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Advances in Clinical Neuroscience & Rehabilitation



Paul Reading

The Neurological Sleep Clinic – Part 1 – The Sleepy Patient

Maurice Curtis, Andrew Naylor, Richard Faull

Manipulation of Neural Stem Cells as a Rehabilitative Therapy

Emma Matthews, Mike Hanna

Possible New Treatments in Muscular Dystrophy

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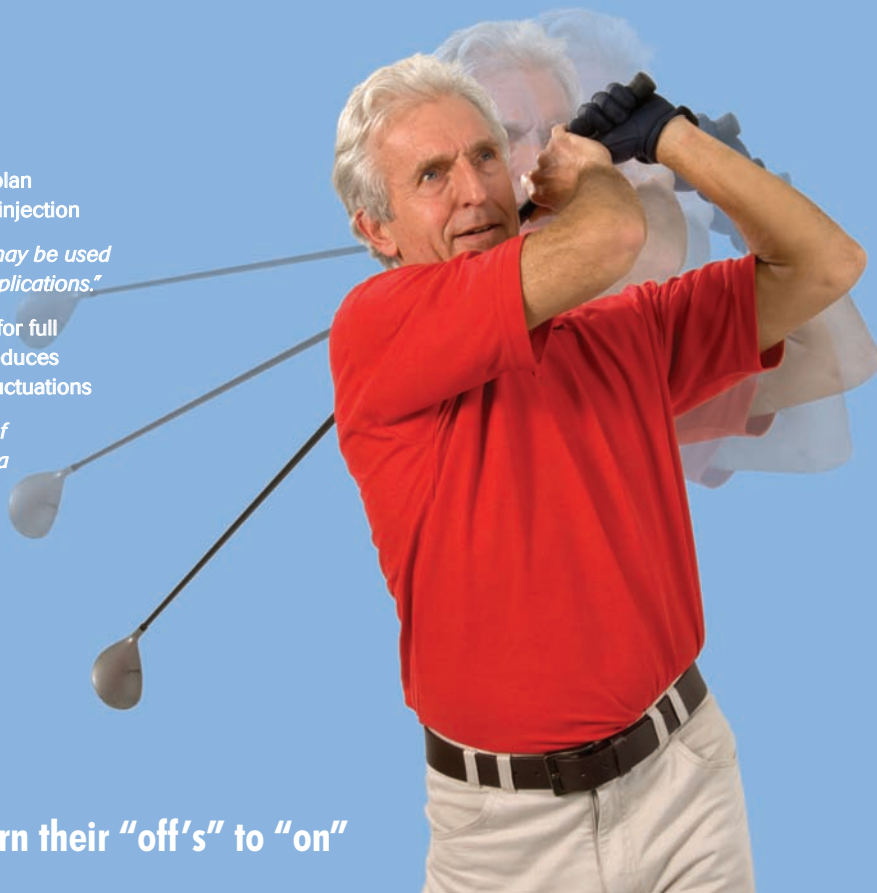
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March/April 2008

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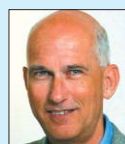
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Paul Reading in the first in his two part series on the Neurological Sleep Clinic takes us through his own views on how best to treat patients who have excessive daytime sleepiness and hypersomnolence. This account, whilst being a very personal one, nevertheless contains a very helpful framework in which to investigate and see patients who complain of this disorder.

Stem cells continue to be a major area of research interest in neuroscience and in their review article Maurice Curtis, Andrew Naylor and Richard Faull discuss the adult neural precursor stem cell. They discuss the evidence for the existence of two populations of such cells in the adult mammalian brain and how they respond to disease and might be manipulated in the future to promote repair. A stimulating article by one of the foremost groups working on this system in human neurodegenerative disorders.

Dysautonomia reflects a disorder of paroxysmal changes in autonomic nervous system activity which may have its origins in a disconnection syndrome targeting the midbrain in a subgroup of patients with severe acquired brain injury. This condition is often not recognised and Iain Perkes and Ian Baguely seek to educate us on this disorder and how it can be treated with a concluding plea for bigger, more multi centre studies into this condition.

Emma Matthews and Mike Hanna in our 'Neurogenetics' series edited by Tom Warner, provide an up to date account of novel therapies for muscular dystrophies. In particular they discuss therapies designed to work on exon skipping, read through of premature stop codons by small molecules that suppress these, transfection of truncated dystrophic mini genes using viral vectors and the blocking of myostatin. This excellent review highlights once more how the better identification of genetic causes of disease can lead to the development of novel disease specific therapies for patients.

Peter Whitfield in our Neurosurgery article in this issue discusses the NICE guidelines on head injury. The guidance is summarized in a series of tables which is an extremely helpful distillation, and to date what is proposed seems not as contentious as other similar guidelines, as Andrew Larner and Mark Doran discuss in their piece for 'Controversies in Neurology'. In this they discuss in detail whether the NICE/SCIE dementia guidelines are as useful as they would initially appear; in particular they question the wisdom in allowing neurological input to be peripheral rather than more central to the future development and management of patients with dementia. This is an interesting, thought-provoking article which again raises questions about the process by which one can best arrive at guidelines for widespread clinical practice.

The Neuropathology article is a clear informative account of the



pathology of intracerebral haemorrhage by Arundhati Chakrabarty and Aditya Shivane. In this article, the authors highlight two important new concepts that have emerged on the pathophysiology of this condition, namely, that many haemorrhages continue to grow and expand over several hours after the onset of symptoms, and secondly that most of the brain injury and swelling occurs after intracerebral haemorrhage as a result of inflammation caused by thrombin and other end products of coagulation. However, even knowing this has not yet altered the poor prognosis associated with this condition.

Whilst MS is common in the United Kingdom, it is much less so in more tropical countries such as India, although Lekha Pandit argues that this might not truly be the case in her illuminating account of MS and related disorders in India. The contrast in the management of MS in the UK and India is brought into sharp focus but with it comes the real belief and excitement that

things are about to change for the better and that Dr Pandit is one of those leading this.

We also have a summary of a roundtable discussion on the cognitive consequences of MS which covers the extent of the problem and how it can be better assessed and integrated into normal patient care is discussed.

In our Neurophysiology series, Antonio Valentín and Gonzalo Alarcón discuss the technique of single pulse electrical stimulation (SPES) to show that delayed responses to cortical stimuli are predictive and thus help identify epileptogenic areas of cortex. They present their data from 125 patients and discuss why the technique may be an important additional investigation in the pre surgical assessment of patients with refractory epilepsy.

Roald Dahl has made two significant contributions to neurology according to the short article by Andrew Larner in this issue of ACNR. Firstly, he helped in the construction of a valve for hydrocephalus, and secondly, developed a method for improving language recovery in aphasic patients.

Finally, we are sad to have to announce the loss of another great British neurologist, with the passing of Professor PK Thomas, who died on the 25th January this year.

We have our usual book, journal and conference reviews as well as our first column from the ABNT. On our website more can be found, including all the previous issues of ACNR a well as case reports. We hope that you continue to enjoy our journal and do let us know if we can improve on it.

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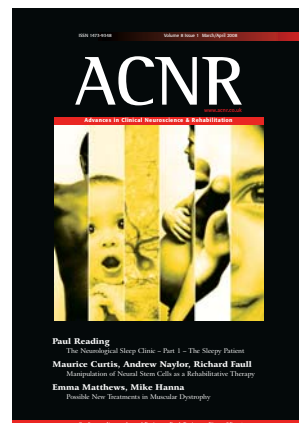
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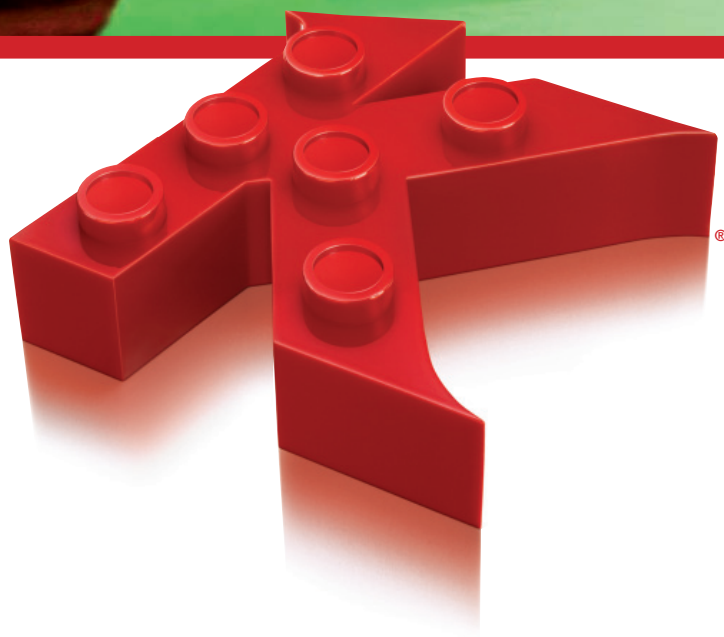
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The Neurological Sleep Clinic – Part 1

The Sleepy Patient

Traditionally, at least in the UK, sleep disorders have received a low profile in neurology training programmes such that only a handful of practising neurologists have an active interest in sleep medicine. As a consequence, most sleep centres are run exclusively by respiratory physicians who understandably focus, to varying degrees, on sleep-related breathing disorders. However, perhaps due to the astonishing developments in the neurobiology of primary sleep disorders, their inherent interest, together with an increasing recognition that abnormal sleep contributes to numerous common neurological conditions such as migraine and epilepsy, the situation is slowly changing. I have held a weekly ‘Sleep Clinic’ for seven years in the North-East of England and propose to summarise my personal approach to the assessment of sleep-related symptoms from a neurological perspective. It is often wrongly assumed that most patients with abnormal sleep require elaborate and expensive investigations in a “sleep laboratory”. In fact, the reverse is true: if the diagnosis is totally unclear despite an accurate history, it is relatively rare for overnight investigations to illuminate the situation. I am particularly fond of an adage from a respected, now retired, doyen of sleep medicine, Professor David Parkes, namely: “A good sleep centre has far more need of a psychiatrist than an EEG machine”.

In this, the first of a two part article, the assessment of sleepy patients will be discussed.

Excessive daytime sleepiness

It is only fairly recently that the symptom of excessive sleepiness has been taken seriously by medical practitioners rather than being seen as a moral failing or sin. In a neurological sleep clinic, it is probably the commonest problem that prompts referral, usually with the implicit underlying question: “Is it narcolepsy?” Narcolepsy is almost certainly massively underdiagnosed, especially if the quoted prevalence rate of 0.05% is accepted. This is partly because there is clearly a spectrum of disease severity. This should not be too surprising given the underlying specific neurochemical deficiency in typical cases. In particular, most narcoleptics lose around 40,000 hypothalamic neurons containing the neuropeptide, hypocretin (or orexin) in adolescence, presumably by an autoimmune process. Although yet to be confirmed, it is entirely possible that a partial deficiency produces less severe or atypical forms of the syndrome that may be more difficult to recognise.

A detailed sleep-wake history, together with a number of directed questions, will usually allow a confident clinical diagnosis. It is important to recognise that the key element of narcolepsy is an inability to maintain stable states of wakefulness (or sleep) for more than a few hours. In other words, it reflects ‘state instability’ with most of the symptoms reflecting an intrusion of sleep elements into wakefulness. For example, visual hallucinations and cataplexy are due to dream imagery and REM sleep paralysis, respectively, occurring when the subject is still awake.

Cataplexy is an extremely specific symptom very rarely seen outside of narcolepsy. It is present to varying degrees in over 60% of narcoleptics, in whom it usually occurs during emotional situations. Laughter in the relaxed presence of friends or family is the commonest trigger, although some report that anticipation of a positive emotion proves to be the most effective precipitant. For example, some narcoleptics have partial attacks in which they cannot reach the punchline of jokes without becoming tongue-tied or

frankly dysarthric. Full blown cataplectic episodes usually start with irregular jerking of the face or head with eye closure but retained awareness. There is subsequent descending paralysis such that the subject slumps to the floor as the knees give way. Because attacks evolve over two or three seconds and narcoleptics usually recognise situations in which they are vulnerable, injury is rare. Similarly, episodes are not generally seen in dangerous or life-threatening situations, presumably because other arousal systems intercede. A variety of emotions can act as triggers including (pleasant) surprise, frustration and anger. However, one should be careful not to over-interpret mild symptoms of knee buckling in extreme laughter or, indeed, anger as this probably reflects a normal reaction.

The nature of the excessive daytime sleepiness in narcolepsy is usually characteristic. It is described as ‘irresistible’ and invariably worse if the subject is unoccupied or bored. Short naps are generally restorative and may contain dreams or hallucinatory experiences. Most narcoleptics will admit to having dropped off in unusual situations. A recent extreme example that comes to mind was a young car mechanic who fell asleep whilst bent over the open bonnet of a car with the engine running!

Vivid or unusual dreams at night due to REM sleep fragmentation and other nocturnal phenomena are also very common. Many narcoleptics report that they can control their dreams to some extent. Indeed, some develop unusual notions that they have paranormal powers and can predict the future. Distinguishing dreams from reality can also be difficult and may produce embarrassing situations. Other nocturnal symptoms such as sleep paralysis are not particularly discriminative symptoms. However, if sleep paralysis occurs as the subject is falling asleep, rather than at the point of waking, narcolepsy should be considered. In keeping with the notion of “state instability”, many narcoleptics wake frequently through the night for no apparent reason and may even have difficulty dropping back to sleep. The full gamut of parasomnias is also relatively common in narcolepsy and includes arousal disorders, sleep talking and dream enactment.

It seems likely that there are subtle metabolic abnormalities in narcolepsy and it is always worth asking about appetite control and the possibility of an eating disorder. Many subjects report cravings for sweet foods in particular which can produce bingeing, especially at night. Narcoleptics tend to be overweight, it seems at least partly as a consequence of altered appetite control.

Finally, from the history, it is worthwhile exploring the concept of ‘automatic’ behaviours. Most narcoleptics complain that they are ‘switched off’ for most of the day, unable to focus, concentrate or take in information effectively. As a result of this, brief so-called ‘micro-sleeps’ are common such that subjects perform complex tasks including writing without full awareness or control. Placing objects in bizarre places or simply losing items around the house are particularly common examples of this.

Because narcolepsy can be disabling and is generally lifelong, some authorities suggest that confirmatory tests are mandatory before treatment is started. This is debatable, especially if appropriate resources are scarce, although investigation is often appropriate in cases where the history is not classical and particularly if cataplexy is absent. The recently published criteria for diagnosing narcolepsy seem clear-cut in that a positive diagnosis is achieved when CSF levels of hypocretin are less than 110pg/ml or if the subject falls asleep in under eight minutes, on average, in a



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Key references for further reading

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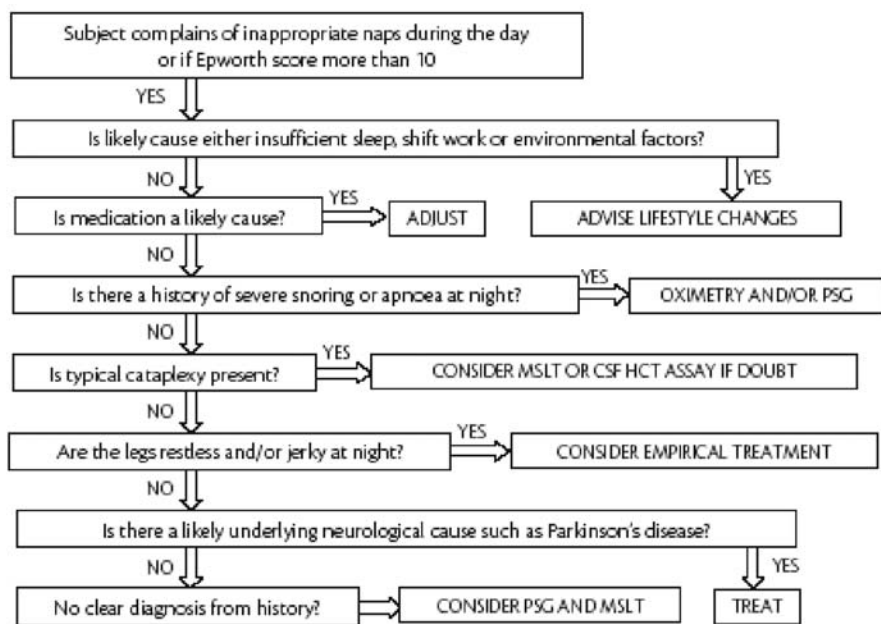


Figure 1: Algorithm for assessing subjects with excessive sleepiness. Oximetry can usually be performed in the home setting. PSG – polysomnography; MSLT – multiple sleep latency test; CSF – cerebrospinal fluid; HCT – hypocretin (also called orexin).

multiple sleep latency test (MSLT) and achieves REM sleep in at least two of the nap opportunities. Unfortunately, at a practical level, these tests are not always very helpful in cases where there is clinical doubt from the history. For example, hypocretin CSF levels may be preserved in mild or atypical cases and, in any case, reliable assays are offered by very few centres. Determining hypocretin levels can be useful, however, if results from a MSLT are surprising or if there are problems with interpretation. It is also useful in diagnosing childhood narcolepsy.

The MSLT is a notoriously fragile investigation and prone to producing false negative results. This is probably because most centres performing the test do not have particular expertise or, indeed, interest in sleep investigations and rarely have strict protocols. Several studies have demonstrated the widely varying results that can be obtained from a MSLT, depending purely on the advice given to the subject or the nature of their activities between nap opportunities. From a diagnostic perspective, I believe a convincing history should hold sway over a 'negative' MSLT.

Given that a very high proportion of narcoleptics have a DQ1B*0602 histocompatibility haplotype, many clinicians believe that HLA testing has an important role in diagnosing narcolepsy. I think this is very rarely the case as I have seen numerous cases of DQ1B*0602-positive sleepy people who are not narcoleptic and a smaller number of 'negative' patients with definite narcolepsy who have turned out to be hypocretin deficient. Despite its relative ease, it is simply not a specific or sensitive enough test to be of general use.

Other causes of excessive sleepiness

A brief algorithm is provided for assessing somnolent patients (Figure 1). Most sleep experts will claim that an identifiable cause will be found for the majority of sleepy subjects, even if it turns out that they are simply 'overdoing it'. Certainly amongst respiratory physi-

cians, the Epworth score is used as a screen to differentiate sleepiness from chronic fatigue, for example, and scores over 10 are usually deemed worthy of further assessment. In my opinion, the most useful discriminatory stem question from the Epworth scale is the one that asks about typical levels of sleepiness if a subject is a passenger in a car for an hour or more. In most populations, the commonest cause of significant daytime somnolence is obstructive sleep apnoea which effectively produces symptoms by severely disrupting overnight sleep. In the typical clinical setting with a good history from a bed partner or family member, the diagnosis

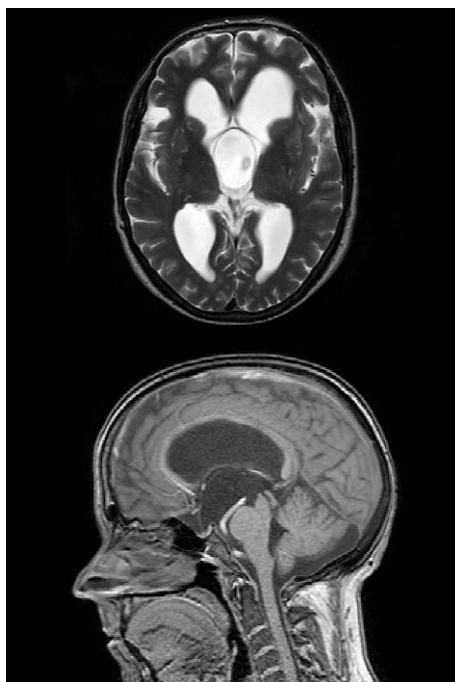


Figure 2: A T2 weighted axial image (top) revealing an arachnoid cyst in the region of the third ventricle in a 45 year-old male patient presenting with excessive sleepiness, headaches and likely cataplexy. Sagittal views (bottom) demonstrate likely compression of the hypothalamus which may well account for his apparent secondary narcolepsy.

is generally straightforward and, as such, patients rarely present to neurologists. However, if the subject is not particularly overweight or if there is no corroborative history, it can easily be missed. Furthermore, it can occur as co-morbidity in patients with other diagnoses, including narcolepsy. If a patient admits to long but unrefreshing sleep and wakes with a dry mouth, feeling 'hungover', it is almost always appropriate to arrange at least overnight oximetry to explore the possibility of significant nocturnal hypopnoea or apnoea.

