to Parkin.[8] Parkin was first described in autosomal recessive juvenile parkinsonism (ARJP) cases. Clinically the phenotype of parkin is very broad, individuals with parkin mutations commonly have atypical features including dystonia at onset, hyperreflexia, diurnal fluctuations, and sleep benefit.[9] Additionally, positive parkin cases with typical PD symptoms and older age of onset have been identified (>45 years).[8] Problems with the preliminary data of parkin were due to low amounts of sequencing performed on the parkin coding exons; currently the spectrum of parkin now involves at least 60 different mutations.[2] Several parkin substrates have been identified and are being followed increasing the focus on the ubiquitin-proteasome pathway and its role in familial and sporadic PD.

Recent reports on Park6 and Park7 suggest that gene mutations on chromosome 1p may account for a proportion of early onset Parkinson's disease. Park6, located on Chromosome 1p35-36 was first discovered in a large Italian kindred (Marsala Kindred). The phenotype of this family includes early disease onset (32-48 yrs), levodopa responsiveness, slow disease progression, and levodopa therapy associated dyskinesias.[10] Signs reported in autosomal recessive juvenile parkinsonism (ARJP) such as dystonia and sleep benefit are absent in the Marsala kindred. After initial reporting of the kindred, an additional eight families with Parkin negative ARJP from four different European countries were confirmed to have linkage to Park6.[11] The phe-

Authors

John Hardy is Professor of Neuroscience at University College, London, and also Chief of the Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland, US. His awards include the Allied Signal Prize for Research into Aging, and The MetLife Prize for Research into Alzheimer's disease. He has written over 260 original articles in refereed journals

Melissa Hanson is a clinical research co-ordinator for the Laboratory of Neurogenetics, NIA. She received her Bachelor of Science degree from the University of Florida in Zoology with a minor in Chemistry. She is currently working on her Masters of Science degree at Johns Hopkins University in Biotechnology. She works to recruit study participants and collect clinical data for laboratory studies, which include movement disorders, dementia and stroke.

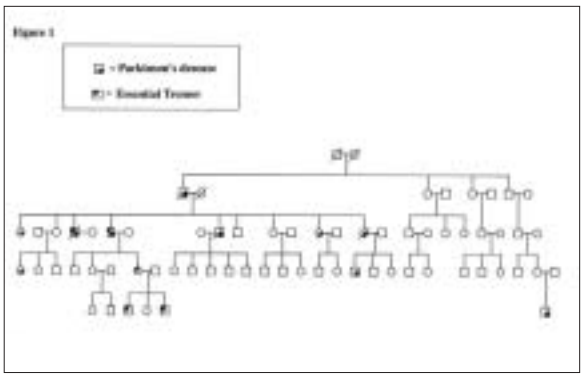
Gene	Chromosome Location	Clinical Diagnosis	Inheritance Pattern	Levodopa Responsive	Asymmetry	Resting Tremor	Dementia	Pathology
Park1 Alpha synuclein (A53T)	4q21-23	PD DLBD	AD	Y	Y	Y	Y	PD, DLB
Park1 Alpha synuclein (A30P)	4q21-23	PD	AD	Y	Y	Y	Variable	PD
Park2 Parkin (deletions or point mutations)	6q25.2-27	PD, dystonia	Variable; mostly recessive	Y	Variable	Variable	N	Neuronal loss in pigmented neurons (one lewy body report)
Park3	2p13	PD	AD, reduced penetrance	Y	Y	Y	Variable	PD
Park4	4p14-16.3	PD	AD, reduced penetrance	Y	Y	Y	Y	PD, DLB
Park6	1p35-36	PD	AR	Y	Y	Y	N	NA
Park7	1p36	PD	AR	Y	Y	Y	N	NA
Park8	12p11.2-q13.1	PD	?, possibly AD	Y	Y	Y	N	NA

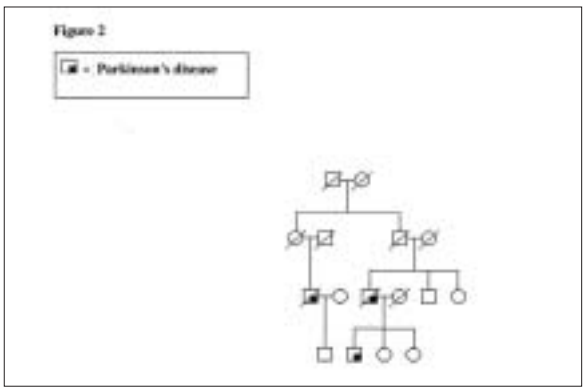
notypes from these eight families overlap with that reported for European parkin cases, including a wide range for age of onset and additionally show slow progression of the disease. A second locus also located on chromosome 1 involved in autosomal recessive early onset parkinsonism, Park7, was discovered in a consanguineous family from an isolated community in the SW region of The Netherlands. The clinical phenotype of this family includes early onset parkinsonism and shows response to both levodopa and dopamine agonist therapy and slow progression of the disease.[12] Park 7 is 25cM telomeric to Park 6. Phenotypes of Park 6 and Park 7 are similar, however, focal dystonia appears as a symptom in Park 7 familial case.

Park 8 was mapped to Chromosome 12p11.2-q13.1 using linkage analysis in a large Japanese family with autosomal dominant PD. Clinical features are comparable to idiopathic PD including favourable response to dopaminergic agents. Neuropathological examination in four cases interestingly showed nigral degeneration without lewy bodies.[13] No other families have been found with the Park 8 locus to date. The Park 8 region contains several relevant genes and varies from any known hereditary PD locus.[13]

Genetics has revolutionised neurological research; our understanding of Parkinson's disease has been better characterised as a result of familial parkinsonism studies. In the future genetic studies will continue to expand our knowledge of parkinsonism and other neurodegenerative diseases and will be key in characterising the biochemical pathways of neurological diseases, which will help to pinpoint therapeutic targets and direct gene-environment interaction studies.

The Laboratory of Neurogenetics (NIA) studies familial cases of parkinsonism and other movement disorders. We would be interested in collaborative efforts in cases with a strong family history of disease or early age of disease onset (<50 years). Examples of families we collect or would be interested in collecting are shown in Figures 1 and 2. Please contact Dr. John Hardy to discuss collaborations or direct interested participants to contact Melissa Hanson.





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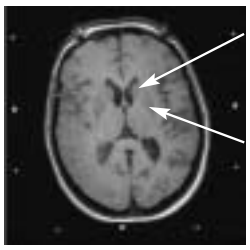
The functional organisation of the basal ganglia

Roger Barker

The **basal ganglia** are made up of a number of subcortical structures that includes the **caudate and putamen** (forming the **neo- or dorsal striatum), the internal and external segments of the globus pallidum (GPi and GPe respectively), the pars reticulata and compacta of the substantia nigra (SNr and SNc respectively) and the subthalamic nucleus (STN).** The neostriatum is the major receiving area of the basal ganglia and receives information from the whole cortex as well as the intralaminar nuclei of the thalamus and a dopaminergic input from the SNc. The major outflow from the basal ganglia is via the GPi and SNr to the ventroanterior and ventrolateral (VA-VL) nuclei of the thalamus which in turn project to cortical areas anterior to the primary motor cortex. In addition there is a projection to the brainstem, especially to the pedunculopontine nucleus (PPN) which may be important in locomotion, and the superior colliculus which is involved with eye movements.

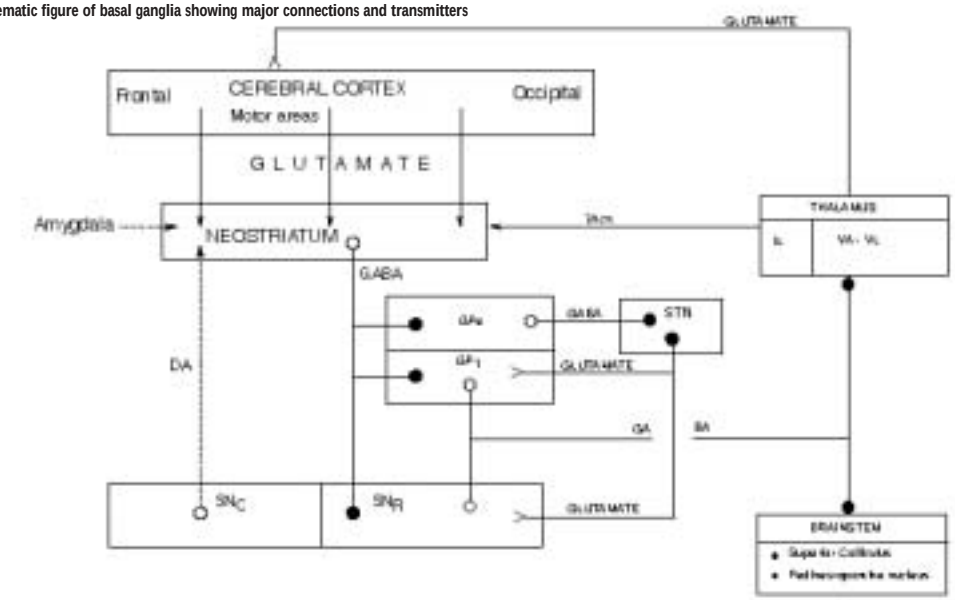


The anatomy of the basal ganglia is complex and the schematic figure is a simplification of their organisation. However a number of points on the anatomical organisation of the basal ganglia need to be made.

1. The neostriatum receives from the whole cortex and intralaminar nuclei of the thalamus as well as a modulating dopaminergic input from the SNc.
2. The basal ganglia have a number of loops within them that are important. There is a striato-nigral-striatal loop with the latter projection being dopaminergic in nature. There is also a loop from the GPe to the STN which then projects back to the GPi and SNr. This pathway is excitatory in nature and is important in controlling the level of activation of the inhibitory output nuclei of the basal ganglia to the thalamus.
3. Whilst there is a marked degree of convergence and divergence of projections throughout the basal ganglia, these can be seen to form parallel pathways, which at the most simplistic level divide into a motor pathway through the putamen and a non-motor pathway through the caudate nucleus.
4. The neostriatum consists of patches or striosomes that are deficient in the enzyme acetylcholinesterase (AChE), these are embedded in an otherwise AChE rich striatum which forms the large extrastriosomal matrix. The relationship of these two components of the neostriatum to any parallel pathways is not clear.
5. There is a ventral extension of the basal ganglia that consists of the ventral striatum (nucleus accumbens), ventral pallidum and substantia innominata (NOT shown in figure for simplicity). It receives a dopaminergic input from the ventral tegmental area that lies adjacent to the SNc in the midbrain, and projects via the thalamus to the prefrontal cortex and frontal eye fields. This part of the basal ganglia is thought to be involved in non-motor functions.
6. Neurophysiologically the basal ganglia take highly processed sensory information and convert it into some form of motor programme. This is supported by the clinical disorders that affect the basal ganglia.

HYPERKINETIC MOVEMENT DISORDERS	HYPOKINETIC MOVEMENT DISORDERS
Chorea Ballismus Tics	Parkinson's disease Dystonia

Schematic figure of basal ganglia showing major connections and transmitters



CLINICAL DISORDERS OF MOVEMENT ASSOCIATED WITH THE BASAL GANGLIA:
One of the simplest way to classify movement disorders associated with the basal ganglia is to consider whether they are hyperkinetic or hypokinetic:

Whilst the pathogenesis of many of these disorders remains obscure, detailed studies in Parkinson's and Huntington's disease has allowed schematic figures of pathological flow within the basal ganglia to be developed. These have proved to be important in some of the newer interventions especially from a neurosurgical point of view, although it must be realised that these figures are gross simplifications of the true disturbance of neuronal activity.

Recent new developments in basal ganglia:

- Anatomical analysis of substantia nigra suggests existence of distinct subdivisions - nigrosomes
- Pharmacological complexity of transmitters within basal ganglia has lead to exploration of novel mechanisms of therapy for dyskinesias in PD
- Cognitive and neuropsychiatric abnormalities are commonly seen with disorders of the basal ganglia

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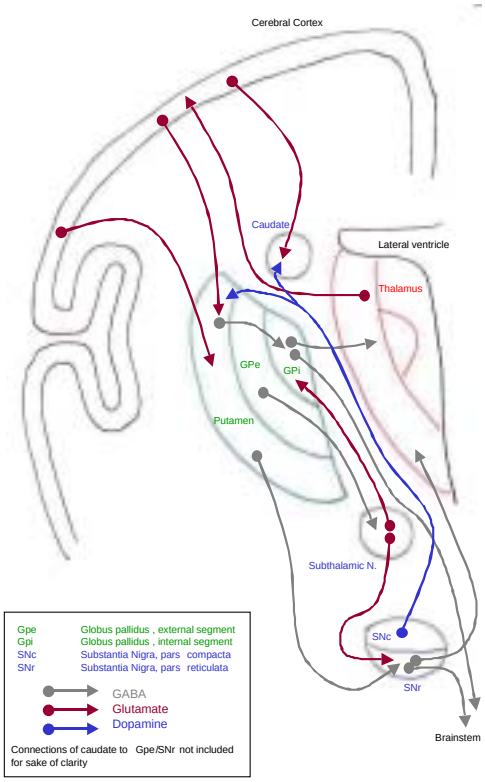

Schematic figure showing layout of major nuclei nad connections of the basal ganglia in humans.

Intrathecal Baclofen in the management of spasticity due to cerebral palsy

Introduction

This article summarises the setting up, the preliminary results and the future of intrathecal baclofen at Queens Medical Centre, the teaching hospital of the University of Nottingham.

Baclofen, a derivative of diazepam was originally developed in the 1920s as an anticonvulsant. The anticonvulsant action proved to be disappointing, but the effect on spasticity of spinal and cerebral origin was noted. Baclofen, in its oral form, became a drug of relevance to rehabilitation. Oral doses vary and so do the side effects. The effect of oral baclofen is generally paired with gastro-intestinal side effects and drowsiness, effects that occasionally outweigh the benefit. Intrathecal delivery of baclofen was initially done by means of single lumbar puncture. The effect of intrathecal baclofen was noted along with the low dose required to relieve the spasticity, but single lumbar puncture is not a comfortable means for chronic delivery. In the eighties reliable drug-delivery systems became available and intrathecal infusion of a variety of drugs eg morphine, methotrexate and baclofen became effective.

Over the past 20 years Intrathecal baclofen (ITB) has gained a steady foothold in the management of spastic disability. The indications vary and include, in decreasing order of importance spasticity due to spinal cord injury, Multiple Sclerosis, stroke and head injury. Baclofen is a Gamma Amino Butyric Acid (GABA) agonist, which is an inhibitory neurotransmitter for the CNS. Baclofen enhances this effect, particularly in the spinal cord, but more widespread effects in the CNS are noted.

Author

Michael Vloeberghs trained in general medicine surgery at the Vrije Universiteit Brussels, Belgium. He then took on Neurosurgical training, partly training in the UK, specifically in Paediatric Neurosurgery. Becoming a consultant in Brussels in 1993 and was offered a position at the University of Nottingham in 1995. He is currently am a Senior Lecturer in Paediatric Neurosurgery and consultant Paediatric Neurosurgeron. His clinical practice involves only children and covers all children's Neurosurgical disorders.

ITB in cerebral palsy

Cerebral palsy affects 2-3 children per 1000. The spasticity of 7% of these children is so severe they are candidates for ITB.

Despite the available literature and proof of effectiveness for the treatment of spasticity in children, the first implants at QMC were seen to be experimental. The resistance for funding this procedure led to the writing of the ScHARR (School of Health and Related Research) report on ITB. The ScHARR group did a meta-analysis of the literature to establish an evidence base. It became clear that there was a definite benefit of ITB to spastic tetraplegic or tetraparetic patients, including children, but there is no proven benefit for diplegic patients eg ITB for gait disturbance is poorly researched and may not be indicated. This is a discrepancy with the, mostly American, literature where the effect on gait improvement is greatly emphasised. The meta-analysis showed the impact to be the greatest on nursing care, quality of life and to a lesser extent on function. This conclusion led to criteria for ITB:

1) Spastic tetraparesis or tetraplegia forms a proven benefit group for ITB and funding should be made available for these patients. This includes children who additionally must be entered in a clinical outcome study.
2) ITB can only be offered to diplegic patients in the framework of a randomised controlled trial for research purposes.

ITB in Nottingham

In order to accommodate the demand for ITB, the process has been streamlined. Once a letter of referral is received describing the neurological condition of the child, funding is sought from the health authority or PCT of origin. Children are only reviewed when the local authority has agreed funding for both the test procedure and the implant of the baclofen pump. Simultaneously, information packages are sent out to the referring clinician and the carers of the child. Once funding is agreed, a date for the baclofen test is set. The process was set up in this way to avoid crowded clinics and disappointment to the patients and their carers if funding is not available for a potentially good candidate.

The test procedure

The test procedure consists of a multidisciplinary assessment of the child eg OT, Physiotherapy and Neurosurgical during a brief admission (24-48h). The child is examined under general anaesthetic, with muscle paralysis (succinylcholine). The muscle paralysis mimics the effect of baclofen and clarifies the Orthopaedic condition of the child. Many children have fixed joint deformities, because of long-standing spasticity, which are to be treated by further Physiotherapy or Orthopaedic surgery. ITB will act on the muscle tension and can make further Physiotherapy or surgery easier, but ITB in itself has no effect on joint deformity.

During the general anaesthetic a lumbar catheter is inserted into the spinal sack. The child is then woken and transferred back to the ward. When the post-operative observations are satisfactory, a bolus dose of baclofen, approximately 30 to 50 micrograms, is given. The peak effect of baclofen can be seen four hours after injection. It is important for the carers to be with the child at that time and the child must also be handled and cared for as usual. This helps in assessing the effect of the bolus dose. The carers must also remain with the child overnight to assess the child on the morning after the test. By the next morning the effect of the baclofen will have disappeared, the child will have returned to its pre-injection state and the effect is even more noticeable to the carers. The only effect of importance to the clinician is whether there is a response to baclofen or not. Quantification of the effect of the bolus is not useful at this stage. The effect of receiving chronic ITB is not comparable to the bolus dose. The catheter is removed on the day of the test and the child is usually discharged the morning after.

Side effects of the bolus dose have been reported eg respiratory depression and meningitis, but none have occurred in this series. So far 40 test procedures have been done according to this in-house protocol. Two did not respond to the bolus dose and the baclofen test did not live up to the expectations of the carers in the latter.

We then enter a negotiation phase where the results of the examination under anaesthetic are discussed along with the effect of the bolus dose. Before embarking into an expensive and invasive procedure eg pump implant, the goals and expectations must be clearly outlined.