If narcolepsy is being considered but the history is not clear cut and cataplexy is absent, for example, the somewhat enigmatic diagnosis of idiopathic hypersomnia often needs to be considered. Typical cases are fairly rare compared to narcolepsy and are characterised by long but unrefreshing overnight sleep that appears ostensibly normal even when monitored in a laboratory setting. The main complaint is usually an extreme difficulty getting up in the morning and a subsequent propensity to long daytime naps. There are no symptoms suggestive of abnormal REM sleep mechanisms in contrast to narcolepsy. Diagnostic criteria require a sleep latency of less than eight minutes. Controversially, idiopathic hypersomnolence is now recognised as occurring with and without long overnight sleep. A number of commentators suggest that the latter category might, instead, reflect a form of monosymptomatic narcolepsy.

Most other causes of daytime somnolence can be attributed to poor quality overnight sleep. Of these, perhaps the most important treatable diagnosis is restless legs syndrome (RLS) and associated periodic limb movement disorder. RLS is a clinical diagnosis and, relatively unusually, both a cause of insomnia and daytime somnolence. If symptoms are severe, a therapeutic trial of a drug before bed is usually warranted, if only for a short period. Occasionally, in the absence of RLS and even if a bed partner is not aware of excessive movement, overnight tests pick up significant periodic leg movements or jerks that can be shown to partially arouse the sleeping subject. Given a number of potentially effective treatment options, this is a relatively rare situation in which overnight polysomnography can be extremely helpful, albeit often in retrospect.

A number of neurological patients will complain of troublesome somnolence and, assuming that breathing-related disorders have been excluded, it is debatable whether thorough investigation will aid management. Examples include patients with parkinsonism, myotonic dystrophy and multiple sclerosis. In many such patients, the ultimate cause of their somnolence is likely to be multi-factorial and an empirical approach, perhaps using wake-promoting agents, is probably justified if symptoms are troublesome. Occasionally, there will be patients with no underlying diagnoses or clues as to the cause of their somnolence. In these, a relatively low threshold for brain imaging is recommended as the author has occasionally picked up otherwise asymptomatic pathologies such as arrested hydrocephalus, arachnoid cysts in the region of the third ventricle (see Figure 2), and various hypothalamic lesions as likely substrates for the sleepiness.

Manipulation of Neural Stem Cells as a Rehabilitative Therapy

The brain develops from stem cells that are born in the medial and lateral ganglionic eminences, migrate towards the pia matter and reside in regionally specific regions of the brain where they differentiate to form neurons and glial cells. Until the last decade the common belief has been that after development ceases, no new neurons are produced in the brain. In reality, new neurons are continually produced in the brain throughout the life of mammals. In response to intrinsic cell death in a particular brain region or as a result of external stimuli, differential regulation of brain-harboured stem cells occurs. Thus in general terms, the stem cell niches in the adult brain remain sensitive to internal and external stimuli encountered by the individual, and this unique function continues throughout life.

The stem cell niches in the adult brain

In the mammalian brain there are two stem cell/neurogenic niche regions: the subventricular zone (SVZ) near the basal ganglia and, the subgranular zone (SGZ) of the hippocampus. In the adult brain, neurogenesis continues in the SVZ throughout adult life, providing ongoing cell replacement in the forebrain, particularly in the olfactory bulb.¹ The proliferation-permissive environment, some fate determinants, and the direction of migration of stem cells are at least, in part, determined in the SVZ.^{2,3} The biology of the SVZ in the normal and diseased human brain demonstrates, similar to the rodent, that the SVZ retains a neurogenic potential. The human SVZ is in close proximity to the nutrients and growth factors in the cerebrospinal fluid of the lateral ventricle from which it is separated only by the ependymal cell layer. The SVZ is enriched in proliferative compounds such as cannabinoids, neuropeptide Y, and growth factors and their receptors, all of which are important for the development and maintenance of multipotent stem cells in the adult brain.⁴

The hippocampus is a brain structure involved in the formation of memory and varied learning tasks; for

instance in rodents, the hippocampus is crucial for spatial memory and contextual discrimination. The hippocampus also harbours stem cells born in the SGZ, which lies immediately beneath the granule cell layer (GCL). The SGZ stem cells migrate into the GCL, differentiate and integrate into the host circuitry and become fully-functioning neurons. Extensive studies have been carried out on the GCL by labelling stem cells with viral vectors in order to follow the progression of a single cell and to determine which type of cell it differentiates into; recent studies have now shown that stem cells can grow to become fully functioning granular neurons.⁵

Stem cells are altered in neurological disorders

Neurodegenerative disorders alter the proliferation and neurogenic potential in the stem cell niche. In Huntington's disease there is a 2.8-fold increase in the number of proliferating cells in the SVZ, which includes increases in the three major classes of cells in the SVZ, namely neuroblast, glial/stem cells and transit amplifying cells. The degeneration of striatal neurons is the major driver of stem cell proliferation, although it still remains unclear as to whether SVZ stem cells migrate toward the striatum in the human brain. However, in the rodent brain, there is clear evidence for migration away from the SVZ toward the affected area with subsequent functional recovery after a Huntington-like lesion in the striatum.⁶ In stroke injury there is as much as a 30-fold increase in the numbers of proliferating cells in the SVZ in animal models and there is substantial migration toward the stroke lesion following occlusion of the middle cerebral artery.⁷ By contrast, in Parkinson's disease, the loss of the dopaminergic projections from the substantia nigra pars compacta leads to denervation of the dopaminergic input to the SVZ and as a result, one of the major proliferative cues is eliminated,⁸ resulting in a reduction in the number of proliferating stem cells in the SVZ. Primarily, the reduction in proliferation occurs due to reduced



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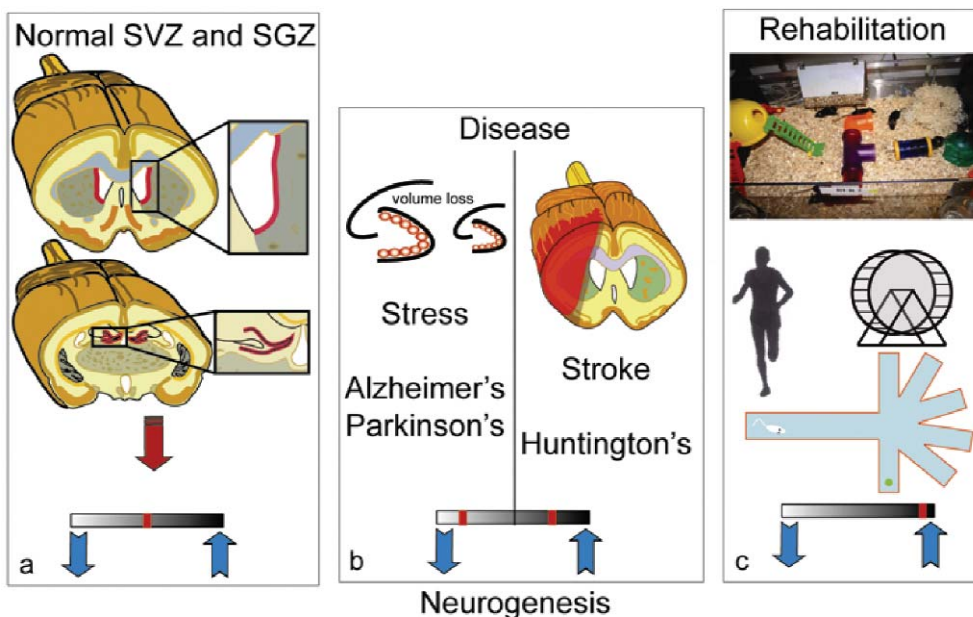


Figure Legend

a. Within the brain there are two stem cell germinal zones; the subventricular zone (SVZ, highlighted in red in the upper illustration) and the subgranular zone (SGZ, in red in the lower illustration). The level of neurogenesis from these germinal zones in the adult brain is moderate. However, b. under the conditions of stress, Alzheimer's or Parkinson's disease there is a reduction in the level of stem cells in the brain whereas in stroke and Huntington's disease there are increased numbers of stem cells. c. when laboratory animals and patients are exposed to an enriched environment and/or regular exercise, the stem cell proliferation is increased and the functional recovery after a brain insult is also improved.

dopamine signalling through the D2 receptors on proliferative cells.⁸ However, whether the lack of proliferation contributes to the symptomatology of Parkinson's disease is dubious due to the long distance from the substantia nigra to the SVZ. Stem cells are equally affected in Alzheimer's disease (AD) where the accumulation of toxic amyloid beta (A β) reduces the number of dividing cells; in addition, A β promotes synaptic dysfunction and death of mature neurons in AD.⁹ Increased A β production and depressed synaptic transmission in hippocampal slices¹⁰ suggest that A β could participate in a negative feedback loop involved in synaptic modulation, since newly formed hippocampal neurons are sensitive to the intensity of synaptic transmission. The reports on stem cells in AD are conflicting, but in severe AD there is a reduction in stem cell production^{11,12} For more detailed review see Curtis et al.¹³

Stem cells in an enriched environment

Stem cells in the brain can be altered by exposing an individual to a range of enhanced external stimuli, such as social and physical / behavioural situations, hence, environmental enrichment. In this context, the key components of an enriched environment are in the novelty and complexity that these type of environments offer. These concepts have now moved forward towards a new and major focus; the enrichment of the environment in order to alter the characteristics of stem cells in the neurogenic niches. Environmental manipulations of the laboratory animal's habitat, using toys, ladders, tunnels, platforms and running wheels, significantly increases animal social interactions, improves learning and memory and promotes stem cell function in the SVZ and hippocampus.¹⁴ Furthermore, enrichment experiences lead to substantial neuron remodelling, with increased dendritic branching, synaptic plasticity (including long-term potentiation) and increased numbers of dendritic spines in cortical and hippocampal regions.

In enriched animals, stem cells are stimulated differentially in the discrete neurogenic compartments of the normal and damaged brain. Under normal conditions in the SVZ, no effect is generally seen on cell proliferation or neurogenic outcome after enrichment. However, environmental enrichment really comes to the fore after damage to the brain, with increased proliferation and neurogenesis seen after experimental stroke¹⁵ and in the enhancing effect that enrichment has on SVZ stem cell integration after stem cell transplantation in experimental stroke.¹⁶ Enriched environments may also play a large role in behavioural alterations in AD. In the hippocampus, enrichment increases proliferation and neurogenesis,¹⁷ increases neurotrophins, such as nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF),¹⁸ mediates effects on angiogenesis and levels of vascular endothelial growth factor (VEGF),¹⁹ and plays a significant role in regulating and boosting cognition and improving spatial memory.

Stem cells respond to physical exercise

One of the major components of the enriched behavioural model for enhanced brain plasticity is the lab animal's free access to a running wheel. Physical exercise strongly and robustly induces hippocampal stem cell proliferation and neurogenesis.¹⁴ The effects of exercise-induced proliferation and neurogenesis is highly dependent on the neurotrophins BDNF and NGF, and the growth factors, insulin-like growth factor I (IGF-I) and levels of VEGF. Exercise also increases dendritic complexity and spine density in the hippocampus, increases angiogenesis and, importantly, significantly improves and enhances cognitive function and spatial memory. However, during periods of stress, increased levels of glucocorticoids significantly decrease hippocampal neurogenesis. The level of progenitor proliferation in running animals is decreased with excessive amounts of running activity. Together with increased levels

of glucocorticoids, hippocampal proliferation levels are highly dependent on the distance run and subsequent negative activation of the hypothalamic pituitary adrenal (HPA)-axis.²⁰ Given these findings, the magnitude of physical exercise should be carefully considered in devising enriched environment regimes.

However, challenges to the brain are well met by the stimulatory actions of exercise and may significantly involve changes in proliferation and neurogenesis. There is overwhelming evidence that regular exercise improves cognitive function in aged mice and elderly humans.²¹ In respect to AD, increased physical activity (walking, swimming and cycling) reduces the risk of cognitive decline. However, current preclinical models of AD suggest a greater effect on improved memory, increased neurogenesis and growth factor levels in animals exposed to the enriched environment compared to physical exercise. The enriched environment still demands greater physical activity and movement compared to more conventionally housed animals and this type of physically-linked behaviour may still play a strong role in enhancing brain function through stem cells.

Conclusion

The adult brain stem cell niches maintain the ability to respond to some neurodegenerative disorders throughout life. The SVZ and SGZ also have the ability to respond to external environmental changes that improve the plasticity of the adult brain. Whilst the virtues of lifelong regular physical exercise and enriching experiences on the prevention of various diseases and illnesses cannot be reiterated enough, adopting practices of healthy lifestyle with the right amount of physical activity and social interaction may prove to be vital for the appropriate rehabilitation of patients with neurological diseases. This focus will improve not only the motor but also the equally important sensory and social needs of the affected individuals.

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Current Understanding of Dysautonomia After Severe Acquired Brain Injury

Dysautonomia is one of a number of names used to describe a clinical syndrome affecting a subgroup of survivors of acquired brain injury (ABI).¹ The syndrome consists of paroxysmal elevations of autonomic nervous system (ANS) parameters, for example, heart rates (HR) up to 190 beats per minute, respiratory rates (RR) of 60 breaths per minute, temperatures to 42°C, arterial blood pressures (BP) of 170/120mmHg and sweating. These signs are accompanied by assorted forms of muscle overactivity such as decerebrate or decorticate posturing, dystonias, rigidity and spasticity.

Traumatic brain injury (TBI) is the most commonly reported causative condition, with an estimated incidence of 8-15% in moderate and severe TBI admitted to an intensive care unit (ICU).² There is no incidence data on other aetiologies, although anecdotally dysautonomia appears to be much rarer. Acute neurological events that have been reported to precipitate dysautonomia include: spontaneous subarachnoid or intracerebral haemorrhages, pressure from tumours, intra-aqueductal abscess, hydrocephalus and cerebral hypoxia in the absence of other trauma.³

In a prospective cohort study,² dysautonomic subjects had a significantly worse outcome, a greater period of hospitalisation and higher estimated costs compared to non-dysautonomic survivors of TBI. However, dysautonomic and non-dysautonomic patients were found to have a comparable degree of improvement with rehabilitation, albeit dysautonomic patients start at a lower point and take longer to improve.¹

There is considerable disparity between the estimated incidence of dysautonomia in prospective research and the quantity of scientific literature. There are a number of plausible explanations for this discrepancy. The most apparent difficulty is the proliferative and synonymous nature of the nomenclature, with at least 10 different names being used for the same condition. These include paroxysmal sympathetic storms, autonomic dysfunction syndrome, acute midbrain syndrome, hypothalamic-midbrain dysregulation syndrome, fever of central origin, hyperpyrexia associated with muscle contraction, dysautonomia, sympathetic or autonomic storming and paroxysmal autonomic instability with dystonia.³

Another explanation for the discrepancy is that dysautonomia is currently a diagnosis of exclusion and relies on a high index of suspicion. Firstly, some degree of autonomic arousal is a common feature during the early post-acute recovery from ABI and there is no clear threshold where this activity should become classified as dysautonomia. Furthermore, dysautonomia shares a high degree of overlap with the presentation of common complications such as opioid withdrawal, epileptic seizures, and sepsis, as well as rarer conditions such as neuroleptic malignant syndrome, malignant hyperthermia and others.³

Natural history / clinical features

Analysis of the hospital course of post TBI dysautonomia suggests that the syndrome follows a common three phase pattern. The first phase runs from admission to ICU to the cessation of paralysis and/or sedation. There is little to differentiate the dysautonomic and non-dysautonomic patients in terms of physiological variables during this stage.¹

The second phase commences with the cessation of regular sedation. The dysautonomic patient will usually have consistently raised HR and temperature, and increasing regional muscle tone. Paroxysms of posturing and ANS

overactivity are superimposed on these elevated baseline levels. In the early parts of this second phase, episodes are frequent, prolonged and intense. Some episodes will be provoked by identifiable stimuli (for example, pain, endotracheal suctioning, passive movements such as turning, bathing and muscle stretching, constipation, a kinked urinary catheter, emotional stimuli, as well as environmental stimuli such as loud noises),³ but others show no overt cause. The pattern of posturing is most often asymmetrical and may not fit into classical decorticate or decerebrate postures.⁴ With increasing time post injury, the paroxysms decrease in duration, frequency and magnitude; resting BP, RR, HR and temperature return to normal. The pattern of posturing may change, revealing an underlying tetraplegia or other focal neurological deficit. Sweating patterns often alter, from whole body to upper trunk, head and neck, before ceasing entirely.⁵ In the majority of patients, background muscle tone increases with variable flexor, extensor or mixed dystonias in the limbs, neck, trunk and facial muscles. The end of phase two is marked by the cessation of regular dysautonomic paroxysms. Extinguishment of episodes usually coincides with improving neurological status, although most are left with some degree of dystonia and spasticity.¹ The high degree of physical disability can prevent voluntary muscle activity, limiting the accuracy of cognitive assessment.

The final phase commences with the termination of regular paroxysms, though by this stage, dysautonomia patients with severe dystonia will have major deformities of joints and markedly reduced range of movement.¹ Although ANS variables are within normal limits, noxious stimuli may still provoke an episode for at least 14 months post injury.⁶ Patients who develop a mechanism for communication often report persistent abnormal painful responses to normally non-noxious stimuli.

Management

Pharmacological management is difficult and there is limited data available to guide decision-making. In the ICU setting, widespread use of paralysis/sedation has been shown to delay the onset of clinical features.¹ Anecdotally, the best available evidence for treatment efficacy includes bromocriptine, gabapentin and intrathecal baclofen (ITB).^{7,8} Intravenous morphine and midazolam are effective but have problematic sedative effects. Drugs with sympathetic activity (particularly clonidine, propranolol and labetalol) are also commonly used; however there are suggestions that these drugs treat the symptoms rather than the underlying disease process. Equally, there is no evidence that anticonvulsants other than gabapentin are effective in this condition. The potential to trigger paroxysms via noxious stimuli has led one author to suggest pre-treatment in this context.⁹

The rehabilitation management of dysautonomia centres on the usual approach of minimising unnecessary disability and complications while maximising the potential for the individual to regain a maximal quality of life. In the rehabilitation setting, this includes adequate fluids, nutrition, and spasticity management including splinting, serial casting and pressure area management. Given the combination of spasticity and nociception, ITB is increasingly being used earlier in the management.

Clinical significance

There are a variety of reasons to believe that dysautonomia warrants active management. A lack of early recognition



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and management contributes to increased morbidity. In particular, core temperatures above 38-39°C produce neuronal death in animal brain injury models.^{10,11} While transient temperatures at these levels occur in 68% of people following severe TBI,¹¹ dysautonomic subjects mean daily maximum temperatures can remain above this level for more than two weeks.¹ The increased metabolic consumption of posturing patients¹² and prolonged irregularities of gastrointestinal tract function¹³ produce a highly catabolic state causing an estimated 25% decrease in body weight.¹ The subsequent malnourishment places the individual at risk of developing critical illness neuropathy. Spastic tetraparesis in patients at rest and dystonic posturing during paroxysms are typical; and combined with weight loss, these lead to increased risk of pain, pressure areas and contractures. Dysautonomic episodes make splinting an extremely difficult prospect, with potential complications such as pressure areas and ruptured tendons. Lack of voluntary movement and the potential for 'locked-in' syndromes to occur^{11,14} can result in under-

managed pain or a misdiagnosis of persistent vegetative state.

Pathophysiology

While the earliest theories proposed an epileptogenic aetiology,¹⁵ multiple attempts to either identify or treat epilepsy in dysautonomic patients have produced negative results.³ There is greater evidence for supporting a disconnection pathogenesis. The limited autopsy and pathophysiological data has recently been reviewed, suggesting that the critical region of interest in dysautonomia is the mesencephalon.³ Conventional disconnection theories suggest that excitatory centre/s located in the upper brainstem and diencephalon drive paroxysms. A more recent disconnection theory, the Excitatory:Inhibitory Ratio (EIR) Model,¹⁶ suggests the causative brainstem/diencephalic centres are inhibitory in nature, with damage releasing excitatory spinal cord processes.

Evidence from literature on dysautonomia and other conditions suggests that disconnection syndromes can result from structural

and/or functional disconnection. Accordingly, functional disconnection may ensue from transient exacerbations of structural change (such as raised ICP) or neurotransmitter abnormalities.

Conclusion

The clinical research clearly shows that dysautonomia places a considerable burden on both patient and health care services and that there is potential for reducing this burden through timely recognition and intervention. However, the field is hampered by under-recognition, misdiagnosis, a poor understanding of pathophysiology and anecdotal management protocols. Recent advances suggest that new physiological investigatory techniques will allow the development of evidence based treatment paradigms for the first time. It is hoped that more effective treatment protocols will, in turn, result in improved outcomes and decreased overall costs. It is recommended that multi-centre research be utilised and targeted towards modifying outcomes for patients with this condition.

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PRIMARY CARE NEUROLOGY

- A Practical Approach

Wed 30th April 2008, Cardiff

One of the highlights of this year's programme is the inclusion of a debate on "Should placebo be used as an active treatment for neurological conditions?" which will involve one of the most highly respected and world renowned experts on complementary medicine, Professor Edzard Ernst, who will be speaking against the use of placebo. Professor Ernst qualified as a physician in Germany in 1978 where he also completed his MD and PhD theses. He has received training in acupuncture, autogenic training, herbalism, massage therapy and spinal manipulation. He was Professor in Physical Medicine and Rehabilitation (PMR) at Hannover Medical School and Head of the PMR Department at the University of Vienna. In 1993 he established the first Chair of Complementary Medicine in the UK, at the University of Exeter.

Talking in favour of placebo is the dynamic Dr Stephen Allen, who has been a pain consultant in Reading for 25 years. Dr Allen has grown his pain clinic in Reading from a very small 'one-man band' into what is now a large unit embracing a multi-disciplinary approach to Pain Management, having significant input from both physiotherapy and psychology. We are in for a fascinating debate!

This year's programme will deal with a number of practical issues including:

- Straightening out Dizziness - a general practice approach
- Dementia and Minimal Cognitive Impairment - Making an accurate assessment
- Commissioning Neurological Services
- Managing Anxiety and Depression in People with Longterm Neurological Conditions
- Yellow Flags and Non-Pharmacological Approaches to Management of Chronic Non Malignant Pain
- Management of Facial Pain - learning the essentials
- Recognition and management of an MS Relapse
- Movement disorders - deciphering the organic from the non-organic.

For full programme details go to

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Single Pulse Electrical Stimulation in Presurgical Assessment of Epilepsy: A New Diagnostic Tool

Epilepsy is a major source of disability amongst all age groups. Although most epilepsies are well controlled on antiepileptic drugs, around 20% of patients fail to gain medical control, and are potential candidates for surgery. However, despite recent technical advances, the overall success rate of surgery for epilepsy remains at about 75%.

At the department of Clinical Neurophysiology at King's College Hospital, we have developed single pulse electrical stimulation (SPES) as a method to identify epileptogenic cortex in the human brain. Cortical responses to SPES (1msec duration pulses, 4-8mA, 0.1-0.2Hz) were studied in 125 consecutive patients evaluated with intracranial electrodes as candidates for resective surgery for the treatment of their epilepsy.

Two main groups of cortical responses were generated by SPES: 1) early responses (ER), starting immediately after the stimulus and considered as responses of normal cortex to stimulation; and 2) late responses (LR), cortical responses seen in some areas after the initial ER. Two different types of LR were seen: a) delayed responses (DR): responses resembling spikes or sharp waves occurring between 100 milliseconds and 1 second after stimulation; and b) repetitive responses (RR): two or more consecutive sharp-and-slow-wave complexes, each resembling the initial early response. DR were seen when stimulating temporal and extratemporal structures and RR when stimulating frontal structures. Late responses to SPES are related to areas where spontaneous seizure onset occurs. They can identify epileptogenic cortex and predict surgical outcome, especially when a frontal or temporal focus is suspected.

Single-pulse electrical stimulation (SPES) could be an important additional investigation during presurgical assessment and can be particularly useful in patients who have widespread or multiple epileptogenic areas, normal neuroimaging, or few seizures during telemetry.

Introduction

Epilepsy is one of the most common neurological disorders, with a prevalence of 4-10/1000 and an incidence of 50-70/100,000 per year.^{1,2} About 20% of patients with epilepsy are not satisfactorily controlled by medical treat-

ment and are potential candidates for surgery.

In focal epilepsies, there is a localised area of abnormal nervous tissue from which seizures originate (epileptogenic cortex). A successful outcome of resective epilepsy surgery depends on accurate identification of the epileptogenic cortex which is structurally and functionally abnormal. Recent developments in medical imaging provide powerful means to localise structural lesions. Identification of functional abnormalities still requires electroencephalographic (EEG) recordings of seizure onset. Despite technical advances in surgical procedures and presurgical assessment over recent decades, the overall success rate of resective surgery of epilepsy remains at about 75% even in the best centres.³ The reasons for a 25% failure rate are unclear, but might be related to difficulties in identifying the area from which the seizures originate. Its location is inferred from clinical, imaging and electrophysiological findings. Sometimes seizure recordings with intracranial electrodes are necessary to identify epileptogenic cortex. As the number of intracranial electrodes implanted is necessarily limited and seizures can rapidly propagate between regions, intracranial recordings can sometimes be misleading in seizures arising from areas where no electrodes were implanted.

Since epilepsy is due to an imbalance between excitation and inhibition, an alternative is to map cortical excitability in order to identify hyperexcitable areas that could be epileptogenic. This can in principle be achieved by recording EEG responses to electrical stimulation in patients with intracranial recordings. Electrical stimulation with trains of pulses at 50-60Hz is routinely used in some centres to map cortical function and after-discharge threshold, and to elicit habitual seizures. However, it is difficult to study cortical excitability with such stimulation parameters because they are likely to produce massive and widespread cortical activation. In the Departments of Clinical Neurophysiology and Neurosurgery at King's College Hospital, we have developed a method to identify hyperexcitable cortex through the study of EEG responses to single pulse electrical stimulation (SPES).^{4,6} In the present article we review the



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The corresponding author has had full access to all the data in the study and has had final responsibility for the decision to submit the paper.

Table 1: Cross tabulation between type of late response and seizure onset.

DR/RR type	Ictal Onset Zone type					Total
	Focal	Regional	Diffuse	Bilateral Indep.	No sz	
Focal DR	18	7	0	3	2	30
Regional DR	6	33*	1	0	0	40
Bilateral DR	4	4**	0	7	3***	18
Only RR	0	5	0	0	0	5
No DR/RR	3	18	7	2	2	32
Total	31	67	8	12	7	125

Patients showing focal and regional ictal onset zones were considered as having regional ictal onset zone. Patients showing focal and regional DR were considered as having regional DR. The ictal onset zone was defined as the region where the initial ictal changes were seen in intracranial recordings.

* Two patients also had repetitive responses (RR).

** One patient also had repetitive responses (RR).

*** One patient had delayed and repetitive responses when stimulating both medial frontal regions.

DR=Delayed Responses; Bilateral DR=independent DR seen on both hemispheres; RR=Repetitive Responses; Indep=independent; sz=seizures.

results of SPES from 125 consecutive patients evaluated with intracranial recordings between 1999 and 2006.

Experimental protocol

SPES was performed between adjacent electrodes with a constant-current neurostimulator (Medelec ST10 Sensor, Oxford Instruments) using monophasic single pulses of 1ms duration and current intensity ranging between 4mA and 8mA (4mA was most often used). A single pulse was delivered every 5-10s and EEG responses to each pulse were recorded by the electrodes not used for stimulation. At least ten pulses were applied to each intracranial electrode. In each patient, all available electrodes located in grey matter were used to stimulate.

SPES responses

Two main groups of cortical responses were generated by SPES:

- 1) Early responses (ER): Responses resembling single sharp-and-slow waves following the stimulus artefact, sometimes associated with a low amplitude sharp wave with a fixed latency. ER can be considered as responses of normal cortex to stimulation (Figure 1).
- 2) Late responses (LR): cortical responses seen in some areas after the initial ER. Two different types of LR were seen:
 - 2.a) Delayed responses (DR): responses resembling spikes or sharp waves occurring between 100 milliseconds and one second after stimulation (Figure 1). DR were not always seen after every identical stimulus and their latency is always variable after each stimulus. DR were seen when stimulating temporal and extratemporal structures.
 - 2.b) Repetitive responses (RR): two or more consecutive sharp-and-slow-wave complexes, each resembling the initial early response (Figure 2). RR were mainly seen when stimulating frontal structures.

Among the 125 patients, 93 had shown late responses to SPES, 84 had exclusively DR, five had exclusively RR, and four patients had both DR and RR (Table 1).

Relation between late responses to SPES and seizure onset

Apart from early responses, DR were the most commonly observed responses to SPES. The relation between the topography of DR and ictal onset zone can be seen in Table 2. The ictal onset zone was defined as the region where the initial ictal changes were seen in intracranial recordings. Ictal onset zone was classified as focal (involving less than three contiguous electrodes), regional (involving three or more contiguous electrodes on one hemisphere), diffuse (involving most electrodes bilaterally), or bilateral independent (different focal seizures starting on different hemispheres). Among the 83 patients with DR and seizures during telemetry, 70 showed DR exclusively within the ictal onset zone (Figure 3), 10 showed DR within and outside the ictal onset zone, and only three showed

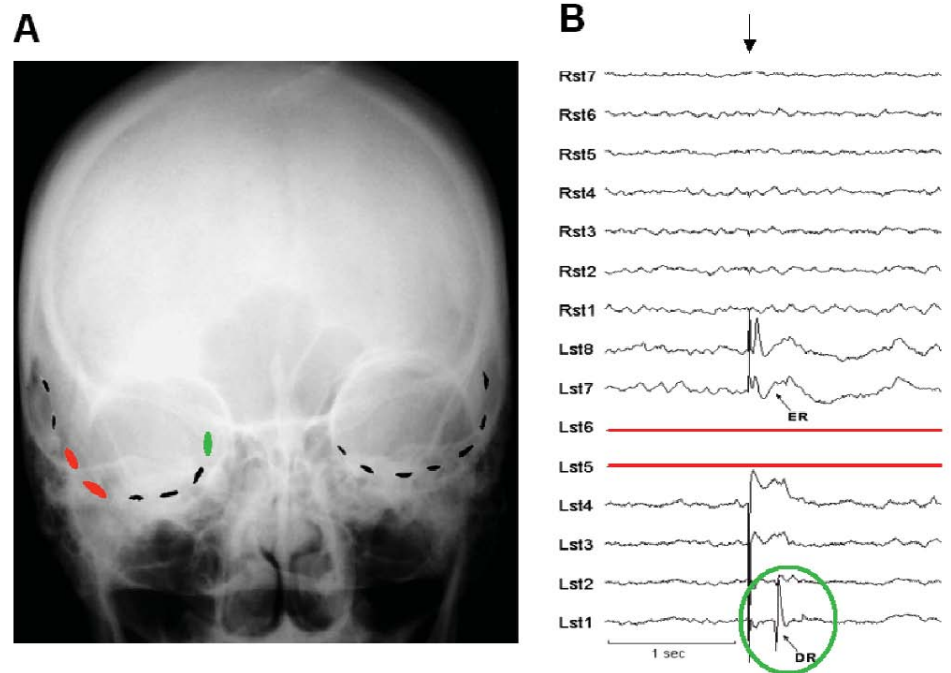


Figure 1: Early and Delayed responses to SPES

A: Frontal radiograph showing implanted subdural subtemporal strips in a patient with left temporal lobe epilepsy. All the contacts of the subdural strips are highlighted. B: Intracranial recordings of early and delayed responses to SPES. Delayed responses were seen at electrode 1 of left subtemporal strip (LsT1, marked as green) when stimulating through electrodes 5 and 6 of same strip (LsT5 and LsT6, marked as red). Early responses were mainly seen at electrodes 3, 4, 7, and 8 of same strip. Electrode 1 was the most distal electrode to the insertion burr hole and closest to mesial temporal structures. Recording displayed in common reference to Pz.

Arrow=electrical stimulation; RsT=right subtemporal strip; LsT=left subtemporal strip; ER=early response; DR=delayed response.

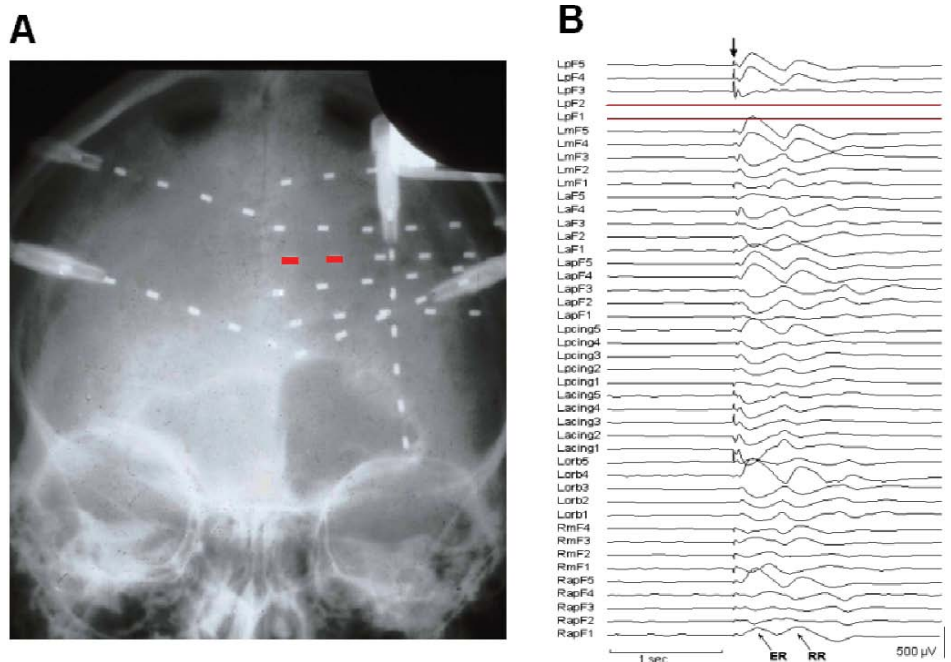


Figure 2: Repetitive responses to SPES

A: Frontal radiograph showing implanted intracerebral (depth) electrode bundles. B: Intracranial recordings of early and repetitive responses to SPES. Repetitive responses were evident when stimulating through electrodes 1 and 2 of the left posterior frontal electrode bundle (LpF1 and LpF2, marked as red). Electrode 1 was the most distal electrode to the insertion burr hole and closest to medial frontal structures. Recording displayed in common reference to Pz.

Arrow=electrical stimulation; RapF=right anterior polar frontal; RmF=right mid frontal; LmF=left mid frontal; LpF=left posterior frontal; LaF=left anterior frontal; Lorb=left orbitofrontal; Lpcing=left posterior cingulate; Lacing=left anterior cingulate; ER=early response; DR=delayed response.

DR exclusively outside the ictal onset zone. Moreover, the vast majority of patients (27/30) without DR did not have a focal onset, probably implying that the electrodes were not in contact with the area of origin for the seizures (Table 1). Therefore, DR appear to be associat-

ed with the ictal onset zone and can be considered as a reliable marker of epileptogenicity.

In a further study of 30 patients with frontal intracranial electrodes, RR and/or frontal DR were seen exclusively in patients with frontal seizure onset.⁵ The best match between seizure

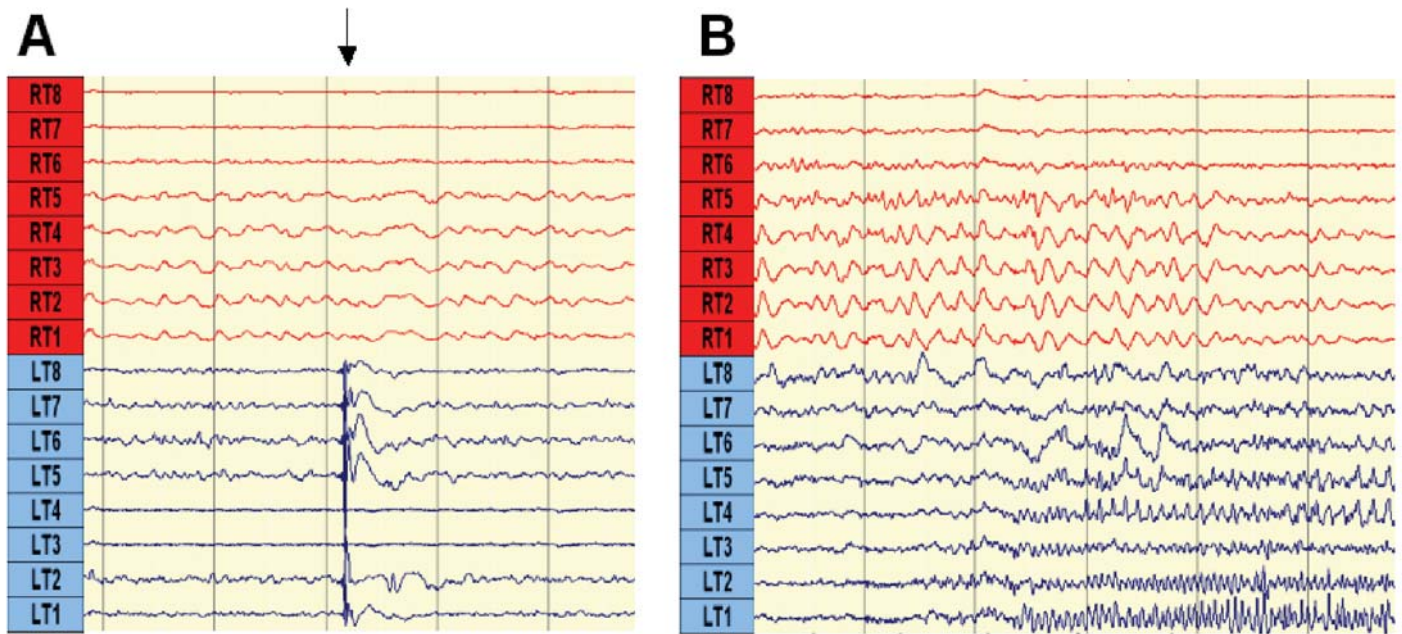


Figure 3: Relation between the distribution and topography of late responses to SPES and seizure onset in a patient with bitemporal subdural strips. A: Intracranial recordings of early and delayed responses to SPES. Delayed responses were seen at contact 2 of left subtemporal strip (LT2) when stimulating through electrodes 3 and 4 of same strip (LT3 and LT4) B: Subdural recording of a focal seizure onset. Note the fast activity building up at electrodes 1 and 2 of the left subtemporal strip (LT1 and 2). Electrode 1 was the most distal electrode to the insertion burr hole and closest to mesial temporal structures Recording displayed in common reference to Pz. Arrow=electrical stimulation; RT=right subtemporal strip; LT=left subtemporal strip.

onset and responses to SPES was seen in the areas where DR were recorded and those which, when stimulated, gave rise to RR (abnormal SPES areas).