In summary: ITB improves nursing care, quality of life for the child and its carers. Added bonus effects are: increased interaction with the environment, improved bulbar function eg swallowing, weight gain and improved control in the upper limbs.

The implant

After the test procedure and when the expectations and goals have been determined, a date is set for the implant. The delivery system is a battery driven programmable pump. The pumps cost approximately £7000, have a battery life of 7 to 10 years and are externally programmable by means of a magnetic wand. The device is inserted through a subcostal incision in the

right flank and can be either subcutaneous or, when the child is very catabolic because of the spasticity, the device is inserted under the fascia of the abdominal muscles. A catheter is inserted into the spinal sack through a small incision over the lumbar area. The catheter is fed into the sack with a Tuhoy needle and tunneled under the skin to the location of the pump. The proximal end of the catheter is then attached to the pump. The only restriction for implanting a baclofen pump is the physical size of the child; age is not a restricting factor. However, the industrially produced drug, baclofen, is not licensed by the manufacturer for use under the age of 4 years. Because of the limited number of cases implanted at that age our local Committee for Ethics in Clinical Practice has advised that the indication for ITB in a child under the age of 4 years is a decision to be made by the clinician, in the best interest of the child. Consent for 'under 4 ITB' is separate from the regular consent for operation and the carers are to be made aware that Baclofen is not licensed in that age group.

Although there are a variety of programming modes, the children are programmed for continuous dose delivery eg the dose received over 24 hours is constant and tailored to the specific need of the child. Doses vary between 150 micrograms/24h to 550 micrograms/24h. The degree of spasticity, the aetiology of the spasticity and even more the weight and size of the child direct the daily dose.

Depending on the delivered dose, refills occur every six weeks to 3 months. Refilling of the pump reservoir is percutaneous and comparable to injecting a "Hickmann" line.

The results

Beginning of the ITB program at QMC, 10/1998
This assessment, 6/2002

All children have severe spastic tetraparesis with Ashworth score >4, with increasing nursing and care demands, compliant with the criteria. All children are entered in a clinical outcome database, which is perpetually updated.
Of the 37 implanted children 10 have mainstream cognition.

40 children assessed and tested
37 tested and implanted
11 are female, 26 male
The age range at pump implant is 2,5 years to 17 years, mean 11.8 years.

Indications

32 children have cerebral palsy due to premature birth
2 children have cerebral palsy and dystonia
1 child has dystonia of unknown origin
1 child suffered a non-accidental injury
1 child was asphyxiated by drowning

Problems

6 spontaneous lumbar catheter migrations
2 children had side effects of baclofen at low dose delivery (headache, GI problems) which were solved by decreasing the delivery dose
1 elective catheter repositioning*
1 catheter fracture
1 pressure sore over the pump leading to infection, requiring removal of the pump and replacement with a new system at later date
1 low battery alarm, leading to replacing of the pump (after 3.5 years)

No primary infections
No procedure related death or incidents related to drug delivery eg overdose

An example of a programmable drug delivery pump. The illustration shows the body of the pump with the spinal catheter connected to it.

*The elective repositioning was done to enhance the effect of ITB to the lower limbs. Initially the catheter was inserted to the mid thoracic level, causing hypotonia in the dorsal spine.

Outcome

The difficulty with assessing outcome in ITB is the inefficacy of most outcome measures. Traditionally spasticity is measured with the Ashworth scale but the Ashworth scale is not helpful during ITB treatment. The Ashworth score can easily be adapted by modifying the delivery dose eg the more baclofen is delivered, the lower the Ashworth score. Dose increase is not always to the advantage of the child, as some children require a degree of spasticity to sit upright or in the extreme to bear their own weight. ITB aims to improve ease and range of movement without interfering with the 'functional' spasticity necessary for activities of daily living.

Other outcome measures such as PEDI scale, Canadian Occupational, WeeFIM and the Child Health Questionnaire are not specific enough as many of the effects of ITB are not easily quantifiable eg improvement in nursing care, swallowing, sleep pattern, seating, writing, use of computer etc. The outcome in Nottingham is measured by combining the above-mentioned tools and keeping track of patient satisfaction.

All children have an improvement in their nursing care and activities of daily living; all had relief of their spasticity.
5 children were mobile before the implant and their mobility improved after the implant (mobility in these children being defined as able to make a few steps with help or a frame)
8 children regained lower limb function allowing weight bearing,
1 child improved so much function that he was able to walk 20m independently.

One family is dissatisfied with the treatment. The child had a pump implant and a catheter migration. The catheter was replaced but migrated again. In the meantime the child had made progress and became more mobile despite the on-off way ITB was given. After the second migration it was jointly decided to leave the pump in place, stop the pump delivering Baclofen but to leave the system implanted. Should the spasticity worsen, the catheter can be replaced and the pump can be restarted.

Conclusion

Intrathecal Baclofen is a safe and effective way of dealing with spastic disability due to cerebral palsy. Complications are few and no children have been harmed by the procedure. The most dreaded complication, which has not occurred in this series, is infection of the system, which may lead to meningitis and requires removal of the pump with the catheter. The most frequent problem is catheter migration, despite adequate anchoring and even suturing the catheter in situ, migrations occur. In this series 7 catheter problems occurred, which amounts to 18%. This lies within the bracket of 10 to 20% catheter problems in the international literature. There is no obvious way to avoid this difficulty. The set up of the ITB service must be logical and comprehensive in order to cater to the occasional troubleshooting and refill activity. The refill activity is done on a walk in basis. Each procedure takes approximately 20 minutes. During the refill the child is reevaluated and in joint consulta-

tion with the carers it is decided whether the daily dose needs to be increased. Initially the dose increases rapidly and reaches a plateau after six months. Physiotherapy needs to be adapted to the post ITB status. Where prior to ITB the physiotherapy is directed at improving range of motion of the joints, the post ITB physiotherapy must also help to build up muscle bulk. Years of spasticity have often wasted muscle bulk, sometimes to the point of fibrosis in some of the older children and every effort needs to be made to recover and strengthen the voluntary movements. The effect of ITB on scoliosis is variable. 4 children, who were reviewed regularly by spinal surgeons prior to operative correction of scoliosis have been discharged from their care. The scoliosis had become less severe in 2 and two children remain stable. This can be anecdotally reported for the other common orthopaedic procedures for ITB patients in this series. After a minimum of 6 months of ITB the need for surgery is reduced in some children. Further study is necessary to objectively assess this observation.

During the initial assessment of an ITB candidate a dietitian is involved. Many of the severely spastic CP children have chronic malnutrition because of reflux, swallowing difficulties due to spasticity of the bulbar muscles and consumption of the normal caloric intake by the spastic muscles. Metabolic studies have shown that ITB decreases the caloric need by 40%. This leads to weight gain, which is a bonus effect in catabolic children but can be undesirable in large and heavy adolescents. Inappropriate weight gain may make the child unmanageable for transfers and activities of daily living. Increase in seizure activity has been noted after ITB. In my experience this is a rare occurrence and occurs because of the gain in weight during which the child outgrows its anticonvulsant requirement and is solved by adapting the dosage.

At the present ITB is only justified in spastic tetraplegic or tetraparetic children with increasing nursing demands. ITB for gait disturbance is not indicated in Britain at the present. This may change in the future when more evidence of effectiveness becomes available. There are otherwise no real contraindications for ITB because the test procedure will, to a certain extent, predict the outcome of the treatment.

The main restriction is funding. All children treated in Nottingham have acquired funding through the process described above and on a named patient basis. Because of the expense involved, this process will be continued indefinitely. The success of ITB depends on patient selection but even more on realistically defining goals and expectations with the child's carers. Carers of a cerebral palsy patient have often been through very difficult times, countless operations and setbacks. The carers are often desperate and wish to offer whatever may be of benefit to the child. The initial assessment and the bolus test cater to this and with these elements in hand a structured plan with realistic outcome can be made.

For further information there is a patient site on *www.baclofen.info*

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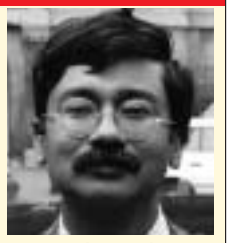
Recent advances in the surgical management of tremor in multiple sclerosis

Authors

Mr Dipankar Nandi studied medicine at the All India Institute of Medical Sciences (AIIMS), New Delhi and qualified in 1989. He then trained in the same Institute in general surgery (M.Ch. Part 1, board certification 1992) and then completed a residency programme in neurosurgery to obtain his M. Ch. Part 2, board certification in 1995. He is currently at Pembroke College, Oxford where he is working towards a D. Phil. in neurophysiology. His research involves investigation of brainstem control of akinesia and application of field potentials in functional neurosurgery.



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

Tremor is estimated to occur in about 50-75% of patients with multiple sclerosis (MS) (Alusi 2001) and is often severely disabling and difficult to treat. This is in part because the tremor is often one component in a more complex movement disorder that includes dysmetria and other ataxic features. Drug therapy for these types of tremor is often disappointing. Kurtzke originally made the observation that isoniazid helped the tremor of MS and occasionally this is still used, but no formal study has shown it to be effective. Nor is propanolol – so useful in essential tremor. Neurologists either declare the tremor of MS untreatable or trawl, with little expectation of success, through a list of drugs that includes clonazepam, carabamazepeine, primidone, valproate and ondansetron. Nor have physical measures, such as wrist weights, or physical restraint, ever proved popular. This has encouraged the exploration for neurosurgical options. In recent years, there has been considerable success in treating tremor in other movement disorders, particularly in Parkinson's disease (PD), by chronic high frequency deep brain stimulation (DBS) of ventrolateral thalamic nuclei - most commonly the ventralis intermedius nucleus (VIM) (Benabid 1991). Using sophisticated stereotactic functional neurosurgical techniques this approach has also been shown to benefit other tremulous conditions like benign essential tremor (BET) and post-traumatic tremor (PTT). However, when the same techniques have been applied to patients with MS tremor the results have been mixed. Those with purely distal limb tremor respond well whilst patients with the more common complex proximal and distal axial and limb tremor combined with dysmetric features do not show satisfactory improvement. Unlike in PD, there are a heterogeneous mixture of lesions which give rise to separate components of the disabling movement disorder and often respond differently to various interventions. The challenge is to effectively alleviate components of tremor, dysmetria and ataxia in the compound involuntary movements that are common in MS and to achieve reasonable functional improvement.

We, in the Oxford Movement Disorder Group at the Radcliffe Infirmary and the University Laboratory of Physiology (OMDG), have developed several refinements in the existing techniques and have re-kindled some therapeutic options tried and discarded in the past, to ensure functional benefit to a greater range of patients with MS tremor and with improved accuracy in predicting functional improvement.

1. Computer-controlled visually-guided arm tracking tasks (VGT) and EMG recording

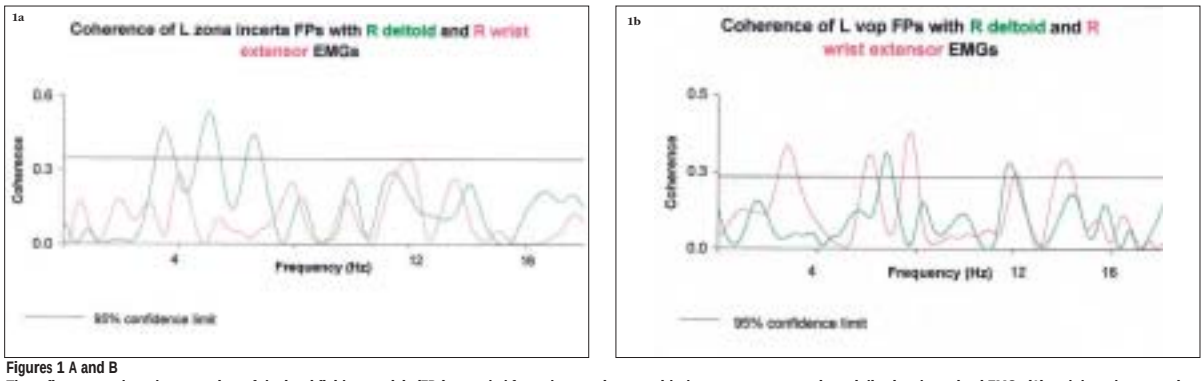
This test, which is conducted both before and after operation for tremor control, has helped us select patients who are most likely to benefit from either thalamotomy or thalamic DBS - nucleus ventro-oralis posterior (VOP) or VIM. It is easy to administer and provides detailed electrophysiological information about each patient's tremor patterns (Liu 2000).

2. Local field potential recording from deep brain nuclei (LFP)

This involves recording the synchronous electrical activity of a group of neurons lying within a few millimetres of the DBS electrode (Medtronic Inc., Minneapolis, Minnesota) used in functional neurosurgery. We have used this technique, which is still in its infancy with respect to its application in clinical neurosurgery, (in conjunction with simultaneous EMG recording) to be able to better localise the appropriate functional target for DBS (Nandi *et al* 2002). This has less risks for the patient than the more conventional electrophysiological tool of micro-electrode recording (MER) with no established loss of efficacy.

3. Zona incerta (ZI) DBS for complex proximal and distal intention tremor

We have focused on this small nucleus (Mundinger 1965), lying between the thalamus and the sub-thalamic nucleus, as a potential target for control of complex tremor, especially in MS.



Figures 1 A and B

These figures are the coherence plots of the local field potentials (FPs) recorded from the zona incerta with the concurrent contralateral distal and proximal EMGs (A) and the coherence plots of the FPs recorded from the thalamic VOP nucleus with the concurrent contralateral distal and proximal EMGs (B). Coherence plots show strength of correlation. They demonstrate that while the strength of correlation between the ZI and the proximal EMGs is significantly high in the tremor frequency range (3-6 Hz), that between the VOP FPs and the distal EMGs is significant in the same range. Thus it appears as if there is a differential oscillatory loop for proximal and distal tremor.

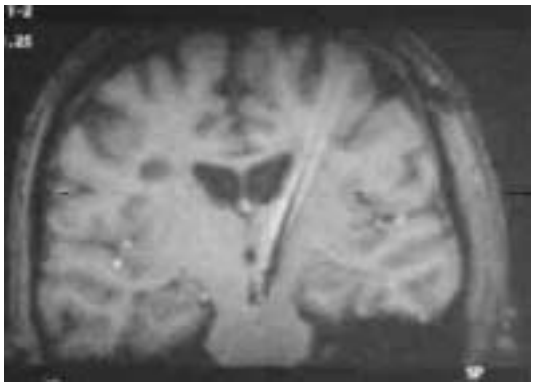


Figure 2
This figure shows the DBS lead straddling the left VOP and ZI. This placement allowed us to stimulate both structures simultaneously.

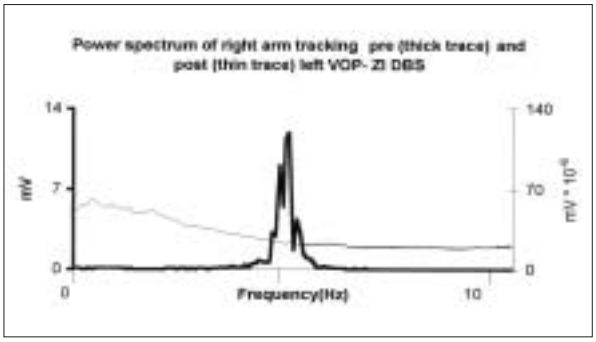


Figure 3
This figure shows the results of the VGT task performed with the right arm before and 6 months after stimulation of the VOP – ZI. There is marked reduction of the dominant 3-6 Hz tremor frequency peak, so much so that the scales needed to plot them in the same figure differ by 105.

Case report: MS with complex proximal and distal intention tremor treated successfully with ZI and VOP DBS using FP monitoring

This 29 year old woman presented with a history of MS diagnosed 5 years previously. She was referred to us with severely disabling involuntary movements affecting her right (dominant) arm. This left her unable to feed or dress herself. She had good motor power in the arm but could not use it to perform even the most basic tasks like using the TV remote control or to write. Extensive drug treatment had not helped. She was assessed clinically, radiologically and with neuropsychological testing according to the standard protocol in the OMDG. She also underwent the VGT and EMG studies. This revealed the complex combined proximal and distal nature of her tremor and based on our previous experience we offered her combined ZI and VOP DBS. She consented to this operation and using FP monitoring conducted intra-op and (following implanting of externalised DBS leads) post-op (figure 1), we successfully started DBS of both the VOP and the ZI (figure 2).

She responded immediately to the DBS and regained good functional control of her right arm. There were no untoward effects from the surgery and she was able to perform many of the routine activities of daily life like feeding herself, dressing, using the TV remote control etc. We have followed her progress for 15 months so far and the benefits are sustained. Her post-op VGT at 6 months shows marked suppression of the dominant tremor frequency peak (figure 3). There is still some residual dysmetria; however her functional status is definitely better. This is also confirmed by her neuropsychological assessment at follow-up.

We have so far successfully operated on 4 patients with complex MS limb tremor using these techniques. There seems to be a growing body of evidence in the literature which links the upper brainstem (and the region of the ZI) with proximal axial motor control. It seems that adequate treatment of complex intention tremor, especially proximal tremor, must influence the cerebellar-basal ganglia balance which is probably abnormally altered in these cases. Further investigation into the electrophysiological and pathological oscillatory circuits operating in these involuntary movement disorders is needed. We feel the way forward is for neurophysiologists to work in close co-operation with clinicians involved in movement disorders, to elicit the pathways of normal and dysfunctional motor control, which may then be influenced to achieve functional benefit for the patients suffering from these incapacitating and frustrating diseases.

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Foramen magnum

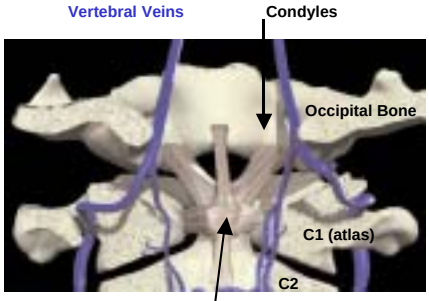
The basics. The foramen magnum (La: big hole) is the large oval opening in the base of the skull through which the spinal cord connects with the brain. It is wider behind than in front where it is encroached upon by the occipital **condyles**. It marks the boundary between the medulla oblongata and cervical cord. It contains:

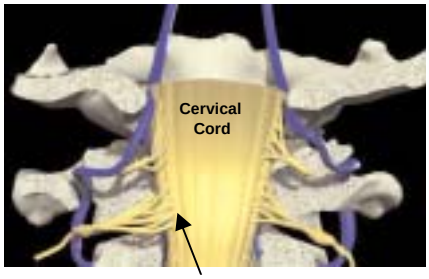
- The cervical cord.
- The spinal division of the accessory nerve ascending to join the cranial division to exit through the jugular foramen.
- The vertebral arteries and veins.
- The anterior and posterior spinal arteries.
- The tectorial membrane (which becomes the posterior longitudinal ligament).
- The cruciform and alar ligaments. These secure the odontoid peg of the axis (the second cervical vertebra) to the atlas (the first cervical vertebra) as well as the condyles of the occipital bone at the lip of the foramen magnum.

Lesions at the foramen magnum give many misleading clinical pictures, with classic presentations being clockface limb weakness, cruciate hemiplegia and wasted hands.

Comparative anatomists study the position of the foramen magnum in the skull as an indicator of how the animal walks. For instance, in apes, the foramen magnum is at the back of the skull, so the spinal cord enters it at 45-degrees. This reflects the `knuckle walking ' posture of apes. Hominoids and humans have a foramen magnum located underneath the skull, where the spinal cord enters at a 90-degree angle as we walk fully upright on two feet.

Foramen magnum, viewed from behind, with posterior surface of vertebral bodies exposed

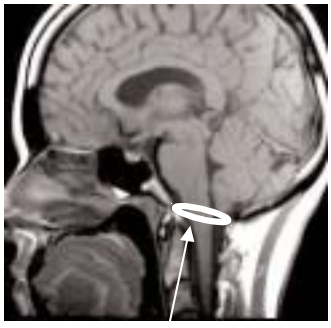




Second cervical nerve roots

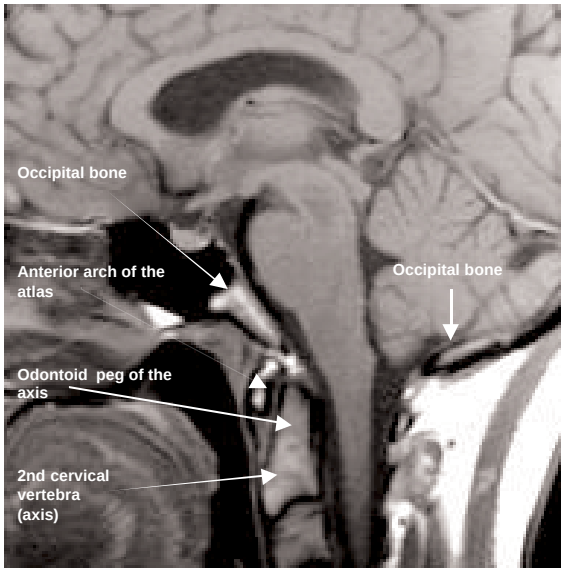
Picture credit: With thanks to Primal Pictures for the above images

Sagittal section of the foramen magnum



Foramen magnum

This shows the normal relation of the tonsils to the foramen magnum as well as the alignment of the peg with the anterior foramen magnum.



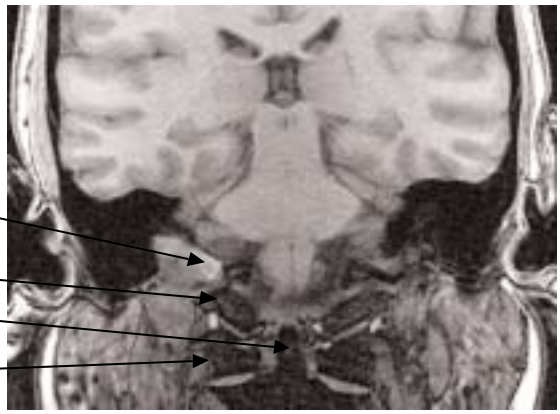
Justin Cross and Alasdair Coles

Coronal section of the foramen magnum

This coronal section shows a large right jugular bulb and its relation to the foramen magnum. The bony structures are quite well seen with the occipital condyles sitting on top of the lateral masses of C1.

Lesions at the foramen magnum

- Meningioma
- Syringobulbia
- Arnold-Chiari malformation
- Atlanto-axial dislocation
- Intrinsic lesions (especially demyelination)



Symptoms of foramen magnum compression
(Meyer & Reese, 1984 and Symonds & Meadows 1937)

- Suboccipital or neck pain (described as a `tight collar '.) (65% in Meyer and Reese's series), often exacerbated by neck movement.
- Pain in the hand (59%) or arm (55%); especially `burning ' along the ulnar border of the contralateral arm in unilateral lesions.
- Pain in the leg (26%) and face (7%) is much less common.
- Gait disturbance (50%).
- Weak arm (40%) or leg (30%).
- Hand clumsiness (27%).
- Bladder dysfunction (22%).
- Dysphagia (13%).
- Headache (11%).
- Dizziness (4%).
- Dysarthria (3%).
- Lhermitte's (3%).

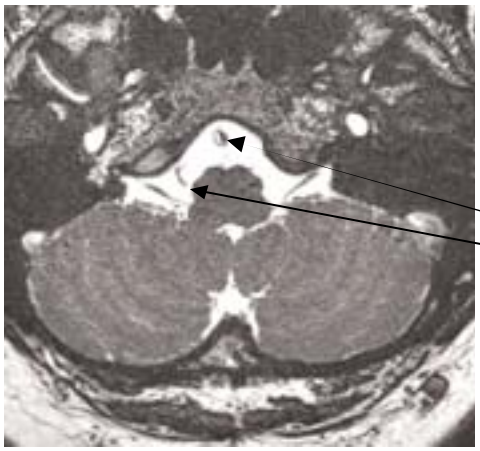
Signs of foramen magnum compression
(Meyer & Reese, 1984 and Symonds & Meadows 1937)

- Hyperreflexia and limb weakness are seen in 70% of cases, with a Babinski sign in 60%.
- Cruciate paraplegia (arms affected more than legs). With unilateral compression, this may present in a ` clockface ' way with ipsilateral arm, then leg, then contralateral leg, then finally contralateral arm weakness.
- Wasting of the hand muscles (13%)
- Disproportionate weakness of sternocleidomastoid and trapezius through compression of the spinal accessory (30%).
- Sensory loss is usually dissociated, with bilateral spinothalamic loss (40%) (caused by ipsilateral root and spinothalamic tract compromise) and dorsal column dysfunction (26%).
- Rarely: papilloedema (7%), Horner's (4%), hiccups (2%).

Intracranial extension of the lesion is indicated by:

- Downbeat nystagmus (25%)
- Cruciate hemiplegia (ipsilateral lower limb and contralateral upper limb weakness caused by a lesion at the motor decussation in the medulla).

Axial section of the foramen magnum



Hand wasting in foramen magnum compression

This intriguing sign has yet to be satisfactorily explained. The most plausible suggestions are ischaemia of the anterior horns following compression of the anterior spinal artery or venous congestion from obstruction of the vertebral veins.

This axial section shows cranial nerves IX,X heading to the jugular foramen as well as the outline of the medulla showing the bulges formed by the pyramids, inferior olive and inferior cerebellar peduncle.

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1. The interactive spine. Primal Pictures.
2. Symonds CP and Meadows SP. *Compression of the spinal cord* in the neighbourhood of the foramen magnum. Brain 1937; 60: 52-84
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Metabolic myopathies

Author

Dr Wojtek Rakowicz is a Specialist Registrar in Neurology. After training in Norwich and Cambridge he worked in the Neuromuscular Division at Washington University in St Louis. He is currently at the National Hospital for Neurology and Neurosurgery.

Metabolic myopathies most often present with either (1) recurrent episodes of acute-onset and reversible muscle dysfunction or (2) progressive muscle weakness (Table 1). In general, episodic abnormalities, such as fatigue, pain, weakness and rhabdomyolysis, correlate well with our knowledge of the underlying defects in energy production (see Box on page 20). The mechanisms by which metabolic abnormalities bring about permanent weakness are poorly understood.

The clinical features of disorders of carbohydrate metabolism (glycogenoses), lipid metabolism (lipidoses) or electron transport chain (mitochondrial) function vary with age at presentation. Defects in cellular energy production in the newborn and infants often give rise to severe multisystem disorders but adult-onset disease is usually restricted to muscle. This review will focus on adult presentations of non-mitochondrial disorders of muscle metabolism.

Presentations of metabolic muscle disease

The most characteristic presentation of metabolic myopathies is episodic muscle dysfunction. Premature fatigue, exertional muscle pain, contractures and rhabdomyolysis are seen in attacks of increasing severity. Those metabolic muscle diseases causing progressive weakness tend to have a more non-specific 'myopathic' phenotype and are less likely to give rise to attacks of rhabdomyolysis.

PREMATURE EXERTIONAL FATIGUE

Defects in carbohydrate metabolism result in an early rise in heart rate, respiratory rate and fatigue within minutes of starting intense exercise while disorders of lipid metabolism only become symptomatic after several hours of sustained submaximal exertion. Muscle disease is clearly not the commonest cause of decreased exercise tolerance which is more likely to be the result of deconditioning or an indicator of primary cardiac or pulmonary disease (Table 2). However, the muscle fatigue in metabolic myopathies has a different and unpleasant quality not reported by normal individuals.

EXERCISE-INDUCED CRAMPS

Individuals with glycogenoses report exertional aching, burning or cramps in muscles which may reach a peak 6 hours after exercise. Continued exercise may result in the muscle 'locking up' due to the development of painful contractures. In contrast to true cramps, a metabolic muscle contracture is hard and tender; the pain is made worse by attempted stretching; the pain lasts for hours rather than minutes; and the EMG is silent.

Muscle pain in lipidoses is characteristically seen during or after sustained exercise but can also be unrelated to exercise, particularly during periods of fasting or dieting, exposure to cold, general anaesthesia and intercurrent infection. Affected individuals may find that the use of glucose tablets or chocolate improves exercise tolerance. In contrast to the glycogenoses, they do not develop painful contractures.

MYALGIA

Muscle pain during exercise is rarely seen in healthy individuals. While a common feature of metabolic muscle disease, it is relatively unusual for exercise-related myalgia in isolation to be the dominant symptom: individuals are more likely to report "weak legs" or "jelly legs." Normal muscle characteristically gives rise to pain 24 to 48 hours after unaccustomed exertion, particularly in individuals who lead a sedentary lifestyle.

RHABDOMYOLYSIS

Muscle pain in individuals with a metabolic myopathy is a harbinger of muscle fibre breakdown and is accompanied by a rise in plasma CK, dark urine and a concomitant risk of renal impairment. In between attacks the plasma CK often remains high in glycolytic disorders but usually returns to normal in disorders of lipid metabolism. However, the CK rise during an attack of rhabdomyolysis is often higher in lipidoses and is more likely to lead to renal failure.

Metabolic myopathies causing episodic muscle dysfunction

Individuals with episodic presentations of glycogenoses and lipidoses are clinically normal between attacks although with time they may become mildly weak. Attacks of rhabdomyolysis are treated symptomatically. Further investigations, especially muscle biopsy, are deferred until at least one month after the episode since muscle necrosis interferes with biochemical analyses and necrotic muscle fibres mask other histochemical findings. The main informative investigations in glycogenoses are raised serum CK levels, myopathic EMG findings and subsarcolemmal vacuoles on muscle histology. In contrast, laboratory investigations in the lipidoses are usually normal between attacks and the diagnosis depends on clinical suspicion leading to muscle enzyme estimation in a specialist laboratory. With the notable exception of phosphofructokinase, episodic weakness is a feature of deficiencies in muscle-specific enzymes.

DISORDERS OF CARBOHYDRATE METABOLISM

Myophosphorylase deficiency (McArdle's disease)

Myophosphorylase deficiency is the commonest defect affecting muscle carbohydrate metabolism. Myophosphorylase is responsible for glycogenolysis in the early stages of intense exercise so affected individuals report fatigue and pain within the first few minutes of strenuous activity. Continued exercise results in increasing pain which is initially deep and aching but rapidly

TABLE 1: The clinical presentation and investigation of the major metabolic myopathies

	EPISODIC MUSCLE DYSFUNCTION #	PROGRESSIVE WEAKNESS
DISORDERS OF CARBOHYDRATE METABOLISM	**Myophosphorylase deficiency Phosphofructokinase deficiency**	**Acid maltase deficiency Debranching enzyme deficiency**
Presentation	premature exertional fatigue, muscle pain, contractures, rhabdomyolysis early during intense exercise	symmetrical muscle weakness, respiratory failure
Investigations	CK raised EMG myopathic Bx subsarcolemmal vacuoles	CK raised EMG myopathic ± irritable* Bx cytoplasmic vacuoles
DISORDERS OF LIPID METABOLISM	**CPT II deficiency VLCAD deficiency**	**Carnitine deficiency**
Presentation	premature exertional fatigue, muscle pain, rhabdomyolysis during/following sustained exercise	symmetrical muscle weakness, cardiomyopathy, encephalopathy
Investigations	CK normal EMG normal Bx normal	CK raised EMG myopathic Bx lipid storage vacuoles

#Investigations should be deferred at least one month after an episode of rhabdomyolysis (see text)
*irritable = fibrillations and positive sharp waves
Abbreviations: CK = serum creatine kinase; Bx = histochemical findings on muscle biopsy

TABLE 2: Differential diagnosis of premature exertional fatigue

Unaccustomed exertion	No pain during exercise Muscle pain occurs 24-48 hrs after exertion
Dystrophinopathies	Fixed weakness Fatigue after exercise is common
Cardiorespiratory problems	Exercise-induced asthma Heart disease
Other disorders	Fibromyalgia Chronic fatigue syndrome

gives way to a painful tightening of the muscle. A second-wind phenomenon is characteristic of the condition: if instead of stopping the subject slows down when they experience fatigue, the symptom will usually subside and the muscle may begin to function more normally allowing prolonged exercise of moderate intensity. Symptoms often improve with a high-carbohydrate meal or glucose.

An absent or blunted rise in serum lactate during exertion is the basis of a forearm exercise test that may confirm a clinical suspicion of a disorder in carbohydrate mechanism. Although performed under standardised laboratory conditions, the traditional ischaemic test has a significant risk of inducing muscle necrosis and is likely to be superseded by a non-ischaemic test. The investigation of choice is the histological demonstration of subsarcolemmal vacuoles (Fig. 1) and absent myophosphorylase staining.

Phosphofructokinase deficiency

Phosphofructokinase (PFK) catalyses the rate-limiting step of glucose breakdown, the conversion of fructose-6-phosphate to fructose-1,6-diphosphate. Symptoms of deficiency are indistinguishable from myophosphorylase deficiency. Descriptions of the second-wind phenomenon are less common while nausea and vomiting are more frequent. Also, the location of the metabolic block means that symptoms are exacerbated rather than ameliorated by a high-carbohydrate meal or glucose: the 'out of wind' phenomenon.

The approach to investigations is similar to myophosphorylase deficiency. The presence of a haemolytic trait (raised serum bilirubin and increased reticulocyte count) is the result of muscle isoforms of PFK normally contributing about 50% of the PFK in red blood cells.

DISORDERS OF LIPID METABOLISM

CPT II and VLCAD deficiency

Carnitine palmitoyltransferase II (CPT II) deficiency is one of the more common biochemical abnormalities in muscle and is the commonest cause of recurrent rhabdomyolysis. Affected individuals have no difficulties with short-lived exercise, which is largely dependent on glycogen, and can even participate in certain competitive sports. Difficulties arise with sustained exercise particularly in the fasting state. Attacks of myoglobinuria tend to be more severe in CPT II deficiency than in the glycogenoses and are more likely to lead to renal dysfunction. Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is paradigmatic of a growing number of described defects of beta-oxidation whose presentation is clinically indistinguishable from CPT II deficiency. At least 25 chain-length-specific enzymes have been identified and symptomatic deficiencies have been described in almost half of these.

Routine laboratory investigations, including muscle histochemistry, are usually normal in CPT II deficiency and VLCAD. Specialised serum biochemical analyses of fatty acid derivatives can help pinpoint the metabolic defect in suspected cases and CPT II activity can be measured in muscle tissue.

Metabolic myopathies causing progressive weakness

Progressive presentations of metabolic muscle disease are difficult to distinguish on clinical grounds from other myopathies such as the limb-girdle muscular dystrophies or polymyositis. In contrast to metabolic myopathies presenting with episodic dysfunction, rhabdomyolysis is rare but cardiac involvement is more frequent. The serum CK is usually raised and the EMG is myopathic but the most characteristic finding is the histological observation of 'storage' vacuoles containing carbohydrate or lipid. In contrast to metabolic myopathies causing episodic weakness, most of the metabolic defects known to cause progressive muscle weakness are in enzymes that are not specific to muscle. The pathogenic significance of this striking biochemical dichotomy is unclear.

Acid maltase deficiency

Adult-onset acid maltase deficiency presents as mild proximal muscle weakness with characteristic respiratory involvement. Respiratory failure is the presenting symptom in up to 30% of affected individuals.

The serum CK tends to be very high and 'irritable' features (spontaneous activity) are often noted on the EMG. The large cytoplasmic vacuoles seen on muscle sections are characteristic (Fig. 1) and enzyme levels can be measured directly in white blood cells, cultured skin fibroblasts or muscle.

Debranching enzyme deficiency

Given its metabolic proximity in glycogenolysis to myophosphorylase, it is somewhat surprising that debranching enzyme deficiency does not usually cause paroxysmal symptoms except in extremely weak individuals. Instead, it presents in the third or fourth decade with muscle wasting that is often distal more than proximal with occasional respiratory involvement, a pattern which can lead to a diagnosis of motor neuron disease although there is usually a concomitant mild sensory axonal polyneuropathy.

The EMG characteristically displays mixed myopathic and

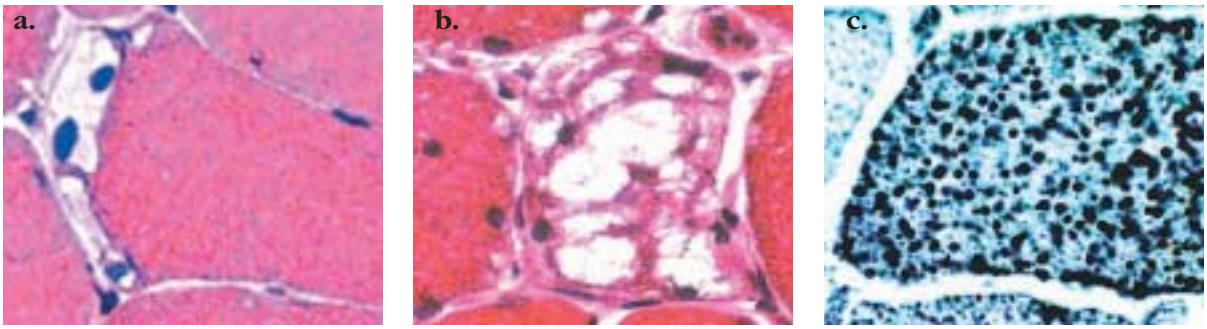

Figure 1: Immunohistochemical characteristics of metabolic muscle disease. a. Myophosphorylase deficiency (McArdle's disease): subsarcolemmal vacuoles (H&E stain); b. Acid maltase deficiency (adult-onset): cytoplasmic and intramyofibrillar vacuoles (H&E stain); c. Carnitine deficiency: lipid storage vacuoles (Sudan black stain).

neuropathic features and nerve conduction studies are often slow. Histochemistry reveals both subsarcolemmal and intermyofibrillar glycogen storage vacuoles.