Neuropathology and prediction of outcome:

We have studied 40 consecutive patients operated on at King’s College Hospital who had previous SPES, and have more than 12 months of follow-up.⁶ A strong relationship between favourable post-surgical seizure control and removal of the abnormal SPES areas was found. Whereas around 96% of patients who had complete removal of abnormal SPES areas enjoyed a favourable outcome, only 71% of patients where these areas were partially removed had a favourable outcome. The three patients where abnormal SPES areas were not removed had poor outcomes (Table 3). More specifically, a

similar relation has been observed after frontal lobe resections.⁵ An important finding was the consistent presence of structural abnormalities demonstrated by neuropathology in the removed abnormal SPES areas despite normal neuroimaging.⁶ This means that delayed and repetitive responses arose from structurally and functionally abnormal regions.

SPES in children

In a study performed in King’s College Hospital and in Great Ormond Street Hospital for Sick Children (London UK), the utility of SPES in the paediatric population has been evaluated in 35 children. We identified cortical responses to SPES that were similar or identical to those reported in adults.⁷ These results are especially important because in children with focal epilepsy there is a compromise between safety and early surgical intervention. SPES

could reduce the duration of intracranial monitoring by optimising electrode placement and by providing reliable information during the interictal period, avoiding long waiting time for multiple seizures to occur.

Early responses and brain connectivity

Since early responses appear to be normal responses to SPES, they can be used to assess connectivity between different cortical regions.⁸⁻¹⁰ We have studied connections between temporal and frontal cortices in 51 patients.¹⁰ Our findings suggest that connections between temporal and ipsilateral frontal regions were relatively uncommon (seen in up to 25% of hemispheres) whereas connections between frontal and ipsilateral temporal cortices were more common, particularly from orbital to ipsilateral medial temporal regions (40%). Contralateral bi-temporal connections were rare (<9%) whereas contralateral bi-frontal connections were very frequent (up to 88%). These findings were assumed to be representative of human brain as no differences were found between epileptogenic and non-epileptogenic hemispheres.

Practical limitations of SPES

We have identified practical limitations of SPES. When stimulating through medial electrodes from subtemporal strips, about 25% of patients experienced brief ipsilateral facial pain or muscle contraction associated with each stimulating pulse. This effect was sometimes disagreeable and the intensity of stimulation had to be reduced, decreasing the sensitivity of SPES. The second limitation applies to patients with focal cortical dysplasia who show regions with nearly continuous spontaneous interictal epileptiform discharges. In these regions it is very difficult to identify DR, since they often have a morphology and topography similar to

Table 2: Comparison between the topographies of DR and ictal onset zones in the 83 patients with DR and seizures during telemetry.

DR topography	Ictal onset zone topography							Total
	Focal		Regional		Bilateral Indep.		Diffuse	
	in	out	in	out	in	out		
Focal	17	1	7	0	3*	0	0	28
Regional	6	0	31**	2	0	0	1	40
Bilateral	4***	0	4***	0	7	0	0	15
Total	27	1	41	2	10	0	1	83

Patients showing focal and regional ictal onset zones were considered as having regional ictal onset zone. Patients showing focal and regional DR were considered as having regional DR
in=DR inside the ictal onset zone; out=DR seen outside ictal onset zone and not within the ictal onset zone; indep=independent
 * All three patients had unilateral focal DR and bilateral seizures.
 ** Two patients had DR inside and outside the ictal onset zone
 *** All patients had DR inside and outside the ictal onset zone

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Date of preparation: January 2008
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Table 3: Relation between seizure outcome and removal of abnormal SPES areas.

	Favourable Outcome (I-II)	Poor Outcome (III-IV)	Total
Completely removed (CR)	21	1	22
Partially removed (PR)	5	2	7
Not removed (NR)	0	3	3
No late responses observed (NL)	5*	3	8
Total	31	9	40

*4 patients showed continuous interictal spikes (cis) suggestive of cortical dysplasia at the areas of seizure onset, which made assessment of the presence of delayed responses at these regions impossible (probably false negatives of SPES).

those of spontaneous epileptiform discharges. Thirdly, at present SPES can only be carried out in patients assessed with intracranial electrodes, and shares with such recordings their limitations with regard to spatial sampling. The combined use of transcranial magnetic stimulation (TMS) and simultaneous EEG could help to study cortical excitability in focal epilepsy.¹¹

Conclusion

Single pulse electrical stimulation is a safe and reliable technique for identifying epileptogenic cortex, as evidenced by the close relationship between the topography of abnormal responses and location of electrographic seizure onset, surgical outcome, and pathological abnormalities. Our findings suggest that surgery should remove abnormal SPES areas. This is of paramount clinical relevance since SPES appears to provide additional evidence of epileptogenicity during the interictal period, and it appears to be a good predictor of pathology and surgical outcome.

At the very least, SPES provides additional evidence that can be used to reduce the need to capture seizures, allowing invasive EEG telemetry to be performed for shorter periods. It may in some instances even replace ictal recording as a method of locating the epileptogenic zone, allowing intraoperative identification of epileptogenic cortex immediately before resection. Furthermore, the technique may also prove of value during electrode implantation to determine whether the sites chosen are likely to lie within the epileptogenic zone.

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(Please consult the Summary of Product Characteristics (SmPC) before prescribing.)

NEUPRO[®] Presentation: Neupro[®] is a thin, matrix-type square transdermal patch. **Active Ingredient:** Rotigotine. *2 mg/24 h transdermal patch* is 10 cm² and contains 4.5 mg rotigotine, releasing 2 mg rotigotine over 24 hours. *4 mg/24 h transdermal patch* is 20 cm² and contains 9.0 mg rotigotine, releasing 4 mg rotigotine over 24 hours. *6 mg/24 h transdermal patch* is 30 cm² and contains 13.5 mg rotigotine, releasing 6 mg rotigotine over 24 hours. *8 mg/24 h transdermal patch* is 40 cm² and contains 18.0 mg rotigotine, releasing 8 mg rotigotine over 24 hours. **Uses:** To treat the signs and symptoms of idiopathic Parkinson's disease, either with or without concomitant levodopa therapy. **Dosage and Administration:** Neupro[®] is applied to the skin once a day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different application site. **Monotherapy:** treatment is initiated with a single daily dose of 2 mg/24 h. Dose increased by 2 mg/24 h each week

(e.g. 2 mg/24h in Week 1, 4 mg/24 h in Week 2, 6 mg/24 h in Week 3 and 8 mg/24 h in Week 4), until an effective dose is reached. Maximal dose is 8 mg/24 h. **Adjunctive therapy (with levodopa):** treatment initiation is at 4 mg/24 h and increased weekly in 2 mg/24 h increments, up to a maximal dose of 16 mg/24 h. **Hepatic and renal impairment:** Adjustment of the dose is not necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment including those requiring dialysis. **Children and adolescents:** not recommended. **Contraindications:** Hypersensitivity to rotigotine or to any of the excipients. Neupro[®] should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns. **Warnings and Precautions:** External heat should not be applied to the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of therapy. Rotate the site of

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References: 1: Watts RL et al. *Neurology* 2007; 68:272-6. 2: Neupro Summary of Product Characteristics. 3: Giladi N et al. Poster presented at EFNS 2006.

Date of literature preparation: February 2008.

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Pathology of Intracerebral Haemorrhage

Intracerebral haemorrhage (ICH) is an acute and spontaneous extravasation of blood into the brain parenchyma. Bleeding may also extend into the ventricles or subarachnoid space.¹ ICH is a subtype of stroke with high morbidity and mortality accounting for about 15% of all deaths from stroke.² Depending on the underlying cause of bleeding, ICH is classified as either primary or secondary. Primary ICH, which accounts for 78-88% of cases, originates from the spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy. Secondary ICH occurs in association with trauma, vascular abnormalities, tumours or impaired coagulation.³ The focus of this article is mainly on the aetiology, pathophysiology and pathology of primary ICH with brief comments on genetics and iatrogenic forms of ICH.

Causes of intracerebral haemorrhage

Table 1 lists the various causes of ICH. Hypertension is still the main cause, being responsible for approximately 55% of cases of ICH.⁴ Cerebral amyloid angiopathy (CAA) is the other major cause of primary ICH/ lobar haemorrhage in the elderly.⁵ Post-traumatic haematomas are usually multiple and about the basal brain surface. Vascular malformations including aneurysms are a common cause of ICH, especially in young normotensive individuals. Coagulopathies may cause multiple or recurrent ICH, sometimes in the presence of systemic bleeding.⁶

Table 1: Causes of ICH

Primary	Secondary
Chronic Hypertension	Trauma
Cerebral Amyloid Angiopathy (CAA)	Ruptured aneurysm
	Vascular malformations
	Tumours (primary and metastatic)
	Coagulopathies
	Drugs or alcohol
	Haemorrhagic conversion of cerebral infarct
	Vasculitis
	Pregnancy (eclampsia, venous thrombosis)
	Others/ unknown

Pathophysiology

ICH was once considered to be a simple, monophasic, rapid bleeding event that stopped quickly as a result of clotting and tamponade.^{1,3} But ICH has now been shown by serial CT scans to be a dynamic and complex process involving several distinct phases. The two most important new concepts are that firstly, many haemorrhages continue to grow and expand over several hours after the onset of symptoms. **Expansion of haematoma:** Most haematomas result from rupture of an artery or arteriole. Their expansion is most likely due to continued bleeding from the primary source and to the mechanical disruption of surrounding vessels. Acute hypertension, a local coagulation deficit, or both may be associated with expansion of the haematoma.^{1,3} Secondly, most of the brain injury and swelling that occurs after ICH is the result of inflammation caused by thrombin and other end products of coagulation.¹ **Secondary brain injury and oedema:** The haematoma initiates oedema and neuronal damage. Oedema typically develops over the first 24-96 hours

and slowly resolves over several weeks. The early oedema is usually secondary to plasma proteins present in the haematoma. Subsequent clotting and complement cascade activation results in disruption of the blood-brain barrier, direct cytotoxicity and more oedema. Lysis of red blood cells with haemoglobin toxicity and formation of free radicals probably accounts for the late onset oedema, which persists for several weeks after the initial haemorrhage.⁷ Neuronal death in the region around the haematoma is predominantly necrotic, with recent evidence suggesting the presence of programmed cell death (apoptosis).³ Unlike primary tissue injury from the haematoma formation, secondary brain injury and oedema are potential therapeutic targets.⁵

Pathology

The most common sites of ICH are cerebral hemispheres, basal ganglia, thalamus, brainstem (predominantly the pons), and cerebellum.³ The gross and microscopic changes in the brain depend on the location of ICH, but the general appearance is similar. In the acute stages, the ICH consists of a liquid or semiliquid mass of blood with surrounding oedema. After a few days, the haematoma changes its consistency and adopts a brown colour, while oedema begins to recede. After several months or years, depending on its size, the haematoma becomes a cavity. Small ICH can be reabsorbed almost completely, leaving behind a small linear scar.⁷

Microscopically, the ICH in its acute stages consists of extravasated well-preserved red blood cells (RBC) without any inflammation. Subsequently, the RBC begins to lyse and neutrophils appear. This is followed by infiltration of macrophages whose main role is to phagocytose blood products and necrotic tissue. The brown discolouration of the slightly older haematomas noted macroscopically is due to the presence of two major haemoglobin-derived pigments, haemosiderin and haematoidin. One of the late events involves proliferation of astrocytes, some containing haemosiderin reflecting their phagocytic activity. The transfer of haemosiderin from macrophages to astrocytes, an event that rarely happens in infants, is common in the adult.⁷ The pathological evolution of ICH is summarised in Table 2 and a knowledge of this temporal sequence helps in estimating the approximate age of a haematoma in the absence of relevant clinical data.⁹

Hypertension

Hypertension-related haemorrhages occur typically in deep areas of the brain such as the basal ganglia and thalamus because vessels in these areas are located close to the high pressure of the circle of Willis.^{9,10} They are less common in the pons, cerebellum or superficial cortex. Pathological studies have shown hyperplasia of the media in artery walls due to proliferation of reactive smooth muscle cells in early hypertension. This has been termed 'hyperplastic arteriosclerosis'. Eventually, the smooth muscle cells die and are replaced by collagen fibres which makes the vessel wall brittle and liable for future leakage.¹⁰ Miliary or microaneurysms, originally described by Charcot and Bouchard, have been recently questioned as the source of haemorrhage, as complex tortuosities of blood vessels affected by hypertensive changes may be misinterpreted as microaneurysms. Fibrinoid necrosis associated with haemorrhage in acute hypertension appears to be haemostatic, whereas in chronic hypertension it has been suggested that fibrinoid necrosis may be a precursor to haemorrhage.⁹



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Table 2: Pathological evolution of ICH (Reproduced with kind permission from Nicoll JAR et al. *Paraneuronal brain haemorrhage. In-Pathology & Genetics-Cerebrovascular Diseases. 2005 ISN, Basel, Switzerland, pp 294-300*)

Time	Macroscopic	Microscopic
Seconds		Rupture of blood vessel wall
Seconds to minutes	Haematoma formation (bright red acute haemorrhage)	Extravasation of blood
Minutes to hours	Space-occupying effect. Distortion and compression of surrounding tissue, (may include: raised intracranial pressure, internal herniations, brain stem compression)	Lysis of erythrocytes
Several hours	Development of peri-haematoma oedema and ischaemia. Increasing space-occupying effect.	Oedema, ischaemia, polymorph infiltrate.
2-3 days to weeks	Brown coloration of haematoma	Haemosiderin formation. Phagocytosis by macrophages. Astrocyte hypertrophy and new blood vessel formation at the haematoma margin.
Weeks to months	Friable brown clot	Organisation of the haematoma with phagocytosis of blood and necrotic tissue by macrophages.
Months to years	Cavity containing dark blood-stained fluid	Continued resorption of blood clot
Months to years	Cavity containing clear fluid resembling CSF with brown haemosiderin-stained cavity wall	Cavity lined by hyperplastic and hypertrophic glial cells; residual macrophages and haemosiderin

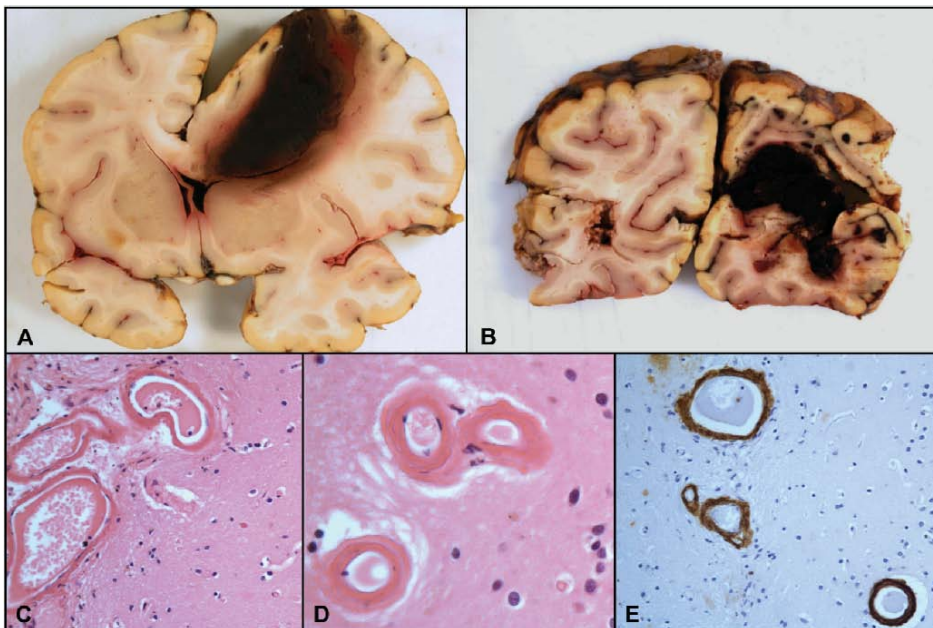


Figure 1: Cerebral amyloid angiopathy. Coronal slice showing a large superficial haemorrhage in the right frontal lobe with extension into the subarachnoid space and ventricle (A). Same case as in (A) showing also a large hematoma in the right occipital lobe (B). Photomicrograph showing thickened hyalinized blood vessels in the leptomeninges (C) and in the brain parenchyma (D) (H&E x200). Immunohistochemistry for beta-amyloid showing strong positivity in the blood vessel walls (E) (x200).

Cerebral amyloid angiopathy (CAA)

CAA results from the deposition of the insoluble amyloid-beta ($A\beta$) peptides (derived from amyloid precursor protein/APP) in the walls of leptomeningeal and cortical arteries, arterioles and capillaries (Figure 1). Replacement of smooth muscle cells in the artery walls by $A\beta$ increases exponentially with age, making the artery less compliant. CAA-associated haemorrhage in some cases may be related to an interaction with other risk factors, notably hypertension. Haemorrhages are superficial, lobar and quite commonly breach the cortical surface resulting in secondary subarachnoid haemorrhage; they can also be multiple or recurrent. Specific vasculopathic complications occur more commonly with CAA-associated haemorrhage than in CAA without haemorrhage. Such complications include concentric splitting of the vessel wall ('double barrel' appearance), fibrinoid necrosis, microaneurysms, stenotic lumina, microhaemorrhages and cortical infarction.^{9,10}

Genetics

Most genetic studies have focussed on the apolipoprotein E alleles $\epsilon 4$ and $\epsilon 2$ that are associated with predisposition to ICH, particularly with CAA and lobar haemorrhages. McCarron and colleagues⁹ found that patients with ICH who carried the apolipoprotein E $\epsilon 4$ allele had a greater hospital mortality rate than non-carriers (40% Vs 25%). The apolipoprotein E $\epsilon 4$ allele is also associated with poor outcome after traumatic brain injury, but there is no such association for ischaemic stroke. Polymorphisms in various other genes such as methylenetetrahydrofolate reductase, angiotensin-converting enzyme, and alpha1-antichymotrypsin have been found to be associated with ICH in other fairly small studies.²

Iatrogenic forms of ICH

The iatrogenic forms of ICH can be broadly divided into two groups: those due to self-administration of substances with toxic effects which include mainly alcohol, drugs like cocaine

and amphetamines; and those due to therapeutic manipulations including anticoagulation, fibrinolytic therapy and carotid endarterectomy. Heavy alcohol consumption predisposes to ICH by inducing hypertension (particularly acutely after a binge), by its inhibiting effects on platelet function or by causing liver dysfunction. Cocaine and amphetamines are sympathomimetic agents known to have effects on pulse and blood pressure. Cocaine also induces a cerebral vasculitis, which may be partly responsible for ICH associated with its use. Most patients with drug-related ICH have an associated vascular lesion such as an aneurysm or an arteriovenous malformation.^{4,7}

Conclusions

The prognosis for patients suffering from ICH is still poor. Size and location of the haemorrhage, together with age and presence of hypertension, represent the main prognostic indicators.⁶ The role of oedema, ischaemia, mass effect, direct cellular toxicity, inflammation, and apoptosis are being evaluated in various experimental studies of ICH.⁵ The future may see the translation of this basic information into clinical trials and also lead to the development of highly effective treatments.

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Tales of the Unexpected: Roald Dahl's Neurological Contributions

Roald Dahl (1916-1990) is best known as an author of children's books, although his oeuvre also extends to other works, including screenplays, ghost tales and novels. It may therefore seem surprising at first sight that he might have made any contributions to neurology. However, in the second volume of his autobiography, *Going solo* (1986), he declares "All my life I have taken an intense and inquisitive interest in every form of medicine", perhaps in part because of the head injury he suffered as a pilot in World War 2. Recovering in Alexandria, he was blind for some time, and reports "Both my senses of smell and of hearing had become very acute since my blindness, and I had developed an instinctive habit of translating sounds and scents into a coloured mental picture".¹ This account suggests the phenomenon of hyperpilaphesie, but not of true ("strong") synaesthesia.

Dahl's book *George's marvellous medicine* (1981) contains the epigraph (in the hardback edition, but not in subsequent paperback editions) "This book is for doctors everywhere". This bold statement is not further elaborated upon, but certainly the book may be read as a salutary lesson about the grave consequences of unregulated experimentation in clinical pharmacology. The author advises readers not to try the recipes reported in the book.

It has been suggested elsewhere (reference 2, case 3) that in his first volume of autobiography, *Boy: tales of childhood* (1984), Dahl portrays a schoolmaster, "Captain Hardcastle", who may have suffered from Tourette syndrome since he seems to manifest both vocal and motor tics. This teacher was almost certainly the inspiration for "Captain Lancaster", also a teacher, who appears in the book *Danny the champion of the world* (1975): "I could hear him snorting and snuffling through his nose like a dog outside a rabbit hole." In the film version, Captain Lancaster (as portrayed by Ronald Pickup) has a larger role than in the book but neither snorting nor snuffling are in evidence. Why Dahl should have recalled this particular teacher is not certain, but of possible note is the fact that Dahl himself had some characteristics which might be suggestive of the obsessive-compulsive spectrum, for example when writing in his famous shed he had to have a particular type of paper (yellow American Legal), and both a particular brand and a specific number (6) of pencils.³

These descriptions may hardly be termed "contributions", but two personal tragedies certainly did lead to developments of clinical import. Whilst living in New York in 1960, Dahl's son Theo, aged 3-4 months, was involved in a road traffic accident which caused some brain damage and secondary hydrocephalus, the latter requiring shunting. Problems with blocked shunts occurred. The family returned to England and Theo came under the care of Kenneth Till, a neurosurgeon at Great Ormond Street Hospital (1956-80). Prompted by Dahl, and in collaboration with Stanley Wade, an hydraulic engineer, a new type of shunt valve was designed. Reported in the *Lancet* by Kenneth Till, under the rubric of "New Inventions", the special characteristics were reported to be "low resistance, ease of sterilisation, no reflux, robust construction, and negligible risk of blockage". The author acknowledged that the valve was

"designed by Mr Stanley C. Wade ... with the assistance of Mr Roald Dahl and myself".⁴ The Wade-Dahl-Till (or WDT) valve became widely used.

Kenneth Till subsequently wrote a preface for a new edition of Valerie Eaton Griffith's book entitled *A stroke in the family*, a manual of home therapy (www.stroke-scheme.ie/articles/reviews/family.htm), wherein lies another Dahl connection. In 1965, Dahl's first wife, the American actress Patricia Neal, suffered a stroke due to a ruptured intracranial aneurysm, one of the consequences of which was marked aphasia, a potential career-ending misfortune for an actress (her illness and recovery are recorded in a book by Barry Farrell⁵). Dahl appealed to Valerie Eaton Griffith, who lived in the same village, for help. With Dahl, she devised a rota of volunteer carers to engage the patient in conversation and hence to stimulate language recovery. This approach, different from formal

speech therapy, was documented in Griffith's book (initially published in 1970, with an introduction by Roald Dahl⁶). It earned the approbation, as "treatment of a surreptitious character", of no less a neurological figure than Macdonald Critchley,⁷ and still has advocates today.⁸ It has been suggested that Patricia Neal's aphasia may have influenced Dahl's creative processes, for example in the neologisms of *The BFG* (1982).⁹

The Roald Dahl Foundation (www.roalddahlfoundation.org) continues to provide charitable grants for neurological conditions affecting young people including epilepsy; acquired brain injury due to benign brain tumour, encephalitis, head injury, hydrocephalus, meningitis, and stroke; and neurodegenerative conditions causing progressive intellectual or neurological deterioration.

Acknowledgements

Thanks to Elizabeth Lerner for drawing my attention to the Wade-Dahl-Till valve.

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Reference: Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease. Arch Neurol 2002; 59: 1937-1943.

impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. **Undesirable effects in clinical trials:** **Monotherapy:** >1%: headache, flu syndrome, malaise, neck pain, dyspepsia, arthralgia, depression, conjunctivitis, allergic reaction, fever, angina pectoris, anorexia, leucopenia, arthritis, vertigo, rhinitis, contact dermatitis, vesiculobullous rash, skin carcinoma, hallucinations, urinary urgency. <1%: cerebrovascular accident, myocardial infarct. **Adjunct therapy:** >1%: abdominal pain, accidental injury, postural hypotension, constipation, vomiting, weight loss, dyskinesia, neck pain, anorexia, dry mouth, arthralgia, tenosynovitis, dystonia, abnormal dreams, ataxia, rash, hallucinations. <1%: angina pectoris, cerebrovascular accident, skin melanoma, confusion. Please refer to the SmPC for a full list of adverse events. **Basic NHS Price:** Azilect[®] (tablets) 1mg x 28 £70.72 **Legal category:** POM **Marketing Authorisation Number:** 1mg tablets (28 pack size) EU/1/04/304/003 **Marketing Authorisation Holder:** Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany **Date last revised:** April 2007 **Further information available from:** Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

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Recent Advances in Genetic Muscle Disease – Possible New Treatments in Muscular Dystrophy

Muscular dystrophies are amongst the most important genetic muscle diseases and patients frequently come under the care of a neurologist. Younger onset muscular dystrophies often result in significant disability and cardiorespiratory complications may be fatal. In the last few years there have been significant advances in the area of gene discovery in muscular dystrophy and this has aided diagnosis. Recent research is now moving from gene discovery to molecular therapy and here we have focussed on new gene intervention treatments and new treatments to promote muscle regeneration. Important phase I/II trials in these areas are either in progress or starting.

Diagnosis

For many neuromuscular diseases diagnosis is based on a combination of clinical features and careful evaluation, including EMG, muscle biopsy and, increasingly, gene testing. Standard light microscopy of a biopsy for diagnosis in muscular dystrophy is now inadequate and careful immunohistochemical evaluation using a range of specific antibodies is mandatory to advance to a precise genetic diagnosis - especially in the limb girdle muscular dystrophies. The discovery of causative genes in this group of muscular disorders has led to more accurate diagnosis, clinical management and genetic counselling¹ (Tables 1 and 2). The recognition of important phenotype-genotype relationships allows selection of patients at risk of cardiorespiratory complications, facilitating early intervention which prolongs life. An accurate genetic diagnosis can enable prenatal diagnosis in carefully selected cases.

New treatment trials in muscular dystrophy - Gene therapy and satellite cell stimulation

Recently two new treatment approaches for muscular dystrophy have reached the stage of phase I/II clinical trials. The first group are new gene therapy approaches in Duchenne muscular dystrophy and the second is the modulation of muscle myostatin levels.

Several gene therapy approaches have been developed in Duchenne muscular dystrophy (DMD); these include exon skipping, transfection of truncated dystrophin mini-genes using viral vectors and “read through” of premature stop codons by small molecules that suppress stop codons. Recognition of myostatin as an inhibitor of muscle growth has led to the development of myostatin antibodies that knock down myostatin production in muscle. There is much interest in the potential of myostatin sup-

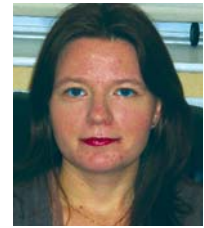
pression as a treatment in a range of genetic muscle diseases including muscular dystrophy.

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is the commonest muscular dystrophy, affecting 1 in 3 500 live male births.² It is an X-linked recessive disorder due to mutations in the dystrophin gene that encode the subsarcolemmal protein dystrophin leading to a lack of dystrophin expression in skeletal and cardiac muscle. It is a progressive muscle wasting disease and death usually occurs in the third decade from respiratory or cardiac muscle involvement. Animal models which also lack dystrophin expression due to premature stop codons in the dystrophin gene have been used extensively to research this disease. The mdx mouse, although having an almost total lack of dystrophin, has a milder phenotype than that seen in humans, with an almost normal life span.³ Thus some caution has to be used when considering how results of trials in mice may relate to human disease. For this reason the mdx dog is often used in treatment trials as its phenotype is much closer to that seen in boys, with a reduced lifespan resulting from cardiac or respiratory involvement. Furthermore, the muscle mass of the dog is more comparable to that of a child with DMD.³

Exon skipping

Mutations of the dystrophin gene in DMD often disrupt the reading frame, resulting in no production of the key membrane structural protein dystrophin. In contrast mutations in the dystrophin gene found in the milder Becker Muscular Dystrophy (BMD) typically do not disrupt the reading frame and there is some production of a semi-functional dystrophin protein, hence the milder phenotype.⁴ The recognition that a significantly truncated dystrophin gene could still produce a functional protein led to the concept of skipping mutated exons in DMD as a therapeutic strategy. In the last few years morpholino anti-sense oligonucleotides have been developed in DMD to do just this with resultant restoration of the reading frame and increased production of dystrophin. Intramuscular delivery of such oligonucleotides in experiments with the mdx mouse model of DMD confirmed a transient local production of the dystrophin protein with no significant immune response.⁵ More recently, systemic delivery to the mdx mouse has produced dystrophin expression in all skeletal muscles with functional improvement, although expression was not uniformly seen.⁶ To



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Table 1: The Dominantly Inherited Limb Girdle Muscular Dystrophies

LGMD	Chromosome	Gene	Protein	Additional Clinical Features
1A	5q22-q34	Myotilin	Myotilin	Dysarthria Cardiomyopathy
1B	1q11-q21	Laminin A/C*	Laminin A/C	Cardiomyopathy
1C	3p25	Caveolin-3	Caveolin-3	Calf Hypertrophy Rippling muscle disease
1D	6q23	Unknown	Unknown	Cardiac arrhythmias and cardiomyopathy
1E	7q	Unknown	Unknown	Dysphagia No associated systemic features

* Mutations in the Laminin A/C gene are also known to cause Emery-Dreifuss Muscular Dystrophy Type 2, Familial Partial Lipodystrophy and peripheral neuropathy.

Table 2: The Recessively Inherited Limb Girdle Muscular Dystrophies

LGMD	Chromosome	Gene	Protein	Additional Clinical Features
2A	15q15.1-q21.1	Calpain-3	Calpain-3	Distribution of weakness cf. FSHD (scapular, pelvis, trunk). Contractures can occur. Cardiac involvement rare.
2B	2p13	Dysferlin*	Dysferlin	Gastrocnemius wasting. Cardiac involvement rare.
2C	13q12	γ -sarcoglycan	γ -sarcoglycan	Phenotype can be similar to Duchenne Muscular Dystrophy. Respiratory Involvement. Cardiac involvement. Neurosensory hearing loss. Death can occur in 2nd decade.
2D	17q12-q21.3	α -sarcoglycan	α -sarcoglycan	Earlier onset more aggressive than later onset. Cardiomyopathy.
2E	4q12	β -sarcoglycan	β -sarcoglycan	Can be severe phenotype. Can be wheelchair bound in teens. Calf hypertrophy. Cardiomyopathy.
2F	5q33-34	δ -sarcoglycan	δ -sarcoglycan	Can be severe phenotype. Calf hypertrophy. Can be wheelchair bound in teens. Death can occur in 2nd decade. Cardiomyopathy.
2G	17q11-12	Telethonin (Titin Cap)	Telethonin	Foot drop. Cardiac involvement.
2H	9q31-q34.1	TRIM-32	TRIM 32	Variable but generally mild phenotype. Facial weakness.
2I	19q13.3	FKRP gene	FKRP	Respiratory failure. Cardiomyopathy. Calf hypertrophy.
2J	2q31	Titin	Titin	Anterior tibial wasting. No cardiomyopathy reported.
2K	9q34.1	POMT-1	POMT-1	Childhood onset. Contractures. Severe mental handicap.
2L	9q31	Fukutin	Fukutin	Infantile onset. Respiratory and cardiac involvement can occur.
2M	11p13	Unknown	Unknown	Exercise induced myalgia.
2N	19q13	POMT-2	POMT-2	Variable phenotype. Learning difficulties can occur.

*Dysferlin gene mutations are also known to cause Miyoshi Distal Myopathy.

Research is moving from gene discovery to molecular therapy

date none of the experiments with anti-sense oligonucleotides have altered dystrophin expression in the heart. The advantages of this approach are that, in animal models, they have proven to be beneficial without any significant adverse effects or unwanted immune response. The limitations are that the beneficial effects seem to be limited to skeletal muscle and do not include the heart. Due to their transient nature repeated doses are required and the long-term effects of this are not known. The oligonucleotides required to achieve skipping have to be specifically synthesised and tailored to the exact deletion in the dystrophin gene in each patient. This underlines the need to have detailed data bases of carefully genotyped patients as an essential requirement for such translational research efforts. Clinical trials employing intramuscular injections of anti-sense oligonucleotides in boys with DMD are now underway in the UK and Europe.⁷

Viral vectors

Another approach to restore some functioning dystrophin to the muscle fibre membrane has been to use viral vectors to deliver 'mini' or 'micro' dystrophin genes. Several viral vectors have been tried but currently adeno-associated viruses are the vectors of choice because of their low pathogenicity in humans and their ability to cross the vascular endothelium and enter skeletal muscle when injected intravenously.⁸ Intravenous administration in the mdx mouse of an rAAV6 – microdystrophin produced uniform distribution of dystrophin not only in

skeletal muscles but also in the heart without provoking an immune response. An improvement in skeletal muscle function and prolonged life expectancy was also observed.⁹ Extension of experiments to canine models however provoked a profound T-cell mediated immunological response to the AAV capsid proteins following IM injection of AAV-mediated transgenes with inhibition of long-term transgene expression.^{10,11} A recent study has indicated that transient immunosuppression may limit the reaction and prevent disruption of transgene expression. This was achieved in canines but required an aggressive immunosuppressant regime of anti-thymocyte globulin, cyclosporine and mycophenolate.¹²

The advantages of the viral vector approach are that uniform expression of dystrophin can be achieved in all skeletal muscles and in the cardiac muscle. There is also prolonged transgene expression, although the exact duration is unclear; it is not considered to be infinite. The major disadvantage is the possibility of a similar immunogenic response that is observed in canines being found in humans. Another potential limitation to clinical use is the current large number of viral particles required to produce a single effective human dose.¹³ Clinical trials are currently underway in France and the USA in limb girdle muscular dystrophy (LGMD) 2C and DMD using viral vectors for transgene delivery.¹⁴

Read through of stop codons

A third approach in the treatment of DMD has

been to consider read through of premature stop codons which could potentially benefit the 10-15% of BMD cases with stop codon mutations. Aminoglycosides are known to achieve this by preventing nonsense mediated mRNA decay leading to increased protein production, but their use is limited by their oto- and nephrotoxicity. This observation however led to the development of PTC124, a new drug that selectively promotes read through of premature stop codons without affecting normal non-premature stop codons.¹⁵ Trials in the mdx mouse confirmed increased dystrophin production in all skeletal muscles tested and the heart with accompanying improvement in muscle function and lack of adverse events. Clinical trials are now underway.

Myostatin

In 1997 a new member of the transforming-growth factor β family of growth and differentiation factors was discovered. Initially labelled as growth/differentiation factor-8 (GDF-8), studies in mice demonstrated a specific effect on skeletal muscle, with null animals exhibiting a uniform dramatic increase in skeletal muscle mass. This negative inhibitor of skeletal muscle growth therefore became known as myostatin.¹⁶ It was predicted that blocking myostatin could be used to increase muscle mass in muscle wasting diseases. Animal studies tested this by weekly intraperitoneal injections of myostatin antibodies in the mdx mouse for three months. Treated mice displayed a significant increase in skeletal muscle mass and strength, with reduc-

tion in serum creatinine kinase to almost control levels.¹⁷

The prospect of myostatin inhibition being used as a therapeutic agent for muscle atrophy from any cause is an exciting one but there may be potential problems with this approach. For example, one recent study evaluating disuse atrophy found that myostatin knockout mice actually lost more muscle mass than control mice.¹⁸ It is clear that myostatin inhibits muscle growth but there are many regulatory factors of myostatin itself and as such its exact role remains to be fully explored.¹⁹ The potential for treatment of muscle atrophy due not only to primary muscle disease but also secondary to systemic illness, drugs or disuse is very attractive, especially for the pharmaceutical industry. However, further work is required to clarify myostatin's specific action in these different mechanisms of muscle damage. The results of a recent Phase II trial in humans with LGMD are awaited.

Conclusion

Recent advances in the genetics of muscular dystrophy have shown that the discovery of causative genes combined with the study of molecular disease mechanisms can identify new therapeutic paradigms. The potential patient benefit of the gene therapy and myostatin pathway manipulation approaches outlined may be significant provided safety can be proved in appropriate trials. Perhaps most promising of all is that some of these approaches, e.g. stop

codon suppression and myostatin pathway manipulation, may have therapeutic potential in a number of different muscular dystrophies and genetic muscle diseases. We are now entering an era of clinical trials for genetic muscle diseases.²⁰

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ABNT - Message from the Chair

Welcome to the first column from the ABNT – a new communicative venture in collaboration with the ACNR.

What is the ABNT?

The Association of British Neurologists Trainees (ABNT) is the trainees group of the Association of British Neurologists (ABN), and is open to all associate members of the ABN who are neurology trainees. We work using a system of regional representatives (elected locally), who act as the first point of contact for matters relating to neurology training in the UK. Policy is devised using a committee, at present with eight positions. Individuals are elected to the committee by ABNT members for a period of two years, and represent trainees interests on all the committees of the ABN, as well as within the BMA and Royal College of Physicians.

What's happening at the moment?

Modernising Medical Careers (MMC)

We can't avoid MMC I'm afraid – this continues to be an enormous problem for neurology trainees nationally. With an average competition ratio of 3:1 for ST3 jobs in the UK, higher in neurology, and run-through training honoured from 2007 in Scotland (and for some of the jobs in England), it's never seemed more difficult to break into higher specialist training.

Extensive lobbying (partly by us but mainly from the ABN President, and Geraint Rees on behalf of the BMA) has resulted in the allocation of around 15 extra ST3 positions in England, which are to be reserved for open competition, along with 2/3 of the posts available via vacated SpR numbers. We know from data that we've collected that this roughly corresponds to the number of research fellows seeking re-entry to training, so this year might be a very good year to apply for specialty training. However, with another 25-30 research fellows projected to 'mature' in 2009/10, and a need to identify consultant vacancies for all the extra training positions created, it's up to all of us to keep the pressure on for the future.

Tooke Inquiry

The final report of the Tooke Inquiry was published recently, and although it is broadly supportive of the issues that we think are important, it remains to be seen

quite how the Department of Health implements it.