Carnitine Deficiency

The importance of carnitine in metabolism is in the regulation of levels of acyl-CoA which can cause damage when present in excess. Typically the deficiency of carnitine is secondary to a defect in another enzyme system that results in the overproduction of acyl-CoA or in a deficiency of acyl-CoA clearance. These disorders can present with a progressive myopathy but this is usually associated with cardiomyopathy and encephalopathy, most strikingly coma after a period of starvation. Exacerbations and fluctuations occur but fatigue, exercise-related symptoms and myoglobinuria are usually absent. The diagnosis is supported by the presence of multiple lipid droplets on muscle histology (Fig.1)

Acknowledgements

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Overview of energy metabolism in muscle

Muscle contraction and relaxation depend primarily on energy derived from hydrolysis of adenosine triphosphate (ATP). The main substrates used by muscle to generate ATP are glycogen, glucose, and free fatty acids (FFAs). The particular energy sources used depend on whether the muscle is at rest or contracting; the intensity, type and duration of exercise; and on diet and physical conditioning. Glycogen and glucose are metabolised in the cytoplasm to pyruvate which can diffuse into the mitochondrion. Short- and medium-chain fatty acids (less than 10 carbon atoms) freely cross the outer and inner mitochondrial membranes. Longer-chain fatty acids have to be transported into the mitochondrial matrix complexed to carnitine to which they are linked and then unlinked by carnitine palmitoyltransferases (CPTs) I and II respectively.

When the oxygen supply is adequate to meet metabolic needs the main energy substrates of muscle are circulating FFAs (at rest and during sustained low intensity exercise) and blood glucose (low intensity exercise). During high intensity submaximal (ie still aerobic) exercise intracellular stores of glycogen are mobilised. Under these conditions acetyl-coenzyme A (acetyl-CoA) in the mitochondrial matrix, the product of oxidative decarboxylation of pyruvate and beta-oxidation of FFAs, enters the Krebs cycle where carbon dioxide and reducing equivalents are generated. The reducing equivalents drive most of the ATP production through the electron transport chain.

During intense isometric exercise the metabolic demand of muscle outstrips the capacity of oxidative metabolism to synthesize ATP. Most of the additional ATP is provided by anaerobic glycolysis during which pyruvate is metabolised to lactate instead of acetyl-CoA. Additional ATP can also be generated by the phosphocreatine pathway and the purine nucleotide cycle. In the former, creatine kinase (CK) catalyses the reaction of phosphocreatine with adenosine diphosphate (ADP) to produce ATP. In the latter, muscle adenylate kinase catalyses the conversion of two molecules of ADP to one each of ATP and adenosine monophosphate (AMP) which is later deaminated by myoadenylate deaminase with concurrent production of ammonia.

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WEDNESDAYS

16 October	Myotonic dystrophy - a disorder of RNA processing? Myotonic dystrophy: clinical aspects	Professor J D Brook, BSc, PhD (University of Nottingham) Dr D Hilton-Jones MD,FRCP,FRCPE (Radcliffe Infirmary, Oxford)
23 October	Diagnostic immunoanalysis of the limb girdle muscular dystrophies The patient with a limb girdle muscular dystrophy – important clinical differential diagnoses	Dr L V B Anderson PhD,MRCPath (University of Newcastle) Dr K M D Bushby MBChB,MSc,MD,FRCP (University of Newcastle)
30 October	Antibodies to different targets at the neuromuscular junction Clinical aspects of myasthenia gravis	Professor A Vincent MBBS,FRCPath (John Radcliffe Hospital, Oxford) Dr J Palace BM,MRCP (Radcliffe Infirmary, Oxford)
6 November	Molecular analysis of muscular dystrophies	Professor K E Davies MA,DPhil,FmedSci, CBE (Dept of Anatomy & Genetics, Oxford)
	Dystrophinopathies: a clinician's view	Professor F Muntoni MD,FRCPCH (RPMS, Hammersmith, IC)
13 November	The role of the motor neurone in Motor Neurone Disease Update on Motor Neurone Disease - molecules and management	Dr L Greensmith BSc,PhD (Institute of Neurology, UCL) Dr C Shaw FRACP,FRCP,MD (King's College London)
20 November	The pathogenesis of vasculitis	Professor C O S Savage MD,PhD,FRCP (University of Birmingham)
	Clinical features and management of peripheral nerve vasculitis	Dr M Donaghy DPhil,FRCP (University of Oxford)
27 November	The pathogenesis of inflammatory demyelinating neuropathies Clinical features and management of inflammatory demyelinating neuropathies	Professor R A C Hughes MD,FRCP,FMedSci (Guy's Hospital, London) Dr J Winer MSc,MD,FRCP (Queen Elizabeth Hospital, Birmingham)
4 December	Amyloidosis and amyloid neuropathies in 2002 Adrenomyeloneuropathy - beyond Lorenzo's oil	Professor M B Pepys FRS (Royal Free & UCL Medical School, UCL) Dr P Lee DM,FRCP,FRCPCH, (National Hospital for Neurology & Neurosurgery)

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EPDA's 10th Anniversary Conference

30–31 May 2002, Ljubljana, Slovenia

This conference focused on the importance of partnership and collaboration and the first day concentrated upon the 'Team Approach' in the management of Parkinson's disease.

Mary G Baker, EPDA President, questioned whether health services knew what families needed and she highlighted the importance of:

- The need to focus more closely on families affected by neurological diseases so that their requirements could be met more appropriately.
- That people with neurological diseases be referred to a doctor with a special interest in their illness to ensure that they receive an accurate diagnosis.
- Patients should be referred to a multidisciplinary team sooner rather than later and should receive continuous care.
- Patients should also be encouraged to play an active part in the management of their illness.

Zvezdan Pirtosek (Slovenia) discussed the results of his History of PD search for possible descriptions of Parkinsonism in centuries before James Parkinson's seminal description in 1817. Fragmentary references were found in the:

- Text of an Egyptian papyrus (c. 1350–1200 BC)
- Bible (Ecclesiastes)
- Sanskrit Ayurvedic medical texts
- Chinese classical works 'Nei Jing' and 'Chan Zen', and clinical observations of Galen

He commented that Rembrandt and Leonardo da Vinci might have suffered from PD.

Both Laszlo Vecsei (Hungary) and Maja Relja (Croatia) addressed The Role of Drugs in the management of PD and it was reported that:

- Liquid preparations of levodopa provide more rapid absorption and can be used in an attempt to control complex patients who are very sensitive to even minor changes in levodopa dosage. Methyl ester and ethyl ester, water-soluble formulations of levodopa are also rapidly absorbed and are now under investigation for use in PD.

A Multidisciplinary Approach included presentations from Lidija Ocepek, PDNS (Slovenia) about the Slovenian 'model'. Mariella Graziano (Luxembourg) emphasised the importance of physiotherapy and addressed four core areas: gait, balance, posture, and transfers whilst Jelka Jansa (Slovenia), Occupational Therapist, stressed the importance of environmental influences, which can either constrain or facilitate everyday functioning for people with PD.

Francoise Lucas, Branko Smid and Mary Baker deep in discussion at the conference

In Sexuality and PD, Gila Bronner (Israel) reported that the Movement Disorder Unit in Tel Aviv is offering in-house counselling services for patients and spouses to discuss sexual issues. The sexual treatment is based on a short-term intervention (usually two to four sessions), which proved to be effective for many patients, and 80% of the patients treated with this approach were satisfied.

In his presentation *Re-emergence of Surgery* Alberto Albanese (Italy) reported the latest data on the long-term follow-up of sub thalamic nucleus stimulation in 22 patients with PD, which registered that in seven patients followed-up for 1 year, medication could be reduced by 65%.

Vladimir Kostic (Serbia), Irena Rektorová (Czech Republic) and Erwin Ott (Austria) in the session *Cognitive and Behavioural Dimensions of PD* covering Depression, Cognitive Disturbance and Dementia, and Pathophysiology and Treatment of Pyschosis reported that:

- Depression and anxiety are the most common and frequently disabling psychiatric conditions that accompany PD, but also, that there is no doubt that depression in PD is a treatable, albeit under-treated, condition.
- The risk for developing dementia is two to six times higher in people with PD than in people without PD. Risk factors for developing dementia include age, severity of Parkinsonism, low education, family history of dementia and, possibly, depression.
- Parkinsonian/dopaminomimetic psychosis is a relatively slow, gradually progressing condition. It should be differentiated from a toxic confusional state, an acute condition characterised by disorientation, impaired concentration, alterations of sleep and usually caused by infection, dehydration or certain drugs. If Parkinsonian psychosis is mild, treatment may not be necessary. Drug management should be initiated when symptoms start to interfere with the patient's daily life.

The second day focused on the EPDA projects including:

Past:

- Participation in Life Survey (Mary Baker, UK)
- Global Parkinson's disease Survey (GPDS) (Leslie Findley, UK)
- Economic and Emotional Cost of Care (Clive Bowman, UK)

Present:

- PD Life (Drug Profiling) (David Burn, UK)
- PD Med (Carl Clarke, UK)
- INFOpark (Pirkko Routasalo, Finland)
- Multilingual Website (Dan Coene, the Netherlands)
- Parkinson's In Europe (Young People and what is needed to improve Quality of Life) (Dinah Gould, UK)
- Centres of Excellence (Nir Giladi, Israel)

Future:

- Complementary Therapies – Conductive Education (Mel Brown, UK)
- Deep Brain Stimulation (DBS) (Guiseppe Carbone, Italy and Mike Robins, UK)
- The REAL-PET Study (Example of Information the new Media Guide will disseminate) (Alan Whone, UK)
- WHO Working Group on Parkinson's disease (Aleksandar Janca, Australia)
- The Role of Phenomenology in Medical Education (Matthew Menken, USA)
- Strategic Alliances – The Global Declaration (Mary Baker, UK)

Lizzie Graham, EPDA Liaison/Project Manager

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7th European Congress of Neuropathology

13-16 July 2002, Helsinki, Finland.

The 7th European Congress of Neuropathology was organised by Dr Matti Haltia, Dr Hanno Kalimo and the Scandinavian Neuropathological Society under the auspices of the European Confederation of Neuropathological Societies (EuroCNS). The abstracts will be published in Clinical Neuropathology. EuroCNS seeks to unify standards of education, diagnosis and research in Neuropathology throughout Europe. To this end, the main Congress was preceded by four-day course on the Pathology of Central Nervous System Tumours brilliantly organised by Dr Dirk Troost (Amsterdam).

Both the Course and the Congress were held in the modern Biomedicum at the University Hospital. Helsinki is a delightful city with beautiful architecture and a distinct maritime air that was enhanced by a week of sunny, warm weather making this Congress one of the most enjoyable of the year.

The scientific sessions of the Congress were composed of 8 plenary lectures, an interactive slide seminar, 18 workshops and 233 posters, 98 of which were on neurodegenerative diseases and 59 on tumours. Some 400 delegates from countries world-wide attended.

Three of the plenary lectures were focused on CNS tumours. V. Peter Collins (Cambridge UK) reviewed the roles of cell cycle pathways in the oncogenesis of astrocytic tumours emphasising how deregulation of p53 occurred in 70% of all astrocytic tumours whereas abnormalities of PTEN and EGFR were more common in glioblastomas. David N Louis (Boston USA) emphasised the impact of molecular genetics on the classification and treatment of CNS tumours. Concentrating mainly upon oligodendrogliomas, he discussed how loss of chromosomes 1p and 19q is associated with a good response to chemotherapy and a favourable prognosis. Optimism was expressed that the combination of histological and molecular genetic techniques would lead to many further benefits for the therapy of CNS tumours. Such work will be greatly aided by the microarray techniques reviewed by Olli-P Kallioniemi (Bethesda USA). Angiogenesis is a hot topic and Karl H Plate (Frankfurt Germany) explored the multiple functions of VEGF in relation to tumours, hypoxia and ontogenesis. Hans Lassmann (Vienna, Austria) showed how Multiple Sclerosis is characterised by an underlying immune attack by cytotoxic T-cells on the CNS with the add-on effects of antibodies, compliment, ischaemia-like disturbances of oligodendrocytes and axonal degeneration determining the variations in clinical and pathological picture. Combining his unique experience of the clinical aspects and pathology of muscle diseases, George Karpati (Canada) gave an excellent update on the molecular basis of genetic muscle diseases. Neurodegenerative diseases were a major focus of the Congress; John Hardy (Bethesda, USA) graphically dissected the genetic bases of tau and / -synuclein-related disorders and presented a framework gathering the tau, synuclein and parkin into a single group of related disorders. Explicit molecular models did much to clarify the relationships between presenilins, €amyloid and its precursor APP. Charles Weissmann (London, UK) gave the final lecture of the Congress in which he analysed the evidence for the protein (prion) theory of CJD and other transmissible spongiform encephalopathies.

The Waterfront in Helsinki with the City Hall in the background and the Lutheran Cathedral towering above.

The workshops covered a wide variety of Neurological disorders concentrating upon the relationships of Neuropathology to other basic and clinical Neuroscience disciplines. There were thorough reviews and discussions on recent advances in the study of CNS tumours and of dementias including prion diseases. Discussions of the new technologies of genetic analysis and proteomics in relation to neuromorphological techniques arose in all fields and in specific workshops. In addition to workshops on trauma, infections, angiogenesis, stem cell research, demyelination, paediatric neuropathology, muscle and nerve diseases, issues such as safety, the legal aspects of Neuropathology and the impact of genetics on the diagnosis and management of Neurological disease were hotly debated.

Posters were the life-blood of the Congress and there was ample time to digest and discuss the contents with presenters. Twenty-two posters were selected for special commendation. Three were awarded prizes: A. Kulla *et al* (Tartu, Estonia and Bonn, Germany) solved the long disputed origin of blood vessels in glioblastomas. They isolated both vessels and tumour from paraffin sections and then by tissue arrays and DNA sequencing showed that TP53 mutations did not correspond. These results suggest that the tumour vasculature is derived from pre-exist-

Dr Matti Haltia, President of the EuroCNS Congress (left), talking to Dr Sam Ludwin, President of the International Society of Neuropathology during the Congress Dinner in the Suomenlinna Sea Fortress.

ing normal vessels rather than via transdifferentiation from primitive glioblastoma cells. This has important implications for tumour therapies directed at angiogenesis. J.F.Poduslo *et al* (Rochester MN and NYU) demonstrated an elegant method for imaging €amyloid (A€) plaques by MRI in transgenic mice. They used a gadolinium-labelled putrescine probe that crosses the blood-brain barrier and binds to A€ with high affinity. This technique has great potential for assessing A€ load in human Alzheimer's disease and for monitoring therapy. P.Lamont *et al* (Australia and the Netherlands) characterised a myopathy in a family of Dutch descent with late onset progressive limb weakness and the presence of rod-bodies and cores in muscle fibres. Linkage to chromosome 15q was obtained. This study demonstrated beautifully how knowledge of muscle disease advances through a careful multidisciplinary clinical, pathological and genetic approach.

Given that most contacts are made at social events, the superb receptions in the Senate House and City Hall, the boat trip and Dinner in the off shore Suomenlinna Sea Fortress ensured the success of the Congress.

Professor Roy O. Weller,
Southampton, UK.

12th Meeting of the European Neurological Society

June 22-26 2002, Berlin, Germany

To anyone who recalls those iconic images of the Berlin Wall being broken down, the opportunity to visit that romantic city, with its exotic associations of espionage and cabaret, would be hard to resist. Too hard apparently for the 3500 neurologists who visited this June under cover of the 12th meeting of the European Neurological Society. They were rewarded with good weather, an excellent meeting and a conference banquet in the Russian Embassy. But above all, this ENS will be remembered for the football. The speakers in one memorable afternoon session had to address a near-empty room, competing with loud reactions to the shifting fortunes of the Germany-South Korea match, watched on a large screen hastily erected at one of the pharmaceutical stalls. As the President pointed out, this was the first time data presented at a pharmaceutical stand were accepted without criticism or the call for meta-analysis from all delegates – South Koreans excepted.

Plenty of work was done as well. My personal prize for the best poster goes to the team from Kragujevac Hospital, Yugoslavia, who carefully documented all 387 cases of Bell's palsy in their region from March 1998 to December 2001. 77 (20%) of these occurred in the three months (March 24th to Jun 23rd 1999) of NATO air strikes. The authors attribute this to the stress of combat or a change in the environment as people took to their basements.

Rudolf Virchow (1821-1902) was educated at the University of Berlin, then was Professor of Pathology at Wurzburg and then Berlin. He was the first person to describe neuroglia.

MULTIPLE SCLEROSIS. The meeting was dominated by multiple sclerosis, both in the academic sessions and the parallel symposia. It was apparent, informally, that (whilst understanding the nature of economic forces) not all delegates favour this emphasis or feel comfortable with the bunching up of satellite symposia with the more academics sessions. Alastair Compston, who took over as President of the ENS on the first day of this meeting, organised a captivating symposium on the clinical science of demyelinating disease. He introduced the provisional results of the **GAMES** project: the European-wide search for susceptibility genes in multiple sclerosis. His team have narrowed the search down to nine areas of the genome for more detailed study taking forward a story that has remained stubbornly recalcitrant for nearly three decades. In this session, Ken Smith (London) gave one of the most elegant talks of the conference. He proposed that axonal death in demyelinating disease results from unhappy coincidence of the need for increased energy to prevent the accumulation of sodium ions within axons (since sodium channels redistribute themselves along the demyelinated axon), and the presence of metabolic inhibitors (like nitric oxide). The therapeutic conclusion is that sodium channel blockade might protect axons; for which reason he and Raj Kapoor are trying to establish a trial of flecainide in secondary progressive multiple sclerosis. The Queen Square MRI unit reported on the MRI effects of 6 months' treatment with **natalizumab** (Antegren) in 213 patients in the US, Canada, and UK. T2 and T1 hypointense lesion volumes increased in the placebo group, but decreased in the natalizumab groups, from months 0-6. However, six months after all therapy stopped, there was no difference between the groups. The use of **intravenous immunoglobulin** in multiple sclerosis received a severe blow when the European multi-centre trial of IVIG in secondary progressive patients (presented by Otto Hommes) showed not only that IVIG failed to reduce the accumulation of disability, but also that the previously reported claim for significant reduction in relapse rate seen in the phase II study could not be replicated. Curiously IVIG did reduce the rate of cerebral atrophy on MRI.