Decoupling has been confirmed at ST2/ST3, in line with the views of many of the medical specialties, and the need to identify transferable competences has been reinforced, important in specialties like ours that attract trainees from a wide range of backgrounds.

The threat of the sub-consultant grade seems to have been downplayed in this final version (compared with previous drafts), but this remains a threat to the provision of neurology care in the UK.

The commission of a new body for postgraduate medical education (NHS Medical Education England) may seem like an extra layer of bureaucracy, but this is a model that has worked well in Scotland for some years, and may also help to safeguard study leave budgets, under threat and essential to our training. Additionally, for specialties that have strong national structures and a common voice (such as ours), it should provide a single portal of entry for negotiation and accountability.

Exit Exam

The Training and Education Committee (TEC) of the ABN has prepared a summative assessment in Neurology, similar to the pilot run in 2006, and is proposed to be compulsory for CCT for ST trainees. It was planned that the first sitting of this exam would be open in May 2008, although recent last-minute concerns of some of the specialist societies allied with the RCP (of which the ABN is one) may delay implementation.

Andrew Kelso is Secretary and Acting Chair of the ABNT. He is an SpR in Neurology in Edinburgh, with a special interest in epilepsy. He is also a member of the BMA Junior Doctors Conference Agenda Committee, Junior Doctors Committee and Scottish Junior Doctors Committee.

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Multiple Sclerosis and Related Demyelinating Disorders in India

Demyelinating disorders of the central nervous system have assumed significance in recent years in India, coinciding with the availability of magnetic resonance imaging facilities (MRI) in teaching and private hospitals in the metropolitan cities of India. Neurologists are in agreement that they see more cases of multiple sclerosis (MS) recently than they did a decade ago. However it is not yet certain whether this is apparent, as a consequence of better diagnostic facilities and greater awareness among specialists, or real. On the other hand post infectious demyelinating disorders or acute disseminated encephalomyelitis (ADEM) are likely to be more common in view of prevailing conditions.

The study of demyelinating disorders of the nervous system in India has been limited by many factors. Neurologists in the past have been significantly influenced by Kurtzke's¹ epidemiological studies which clearly showed India among other tropical countries to have a low prevalence for MS. The diagnosis of MS in India has relied heavily on clinical criteria. Lack of facilities and or financial constraints have prevented the use of radiological and other paraclinical tests on a wide scale in diagnosis. Evaluation of optic neuritis in a tropical setting is beset with problems. Toxic, nutritional and infectious causes of optic neuritis are under-diagnosed. Most patients presenting with acute visual loss are evaluated by ophthalmologists and evaluation of the central nervous system by imaging and lumbar puncture are seldom considered. Record keeping and long term follow up of patients have seen serious limitations in all but the teaching hospitals and continue to hinder data collection and analysis of diseases in India, including demyelinating disorders. One of the direct fall outs for this problem is that there are no longitudinal studies on clinically isolated syndromes (CIS) suggestive of demyelination in India.

In this article a brief overview of demyelinating disorders seen in India is discussed, particularly the prevalence of MS, the contentious issues of optico-spinal MS and neuromyelitis optica, and the available data on immunogenetics of MS. There are many mimics for CNS demyelinating disorders in a tropical set up which are also highlighted.

Multiple Sclerosis

There are no large scale epidemiological studies from India on the incidence and prevalence of Multiple sclerosis. Based on hospital statistics a prevalence of approximately 1.33/100,000 was reported by Singhal et al² in the mid eighties from the west coast of India. An indication to suggest that more cases are being diagnosed in recent times comes from data published from the northwest of India.^{3,4} The incidence of hospitalised MS patients seen at a premier teaching hospital, nearly doubled within a span

of 15 years. In the Parsi population of India, Wadia⁵ observed a prevalence of 26/100,000. Parsis are a closely knit community which migrated to and settled predominantly in the west coast of India, between the 7th and 8th century and more recently in the 19th century, from the Pars province of Iran. Recently a high prevalence of MS was detected in Isfahan, a province that adjoins Pars in Iran, supporting the notion of genetic susceptibility in this community.⁶

Is MS seen in India different from that in the west? Results of some of the recent Indian studies^{7,8} done in the MRI era have found relatively few differences from the west, lending support to the theory that the differences between MS in the West and Indian population are more apparent than real. However what cannot be ignored is the report of high frequency of optic and spinal cord involvement in several Indian studies.⁹ In a recent prospective and longitudinal study of CNS demyelinating disorders which included 51 patients, Pandit et al¹⁰ found 47% of their MS cases to have clinical attacks confined to the optic nerve and spinal cord. The MRI of brain and spinal cord was indistinguishable from conventional MS in all. A larger prospective study with careful documentation of clinical events supported by MRI imaging of brain and spinal cord is important to settle the issue of optico-spinal phenotype of MS and its prominence in Indian MS. The results of one such study, which will be completed by 2010, are awaited. Immunogenetics of MS in India have not been studied in detail. Class II HLA association studies were done for the first time recently in 23 MS patients of non Parsi origin in whom the commonly reported association was with DRB1*1501 (50%) similar to western studies.¹¹

Neuromyelitis optica

In earlier studies neuromyelitis optica was diagnosed as a monophasic illness with involvement of both optic nerve and spinal cord and an interval not exceeding a month between involvement of both sites.^{9,12} Most studies have collectively shown an incidence of 20% or fewer cases of neuromyelitis optica defined by these criteria. A paper by Jain et al¹³ has been widely quoted in western literature as evidence for high prevalence of NMO in India. A careful review of their data of 354 cases of MS collected from nine centres reveal that 33 cases (10.1%) were neuromyelitis optica, defined according to the above mentioned criteria. Prospective studies¹⁰ using the newer diagnostic criteria of Wingerchuck have shown an incidence of 9.5% of NMO. Recurrent myelitis, which is probably a variant of NMO has been reported from the India.¹⁴ Whilst it is probable that NMO is seen more commonly than in western countries, it is certainly not seen in the magnitude reported from other Asian countries, especially Japan.



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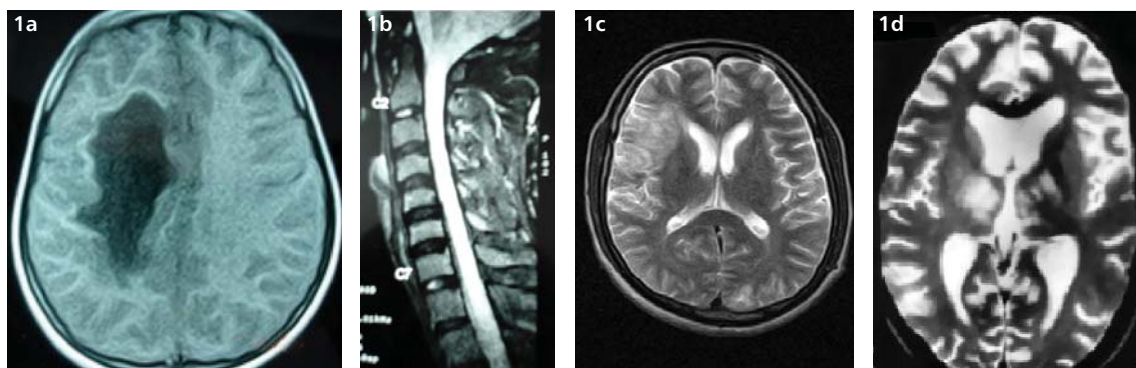
Differential diagnosis of white matter diseases in the tropics

From left – Figure 1a: A case of biopsy proven ADEM, MRI brain with contrast showing incomplete ring enhancing lesion with mass effect.

Figure 1b: A case of Neuromyelitis optica, with MRI spine showing longitudinally extensive transverse myelitis.

Figure 1c: An asymmetric white matter lesion on brain MRI of an HIV positive patient with progressive multifocal leucoencephalopathy.

Figure 1d: A case of Japanese B encephalitis with bilateral thalamic lesions.



Acute disseminated encephalomyelitis (ADEM)

ADEM is a commonly made diagnosis in tropical countries like India where infections abound and vaccinations, especially anti-rabies vaccination (Semple's vaccine) are still freely in use. ADEM as an entity has no definite diagnostic criteria and has a heterogeneous clinical presentation. Most importantly it is a diagnosis of exclusion. Infections, especially HIV, neurosyphilis, Arboviral encephalitides, especially Japanese B encephalitis, which target the basal ganglia and thalamus, tuberculosis of the CNS presenting as isolated parenchymal white matter disease, neurosyphilis and cystic infective brain lesions such as neurocysticercosis can mimic ADEM. Osmotic demyelinating syndrome, especially of the extrapontine type, vitamin B12 deficiency and occasionally mitochondrial disorders which flare up in the background of systemic infections can cause diagnostic confusion.

Conclusion

One of the priorities for specialists working in demyelinating disorders in India is to collect data using uniform criteria, especially when defining conditions such as opticospinal MS and neuromyelitis optica. Clinical descriptions have to be correlated with MRI data of both the cord and brain. This is particularly important in the context of choosing the appropriate disease modifying agents and while recruiting patients for clinical trials for drugs with potentially disease modifying effect. While it is true that only a fraction of diagnosed patients in India are able to afford beta interferon or glatiramer acetate, alternate therapies such as mitoxantrone¹⁵ are being tried with varying degree of short term success. The MS society has 4000 registered patients and it is estimated that there are approximately 40,000 more in the community. Epidemiological studies are urgently warranted to establish the burden of disease in the country. In India, issues regarding health insurance for MS patients (which is not currently available), subsidies for disease modifying agents, disease awareness and rehabilitation of affected patients are concerns which have to be addressed jointly by health professionals, MS societies, the pharmaceutical industry and governmental agencies. The Multiple Sclerosis Society of India, having over ten branches in Indian cities, is very active in arranging social and financial help for the patients and acts as an effective interface between the doctors and the patients.

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The National Institute of Clinical Excellence Head Injury Guidelines: A Summary to Assist Implementation

The National Institute for Clinical Excellence guidelines aim to improve the quality of healthcare. They provide evidence based recommendations for the treatment and care of patients with specific disorders. The guidelines can be used to develop standards of care and provide a useful tool for auditing clinical practice. In 2003, NICE first published guidelines for the management of head injured patients (Clinical Guideline 4).¹ In September, 2007, an extensive update including amendments to existing advice and new recommendations was published (CG 56).² The guidelines and the update were compiled by a large panel of interested parties after an exhaustive review of the available literature. This paper aims to summarise the features of head injury care as recommended by the guidelines.

The objective of care for head injured patients is to ensure timely recognition and treatment of significant injuries in an appropriate healthcare setting. The NICE guidelines have led to a shift in management from an "admit and observe" strategy to a "diagnose and decide" approach. The guidelines provide advice on pre-hospital management, assessment in the emergency department, investigation for brain and cervical spine injuries (see

Boxes 1, 2 and 3), recommendations for referral and transfer to a neurosurgical unit (see Box 4) and guidelines regarding the admission, care and discharge of brain injured patients (see Box 5).

The key features of the guidelines include the following:

- Head injured patients should be transported to a facility with the resources to resuscitate, investigate and provide initial management of multiple injuries. The initial assessment and management should follow the principles of the Advance Trauma Life Support system. For patients with a GCS 3-8 the paramedic crew should make a stand-by call to ensure that appropriate personnel are available to treat the patient at the receiving hospital.



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With reference to boxes

NAI = non-accidental injury
= fracture

Box 1 – CT head imaging in adults

CT Head Imaging in adults

Immediate CT (within 1 hour of request):

GCS <13 when assessed in Emergency Department
GCS <15 2 hours after Emergency Department assessment
Suspected open or depressed #
Signs of basal skull #
Seizure
Focal neurological deficit
>1 episode of vomiting
Anticoagulant therapy or coagulopathy

CT within 8 hours:

Pre-traumatic amnesia >30 min
Age >65 years if any amnesia or loss of consciousness since the injury
Dangerous mechanism if any amnesia or loss of consciousness since the injury (e.g. pedestrian or cyclist hit by motor vehicle; ejected vehicle occupant; fall >1m or 5 stairs)

Box 2 – CT head scanning in children

CT Head in Children (under 16):

Age <1 year; GCS <15 on assessment in Emergency Department (Paediatric GCS)
Age >1 year; GCS <14 on assessment in Emergency Department (Paediatric GCS)
Age <1 year; bruise, swelling or >5cm scalp laceration
Dangerous mechanism (high speed RTA, fall >3m, high speed projectile injury)
?NAI (personnel should be trained to recognise NAI)
Witnessed loss of consciousness >5 min
Seizure (with no history of epilepsy)
Suspicion of open or depressed #
Tense fontanelle
Signs of basal skull #
Focal neurological deficit

Box 3

Cervical Spine Clearance

If undertaking urgent head CT the cervical spine should also be scanned

In patients who are alert it is safe to fully examine the neck if:

- Simple rear end collision
- Patient has been ambulant at any time since injury and there is no midline tenderness
- Patient can sit comfortably in emergency department
- Patient presents with delayed onset of neck pain

Requests for cervical spine radiographs in adults and children

For adults and children age 10-16 years use AP, lateral and odontoid peg views

For children age <10 years request AP and lateral views (no peg view)

Radiographs should be requested if:

- Not safe to assess neck (see above) and CT not indicated
- Active neck rotation is limited to <45 degrees to left and right
- Neck pain/midline tenderness + age >65
- Neck pain/midline tenderness + dangerous mechanism (fall > 1m or 5 stairs; axial load; high speed RTA; ejection from vehicle; rollover; bicycle collision; recreational vehicle)
- Cervical spine status required e.g. pre-surgery

CT Cervical Spine requests in adults and children 10 years or older

CT Cervical Spine should be requested if:

- GCS <13 on initial assessment
- Patient is intubated
- Inadequate plain films
- Clinical suspicion persists despite normal plain films
- Undertaking scans for multi-region trauma

CT Cervical Spine requests in children under 10 years

Request CT Cervical spine if:

- GCS <9
- Inadequate plain films
- Strong clinical suspicion of injury despite normal plain films

- The spine should be immobilised for all patients with GCS < 15, any history of neck pain or tenderness, any extremity paraesthesia, any focal neurological deficit or any other suspicion of a cervical spine injury. Immobilisation should remain in place until a full assessment has been conducted (Box 3).
- Immediate clinical assessment should be conducted in the Emergency Department for all patients with a GCS <15. All patients with a GCS of 15 should be assessed by trained staff within 15 minutes of arrival.
- The admitting team should be competent to assess, observe, investigate and transfer patients. If the patient has sustained poly-trauma, admission should be under the care of the team who are dealing with the most severe and urgent clinical problem.
- All serious head injuries (GCS 3-8) should be transferred to a neuroscience unit. If logistics prevent transfer, neurosurgeons should assist and advise.
- Patients and carers should be aware of potential long-term symptoms and disabilities and should know how to seek help. GPs should be able to refer patients with long term sequelae to a suitable healthcare professional for specialist advice.

ERNIE database

The Evaluation and Review of NICE Implementation Evidence (ERNIE) database summarises the literature concerning the uptake of NICE guidance. References to external literature and a simple classification system are provided. ERNIE identifies 11 references that have assessed the implementation of the head injury guidelines.³ Although this information is far from complete, it provides a sound introduction to further investigation and dissemination of knowledge about the impact of the guidelines. Initially an increased use in resources was considered likely.^{4,5} However, this prediction has not been evident in studies published to date. The 2 to 5 times increased use of CT scans has been associated with a large decrease in admission rate. This has therefore led to a redistribution of patient management from the observation ward to the radiology department with no net increase in cost of care.^{6,7}

Areas for future research

The Guideline Development Group made several recommendations for further research to improve the evidence in specific areas of care. These are summarised below.

1. Should patients be transferred directly to a specialist neuroscience centre or to the nearest district general hospital?
2. The new guidelines regarding the use of CT head scans in children need validation in clinical practice.
3. The role of surgery vs. ICP and intensive care monitoring in patients with 'non-surgical' mass lesions requires further elucidation. Is there a role for 'pre-emptive' surgery?
4. Some evidence supports the transfer of patients with 'non-surgical' traumatic brain injury to a specialist neurosciences unit. This practice is not universal and further work is required to evaluate whether the

Box 4

When to involve a neurosurgeon

- All mass lesions on CT (including those of obvious and those of uncertain significance)
- GCS 3-8 after initial resuscitation
- Unexplained confusion >4 hours
- Deterioration in GCS after admission
- Progressive focal neurological signs
- Seizure without full recovery
- CSF leak
- Definite or suspected penetrating injury

The South West Neurosurgery Centre recommends that all patients not obeying commands after resuscitation and imaging are discussed with on-call neurosurgical SpR.

Transfer of Patients to the Neuroscience Unit

- All patients with GCS <9 should be transferred (unless GCS 3 with fixed and dilated pupils)
- Many other patients will be transferred depending on GCS and scan findings.
- Most transfers should be intubated and ventilated and managed according to AAGBI guidelines.
- Patients with persistent refractory hypotension should not be transferred until the cause has been identified and the patient stabilised.
- Maintain mean BP of 80 mmHg; PaO₂ >13 kPa and PaCO₂ 4.5-5.0 kPa

reported improvements in outcome can be achieved across the board.

5. Robust clinical decision tools need to be developed to help predict those patients with mild injury who are likely to develop long term sequelae.

Conclusion

In summary, the NICE Head Injury Guidelines provide the many clinicians involved in the care of brain-injured patients with a sound foundation upon which to build patient care. The challenge for neurosurgeons is to improve the efficacy of management for patients with intracranial mass lesions and to conduct further work to establish the best pathway of care for patients with diffuse brain injury. Neurosurgeons are well placed to aid national guideline implementation.

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Box 5 – Criteria for admission, observation, medical review and discharge

Admission Criteria

- New, significant abnormalities on imaging
- GCS <15 after imaging (even if imaging normal)
- Persistent vomiting or severe headache
- Other concerns e.g. drugs; alcohol; shock; meningism; CSF leak; other injuries; ?NAI
- Criteria for CT fulfilled but scan not performed within appropriate time period (e.g. non-availability; uncooperative patient).

Observations by trained, capable staff

Observations should include: GCS, pupils, limb movements, vital signs including oxygen saturations. The frequency of observations should be:

- GCS every 30 minutes until GCS = 15
- When GCS = 15; observe every 30 mins for 2 hours then 1 hourly for 4 hours; then 2 hourly.
- If GCS falls to <15 resume observations every 30 minutes.

Urgent Medical Review should be conducted if:

- Agitation or abnormal behaviour develop
- GCS drops by 1 point for 30 minutes duration
- Motor score drops by 2 points
- Verbal or eye opening score drop by 3 points
- Severe or increasing headache occur
- Persistent vomiting occurs
- New signs e.g. pupil changes, facial weakness are detected

Discharge of Mild and Moderate Head Injured Cases

- All patients must be GCS 15
- Ensure a support structure exists to avoid a "home alone" situation
- If the patient met the criteria for a CT scan or hospital admission a review should be conducted by the GP after 1 week. The GP should receive written details of the episode.
- All patients should receive a head injury advice card and be aware that some patients can develop delayed complications warranting further medical advice.

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NICE/SCIE Dementia Guidance: Time to Reconsider

In November 2006, the National Institute for Health and Clinical Excellence and the Social Care Institute for Excellence (NICE/SCIE) jointly published guidance on the identification, treatment, and care of people with dementia.¹ This document has been somewhat overshadowed by the concurrently issued recommendations of NICE regarding the use of cholinesterase inhibitors (ChEIs) and memantine for the treatment of Alzheimer's disease (AD).^{2,3} However, as NICE/SCIE guidance is implemented by commissioning bodies, its implications are being brought into sharper focus since, though titled 'guidance', adherence is required rather than optional, and will be used as a marker of a Trust's 'performance'.

The system of NICE guidance in various domains of medical practice is in general to be welcomed. It is helpful to have available a systematic approach to diseases and treatments in order to ensure that practising clinicians are aware of best practice. However, in a subject as complex as medicine, where patients do not always fit neatly into simply defined problems, guidelines may, like all other medical interventions, have unintended adverse effects as well as possible benefits. Often what is offered as guidance becomes de facto a prescription of rigidly-defined limitations against which Trusts are judged.

In the specific case of dementia, the aspiration to effect a seamless transition between the medical/diagnostic and social/pastoral aspects of patient care, to bridge the health care/social care divide, so often previously a stumbling block, is one that all involved clinicians – old age psychiatrists, geriatricians, neurologists – will share; likewise patients, families, carers and patient organisations. However, the care pathway is not so linear as the NICE/SCIE guidance seems to envisage, such that the required service restructuring runs the risk of disadvantaging patients who fall outside the 'typical'. In particular, the proposal that there be 'a single point of referral' for all suspected cases of dementia, to wit generic 'memory assessment services' which may be provided by a 'memory assessment clinic or by community mental health teams' (p10), requires careful examination.

Dementia is not a unitary, homogeneous condition but a syndrome with many different causes. Although neurodegenerative disorders in which cognitive impairment and dementia are the predominant features, the so-called primary dementias, account for the majority of cases, in particular AD, many other neurological and medical conditions may present with cognitive complaints and/or cognitive decline, including cerebrovascular disease, Parkinson's disease and parkinsonian syndromes, multiple sclerosis, epilepsy syndromes, motor neurone disease, Huntington's disease, prion diseases,

HIV, certain autoimmune, endocrinological and inflammatory conditions, and structural lesions such as tumours, subdural haematoma and hydrocephalus, the so-called secondary dementias.^{4,5} Hence, treatment of dementia syndromes extends well beyond simply ChEIs, and the inputs required for patients as disparate as, say, an 80-year-old with AD and a 40-year-old with prion disease or HIV, are manifestly not the same.

In dementia of early onset (arbitrarily defined as occurring before 65 years of age), which recent estimates suggest accounts for 2.2% of all dementia cases,⁶ the differential diagnostic possibilities become even broader,^{4,7} including an increased frequency of genetically-determined diseases such as familial AD, frontotemporal dementia, Huntington's disease, and CADASIL. It was previously acknowledged in a joint report from the Royal College of Psychiatrists and the Alzheimer's Disease Society that patients with early-onset dementia and their families have special requirements and that specialist resources, under the auspices of neurologists, psychiatrists, or jointly in multidisciplinary teams, are required to address them,⁸ conclusions with which NICE/SCIE seem to agree ("specialist multidisciplinary services should be developed", p13).

Most 'memory assessment services' and 'community mental health teams' are under the auspices of old age psychiatrists. It is not clear whether these clinicians have the appropriate training to diagnose and manage neurological conditions, some of which are not even acknowledged as possible causes of dementia in the Diagnostic and Statistical Manual of Mental Disorders (e.g. MND).⁹ Furthermore, even so-called primary psychiatric disorders associated with cognitive decline, such as depression and schizophrenia, may be referred to neurology-led cognitive clinics for assessment. A recent study showed that not less than 20% of referrals to such a clinic over a 5-year period were from psychiatrists.¹⁰

The diagnosis of dementia often requires specialist investigations, including structural (CT, MRI) and functional (SPECT, PET) brain imaging, cerebrospinal fluid studies, neurogenetic testing, neurophysiological studies (EMG, EEG) and sometimes tissue biopsy (brain, bone marrow, skin, rectum) as well as detailed neuropsychological assessment. Some of these are acknowledged by NICE/SCIE (p24-26). Incorporation of such biomarkers into diagnostic criteria is now recommended for AD.¹¹ Again it is not clear whether, outside specialist centres, a 'single point of referral' will be equipped to provide these services.

The heterogeneity and complexity of the dementia syndrome at the clinical, aetiological, therapeutic and prognostic levels^{4,7} argues the need for a flexible yet

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The problem lies in giving the impression, which may be acted upon by commissioning bodies, that this is a universal approach to dementia irrespective of age or other attendant neurological disorder

structured approach to case management. Dementia is neither a neurological nor a psychiatric disease – neurology and psychiatry being cultural artefacts and political constructs – but a brain disease. A “single point of referral”, with its connotations of “one size fits all” – so definitively rejected in the sphere of education policy – will not suffice. An integrated care pathway which encompasses the various clinical disciplines with an interest in dementia has been proposed.¹²

The NICE/SCIE guidance is sensible with regards to the provision of care services for elderly people with dementia of neurodegenerative and cerebrovascular aetiology. The problem lies in giving the impression, which

may be acted upon by commissioning bodies, that this is a universal approach to dementia (“recommendations that apply to all types of dementia” p4) irrespective of age or other attendant neurological disorder.

Whatever the original intentions of NICE/SCIE, the consequence of implementation of their guidance by commissioning bodies who may know no better is to marginalise, if not abandon altogether, neurological input into the diagnosis and management of dementia syndromes (neurologists are mentioned only once in the document, in the context of initiation of pharmacological therapy for the cognitive symptoms of AD, p30). We believe that such a prescription will inevitably

lead to a reduction in the quality of service provision for this vulnerable group of patients.

These oversights are easily understandable – wittingly or otherwise, there was no neurologist on the Guideline Development Group or Review Panel – and easily rectified in future guidance. In the meantime, we suggest confusion may be avoided by NICE/SCIE explicitly re-titling their current guidance as applicable to typical dementias in adults over age 65. This would alert clinicians to the need for critical evaluation of all individuals with dementia or cognitive decline, irrespective of age, so that the highest standards of medical care provision are available to all.

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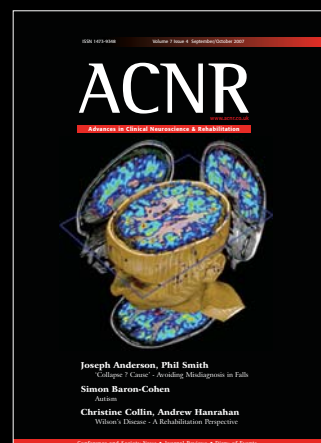
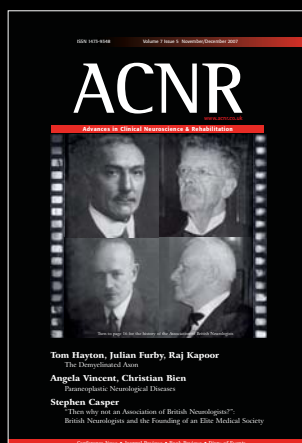
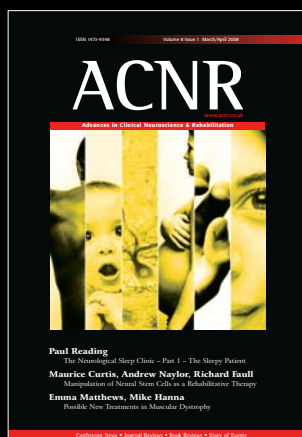
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Cognitive Function in Multiple Sclerosis – A Roundtable Discussion

In June 2007, a panel of healthcare professionals with a strong interest in and/or practical experience of cognitive problems in people with multiple sclerosis (MS) met to explore the potential for routine screening of cognitive function in the clinical management of people with MS. The purpose would be to examine whether changes in cognitive function were significantly affecting a person's life. This paper provides a summary report of the group's discussion and views on cognitive function and screening, including the measures being used, their appropriateness for use in MS clinical services and the potential for a measure that encourages healthcare professionals to monitor cognitive function routinely.

Cognitive dysfunction affects up to 65% of people with MS.¹ It threatens confidence and self-esteem and can disrupt employment, social interactions, and daily routines.^{2,3} Symptoms of cognitive dysfunction, which can cause significant upset for patients and families, are subtle and complex and therefore, can be challenging to identify. They may produce memory decline which affects 40-60% of individuals,⁴ reduction in: new learning capacity,¹ verbal working memory,⁵ visual memory and auditory memory.⁶ Other changes include dysexecutive symptoms, with a reduced ability to engage in testing,⁷ attention deficits,⁸ reduction in processing speed⁹ and intellectual decline.¹⁰ There was a view during the discussion that many people with MS are unaware of the meaning of cognitive changes and may confuse them with symptoms of mental health problems.

Rehabilitation and cognitive decline

Rehabilitation can be regarded as a problem solving and educational process aimed at reducing the level of disability and increasing the level of independence. However, this is always within the limitations imposed both by available resources and by the underlying disease process.¹¹ It encompasses the ability to learn new

healthcare providers
should offer periodic
screening and/or
assessment of cognitive
function

information and adapt to new ways of functioning, which utilises feedback, taking into account cognitive ability. Therefore, cognitive and related impairments are likely to have an impact on rehabilitation when domains of cognition such as communication, recall, processing speed, problems in abstract thinking, coping strategies, mood and relationships are affected.

According to a recent observation of one of the group members, approximately 90% of people with MS who were admitted to a rehabilitation centre agree with the following statements to some degree: 'I begin to talk and forget what I was going to say' and 'I have difficulty finding words when trying to explain things'.¹¹ However, when the same patients were asked if they had speech problems, there was a lack of awareness of such problems, suggesting that cognitive impairment may limit the strategies which can be adopted to cope with illness, such as problem solving (if working memory is impaired) and organisation, if there are dysexecutive problems. Given that people with MS deteriorate, learning to cope and adjust is an important part of maintaining a person's quality of life. From the group's experience it was felt that people generally cope better if they feel they have control over what happens to them and a choice in their lifestyle.¹¹

Mood changes are common in people with MS, with up to 42% reported to suffer significant depression.¹² Depression itself can affect short term memory, learning and attention¹² and anxiety may also impair attention¹⁴ but the relationship between cognition and mood is complex. One viewpoint at the meeting was that a person's lack of expression of distress could be due to communication or cognitive problems.

The group generally felt that there is a relation between fatigue and cognitive problems and that recognising these links, treating the fatigue and/or associated depression, may reduce the impact of cognitive decline on daily life.¹⁵ Developing and using strategies for dealing with cognitive problems, such as memory impairment, may also help improve general well-being.

Cognitive impairment may put a strain on the carer/patient relationship. For example forgetting,

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Table A: Reasons for cognitive screening

• <i>To provide a baseline as a measure of deterioration</i>
• <i>To give reassurance</i>
• <i>To inform how a multidisciplinary team should work with a patient.</i>
• <i>To inform on intervention/medical treatment</i>
• <i>Cognitive Rehabilitation</i> - Individual - Groups - Carer Support/education
• <i>Research</i>
• <i>Highlighting to commissioners the need for resources and coherent psychological services to address the various problems arising as a result of cognitive impairment.</i>

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repeating one-self and confusion can lead to the need to work with patients and their carers on ways to manage the cognitive problems together. Executive problems may also affect behaviour, leading to difficulties in relationships with staff and others.

Monitoring cognitive function in clinical practice

The experience of practicing Clinical Neuropsychology within a Neuro-rehabilitation Service highlighted several practical reasons why assessment of cognitive function is not routinely performed, including the fact that tests are long and not standardised for people with MS, the limited availability of assessments for people with physical difficulties, including poor vision, communication problems and fatigue, and lack of resources. The rationale for cognitive assessment needs to be established and consideration needs to be given to when, where, why and how to carry out cognitive assessment as well by whom. One view was that it is important to take into consideration that screening someone has the potential to unnecessarily high-

light a cognitive problem.

It has been recommended that healthcare providers should offer periodic screening and/or assessment of cognitive function,¹⁶ as deficits may not always be reported or noticed. For example, The NICE guidelines state: ‘Any person with MS complaining of cognitive problems... should be offered a formal cognitive assessment’ and yet it is an area that is not assessed routinely.¹⁷ Early screening would be helpful and it may be useful to ask questions both to elicit information and also to give reassurance. Patients are often relieved to be told that cognitive changes they may be experiencing, are not dementia and that they are not ‘going mad’.

At the meeting, several reasons why screening for changes in cognitive function may be helpful were raised (Table A). Although consultation rates have been found to increase as cognitive function worsens, the generally held view was that once an appropriate care package is put in place the rate of consultation lessens thereafter. It is feasible that early recognition and intervention in cognitive dysfunction can have a positive impact, because

people are likely to be able to stay in work for longer and maintain relationships for longer. Early recognition of cognitive function decline enables early intervention. Once memory loss becomes too impaired, teaching strategies to cope become of little use.

The most appropriate format for cognitive assessment remains unclear. Asking specific questions about problems at work, in daily life and hobbies may be beneficial. However, asking global questions such as “Are you having memory problems?” can be inappropriate as they may lead to false positives and conflicting information. Subtle enquiry with a patient or carer may educate patients and carers, highlight concerns and reduce anxiety. Although the necessity to perform in-depth assessments at the point of diagnosis remains debatable, performing in-depth neuropsychological assessments soon after a diagnosis of MS may sometimes be helpful especially when employment is threatened, there are difficulties with independence in the home or education problems.

Routine screening for cognitive dysfunction in MS

To encourage cognitive screening of people diagnosed with MS, the measure should ideally be brief, sensitive, and specific, with a clear cut-off point (i.e. provide a score to indicate that further evaluation is required) and be independently validated. It should also be able to evaluate specific cognitive domains including: memory, attention, executive abilities and speed of processing. It should be independent of mood, fatigue and disability. It is clear that there is a drive for something brief and which does not necessarily require the involvement of a neuropsychologist, although it is important not to overemphasise the need to save time. Detailed assessment of cognitive function requires the appropriate time. It is difficult to know from the outset which cognitive functions are impaired and consequently measures of most cognitive domains should be included.

Two main strategies have been used to assess cognitive function in people with MS. These are self-report measures e.g. MSNQ (MS Neuropsychological Questionnaire),¹⁸ and short batteries of cognitive tests.

Discussion focussed on the MSNQ, which had general appeal because it is short and easy to administer. There are only 15 questions rated on a 5 point scale. It is non-invasive, standardised and validated.¹⁸ However, with the self report form of the MSNQ, a replication study found the specificity to be only 0.6, with false negatives seen in people with low mood.¹⁹ The self report version was highly correlated with mood and not significantly correlated with cognitive tests.¹⁹ The informant MSNQ shows higher sensitivity and speci-

Table B: Neuropsychological Tests included in the MACFIMS

Test	Domain
<i>Benton Judgement of Line Orientation Test</i>	<i>Visual/Spatial Perception</i>
<i>Controlled Oral Word Association Test</i>	<i>Generative Verbal Fluency</i>
<i>California Verbal Learning Test, Second Edition</i>	<i>Auditory/Verbal Learning and Memory</i>
<i>Brief Visuospatial Memory Test – Revised</i>	<i>Visual/Spatial Learning and Memory</i>
<i>Paced Auditory Serial Addition Test</i>	<i>Processing Speed and Working Memory</i>
<i>Symbol Digit Modalities Test</i>	<i>Processing Speed and Working Memory</i>
<i>Delis Kaplan Executive Function System</i>	<i>Executive Function</i>

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Identification of cognitive deficits in people with MS requires greater emphasis

ficity than the self report version¹⁹ and is significantly correlated with cognitive tests and not with mood. Self report and informant measures can lead to conflicting results, but each provides useful information.

Cognitive tests have the advantage of standardisation and are usually independent of mood. The Addenbrookes Cognitive Examination – Revised (ACE-R), is used in clinical practice to monitor cognitive function and takes between 10 minutes to half an hour. Although the ACE-R has not been validated for use with MS patients it had been used by a member of the group. It is not sensitive to mild cognitive decline. There are timed elements within the assessment, which is an advantage, as slowness is a common problem in MS patients.¹³ The ACE-R includes a drawing which the group felt may limit the completion of the assessment, although it is unlikely to misclassify patients on the basis of one item.

Undue length is a concern with some cognitive test batteries, a disadvantage in fatigued patients especially. They take from 20 minutes, for example for the MMSE, up to 90 minutes for the MACFIMS (Minimum Assessment of Cognitive Function in MS),

because they assess a number of different domains (Table B).¹⁹ Furthermore, some tests require motor skills that limit their applicability to severely physically disabled patients. Other drawbacks include poor specificity and sensitivity; and the batteries are not always relevant to the usual pattern of cognitive impairment in people with MS,

There have been attempts to compare the effectiveness of the tests. Aupperle et al²⁰ found that the sensitivity of the Neuropsychological Screening Battery for Multiple Sclerosis (NPSBMS) and the Screening Examination for Cognitive Impairment (SEFCI) was greater than the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The best sensitivity was achieved from a combination of the NPSBMS and Symbol Digit Modalities Test (SDMT). They suggested that if one test is to be used the Symbol Digit Modalities Test (SDMT) may be the most sensitive.

Conclusion and summary

The identification of cognitive deficits in people with MS requires greater emphasis. However, to introduce cognitive assessment into routine clinical management is challeng-

ing. One approach may be to develop a simple measure that incorporates questions pertaining to cognitive function while at the same time going over the main challenges that a person with MS has to cope with. If at this initial screen a decline in cognitive function is identified, then further cognitive screening (e.g the MSNQ) could be implemented. The development of a measure would help to raise awareness of cognitive problems and would guide professionals when attempting to determine overall priorities for the patient, carer and healthcare professionals. It should therefore, be designed to monitor the patient's, carer's and healthcare professional's perspectives.

Enabling patients, professionals and carers to contribute equally to the assessment of cognitive function may help to provide a more balanced perspective. This balanced approach could encourage a discussion of areas where the patient and carer would wish to concentrate, but also it could help the healthcare professionals to identify other areas of concern. It is therefore vital that any screening or assessment should be patient led and done within the context of a professional relationship.

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Recent Advances in Assistive Technology and Engineering (RAatE) 2007

26-27 November, 2007; Sheffield, UK.

RAatE 2007 is the only UK conference focused on the latest innovations in assistive technology and is attended by people who use, work with, develop and research on assistive technology (AT). RAatE is held annually and attracts a regular but diverse audience, with this year's audience approaching 150 over two days. The ACT Programme, a South Yorkshire based programme of research and development and knowledge transfer, acted as co-sponsors for 2007, and enabled a number of overseas based keynote speakers to be brought to the conference.

The conference started with training courses on various areas of AT delivered by key professionals and organisations. These short courses enabled people to reinforce or extend their skills in some key areas. Topics covered were Alternative and Augmentative Communication (AAC); Accessing Technology; Paediatric Postural Management; and a workshop on Outcome Measures in AT. The keynotes throughout the conference were all stimulating and delivered by well renowned presenters: Dr Branko Cellar from the Laboratory for Health Telematics in New South Wales, Australia delivered a talk around his founding work in Telecare; Dr Jeff Jutai, from the Lawson Health Research Institute in London, Ontario, Canada discussed Outcome Measures in Assistive Technology including his PIADS measure; and Adam Walker, assistant director of Triangle, gave a user's perspective on AT, particularly how persistent one has to be to secure adequate funding.

Paper sessions demonstrated the range and depth of work occurring within AT – the number of paper submissions having increased substantially over previous years and the high quality of papers presented reflected this. Themes for the papers included:

- AAC – an innovative communication aid, project review and task analysis were presented;
- Outcomes – including different services' experiences and perspectives of different measures;
- Telecare and housing – innovative monitoring technology in addition to large scale research projects in housing technology were addressed;
- Trade presentations – the latest innovations from companies in AAC, telecare and powered mobility;
- New Research Programmes – updates from two new, large, AT research, development and funding programmes;
- Eye Gaze – two case studies of the application of this new technology as well as development of a new eye-gaze based device;
- Cognitive Support – the research and development of different systems to support people with various cognitive difficulties;
- Wheelchairs – research innovations in control of manual and powered chairs, navigating and also analysing attendant propulsion of chairs;
- ICT – the impact of new and emerging information technology on people with disabilities, novel AT software applications and modelling;
- AT devices – a wide variety of device development, including a novel urine collection device, switch input method and tremor compensation;
- Telecare – evaluation of smart home technology and location-independent monitoring using GPS.