GUILLAIN-BARRÉ SYNDROME. The Dutch GBS Study Group showed – against orthodoxy - that **intravenous methylprednisolone** 500mg daily for five days is useful in GBS. In a placebo-controlled study of 225 patients unable to walk independently, and

Professor Alastair Compston, new President of the ENS

treated within 14 days after onset of weakness, the addition of steroids to standard IVIG significantly improved the outcome at 4 weeks. (Steroid patients were three times more likely than placebo patients to have improved on the Hughes' scale.) The longer-term outcome was not reported.

STROKE. A team in Frankfurt reported their experience of treating 205 patients with high-grade carotid stenosis using **carotid angioplasty and stent implantation** since 1994. They concluded that the results were no different to endarterectomy. A rather depressing presentation from the European SAFEII investigators revealed that, of 300 consecutive patients with **stroke and atrial fibrillation** who should have been put on warfarin – by agreed guidelines, only 60 in fact were anti-coagulated. The explanation, it seems, is ignorance. Oh dear.

PARKINSON'S DISEASE. Sleep attacks occurring on dopamine agonists were much discussed a couple of years ago. A German group has surveyed 2952 patients, of whom 171 were found to have developed sudden irresistible sleep attacks during activity. They occurred equally commonly with all the dopamine agonists, less frequently with L-dopa alone, and not at all with selegiline and amantadine. The **REAL-PET study** of 186 new Parkinson's disease patients studied over two years showed that **ropinirole** was associated with less reduction of 18F-dopa signal in the putamen and nigra than occurred with L-dopa. Unsurprisingly, L-dopa induced better changes on clinical motor scores, but also more dyskinesias (27% versus 3%).

EPILEPSY. The new anticonvulsant drug, **levetiracetam**, received much attention during the conference. Its mechanism of action remains unknown. In a pragmatic study of efficacy, O'Rourke reported on its use as add-on therapy in adults with mental retardation and epilepsy. Levetiracetam rendered 14% of punters seizure-free and gave a 64% seizure reduction by > 50%. These figures are higher than for topiramate and gabapentin in the same population, but not as good as lamotrigine (21% and 25% respectively). Tim Betts from Birmingham reported an "impressive result" from an open-label study of its use in juvenile myoclonic epilepsy.

NEURO-OPHTHALMOLOGY. In an epidemiological study, some Berlin neurologists found that **benign positional vertigo** tended to last for three years, during which patients had 2.4 episodes of vertigo. In only 4% had the Epley manoeuvre been tried, which is almost criminal given that it is the most successful of all neurological treatments for this horrible symptom. Would a survey in the UK give any better results? Thomas Brandt's team reported a case that should also worry us: a patient with apparent **"idiopathic vestibulopathy"** who turned out to have autoantibodies against the inner ear structures and who improved on immunosuppressive therapy.

DEMENTIA. There were no less than seven posters on galantamine, a novel acetylcholinesterase inhibitor that also acts as an agonist at nicotinic acetylcholine receptors. Perhaps the most interesting was from Helsinki, indicating that galantamine maintains cognitive function for a year in patients with both Alzheimer's disease and vascular dementia, as well as those diagnosed with vascular dementia alone.

The next meeting of the ENS is in June 14-18, 2003 in Istanbul. Early signs are that it will be just as stimulating and enjoyable as this one was. Get it in your diary!

Alasdair Coles & Alastair Compston

LETTERS

We welcome your letters and comments about ACNR. Please write to The Editors, ACNR magazine, c/o 7 Alderbank Terrace, Edinburgh EH11 1SX, or e-mail. AdvancesinCNR@aol.com

Dear Dr Coles

In your recent cerebellar pontine angle anatomy primer (pg 16-17, vol 2, issue 3, July/Aug. 2002), your introduction declares that amongst other signs, an acoustic neuroma classically gives rise to ipsilateral facial palsy. I can only imagine that this was a slip of the pen for an ipsilateral facial palsy is an excessively rare presentation of the lesion and is almost always the stamp of therapeutic intervention.

Yours sincerely

Charles G H West
Consultant Neurological Surgeon
Royal Manchester Children's Hospital

INTERNATIONAL SYNCOPE SYMPOSIUM

STARS
Syncope Trust And Reflex anoxic Seizures

Friday 27th September 2002, Birmingham NEC

Medical professionals are often faced with the difficult task of distinguishing between epilepsy and the vast and varied forms of syncopes. Understanding the mechanisms and presentation of these conditions is essential to diagnosis. The successful management and treatment of these patients also requires a comprehension of the issues faced by families, teachers, employers and health professionals.

Speakers

Professor Christopher J Mathias, Professor of Neurovascular Medicine, Imperial College School of Medicine at St Mary's Hospital, London, National Hospital and Institute of Neurology, Queen Square, London, UK will introduce *dysfunctions of the autonomic nervous system*

Professor Julian M Stewart, Professor of Paediatrics and Research Professor of Physiology, Centre for Paediatric Hypotension, New York Medical College, New York, US will explore *paediatric orthostatic intolerance*

Professor Gert van Dijk, Professor of Clinical Neurophysiology,Leiden University Medical Centre, The Netherlands will consider '*Does hyperventilation cause fainting?'*

Dr William Whitehouse, Senior Lecturer in Paediatric Neurology, Queen's Medical Centre, Nottingham, UK will present the results of an extensive *new survey of Reflex Asystolic Syncope*

Dr Gordon Bates, Adolescent Psychiatrist
Park View Clinic, Birmingham Children's Hospital, UK will take into account *the psychological effects of living with syncope*

Mr John L Firth, Consultant Neurosurgeon, Orkney, UK will address *the 'GLOC-STARS' connection*

Dr Wonter Wieling, Academic Medical Centre, Dept of Internal Medicine, Amsterdam, The Netherlands will speak on '*Physical counter-manoeuvres: the muscle pump as our second heart*'

Professor John B P Stephenson, Visiting Neurologist
Royal Hospital for Sick Children, Glasgow and Hammersmith Hospital, London, UK
Founder Patron of STARS will lead the symposium debate *'To Treat or Not To Treat?'*

6 CPD points and attendance certificate for all delegates

STARS INTERNATIONAL SYNCOPE SYMPOSIUM

Application Form - Information Request - Medical Professionals only

- ☐ Please register me for the Symposium - I enclose a cheque for **£95**
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- ☐ Please send details of the STARS National Conference to be held on 28/09/02 at the NEC, Birmingham
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Inaugural meeting at new UK epilepsy assessment centre

25 April, 2002, Buckinghamshire, UK

The world's leading medical centre for assessing and treating people with epilepsy was officially opened at The National Society for Epilepsy in Chalfont, Buckinghamshire, on Thursday 25 April 2002 by HRH the Duchess of Gloucester.

HRH the Duchess of Gloucester unveiling the plaque at the opening of the Sir William Gowers Centre, NSE, Chalfont, Buckinghamshire.

The Sir William Gowers Centre

This purpose-built Assessment Centre providing 26 beds and five outpatient rooms at the National Society for Epilepsy (NSE) is linked to the state-of-the art MRI Unit, which was completed in 1995. The Sir William Gowers Centre – named after one of the 19th century founders of the NSE, to commemorate his role in establishing modern understanding of epilepsy and its treatment – is the first centre anywhere in the world where an MRI scan can be performed immediately after a seizure. The proximity of patients 'on site' minimises the time between seizure occurrence and scan, providing exciting new possibilities for scientific understanding of ictal activity. Other facilities at the centre include EEG and pharmacology laboratories, video-EEG telemetry, neuropsychological testing and occupational therapy. Patients are referred for a number of reasons such as clarification of their diagnosis, classification of seizure type, supervised optimisation of antiepileptic drug (AED) treatment and formulation of a longer term social and medical care plan.

Although an assessment unit has existed at the NSE since 1972, previous accommodation was inadequate for the 280 inpatients and 2000 outpatients who are referred there each year. It took 10 years to plan, design, raise the necessary £2.4 million, build and complete the Sir William Gowers Centre. Funding for the new seminar room at the centre was donated by GlaxoSmithKline. The inaugural meeting in this room, attended by about 60 neurologists from the UK, took place on 26 April 2002.

Professor John Duncan
Medical Director, National Society for Epilepsy

National Society for Epilepsy: past, present and future

The NSE is integrated with the National Hospital for Neurology and Neurosurgery, London, and provides valuable inpatient and residential facilities. Professor Ley Sander (UCL Institute of Neurology, London) presented a fascinating insight into the history of the NSE and the links between the two establishments.

In the 19th century, people with epilepsy were regarded as being possessed by the Devil and were often consigned to poorhouses, lunatic asylums or jails. By the mid-1880s physicians at Queen Square in London had recognised the existence of 'sane epileptics', and in 1892 William Gowers and others founded a society to provide employment for 'able epileptics'. An appeal was launched to establish a 'colony for the epileptics', and the current site at Chalfont opened in 1894. Junior physicians at Queen Square paid weekly visits there – a tradition that strengthened the medical and scientific standing of the establishment and that still continues today.

Sir William R Gowers, FRS (1845–1915) – one of the Founders of the National Society for Epilepsy

Early research at Chalfont (by Aldren Turner, 1894–1910) suggested that seizures were more likely between 10 pm and midnight and that salt deprivation decreased seizures by 30%. Current research is wide-ranging, covering areas such as neuroimaging, neurogenetics, epidemiology and pharmacology. Patients at the National Society for Epilepsy are often among the first to try new AEDs, and several experimental agents are currently under evaluation.

Emerging treatments for epilepsy

Professor Sander also presented a detailed review of current and pipeline drugs for epilepsy. Major goals of AED treatment are:

- complete seizure freedom
- no adverse effects (including cognitive effects and teratogenicity)
- maintenance of a normal lifestyle
- reduction in morbidity and mortality.

Conventional AEDs do not control seizures in 30% of patients. A number of 'new' AEDs have been licensed since 1990, but these drugs too have some limitations. In chronic epilepsy, the most successful new agents are Lamictal® (lamotrigine), Keppra™ (levetiracetam) and Topamax® (topiramate). In newly diagnosed epilepsy, the efficacy of new and conventional AEDs is comparable, but new AEDs are generally better tolerated. However, currently available treatments manage the seizures but not the underlying epilepsy, so there is an urgent need for 'curative', disease-modifying drugs.

The quest for potential new AEDs is not only revisiting old targets (the GABAergic system, NMDA receptors, ion channels) but also seeking to identify novel approaches to drug delivery, immunological targets, mechanisms of drug resistance, 'new' neurotransmitter systems (eg adenosine) and pharmacogenetic mechanisms. A large number of AEDs are currently in development – 4 in Phase I, 9 in Phase II and 4 in Phase III – and some of these are simultaneously being developed for other indications such as neuropathic pain, migraine, anxiety or mood stabilisation. A number of these pipeline AEDs – alongside recent genetic discoveries offer promising developments in treatment.

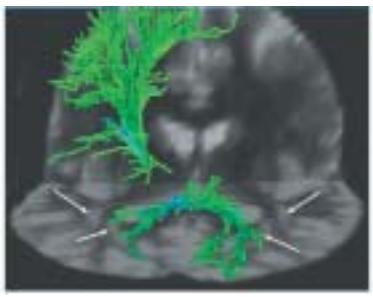
Professor Nicholas Wood (Institute of Neurology, London) explained how pharmacogenomics could provide more information on disease risk and drug responsiveness within the next 2 years. For Mendelian epilepsies, genes have been mapped at

more than 33 loci, including at least 10 genes for ligand- or voltage-gated ion channels. Mutations at these sites give rise to a variety of seizure types. For complex (non-Mendelian) traits, linkage disequilibrium mapping can help to localise large numbers of polymorphisms using a few markers.[1] Candidates for further investigation are all the Mendelian epilepsy genes, all 160 CNS-expressed ion channels, genes involved in signalling pathways (eg GABA) and sites of action of AEDs.

New imaging in epilepsy

MRI is used to establish the cause of epilepsy, assess its consequences, study the genetics and enhance surgical selection. It can identify structural abnormalities in 80% of cases of focal epilepsy. Dr Sanjay Sisodiya (Institute of Neurology, London) gave some specific examples of the use of new MRI sequences (diffusion tensor imaging [DTI], T2 mapping, magnetisation transfer ratio imaging and double inversion recovery) that can reveal subtle abnormalities in previously MRI-negative cases of epilepsy.

Imaging can increase our knowledge of the mechanisms underlying brain function, connectivity and biochemistry. Functional MRI (fMRI) combined with other types of imaging can give more information about function and structure. For example, tractography, an extension of DTI, can trace axon tracts within the human brain *in vivo* to reveal the putative distributed network that is contributing to epileptogenesis and identify the connections responsible for that network.



Tractography reveals the connections of the posterior corpus callosum and the pyramidal tracts in a patient with bilateral subcortical band heterotopia. The occipital region has been 'cut away' in this 3D reconstruction to show the forceps fibres of the corpus callosum passing through the splenium and into the occipital lobe. The axons traversing the heterotopic regions (white arrows) demonstrate the connections between the malformation and other parts of the brain.

Continuous EEG recording performed while a patient is undergoing fMRI scanning can help to pinpoint brain areas where there are signal changes associated with specific EEG discharges, providing additional localising information about seizures.

Teratogenic effects of antiepileptic drugs

About 3–4 pregnancies in every 1000 involve women with active epilepsy, giving a total of about 1800–2400 live births each year to women in the UK with the condition. AEDs administered during pregnancy can sometimes cause major malformations, minor abnormalities, and adversely affect psychomotor development and intra-uterine growth. Major malformations such as cleft palate and spina bifida occur in 1–2% of pregnancies not exposed to AEDs, but in AED-exposed pregnancies the overall risk for major malformations is thought to be around 2–3 times higher than the background rate. This estimate is based on several retrospective and prospective studies with varying methodologies. As such, it does not provide a firm basis on which to make recommendations to women with epilepsy who are taking particular AEDs, either singly or in combination, and who are contemplating pregnancy.

Dr John Craig (Royal Victoria Hospital, Belfast) described how he and colleagues set up the UK Epilepsy and Pregnancy Register about 5 years ago, to obtain accurate information on the relative risks and types of major congenital malformations associated with specific AEDs, and the effects of modifying dosage. A primary objective of their study is to investigate whether some AEDs pose a lower risk in pregnancy than others. Animal studies indicate that lamotrigine and gabapentin appear to cause fewer abnormalities than other AEDs. However, more data from humans is essential before firm conclusions can be drawn or recommendations made. So far, almost 2500 pregnancies in epilepsy have been reported to the register, and full outcome data are available for around 1910 (73% receiving monotherapy, 21.5% polytherapy and 5.5% untreated with an AED). Dr Craig encourages doctors to register all new pregnancies in women with epilepsy by ringing Freephone 0800 389 1248.

Informed choice: medico-legal implications

Changing relationships between doctors and patients mean that cases where personal autonomy confronts paternalism can make headline news and sometimes cost the NHS millions of pounds in medical negligence settlements. David Evans (Middlesex), a specialist healthcare lawyer, gave a highly informative presentation covering some implications of the Human Rights Act and issues surrounding patient consent, including the definition of 'capacity' (or lack of it) to make health-related choices.

Obtaining consent prior to treatment helps to protect doctors against two potentially damaging allegations: trespass (touching or attempting to touch a patient without consent) and negligence. A number of classical cases have set medico-legal precedents. In *Bolam v. Friern Hospital Management Committee* (1957), a patient who received ECT treatment without a relaxant drug dislocated both his hips. However, because the use of sedatives was not commonplace in the early 1950s, the court eventually ruled that the duty of care had *not* been breached. Much criticism followed this case, however, and 40 years later the House of Lords ruled that a court is not bound to absolve a doctor of liability just because experts agree that treatment has been in accord with sound medical practice (*Bolitho v. City and Hackney Health Authority*, 1997). The expert opinion must be logically justifiable. Current best practice requires that patients receive adequate information prior to consent.

This presentation provoked much lively discussion, particularly in relation to the issue of AED-related teratogenicity. There was a consensus that appropriate information needs to be given regularly and should be well documented. A woman may be advised about the potential risks of one agent in pregnancy and be offered an alternative. However, if she decides that she wishes to continue taking her current medication, the audience suggested that the specialist should record this conversation in a letter to the GP, with a copy to the patient.

The need to keep up-to-date with new developments and to provide clearly written patient information leaflets and was stressed. This meeting certainly helped attendees to achieve the first of these objectives.

Reference

1. Jeffreys AJ, Kauppi L, Neumann R. *Intensely punctate meiotic recombination in the class II region of the major histocompatibility complex*. Nat Genet 2001 Oct 29:217-22.

We would like to thank GlaxoSmithKline for sponsoring this report

Forum of European Neuroscience (FENS 2002)

13-17 July 2002 Paris, France

The 3rd Forum of European Neuroscience (FENS 2002) was hailed as a success. "It was a great meeting," said Pierre Magistretti, the new president of the Federation of European Neuroscience Societies. "And it can grow. FENS has been able to provide a new opportunity for European neuroscientists. It generates a synergy amongst societies."

Hosted this year by La Société des Neurosciences at Palais des Congrès in Paris, FENS 2002 brought together nearly 6000 people from around the world – the largest gathering yet. The previous two meetings were held in Berlin and Brighton with the aim of raising the status of neuroscience in Europe.

Delegates were not disappointed! There were around 3,500 sessions and posters covering a diverse range of topics:

- For people severely or partially paralysed the ability to communicate helps to improve their quality of life. For the first time, Professor Niels Birbaumer (Institute of Medical Psychology and Behavioural Neurobiology, Tuenbingen, Germany) has found a way to use the brain as an instrument with a 'thought translation' device operated by the patient's brain waves alone.
- The central ethical principle in human embryonic stem cells research is that of beneficence, said Professor John Harris (Manchester University, UK). A key aspect of ethical debates is the variety, diversity and strength of the various interests involved and the many stakeholders whose concerns require attention. According to Dr Glyn Stacey (National Institute for Biological Standards and Control, UK), the safety of stem cell therapy is as important as the ethical aspects. Regulatory guidance must be developed to ensure safety of stem cells intended for clinical application. Embryonic stem cell banks must be prepared and validated to provide a reproduceable source of quality stem cells. Professor Patrick Brundin (Lund University, Sweden) believes that the future of stem cell grafting for Parkinson's disease is very promising. The criteria for selecting patients and the way the tissue is handled are among the factors to affect the outcome.
- Understanding the biology of drug addiction and relapse is important in helping to inform social and clinical strategies to treat these chronic disorders. The knock-out mouse model with a gene deleted involved with the dopamine – or reward – system of the brain indicates to Dr Beatriz Rocha (National Institute of Drug Abuse, USA) that cocaine is still able to induce its effects by interacting with other brain chemicals. Her research shows that new therapies must be more wide-ranging to take into account these and other psychiatric conditions that reinforce cocaine addiction. Dr Taco De Vries (Vrije University, Amsterdam, The Netherlands) discovered recently that the cannabinoid system, which exists in the brain and regulates normal body and cognitive functions, also plays a role in relapse to cocaine and heroin abuse, possibly by altering the way nerve cells communicate with each other.

The BNA stand in the exhibition hall

Pierre Magistretti, the new president of the FENS.

Picture: Duncan Banks

- The genetic variation involved in causing ADHD points the way towards the development of new drug treatment and related disorders based on the dopamine (the reward) system in the brain, according to Dr David Collier (Institute of Psychiatry, UK). Pharmacogenetics is the science of relating the reaction to a pharmaceutical treatment to the specific genetic make-up of a person and, said Professor Philip Gorwood (CNRS, Colombes, France), is beginning to show promise for some groups of patients with schizophrenia and other psychiatric disorders.
- Serotonin is essential for functions such as body temperature, arousal and satiety. Dr Annie Daszuta (LNCF, Marseille, France) and her team have shown that the interaction of serotonin and estrogen could be significant in the treatment of depression and postmenopausal conditions.
- Professor Gareth Williams (Liverpool University, UK) has shown that orexins that partly regulate mood, appetite and sleep, are stimulated by low glucose in the body but when feeding is underway, they are switched off, thereby regulating short-term feeding habits. Narcolepsy is caused by a lack of orexins (also known as hypocretins) and affects around 1 in 2000 people and also affects certain breeds of dog. Dr Emmanuel Mignot (Stanford University, USA) has discovered that whereas in the Doberman dog there is a clear genetic link, in humans, the immune system plays a far more important role than genes and that narcolepsy appears to be an auto-immune disease. This knowledge could eventually lead to an entirely new approach to treatment.
- Around 2,500,000 people around the world have multiple sclerosis. Dr Robin Franklin (University of Cambridge, UK) has shown that there are changes in the inflammatory processes in response to MS and that repair of the damaged myelin sheath is best when the inflammatory processes are most active. This indicates that drugs that suppress inflammation could, in fact, hamper potential regeneration.

At a meeting such as this, national and European issues can be blended together. "There was a lot of positive energy this year at FENS and a good spirit for exchanges," said Professor Magistretti.

Elaine Snell

If you would like your event listed in the next issue, send details to: Rachael Hansford on Fax: 0131 3131110 or E-Mail: AdvancesinCNR@aol.com by October 8th, 2002.

2002

September

Better Care for Children & Adults with Epilepsy - A Consensus Conference
4-5 September, 2002; Edinburgh, Scotland
Rosemary Hector, Tel. 0131 247 3636, Fax. 0131 220 4393, E. r.hector@rcpe.ac.uk

5th Congress of the European Association for Neuro-Oncology
7-11 September, 2002; Florence, Italy
Tel. Carmine Carapella, Tel. 39 064 173 4412, Fax. 39 064 179 6897,
E. eano2002@ifo.it

5th International Congress International Society for Neuroimmunomodulation
8-11 September, 2002; Montpellier, France
E. Craig Smith, ccs@codon.nih.gov

Signal Transduction in the Blood-Brain Barriers
12-15 September, 2002; Berlin, Germany
E. bbb@fmp-berlin.de

4th World Congress on Stress
12-15 September, 2002; Edinburgh, UK
Tel. 01355 244966, Fax. 01355 249959, E. stress@glasconf.demon.co.uk

10th Meeting of the European Neuroendocrine Association
12-14 September, 2002; Munich, Germany
Tel. 49 89 5 482 340, Fax. 49 89 54 823 444, E. ena2002@i-plan.de

BSRM/University of Nottingham Advanced Rehabilitation Course
10-13 September, 2002; Nottingham, UK
E. info@bsrm.co.uk

Epilepsy Specialist Nurses Association Conference
16-17 September, 2002; Sheffield, UK
Tel. Chris Morley on 01482 587011

4th Asian & Oceanian Epilepsy Congress
12-14 September, 2002; Nagano, Japan
Tel. +81 3 3255 0900, Fax. +81 3 3255 7377, E. aoecsecret@gp.knt.co.jp

International Conference on Transmissible Spongiform Encephalopathies
15-18 September, 2002; Edinburgh, UK
www.tse2002.com, E. info@tse2002.com

Effectiveness of Rehabilitation for Cognitive Deficits
17-19 September, 2002; Cardiff, UK
Tel. Kath Giblin, 029 2087 5356, Fax. 029 2087 4858

British Sleep Society Annual Scientific Meeting
18-20 September, 2002; Cambridge, UK
E. bssoffice@huntingdon52.freeserve.co.uk

Neuroscan Scan School
18-20 September, 2002, London, UK
Med-Tech Systems Ltd, Tel. 01306-627171, Fax. 01306-627411, E. miguel@medtech-systems.com

SMART Introductory & Assessors Course
18-20 September, 2002, London, UK
Conference administrator, Royal Hospital for Neurodisability, Tel. 020 8780 4500 ext 5236, E. conferences@rhn.org.uk

ACTRIMS/ECTRIMS
18-21 September, 2002; Baltimore, US
Tel. 001 212 476 0465, E.ae2002@nmss.org

Neurobiological Background to Rehabilitation
19-21 September, 2002; Goteborg, Sweden
Tel. +46 31 81 82 20, Fax. +46 31 81 82 25, E. rehab2002@gbg.congrex.se

Nordic Movement Disorder Symposium
20-21 September, 2002; Oslo, Norway
Tel. 47 22 561 930, Fax. 47 22 560 541,
E. congrex@congrex.no

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

30th Annual Scientific Annual Congress of Neurological Surgeons
22-25 September, 2002; Philadelphia, US
Tel. 847 692 9500, Fax. 847 692 2589

British Human Genetics Conference
22-25 September, 2002; York, UK
Tel. 01216 272 634, Fax. 01216 272 634, E. york2002@bshg.org.uk

4th International Symposium on Experimental & Neurobiology
22-26 September, 2002; Tatranska, Slovakia
Tel. 42 556 785 074

Meeting of British Psychophysiology Society
23-25 September, 2002; Glasgow, UK
Hartmut Leuthold, Tel. 0141 330 6847, Fax. 0141 330 4606,
E. h.leuthold@psy.gla.ac.uk

Genetics & Dystonia
24 September, London, UK
E. j.townsend@ion.ucl.ac.uk,
www.ion.ucl.ac.uk/cgi-bin/seminars

Glial Cells and Progression of Neurodegeneration
24 September, 2002; London, UK
E. j.townsend@ion.ucl.ac.uk,
www.ion.ucl.ac.uk/cgi-bin/seminars

Management of Advanced Disease
24 September, 2002; London, UK
RSM, Fleur Raggatt, Tel. 020 7290 2984, E. geriatrics@rsm.ac.uk

Peripheral MRI Symposium
25 September, 2002; Warwick, UK
Clare Cooper, Tel. 01628 851532, E. clare.cooper@bracco.co.uk

2nd International Conference on Metals and the Brain
25-28 September, 2002; Fez, Morocco
Tel. 00 21 255 930 499, E. kingcon-gres2002@iam.net.ma

Epilepsy & Pregnancy Seminar
26 September, 2002; London, UK
Tel. Leigh Slocombe, ERF on 0208 995 4781.

International Syncope Symposium
27 September, 2002; Birmingham, UK
Tel. 01789 450 564, Fax. 01789 450 564, E. trudie@stars.org.uk

October

Nikon Digital Imaging Seminar
1 October, 2002; Oxford, UK
Tel. Clare Williams on 0208 541 4440.

Violence & Agression Awareness for Public Sector Employees
1 October, 2002; London, UK
Conference administrator, Royal Hospital for Neurodisability, Tel. 020 8780 4500 ext 5236, E. conferences@rhn.org.uk

Epilepsy: The Issues for Women & Girls
2 October, 2002; Truro, UK
www.epilepsy.org.uk/bea/seminarfrm.html

Facial Oral Tract Therapy
2-3 October, 2002; London, UK
Conference administrator, Royal Hospital for Neurodisability, Tel. 020 8780 4500 ext 5236, E. conferences@rhn.org.uk

Diagnosis & Management of Epileptic Syndromes
3 October, 2002; Copenhagen, Denmark
Dr Simona Tigaran, Fax. +45 89 493 300,
E. mona@akhphd.au.dk

ABN Autumn Meeting/British Neuropsychiatry Association
2-4 October, 2002; London, UK
Susan Tann, ABN, Tel. 020 7405 4060, Fax. 020 7405 4070,
E. abn@abnoffice.demon.co.uk

Prevention in Physical Medicine & Rehabilitation: Innovation in Ergotherapy
2-5 October, 2002; Hannover, Germany
Fax. +49 511 532-8124, E.
kongress2002.dgpmr-dve@mh-hannover.de

7th International Congress of the World Muscle Society
2-5 October, 2002
Mr Jacob Muller, Tel. 0031 71 527 52 97, Fax. 0031 71 527 52 62,
E. j.j.l.muller@lumc.nl

Workshop Function and Dysfunction of the Basal Ganglia
3 October, 2002; London, UK
E. j.townsend@ion.ucl.ac.uk,
www.ion.ucl.ac.uk/cgi-bin/seminars

BAS-BNS Autumn Meeting 2002
3-4 October, 2002; York, UK
Audrey Bowen, Tel. 0161 275 3401.

9th Annual Meeting of the American Society of Neurorehabilitation
4-5 October, 2002; Philadelphia, USA
Fax. 001 952 5456073, www.asnr.com

EPTA Autumn Scientific Meeting
5 October, 2002; York, UK
E. nigel.hudson@phnt.swest.nhs.uk

15th Congress of the European College of Neuropsychopharmacology
5-9 October, 2002; Barcelona, Spain
Tel. +31 205 040 207,
E. ecnp@congrex.nl

Stroke Beacon Conference
7th October, 2002; London,UK
Dr S M Tauzeeh, Tel. 020 8349 6303, Fax. 020 8343 4498,
E. anil.sohun@barnet-pct.nhs.uk

Approaches to the Cervical Spine
7-9 October, 2002; London, UK
Neurosurgery Courses Assistant, RCSE, Tel. 0207 869 6335, Fax. 0207 869 6329,
E. neurosurgery@rcseng.ac.uk

Xth World Congress on Psychiatric Genetics
8-12 October, 2002; Brussels, Belgium
Fax. +32 2779 5960,
E. wcpg2002@iceo.be

Recent Advances in Brain Injury Rehabilitation
9 October, 2002; London, UK
The Homerton Hospital, Tel. Dr Polly Phillipson on Tel. 020 8510 7453, Fax. 020 8510 7318.

15th Meeting of the European Society for Stereotactic and Functional Neurosurgery
9-12 October, 2002; Toulouse, France
Tel. +33 5 61 32 26 16,
E. ylazorth@cict.fr

Annual Conference on Alzheimer's
9-15 October, 2002; Barcelona, Spain
Tel. +49 0 605 097 220, www.alz.org

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

British Society of Neuroradiologists Annual Meeting
10-11 October, 2002; Winchester, UK
Drs Millar or Barker, Wessex Neurological Centre, Tremona Road, Southampton, SO16 6YD

Current & Future Trends in Stroke Treatment
12 October, 2002; New York, US
Fax. 001 212 781 6047,
E. cme@columbia.edu

Annual Meeting of the American Neurological Association
13-16 October, 2002; New York, US
Tel. 952 545 6284,
Fax. 952 545 6073,
E. lorijanderson@msn.com

Mount Sinai 2002 Update; Brain, Spine, Neurovascular Imaging
16-19 October, 2002; New York, US
Ryan Gibson,
Fax. 001 770 552 9859,
E. info@ryalsmeet.com

Practical Management of Memory Problems following Acquired Brain Injury
17-18 October, 2002; Ely, UK
Alison Gamble, Tel. 01353 652173, Fax. 01353 652164, E-Mail.
alison.gamble@pow.lifespan-tr.anglox.nhs.uk

British Geriatrics Society Autumn Meeting
17-18 October, 2002
Tel. 020 8977 0011, Fax. 020 8977 0055,
E. hmc@hamptonmedical.com

Peptides and Non-peptides of Neuroendocrine and relevance
17-19 October, 2002; Como, Italy
Eugeno Muller, Tel. +39 0 258 357 010,
E. eugenio.muller@unimi.it

ECNR - European Course in Neuroradiology
19-24 October, 2002; Crieff, Scotland
Dr Wendy Taylor, Tel. 01718 377 660, Fax. 01712 785 122, E. w.taylor@ion.ucl.ac.uk

Alzheimer's Disease International's 18th Annual Conference
23-26 October, 2002; Barcelona, Spain
Tel. 0034 93 201 7571, Fax. 0034 93 201 9789, www.alz.org

European Academy of Childhood Disability
24-26 October, 2002; Pisa, Italy
www.inpe.unipi.it/eacd2002

The Southern Meeting of Minds: A Review of ITB Therapy
25 October, 2002; London, UK
Dr Sylvia Bartley, Tel. 01923 212213.

Physiotherapy Treatment in the Overall Management of Parkinson's Disease
26 October, 2002; Vienna, Austria
Tel. 352 26 53 15 51, Fax. 352 26 53 15 52, E. mariella.graziano@internet.lu

European Federation of Neurological Societies Congress
26-30 October, 2002; Vienna, Austria
EFNS, Tel. 43 1 880 00270, Fax. 43 1 888 925581, E. headoffice@efns.org

12th World Congress of the International Society for Brain Electromagnetic Topography
27-29 October, 2002; Naples, Italy
Tel. 39 081 566 6504, Fax. 39 081 566 6523, E. isbet 2002@virgilio.it

20th Annual National Neurotrauma Society & The Sixth International Neurotrauma Symposium
27 October-1 November, 2002; Florida, US
E. nints@dprice.com, www.dprice.com

EDITOR'S CHOICE

The neuroscience of pleasurable caresses

It remains true that close observations of patients with neurological diseases can inform basic neuroscience. Take, for instance, the case of GL, now aged 54. At the age of 31, she had several episodes, apparently, of "polyradiculitis and polyneuropathy" that has been stable ever since: presumably a form of Guillain-Barre syndrome. Curiously, the immune attack was directed only against large myelinated fibres; a sural nerve biopsy showed preservation of small myelinated and unmyelinated fibres. Interestingly, and in contrast to the predictions of the gate-control theory of pain, her appreciation of noxious stimuli was no different from controls. Another prediction would be that she could only perceive pain and temperature sensations. But this Canadian-Swedish group decided to exploit the patient's unique deficit and explore whether she –like some animal studies have claimed- had some form of tactile sensation subserved by small fibres: "C tactile afferents" which are found only in hairy skin. And indeed she could detect a soft brushing motion on hairy skin, such as the forearm, but not on the palm. She could not identify the brushing stimulus, or describe the path that brush took across her skin, or detect vibration on hairy skin. She perceived the brushing as a very faint "touch", but she strongly felt a pleasant ill-defined sensation. In a functional MRI study, stroking hairy skin activated GL's insular cortex but not the somatosensory areas. The authors suggest that the C tactile afferents are not involved in discriminative sensation, but rather subserve a system for "limbic touch" where caress-like sensations arouse pleasure. ***-AJC***

Olausson H, Lamarre Y, Backlund H, Morin C, Wallin BG, Starck G, Ekholm S, Strigo I, Worsley K, Vallbo AB, Bushnell MC.
Unmyelinated tactile afferents signal touch and project to insular cortex.
NATURE NEUROSCIENCE
2002 Jul 29 (E-publication on-line)

PERIPERHAL NERVE

★★★ RECOMMENDED

Hereditary neuropathies: all sorted?

The last decade has seen major advances in our understanding of the genetic basis of hereditary neuropathies. Many of us routinely request peripheral myelin protein 22 (PMP22) gene analysis in patients with an inherited severe demyelinating sensori-motor neuropathy and suspected Charcot Marie Tooth disease (CMT 1a, MIM 118200). Often the test comes back negative – so what do we do then? Boerkeol et al. in Houston have addressed this question by carrying out a thorough molecular genetic analysis of their cohort of 153 genealogically unrelated patients with a suspected inherited neuropathy. The authors acknowledge that their specialist interest in inherited disorders will have led to a biased cohort, but a similar bias probably reflects the kind of patients that UK neurologists would consider referring for genetic testing in any case. In the Houston cohort, 91% of cases had a family history suggestive of a dominant neuropathy, 3% had a family history suggestive of a recessive neuropathy, and 6% were sporadic cases. Interestingly, they did not classify their patients neurophysiologically prior to genetic testing. The results confirm that the 17p12 duplication in PMP22 is the most common cause of an inherited neuropathy (51.6% of the 153 cases). The second most common cause were mutations in the gap junction protein b1 gene (GJB1, or connexin 32, 7.2%). Point mutations in myelin protein zero (MPZ) accounted for 3.3%, and point mutations in PMP22 also accounted for 3.3%. Mutations in the other genes known to cause peripheral neuropathy were extremely rare, causing <1% each of the 153 cases (these included the genes for early growth response factor 2, EGR2; periaxin, PRX; myotubularin related protein 2, MTMR2; and N-myc downstream regulated gene, NEFL). No mutations were found in 32.7% of the 153 cases – approximately 1/3. This is an important paper, but it raises more questions than it answers. What causes the remaining 1/3 of presumed inherited neuropathies, how can we explain the extreme clinical variation between family members harbouring the same gene defect, and why can different mutations in the same gene (MPZ) cause a predominantly axonopathic picture in some and a predominantly demyelinating neuropathy in others? Finally, studies such as this one raise the provocative question: should we think about a blood test first, and reserve neurophysiology for the difficult cases? This may be unrealistic at present, but now we have identified most of the genes involved in hereditary neuropathies, we simply need to wait for high throughput molecular genetic diagnostic technology to catch up. ***–PFC***

Boerkoel CF, Takashima H, Garcia CA, Olney RK, Johnson J, Berry K, Russo P, Kennedy S, Teebi AS, Scavina M, Williams LL, Mancias P, Butler IJ, Krajewski K, Shy M, Lupski JR.
Charcot-Marie-Tooth disease and related neuropathies: mutation distribution and genotype-phenotype correlation.
ANNALS OF NEUROLOGY
2002;51:190-201

How do intravenous immunoglobulins work in Guillain-Barre?

Guillain-Barre is usually envisaged as a T cell-driven autoimmune disease that leads to inflammation and demyelination of proximal nerve root and peripheral nerve. However Angela Vincent's group in Oxford, as well as the authors of this study, have shown in the past that antibodies circulating in patients with Guillain-Barre syndrome cause electrical conduction block in animal models of neuromuscular transmission. Klaus Toyka's group in Wurzburg have now investigated whether IVIG in Guillain-Barre operates on this pathogenic mechanism. They studied the effect of sera from seven patients, both before and after IVIG, on neuromuscular transmis-

sion in the mouse hemidiaphragm model. With a "macro" patch-clamp (larger than the conventional sort), the electrode can perfuse, and record from, both the pre- and post-synaptic membranes. They showed that sera from patients before IVIG reduced the quantal release of acetyl-choline and blocked neuromuscular conduction. Sera taken after IVIG did not have the same effect. Most interesting of all, mixing the pre- and post-IVIG serum samples abolished the former's blocking effect, as did incubation of the pre-infusion specimen with therapeutic-grade IVIG.

This suggests that part of the effect of therapeutic IVIG on Guillain-Barre may be the restoration of conduction at neuromuscular junctions. This should be eminently testable by serial electrophysiological analyses of patients. Perhaps this explains why some patients with Guillain-Barre improve so quickly after IVIG, far quicker than could be accounted for by a cellular repair process.-***AJC***

Buchwald B, Ahangari R, Weishaupt A, Toyka K.
Intravenous immunoglobulins neutralize blocking antibodies in Guillain-Barré syndrome.
ANNALS OF NEUROLOGY
2002 51: 673-680

NEUROGENETICS

★★★ RECOMMENDED

Vanishing white matter disease

The widespread use of Magnetic Resonance Imaging has led to identification of many patients with unexplained leukodystrophies, particularly in childhood. At present it is only possible to reach a specific biochemical or molecular diagnosis in a small proportion of these cases. Vanishing white matter disease (VWM, MIM 603896, also called childhood ataxia with central hypomyelination) is one of these disorders. It is instantly recognisable by the striking appearance of the white matter on MRI, with large areas that have the same signal intensity as CSF on all pulse sequences, including proton density and FLAIR images. In sagittal section, the brain appears to have large cavities extending throughout the white matter, separated by fine septae radiating from the corpus callosum. VWM disease usually presents in childhood with ataxia, spasticity, seizures and optic atrophy with mild cognitive decline. Sudden deterioration in VWM disease is well described following head injury or in association with viral infections. Interestingly, presymptomatic young adults have been described with the disorder, and it may present in middle age with a slowly progressive dementia. The inheritance pattern of VWM is autosomal recessive, and the molecular basis has just been identified. Mutations in each of the five subunits of the eukaryotic translation initiation factor (eIF2B) gene have been described in patients with VMW disease. IF2 initiates and regulates the translation of messenger RNA within the cytoplasm, and the mutations in patients with VWM are the first gene defects to disrupt this critical cellular process. It is intriguing why this should cause a disease that solely affects the white matter of the brain. Although VWM will probably turn out to be a rare disorder, it may present in adult life, and it is worth looking at the images in the clinical papers. Once seen – never forgotten. ***-PFC***

Leegwater PA, Vermeulen G, Konst AA, Naidu S, Mulders J, Visser A, Kersbergen P, Mobach D, Fonds D, van Berkel CG, Lemmers RJ, Frants RR, Oudejans CB, Schutgens RB, Pronk JC, van der Knaap MS.
Subunits of the translation initiation factor eIF2B are mutated in leukoencephalopathy with vanishing white matter.
NATURE GENETICS
2001;29:383-388

Prass K, Bruck W, Schroder NW, Bender A, Prass M, Wolf T, Van der Knaap MS, Zschenderlein R.
Adult-onset leukoencephalopathy with vanishing white matter presenting with dementia.
ANNALS OF NEUROLOGY
2001;50:665-668

van der Knaap MS, Leegwater PA, Konst AA, Visser A, Naidu S, Oudejans CB, Schutgens RB, Pronk JC.
Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter.
ANNALS OF NEUROLOGY
2002;51:264-270.

★★★ RECOMMENDED

Huntington's disease-like 2 - how common is this?

There are an ever-growing number of patients who develop what looks like Huntington's disease but don't have the appropriate CAG repeat in the huntingtin gene. These cases represent a heterogeneous group of patients, some of whom display clear inheritance. In 2001 Margolis et al (Ann.Neurol. 50:373-380) described an HD like disorder that mapped to chromosome 16 and was associated with a CAG/CTG repeat in the gene coding for junctophilin-3. This condition has been termed Huntington disease-like 2 and to date has only been found in families of African origin. In order to ascertain how common it is in Europe, Bauer et al report their findings in a short letter to the Annals of Neurology (which is easy to overlook) on the frequency of this gene defect in the cohort of patients from Austria and Germany who have "gene negative" HD. This group consists of a staggering 1,600 patients referred by neurologists for HD testing that were negative for the gene, in so much as they had a CAG repeat length in exon 1 of huntingtin of less that 37. On testing, none of the patients had an expanded allele in the junctophilin-3 gene, which explains its reporting as a letter rather than a full report.

This paper is important for those involved in HD, as it means that this gene defect is unlikely to be of significance in individuals of a non-African background who present with an HD like illness. It is also important in highlighting the fact that negative results can often be overlooked because they are deemed to be low priority publications, and as such biases can be left in the literature and so in clinical practice - ***RAB.***

Bauer I, Gencik M, Laccone F, Peters H, Weber BH, Feder EH, Weirich H, Morris-Rosendahl DJ, Rolfs A, Gencikova A, Bauer P, Wenning GK, Epplen JT, Holmes SE, Margolis RL, Ross CA, Riess O.
Trinucleotide repeat expansions in the junctophilin-3 gene are not found in Caucasian patients with a Huntington's disease-like phenotype.
ANNALS OF NEUROLOGY
2002 51:662.

★★★ RECOMMENDED

Copy a flower or draw a clock?

Unilateral neglect is common after right hemisphere stroke and is associated with poor functional outcome. It is therefore important to identify the problem early and monitor it. However screening is often haphazard. Clinicians may choose a single quick and easy bedside test such as asking the patient to draw a flower or to spot a wiggling finger, when they are examined on admission, but very often the neglect is discovered later by observation from staff. Choosing the best early detection test is a problem, since there are many and the tests' sensitivities are often unknown.

19 centres in France and Belgium have collaborated to assess the sensitivity of a battery of tests for spatial neglect and compare

the results with performance on a behavioural test comprising 10 daily living tasks. 206 consecutive patients suffering from first ever unilateral right hemisphere stroke were included. Most were in rehabilitation settings. The patients were tested on pencil and paper tests: bells cancellation test, figure copying, clock drawing, line bisection and writing, a reading test, recognition of overlapping figures as well as assessments to determine gaze orientation, the ability to find the left hand using the right and bilateral finger wiggling for extinction. In two of the participating centres a standardised behavioural assessment was also performed.

According to the behavioural assessment, neglect was considered as clinically significant in about one third of cases but detection of neglect varied greatly between the pencil and paper tests. The proportion of patients who scored below normal ranged from 19-50 %. More than 85% of patients presented with some degree of neglect on at least one test. The bell's test was found to be the most sensitive, in particular the measurement of the patient's starting point of cancellation. The line bisection test was the least sensitive. The presence of neglect was found to be task dependent and the results of this study support the view that neglect is not a simple unitary disorder. It follows then that several tests done by the bedside are more likely than a single test to detect neglect that will affect behavioural performance. Following the results of multiple regression from this large study the French Study Group suggest that the bells cancellation test, figure copying and clock drawing used together as a battery would pick up neglect in the majority of cases. ***–AJT***

Azouvi P, Samuel C, Louis-Dreyfus A et al., for the French Collaborative Study Group on Assessment of Unilateral Neglect
Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke.
JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2002: 73: 160-66

Chiropractic Manipulation And Stroke

There are many reports of posterior circulation stroke secondary to vertebral artery dissection seemingly provoked by chiropractic manipulation of the neck. However these are generally anecdotal cases or small series. Thus the true relationship of chiropractic manipulation as a cause of stroke is open to publication, selection and recall bias. This study seeks to determine whether, and if so with what risk, chiropractic manipulation of the neck really does lead to vertebrobasilar infarction.

Each of 582 patients with a posterior circulation infarct admitted to hospital in Ontario were identified retrospectively and matched to 4 controls from the local population. Public health billing records were used to identify all persons having chiropractic manipulation prior to the event date.

Patients under the age of 45 were five times (95% CI 1.32-43.87) more likely to have undergone chiropractic manipulation than controls in the week before stroke onset and were five times as likely (95% CI 1.34-18.57) to have made 3 or more visits to a chiropracter for neck manipulation in the previous month. There was no association for patients over the age of 45 yrs.

This is the first population based control study to test the association between chiropractic manipulation and vertebrobasilar stroke and does demonstrate an association for young people. The results correspond to an incidence of 1.3 cases of stroke within 1 week of manipulation per 100 000 (greater than the 1 per million previously suggested). However biases do exist – patients who may have had a subarachnoid haemorrhage from intracranial extension of the vertebral dissection and patients with carotid dissections were excluded. The vertebrobasilar strokes were not all proven dissections. The visit to the chiropracter may have been due to the initial neck pain of a spontaneous dissection and the manipulation was not actually the cause of the dissection (although may have aggravated it). Clearly a large prospective population based case control study is the only way to eliminate such bias but this would require a long study period. Meantime the neurologist who sees a patient with a posterior circulation stroke needs to consider a dissection as a likely cause, patients who have had a previous spontaneous dissection should probably avoid chiropracters and chiropracters should refer on any patient who develops neurological symptoms between or after treatment sessions. Should they warn patients of the risk? Since it is 1:100 000 presumably not. ***-PM***

Rothwell DM, Bondy SJ, Williams JI.
Chiropractic manipulation and stroke: a population-based case-control study.
STROKE
2001;32:1054-1059

DEMENTIA

BACE: a therapeutic target in Alzheimer's disease

The amyloid b-peptide (Ab) that accumulates in the plaques in Alzheimer's disease (AD) brain is derived from the amyloid precursor protein (APP) by sequential activity of b- and g-secretases. A novel transmembrane aspartyl protease, b-site APP cleaving enzyme or BACE, also known as Asp2, has been characterised as b-secretase. This study examined BACE in human brain (sporadic AD, normal, and neurological controls).

BACE immunoreactivity in Western blots was quantified by image densitometry. Compared to b-tubulin, whose signal did not differ between AD and the control groups, BACE showed a 2.7 fold increase in expression in AD brain, and a 2.5 fold increase compared to a-synuclein. Consistent with increased BACE expression, there was a 1.8 fold increase in the signal for b-CTF/b-tubulin; b-CTF is the C-terminal fragment of APP produced by b-secretase cleavage, and the direct precursor of Ab.

Competitive reverse transcription polymerase chain reaction was used to quantify BACE mRNA levels. Similar results were found in AD and controls, suggesting no increase in message expression. Hence an alteration in protein metabolism would seem to be the cause of increased BACE expression.

Although the precise mechanism of increased BACE expression in AD brain is unknown, this study does suggest that BACE is a logical target for AD treatment. BACE knockout animals are viable and normal although devoid of Ab generation. Patents claiming BACE inhibitors for the treatment of AD have already been filed. ***-AJL***

Holsinger RMD, McLean CA, Beyreuther K, Masters CL, Evin G.
Increased expression of the amyloid precursor b-secretase in Alzheimer's disease.
ANNALS OF NEUROLOGY
2002;51(6):783-786

MULTIPLE SCLEROSIS

★★★ RECOMMENDED

How pregnancy protects mum in MS

It has long been recognized that women with multiple sclerosis experience fewer relapses during the third trimester of pregnancy compared to any other time. In a small study, in which two pregnant women with MS underwent serial MRI scans, a parallel reduction in T2-weighted lesions was demonstrated in the third trimester. A recent prospective study, published in the New England Journal of Medicine (1998) by Christian Confavreux, followed over 200 women with MS through their pregnancies and confirmed a statistically significant reduction in relapse rate during pregnancy, and an equal increase immediately afterwards.

Uncovering the mechanism by which relapses are reduced in late pregnancy would reveal a potential treatment that is more

effective than any of the currently licensed disease modifying drugs. To identify the mechanism by which pregnancy reduces disease activity in MS, Langer-Gould et al from Stanford used a mouse model of relapsing remitting multiple sclerosis (Relapsing Remitting Experimental Autoimmune Encephalitis – EAE). They then explored the effect of pregnancy on (i) the susceptibility to EAE; (ii) relapse rate; and (iii) the phenotype of the T cells driving the autoimmune process. They clearly demonstrated a reduction in relapse rate in late pregnancy as expected, and also a marked reduction in disease susceptibility if induction was attempted during mid/late pregnancy. (Interestingly, it has been observed that women whose first MS relapse is during pregnancy tend to follow a more benign disease course.) On the analysis of T cell function from pregnant 'protected' mice compared with virgin mice the group found no difference. They demonstrated the T cells had a Th1-cytotoxic- phenotype irrespective of whether or not the animal was pregnant. This was a surprise: hitherto the explanation for the protective effect of pregnancy had been a shift in the phenotype of T cells form Th1 to Th2. However, when serum from a pregnant mouse was added to cells from a virgin or pregnant mouse there was a reduction in the cytotoxicity of cells from both pregnant and non-pregnant mice. This phenomenon was not seen when serum was used from the non-pregnant mice. They concluded that a substance present in the serum during pregnancy was responsible for preventing the cytotoxic T cells from causing inflammation in the central nervous system.

The hunt is now on to identify the pregnancy related serum factor that keeps the self-reactive T cells in check. If it can be bottled, a treatment significantly more effective than currently available disease modifying drugs may emerge.

Langer-Gould A, Garren H, Slansky A, Ruiz PJ, Steinman L.
Late pregnancy suppresses relapses in experimental autoimmune encephalomyelitis: evidence for a suppressive pregancy-related serum factor.
JOURNAL OF IMMUNOLOGY
2002 Jul 15;169(2):1084-91.

EPILEPSY

Towards a mechanism of antiepileptic drug teratogenicity:

Any article involving the human ether-a-go-go-related gene (HERG) is bound to draw my attention. Though sadly not related to the Moulin Rouge, this article provides an insight into a possible mechanism of antiepileptic drug teratogenicity, an issue faced daily by most neurologists. The gene encodes the major human cardiac repolarisation channel (Ikr). During weeks 5-9 of development, class III anti-arrhythmics (blocking Ikr), trimethadione and phenytoin will induce identical embryonic arrhythmias at concentrations not affecting the maternal heart. Episodic hypoxia causes similar teratogenic changes and it is proposed that arrhythmia-induced hypoxia underlies the teratogenicity of these drugs. The pathological changes of vascular disruption and haemorrhage into the palate are similar for phenytoin and induced episodic hypoxia.

The current experiment was to explore the teratogenic properties of dimethadione (DMO), the active metabolite of the antiepileptic drug trimethadione. DMO was given intraperitoneally to mice on gestational day 9-16 at 1000mg/Kg, to identify the sensitive period. DMO was given at 125-1000mg/kg on day 12, which seemed to be the most sensitive day, to test dose effect relationships. Some mice were pre-treated with a-phenyl-N-tert-butyl-nitrone (BPN) a scavenger of reactive oxygen species. A placebo arm received just saline. Mice were sacrificed 24-28hrs after the dose of DMO. Observations on the mice included heart rate measurements, patch clamping to assess prolongation of the Q-T interval, which is a measure of abnormal cardiac repolarisation. Pathological examinations were made including somite number and assessment for palatal haemorrhage. In this study DMO caused early embryonic deaths in 16%, late foetal deaths in 9% and cleft palate. The main effect of PBN was to reduce cleft palate in a dose dependent fashion with a less clear effect on embryonic deaths.

The effect of DMO on heart rate was dramatic, with dose-dependent bradycardia (69% reduction in HR at the highest dose) and arrhythmia (29% at the highest dose), without affecting maternal heart rate. DMO had a clear dose-dependent effect on Ikr although the effect of TMO was less clear. The maximal effect of these drugs was at gestational day 12 and it disappeared after GD 13. These data support the view that DMO interferes with foetal heart rate. The timing of this effect coincides with the timing of development of cleft palate and corresponds to the appropriate period in humans. Although this effect is commoner in animals treated with trimethadione than phenytoin, it is fundamentally similar. Real progress is being made towards our understanding of foetal abnormalities with this group of drugs, which may help in anticipating problems with other drugs, if they can be tested against this model. ***-MRAM***

Azarbayjani F and Danielsson BR.
Embryonic arrhythmia by inhibition of HERG channels: a common hypoxia-related teratogenic mechanism for antiepileptic drugs.
EPILEPSIA
2002;43:457-268

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Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP. Tel. 01865 267154, Fax. 01865 267985.

Clinical Rehabilitation, Multiple Sclerosis
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E-Mail.arnoldjournals@hodder.co.uk,www.arnoldpublishers.com/journals

Current Opinion in Neurology
Lippincott Williams & Wilkins, 241 Borough High Street, London, SE1 1GB. Tel 0207 940 7564, Fax 0207 940 7530
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Epilepsia
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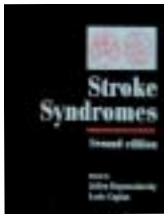
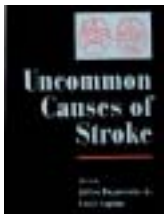
Book Reviews

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

Stroke syndromes (Second Edition) & Uncommon Causes of Stroke





Edited by: Julien Bogousslavsky & L. Caplan
Publisher: Cambridge University Press
ISBN No: 0 521 80258 X
Price: £240

The Stroke Syndromes book has been modified for its second edition: what used to be part III has now been split off into a separate book, "Uncommon Causes of Stroke". Chapters have been re-written and new ones added, and both books are very substantial. Stroke Syndromes runs to 53 chapters and 768 pages, with a thousand illustrations, whereas "Uncommon Causes of Stroke" is a mere 422 pages with 190 illustrations. Each retails at £150, or the publishers, Cambridge University Press, offer a magnanimous £20 saving if you buy both together at £280. In both books, individual chapters are written by one or more authors, with the editors fortunately contributing greatly, and they are to be congratulated in assembling some of the best known names in stroke neurology (though sadly few are British).

As its name suggests, Stroke Syndromes is almost entirely weighted towards clinical aspects of stroke neurology. Indeed Part I is devoted entirely to the clinical manifestations, including the whole gamut of possible symptoms arising in stroke, each discussed in chapters of between about 10 and 15 pages. Predictably, some chapters are well written, concise and clear (for example Hankey discussing TIA's and Wray discussing vascular ocular disease) whereas others are more heavy going. I did not find this a book to be delved into quickly or lightly, but its concentration on clinical features makes the effort worthwhile in almost all the chapters I sampled. The correlation of neurological features with acute lesion site is the stuff of traditional neurology and one comes away with the feeling of having one's neurological knowledge refreshed (or, in my case, extended) in general, let alone in the context of stroke medicine. The only glaring omission in this first part of the book is a chapter dealing with non-organic syndromes masquerading as strokes or TIAs. Experience suggests that this is a not uncommon clinical setting that is usually not realised by many of those who routinely care for stroke patients.

Part II moves away from clinical manifestations themselves, and considers the syndromes that arise according to the topography of the blood vessels. There is a useful reminder of the relevant vascular anatomy in a preliminary chapter and thereafter in subsequent chapters. Of course this works well in many of the vascular territories, but in others, the inter-patient variation in vascular supply introduces considerable complexities in the clinical pictures and makes the exercise of reduced value in clinical practice. Most chapters deal with this quite critically but it remains a major weakness of this approach. Nevertheless the chapters are detailed in outlining the deficits usually seen with vascular lesions in the different vascular territories throughout the central nervous system.

The range of causes covered in "Uncommon Causes of Stroke" is extremely wide and comprehensive, from the not so common (dissection, temporal arteritis, cerebral amyloid angiopathy) to the exceedingly rare. In many of these, the angiopathy extends to the eye, and the ocular manifestations are outlined well.

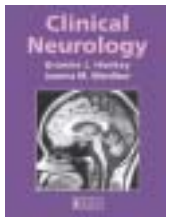
Sensibly, the authors of each chapter do not attempt exhaustive reviews. Most are quite short and punchy and referenced reasonably (the reader can take further if needed). In some, the number of references seems inversely proportional to the author's clarity of thought and expression, but in most chapters the writing is quite tight. I thought a greater use of small tables could have been made, emphasising essential points from the occasional morass of case reports, small print and uncertainty. Many chapters follow a standard format: introduction (including non-neurological features), pathology and pathogenesis, clinical features, investigations, treatment and prognosis. One can read all these in concise form, in one book covering a wide range of disorders, and come away with greatly increased knowledge. But will this be useful? Most definitely if the underlying diagnosis is already known because of previous non-neurological features in a multi-system disease, or because of a relevant family history. But what about the clinical neurologist's real problems: those patients in whom the neurological features occur very early, or worse, if they are the sole manifestation of this rare disorder? This is where the clinical `nouse' is needed and what I most wanted to find in these chapters: a little less knowledge and a bit more wisdom, informing me of the flavour of the cases, the differential diagnosis and most importantly the `red flags' which are going to alert me in the first place. These are unfortunately lacking in some of the chapters, whereas the experienced clinician's perspective shines through in others, for example the contributions from Davis, the editors and from Mokri (the clearest short article on arterial dissection I have seen).

By the essential nature of its topics, `Uncommon Causes of Stroke' is the antithesis of the book written by Charles Warlow and colleagues, `Stroke: a practical guide to management.' Each should have its place. Warlow's book will help neurologists through everyday practice, providing a very good evidence-base as it does so. This book will be used less often, but for individual patient care may well prove just as valuable.

These books will appeal to the neurologist, and in particular the neurologist with an interest in vascular disease, more than those physicians in the UK who routinely look after stroke patients. At £280, departmental libraries should consider them, though their appeal otherwise will be very much to the Stroke Neurologists, a rare breed in the UK.

Dr T Enevoldson, The Walton Centre for Neurology & Neurosurgery, Liverpool

Clinical Neurology



Authors: Graeme Hankey and Joanna Wardlaw
Publisher: Manson Publishing
Pages: 798 hardback
ISBN No: 1-84076-010-9
Price: £85

Alluring from the first idle flick through its glossy pages, this new textbook makes a profound and immediate visual impact. It is sumptuously illustrated: 'a speaking picture, with this end: to teach and to delight.' There are over 800 illustrations in fewer than 700 pages. The text, condensed into tables and bullet points, is often reduced to a few paltry lines on a page crammed with beautiful clinical photographs, line drawings, scans, angiograms and pathological slides. The authors and production team should all be congratulated. Many of the clinical photographs and radiological images come from the authors' personal collections. For instance they have contributed photographs on ulnar nerve palsies, syphilitic rash, Kennedy's syndrome, leprosy, Pott's disease and even the ascites of hepatic failure! This betrays a curiosity and enthusiasm for areas of clinical neurology well outside the authors' academic interest of stroke. This engaging keenness permeates the book and will undoubtedly project it into the neurological bestseller list. Much more so than the dutiful cap doffed at Evidence Based Medicine in the foreword, where the authors claim that they only recommend therapies on the basis of systematic reviews. They soon lose their inhibitions; for instance, second on their list of seven drugs to treat the ataxia of multiple sclerosis is thioridazine, for which there is no literature let alone clinical trial evidence.

Graeme Hankey and Joanna Wardlaw, from Perth and Edinburgh respectively, were aiming to produce a 'middle-sized clinical neurology' text, suitable for neurologists-in-training and practising neurologists. They have only one competitor for this slot. The likes of Geraint Fuller, Lionel Ginsberg and, especially, Ian Wilkinson have written condense readable texts at prices affordable by a medical student. At the other end of the market are the authoritative multi-volume textbooks from Bradley, Daroff, Fenichel & Marsden (£324) in its 1999 3rd edition, or Swash & Oxbury (£328). Hankey and Wardlaw's nearest rival is the superb Victor & Adams, whose 1997 6th edition has just come out in paperback costing £65. It is hard to think of a greater contrast. Victor & Adams draws on depths of historical and scientific scholarship, as well as personal experience, that Hankey and Wardlaw cannot yet match. But the illustrations in Victor & Adams are embarrassingly scanty and poorly produced. Gilded loam and painted clay. Personally, I will have to have both.

Alasdair Coles, Addenbrooke's Hospital, Cambridge

Symphony at BUPA Bushey

BUPA Hospital in Bushey, Hertfordshire recently held a celebration to mark the official opening of their new MRI Centre.

Neil Cox and Nigel Gibbs of Watford Football Club cut the ribbon to officially open the centre. Also present at the opening were Richard Jones, the Director of Operations for BUPA Hospitals and Andrew Gore, the hospital's General Manager.

The MRI centre is equipped with a Siemens MAGNETOM Symphony with Quantum Gradients and will perform a wide range of examinations including sports medicine, orthopaedics, neurology, vascular and abdominal imaging.

The opening in Bushey coincided with the BUPA Hospital in Manchester commencing its first clinical scanning. This installation in Manchester was the fourth Siemens MR scanner to be installed in a BUPA hospital.

For more information contact Mike Bell on Tel. 01344 396317, or see www.siemensmedical.com.

Pictured at the recent opening of the MRI Centre at BUPA Hospital Bushey are, (L to R) Richard Jones, Operations Director, BUPA Hospitals, Helen Gingell, MRI Manager, BUPA Bushey, Jonathon Gifford, Corporate Accounts Manager, Siemens Medical Solutions, Neil Cox and Nigel Gibbs of Watford FC and Andrew Gore, General Manager, BUPA Bushey.

Survey shows MS treatment still delayed

A survey of over 300 neurologists in 7 EC countries has revealed that, on average, disease-modifying beta interferon treatment for multiple sclerosis is not initiated until a patient has experienced between 4 and 5 documented MS relapses, despite current knowledge supporting earlier treatment. However, experts at the European Neurological Society (ENS) meeting predicted that this situation would change in the light of the recent extension of indication of Avonex" (Interferon beta-1a) for high risk MS patients.

Presenting the findings, Professor Hans-Peter Hartung from Germany said, "There is clearly a trend towards earlier treatment, but there continue to be barriers for prescribers to contend with." He expressed the hope, however, that this situation should change significantly as a consequence of the extension of indication for Avonex to include patients who have experienced only one attack or demyelinating event, who are judged to be at high risk of progressing to clinically definite MS.

For further information contact Biogen on Tel. 01628 501000, Fax. 01628 501010.

The Handbook of Neurological Rehabilitation, 2nd Ed.

Editors: Richard Greenwood (The National Hospital for Neurology and Neurosurgery, London), Michael P. Barnes (Huntersmoor Regional Rehabilitation Centre, Newcastle), Thomas M. McMillan (Department of Psychological Medicine, University of Glasgow), Christopher D. Ward (University of Nottingham).

This book is said by the publishers to be "An essential resource for anyone involved in the management of chronic neurological disease." This new edition comprises three thoroughly updated and expanded sections:

- Principles of Practice explores the clinical and biological principles underpinning rehabilitation practice in the context of neurological disablement.
- Assessment and Treatment of Functional Deficits describes the assessment, treatment, and management of the major physical, cognitive and behavioural impairments and resulting functional deficits that accompany neurological disease.
- Specific Disorders explores in detail problems and their management in the more common specific disorders of the nervous system.

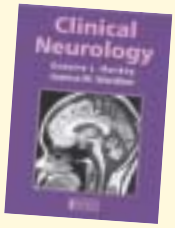
For more details, visit www.psypress.co.uk, Published January 2003. To pre-order, please Tel. 01264 343071.

Forthcoming prizes & awards

The Gordon Holmes Prize: Trainees in neurology, neurosurgery, neurophysiology, neuropathology or neuroradiology are invited by the RSM to submit summaries of their research in application for The Gordon Holmes Prize (value £100). The winners will be invited to give a 15 minute presentation (including 5 minute discussion) at a meeting of the Clinical Neurosciences Section on 6th February 2003. For submissions, please write to Fleur Raggatt, RSM, 1 Wimpole Street, London W1G 0AE by Friday 8th November.

European Academy of Rehabilitation Medicine, Prize 2002: The annual prize of the European Academy, up to 10,000 Swiss Francs, will be awared to an original work about rehabilitation, or to a project of research concerning a present study. The text or protocol typewritten, in French or English (including a summary in both languages) should be sent by 31st December 2002 to: Professeur Alex Chantraine, 3, rue Emile Yung, 1205 Geneve, Switzerland.

Clinical Neurology



Clinical Neurology is a concise yet comprehensive new reference guide combining the key elements of a textbook and colour atlas. The authors, Dr Graeme Hankey (Royal Perth Hospital, Australia) a neurologist, and Professor Joanna Wardlaw (Western General Hospital, Edinburgh) a neuroradiologist, provide practical and patient-oriented text integrating presentation, pathology, radiology, diagnosis and treatment options. The book contains over 800 quality illustrations, ranging from anatomical drawings to clinical photographs and pathology specimens, plus imaging using the latest techniques.

While emphasising the more common conditions, the book is said by the publisher to be a major source for trainees in neurology, and a valuable reference for neurologists, radiologists and general physicians.

Doody's Medical Reviews described the book as "An amazing tour-de-force of clinical neurology."

For more information, visit www.manson-publishing.co.uk or contact Manson Publishing Ltd on 020 8905 5150. See also our review on page 36.

FOCUS ON NEUROSCIENCE

The British Neuroscience Association

The British Neuroscience Association (formerly known as the Brain Research Association) is a professional organisation designed to represent the interests of neuroscientists in research, education, publishing, medicine and industry. It now has approaching 2000 members and is the fastest growing learned society, increasing its membership by 40% since its relaunch as the BNA in 1997. Members are primarily based in the UK but, increasingly, from further afield as well. The primary aims and objectives of the BNA are: to promote a multi-disciplinary approach to the study of the structure and function of the nervous system; to assist in the dissemination of research findings by means of lectures, discussions and meetings; to enhance the public understanding and awareness of progress in brain research; to support the education and training of young neuroscientists in schools, colleges, universities and in industry.

The BNA would welcome more members with a clinical background to foster a closer liaison with basic neuroscience researchers for mutual gain. For this reason, ACNR is now being circulated to all BNA members free of charge and clinicians are cordially invited to join the BNA.

In addition to discounted journals and books and other occasional 'special offers', benefits of membership now include the following: Reduced (50%) registration fees to the National Meeting and free admission to One-Day Symposia held throughout the year, including the popular Christmas Symposium; Regular newsletter and other relevant mailings; Regular 'BNA News Email Alert' service; Student prizes, and bursaries for attendance at BNA and FENS meetings; free on-line access to European Journal of Neuroscience; Concessionary (SFN membership rate) registration fees and sponsored abstract forms for Society for Neuroscience meetings; free advertising in 'BNA News Email Alert', the BNA Newsletter and on the BNA Website; free inclusive membership of the Federation of European Neuroscience Societies (FENS) and the International Brain Research Organisation (IBRO).

For further information E-Mail membership@bna.org.uk, or visit www.bna.org.uk. Annual membership fees start from as little as £15 for student members, £45 for full members. Membership applications can be made online, or forms can be obtained from The BNA Conference Office, Sherrington Buildings, Ashton Street, Liverpool, L69 3GE. Tel: 0151 794 4943 Fax: 0151 794 5516.

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The Cambridge BioScience website features a fully searchable database that covers over 16,000 products for life science research. This facility enables researchers to browse the extensive selection of neurobiology reagents on offer, not only from ABR but also from a variety of other suppliers, and order these products online.

For more information contact Rick Bhatt, Business Development Manager, Cambridge BioScience, 24-25 Signet Court, Newmarket Road, Cambridge CB5 8LA, Tel. 01223 316855, Fax. 01223 360732, E-Mail. tech@cbio.co.uk, www.bioscience.co.uk

R U *UP* 2 IT?

Texters (=those whose send and receive text messages) reduce words to character strings which are intelligible to the reader. Within cells, many proteins are subject to post-translational modifications and, once modified, become able to transduce messages. Ubiquitin (U) and ubiquitin-like proteins are known to direct redundant, mutant or misfolded proteins into a large multicatalytic complex, the proteasome (P) where they are enzymatically degraded. However, there is increasing evidence to suggest that U and U-like proteins do not necessarily only target proteins for destruction, but that the manner in which proteins are tagged may regulate many intracellular events other than degradation. There is currently intense research interest in the ubiquitin-proteasome pathway amongst neuroscientists and neurologists.

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For more information contact Olympus Optical Co. (UK) Ltd on Tel. 020 7250 4697, E-Mail. microscope@olympus.co.uk

Dedicated pulse generator for in ovo work

A new square wave pulse generator specifically designed for in ovo electroporation has been introduced by Intracel, specialist suppliers of products for electrophysiology and transgenesis.

The TSS20 Ovodyne is an up-to-the-minute electronic design offering simplicity of operation and low cost. It is based on experience and customer feedback from Intracel's TSS10 pulse generator, a mainstay of this application for a number of years, despite having been designed as a more general purpose instrument.

All the features normally required for in ovo electroporation are incorporated in the TSS20 Ovodyne, including multi-pulse programming, with adjustable voltage to a resolution of 0.1 v and adjustable space between pulses.

Operating parameters, which are shown on the matrix display, also include resistance measurement and a re-settable pulse indicator that confirms the number of pulses delivered. Remote hand and foot switches are optional.

For further information contact Tim Scot, Intracel Ltd, Tel. 01763 262680, Fax. 01763 262676, E-Mail. intracel@intracel.co.uk, www.intracel.co.uk

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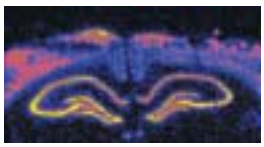
For more information contact World Precision Instruments on Tel. 01438 880025, Fax. 01438 880026, www.wpi-europe.com/stimulators/DS8000.htm

Digital autoradiography systems for basic neuroscience research



LabLogic Systems Ltd are UK distributors for the Micro Imager and Beta Imager. These two new systems reduce autoradiography imaging times to only a few hours, even when using low energy beta emitters. A spatial resolution of 15mm is achieved making the systems ideally suited to applications such as radio-ligand binding studies and in-situ hybridisation. Both instruments use direct beta counting to provide precise quantitation and the capability of imaging dual-labelled samples.

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For further information or to discuss applications in more detail contact LabLogic Ltd on Tel. 0114 2500419, Fax. 0114 2500291, E-Mail. hlyon@lablogic.com, www.lablogic.com

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REQUIP (ropinirole) Prescribing Information
Presentation 'Requip' Tablets, PL 10592/0085, 0087-0089, each containing ropinirole hydrochloride equivalent to either 0.25, 1, 2 or 5 mg ropinirole. 0.25 mg tablets - 210 tablets starter pack, £43.12; 1 mg tablets - 84 tablets, £46.20; 2 mg tablets - 84 tablets, £92.40; 5 mg tablets - 84 tablets, £184.80. **Indications** Treatment of idiopathic Parkinson's disease. May be used alone (without L-dopa) or in addition to L-dopa to control "on-off" fluctuations and permit a reduction in the L-dopa dose. **Dosage** *Adults:* Three times a day, with meals. Titrate dose against efficacy and tolerability. Initial dose for 1st week should be 0.25 mg t.i.d., 2nd week 0.5 mg t.i.d., 3rd week 0.75 mg t.i.d., 4th week 1 mg t.i.d. After initial titration, dose may be increased in gradual weekly increments of up to 3mg/day, until acceptable therapeutic response established. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually by around 20%. When switching from another dopamine agonist follow manufacturer's guidance on discontinuation. Discontinue ropinirole by reducing doses over one week. *Renal or hepatic impairment:* No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment - administration not recommended. *Elderly:* Titrate dose in normal manner. *Children:* Parkinson's disease does not occur in children - do not give to children. **Contra-indications** Hypersensitivity to ropinirole, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Ropinirole has been associated with somnolence and episodes of sudden sleep onset. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole - avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction seen with other Parkinson's disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme - ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol - as with other centrally active medications, caution patients against taking ropinirole with alcohol. **Pregnancy and lactation** Do not use during pregnancy - based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. Adverse reactions In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo, however, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see 'Precautions' and 'Effects on ability to drive and use machines'). **Effects on ability to drive and use machines** Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Overdosage** No incidences reported. Symptoms of overdose likely to be related to dopaminergic activity.

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