Workshops covered a number of areas and brought about a range of discussion, as did the parallel papers on projects run by the ACT programme. Workshops covered:



RAATE is the only UK conference focused on the latest innovations in Assistive Technology and is attended by people who use, work with, develop and research on Assistive Technology (AT)

- Speech driven assistive technology – looking at the reasons that voice is not heavily used as an access method and feeding into the development of a new speech controlled product;
- Workforce development – examining the workforce requirements for training and discussing recent initiatives in this area;
- Bringing an AT device to market – the process of designing, developing, manufacturing and testing an AT device and the steps required to bring this to market were discussed.

Of note, too, was the exhibition, which was constantly 'buzzing' with activity during the breaks and had an excellent range of over 20 AT exhibitors. Areas covered within the exhibition included: powered mobility; posture management systems; alternative and augmentative communication; voluntary sector; environmental control; eye-gaze; telecare and telehealth.

RAatE is organised by IPEM and the RAatE Committee: Donna Cowan (Chailey Heritage Clinical Services), Keren Down (FAST), Paul Dryer (Kings College Foundation Trust), Colin Clayton, Sarah Vines (Croydon Wheelchair Services), Ruth E Mayagoitia (King's College London) & Simon Judge (Barnsley AT Team). Check the RAatE website for details of future conferences.

*Simon Judge,
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RAatE 2007 – Key topic – Eye Gaze

One of the most talked about topics at RAatE this year was the use of eye gaze for control of computers or AAC. This technology has been available for some time in different fields, however technological and cost improvements have raised its profile as a method of control. The COGAIN project - an EU wide 'network of excellence' - and the ACE Centre-led user-involvement work package has also done much in recent years to progress eye gaze within AT.

RAatE 2007 featured a paper session on eye gaze, in addition to several systems and suppliers demonstrating systems in the exhibition and eye gaze forming part of the ACE Centre's training package on accessing AT. The papers presented featured two interesting case studies of recent use of eye gaze. The cases presented were both 'challenging' cases – the Barnsley Assistive Technology Team presented the successful use of a system with a client who has only a single up-down eye movement,

they also detailed the system the team had developed to enable him to communicate using this limited eye gaze data. Chailey Heritage Clinical Services presented the second case study of a child who used an existing paper based eye-pointing system but wished to investigate options which would allow more autonomous communication. The rationale behind choice of system was discussed and the client's case history, which eventually ended in rejection of eye gaze as a method, helped build the case history of where eye gaze is appropriate. To complete the session, a novel new eye gaze system was presented designed for environmental control, demonstrating the continued research interest in this area.

Eye gaze will undoubtedly continue to make an impact in the AT field over the next years and RAatE will, no doubt, have more papers and exciting innovations in the future on this theme.



Resources:

The RAatE website – for details of future conferences and conference proceedings: www.raate.org.uk
www.raate.org.uk/raate-programme
www.raate.org.uk/exhibition

The ACT Programme: www.actprogramme.org.uk

A blog entry about RAatE:
<http://eduspaces.net/stevelee/weblog/225753.html>

Cogain: www.cogain.org
 A number of papers from RAatE will feature in the new Journal of Assistive Technologies: www.pavpub.com/pavpub/journals/JAT/

18th International Symposium on ALS/MND

1-3 December, 2007; Toronto, Canada.

This year's annual International Symposium on ALS/MND was held in a cold, overcast Toronto. As ever, the meeting was extremely well-organised by the Motor Neurone Disease (MND) Association UK, in co-operation with the International Alliance of ALS/MND Associations. The only hitch was the late arrival of the conference abstract booklets, which finally pitched up on the last morning of the meeting, having spent several days in scrutiny by Canadian customs. The dreariness of the grey Toronto December weather was more than compensated for by the excellent hotel and conference facilities and the liveliness of the meeting. As in previous years the programme was run mainly as parallel sessions, with emphasis on basic research and clinical aspects respectively, catering to the 750 basic scientists, clinical researchers, clinicians and health care professionals attending.

TDP-43 – Innocent bystander or key in pathogenesis?

The meeting opened with a clinical and pathological review by Michael Strong, (London, Canada) in which he emphasised the heterogeneous clinical disease we term ALS, and the varying biochemical abnormalities. A highlight of his overview was his discussion of the role of TDP-43 in the disease. Intracytoplasmic, ubiquitinated inclusions are a pathological hall mark of ALS/MND, and similar ubiquitinated inclusions are also evident in the clinical disorder of frontotemporal lobar dementia. In late 2006 hyperphosphorylated forms of the DNA and RNA binding protein TDP-43 were identified in these inclusions in both disorders, and several recent papers have since confirmed these findings. Interestingly, the inclusions evident in SOD-1 mutation positive cases of familial ALS do not seem to stain with antibodies to TDP-43, suggesting that the inclusions (and possibly the pathogenic mechanisms) in this familial variant differ from those seen in sporadic ALS. Some have suggested that this casts doubt on the validity of the mutant SOD-1 overexpressing mouse model as a useful model for the sporadic disease. Professor Strong outlined elegant studies in his laboratory showing that TDP-43 binds to and stabilises neurofilament light chain



mRNA, and forms complexes with both SOD1 and 14-3-3 protein. He also showed data suggesting that TDP-43 and ubiquitin do not always co-localise in ALS, and suggested that cytoplasmic TDP-43 aggregation may be the earlier event, with the inclusions subsequently being decorated by ubiquitin. Merely showing the presence of abnormally hyperphosphorylated TDP-43 in these inclusions does not of course confirm their pathogenicity, and it is anticipated that ongoing studies will shed light on whether and how this abnormal protein may cause disease.

Genetics of ALS

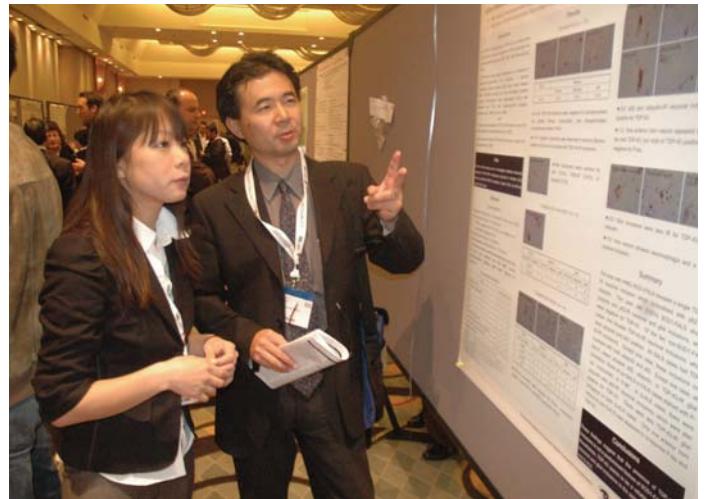
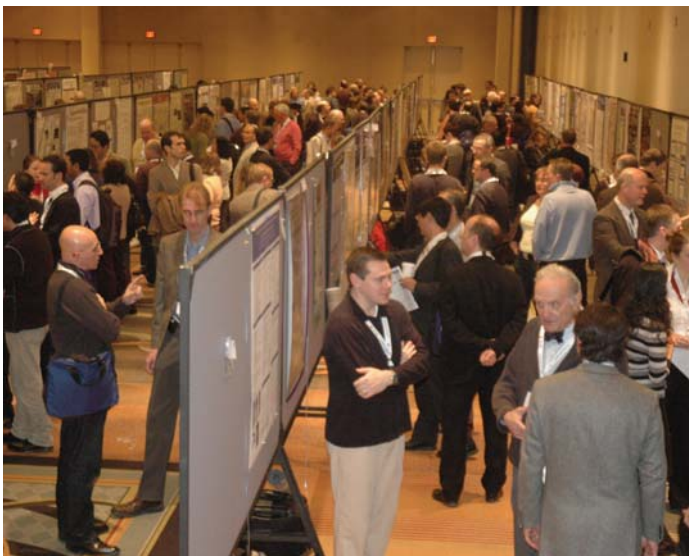
The other plenary presentation at the Opening Session was devoted to the genetics of ALS. Peter Andersen (Umeo, Sweden) gave an excellent, if very detailed, over-view of SOD-1 mutations in familial ALS. It has now been over 15 years since such mutations were first identified and some 156 different mutations have been detailed. Most of these mutants are 'missense', 17 are 'nonsense', 8 are 'silent', 8 are intronic and 2 are thought to affect intronic splice sites. Their identification has allowed specific molecular diagnosis, earlier clinical diagnosis, some prognostic information (e.g. rapid disease progression associated with

the A4V mutation) and the development of the mutant SOD-1 mouse model, but unfortunately no effective therapies as yet. He presented a study showing that more individuals with ALS had a family history of the disease (23%) when this was carefully inquired about, compared to 5% previously recorded in that same population. While this discrepancy may not be so large elsewhere, I think it behoves all of us to ensure that we take adequate family histories and document when the family history is simply not known, rather than assume it is negative.

Highlights of the genetics presentations elsewhere in the meeting included discussion of the genome wide association studies (GWAS) performed in the last year. There have been a number of these (from the US, Holland and Ireland), all now published, and following the example of Traynor et al, data is being made publicly available to allow subsequent meta-analysis. My take on the GWAS in ALS to date is that no study has as yet had sufficient sample numbers, and further collaboration is required. Extrapolating from the recent GWAS in type II diabetes, Frayling has suggested that 'hits' with p values $< 5 \times 10^{-7}$ tend to be replicated in different populations, and are probably significant. None of the studies in ALS has yielded association with such certainty as this, but again, with collaboration and pooling of resources, adequately powered studies in ALS should soon be achievable. If however susceptibility to the heterogeneous disorder of ALS is due to multiple rare genetic variants, standard genome wide approaches which depend on common alleles conferring susceptibility are unlikely to prove successful.

Hypermetabolism in ALS

Another interesting session considered hypermetabolism in ALS. Jean-Philippe Loeffler (Strasbourg, France) reviewed the evidence for a hypermetabolic state in some ALS patients, a state that seems to confer survival advantage. His group has recently reported that hyperlipidaemia is a typical feature of ALS patients and that an abnormally elevated LDL/HDL ratio significantly increases survival by more than 12 months. A high fat diet early in the disease improves survival in mutant SOD-1 mice, and he presented data to suggest that increased energy demand of itself is sufficient to damage the motor unit. Clinical recommendations which might follow on from these observations would be that high lipids might be protective in ALS, and that patients with ALS should not be on lipid-lowering agents. A poster by Zinman et al (Toronto) showed data that agrees with this advice. This group observed that the rate of decline in ALS-FRS in patients in their clinic who were taking statins was 1.29 units/month, compared to a decline of 0.77 units/month in patients not on statins. Patients on statins also reported greater frequency and severity of muscle cramps. I have certainly seen patients with ALS who relate onset of their symptoms to starting a statin, and I think it is prudent to advise patients with ALS to consider stopping these drugs.



Clinical trials

In this short review it is impossible to do justice to the many other good sessions at the meeting. In the session on clinical trials, no new effective agents were reported. The disappointing results of the US minocycline trial were presented (Gordon et al, New York). Analysis showed a 25% faster deterioration in the decline in ALS-FRS in the minocycline group compared to placebo. This has been interpreted as perhaps being due to an adverse interaction of minocycline with riluzole, and there are additional concerns about an inappropriately high dose of minocycline having been used. Nevertheless, the data at present are such that we cannot recommend minocycline to patients.

I managed to get to some of the session on 'Evaluating Unproven Treatments', in which Leonard Van den Berg (Utrecht) gave an excellent update on the use of olfactory ensheathing cell transplants in the disease. He reviewed the two studies by Huang that have been published in Chinese journals, one of which reports improvements in the ALS-FRS scores within four weeks in 77% of 327 patients who received such transplants. As outlined by Van den Berg, these publications were not peer-reviewed, the follow-up was too short, the intervention was not placebo-controlled, and it is not clear that appropriate consent procedures were followed. He then reported his follow-up of 13 Dutch patients who had received cell transplants in China. Seven of these reported a subjective increase in well-being and muscle strength within 24 hours of the procedure (possibly due to the steroid therapy given at the time of transplant), but none of them showed any improvements at 4 or 12 month post-procedure assessments in Holland. Leonard gave a straightforward plea for clinicians to tell patients of placebo effects, to warn of the high costs of such unproven therapies (\$25,000 upwards for ensheathing cell transplants), to outline the side-effects if known and to defend to patients our system of ethical scrutiny of the research we do. Yes, ethics applications are cumbersome, but they do afford our patients some protection. While not wanting to dash patients' hopes, we have a duty to tell them when proposed treatments have not been shown to work.

And to next year...

The meeting included a video by Steven Hawking inviting delegates to reconvene for the 19th International ALS/MDS Symposium next year. The venue – a sunny Birmingham, UK, the city which hosted the first two of these symposia back in the 1990s with a handful of delegates in attendance. I hope that many UK neuroscientists and clinicians will come along from 3-5 November, 2008. ALS has not yet been cracked, and attracting more minds to the research and care of this progressive disease can only be a good thing.

*Karen E Morrison, Professor of Neurology,
University of Birmingham,
Honorary Consultant Neurologist,
University Hospitals Birmingham NHS Foundation Trust,
Co-Director of Birmingham MND Care and Research Centre.*

The UK Stroke Forum Conference

4-6 December, 2007; Harrogate, UK.

The second annual conference of the UK Stroke Forum hosted by The Stroke Association met at the Harrogate International Centre for three days in the first week of December – a historic week for UK stroke services that saw the launch of the Department of Health's National Stroke Strategy for England.

Building on the success of last year's inaugural conference, this year's conference welcomed around 1300 delegates from the stroke community to share best practice and expertise, to network with colleagues, and to enjoy a varied programme which attracted some of the leading experts in their field sharing their knowledge and updating the conference on the latest research.

In response to delegate feedback, this year's conference was expanded to include additional educational sessions as part of a training programme offering designated sessions for stroke physicians, nurses, and rehabilitation specialists. On Tuesday 4 December, the British Association of Stroke Physicians organised training sessions on identifying and treating the complications of stroke, the National Stroke Nursing Forum organised sessions on hyperacute care, continence and medication management, and a rehabilitation session covered managing the delivery of therapy and rehabilitation for people who have impaired communication and cognition.

Later in the day there was a Community Stroke Research and TRACS drop-in session, and both the British Association of Stroke Physicians and the National Stroke Nursing Forum held their respective annual general meetings.

On Wednesday 5 December, the opening plenary session organised by The Stroke Research Network focussed on ethical issues in stroke care and research, including presentations on the ethical justification for resource allocation to stroke, and a legal perspective on assessing incapacity and its implications for stroke research.

Parallel sessions on the second day of the conference covered a wide range of topics including neuroradiology, participating in the community and returning to work after stroke, the future of stroke nursing, and psychological support. A free papers session updated delegates on the latest developments in various aspects of stroke research, and there was a showcase of recent rehabilitation trials.

The day closed with the Princess Margaret Memorial Lecture, with guest lecturer Professor Willy de Weerd from the Department of Rehabilitation Sciences, KU Leven, Belgium, presenting a collaborative evaluation of rehabilitation in stroke across Europe.

In the evening, Harrogate's Majestic Hotel was the venue for the UK Stroke Forum Gala Dinner attended by 650 of the delegates.

The following day's opening plenary session focussed on the implementation of a national stroke strategy. The Secretary of State for Health, Alan Johnson, addressed the conference to introduce the National Stroke Strategy for England and to mark its launch. Professor Martin Dennis (Chair of the National Advisory Committee for the Scottish Stroke Strategy) updated the conference on the progress of the Scottish Stroke Strategy, and Professor Mike Harmer (Deputy Chief Medical Officer, Wales) and Dr Carolyn Harper (Deputy Chief Medical Officer, Northern Ireland) also made presentations.

Parallel sessions on the final day again covered a wide range of topics including driving and vision, atrial fibrillation and glucose, acute stroke management, delivering augmented rehabilitation therapy, and good practice in user involvement. There was also a further free papers session.

The final plenary session in the afternoon began with a speech by The Duke of Kent and the presentation of the British Stroke Research Group prizes, followed by a showcase of research funded by UK Stroke Forum charities with presentations by Professor Charles Wolfe (King's College London) on the South London Stroke Secondary Prevention Programme, Jacqui Crosbie (University of Ulster) on virtual reality in the rehabilitation of the upper limb following stroke, Professor Fenella



Secretary of State for Health, Alan Johnson.



The auditorium.

Kirkham (University College London Institute of Child Health) on the prevention of morbidity in sickle cell anaemia, Professor Peter Langhorne (Glasgow Royal Infirmary) on the development of the stroke unit, and Dr Wendy Best (University College London) on aphasia therapy.

Certainly, the feeling at this year's conference was that the event had been even bigger and better than last year, bringing together even more people from the stroke community and establishing the UK Stroke Forum Conference as an invaluable and truly multidisciplinary occasion. With a lively exhibition hall, ideas fair, and poster displays covering acute care, clinical trials, cognitive and emotional issues, good practice in user involvement, hyperacute care, nursing, swallowing, and vision, delegates were offered a varied programme throughout the three days with the programme highlight being the launch of the National Stroke Strategy for England.

For further information on the 2007 conference, and to download speaker presentations, please visit www.ukstrokeforum.org

Matthew King, The Stroke Association.

Specific examples of research presented at the conference include:

- A new study has found that that Post Traumatic Stress Disorder is the likely cause of psychological problems affecting some carers of stroke survivors. The study, which focused on stroke survivors with subarachnoid brain haemorrhage, was conducted by Doctoral Research Student Adam Noble and colleagues at Durham University (in collaboration with Newcastle General Hospital and James Cook University Hospital in Middlesbrough).
- A study comparing the benefits of surgery (endarterectomy) to endovascular therapy (angioplasty) to reopen a blocked carotid artery has found that over a follow up period of eight years, a recurrent distinct narrowing of the artery (by 70% or more) was three times more likely after endovascular therapy than surgery. The study was conducted by the Stroke Research Group at the UCL Institute of Neurology in London
- A new NHS clinical service which helps stroke patients with dropped foot is being used at the Salisbury NHS Foundation Trust. The conference provided the opportunity for staff from the Trust to explain the condition and how this new clinical service is proving of benefit to many stroke survivors.

Encephalitis – the Broader Spectrum: Rare Forms of Encephalitis

22 January, 2008; London, UK

The Encephalitis Society started out 15 years ago as a fairly modest support group, in response to the very limited help available for people, and their families, who had been affected by encephalitis. Since then, it has expanded its activities very substantially and is the only resource of its kind in the world, providing evidence-based information, education and support services. The Society has also supported and funded a number of research studies and is currently involved in a large scale collaborative study of the outcome of encephalitis with the University of York. The society organises an annual seminar, which this year had as its topic some of the less familiar varieties of encephalitis.

Professor Tom Solomon from the new Liverpool Brain Infections Group (www.liv.ac/braininfections) opened the meeting with a presentation on Encephalitis in the Global Village, which highlighted the threat of emerging viruses. He has worked extensively on Japanese encephalitis in Vietnam and, although still a rarity in the UK, this is actually one of the more important brain infections on a worldwide scale. There are anything from 35,000 to 50,000 cases each year with a 30% mortality and 30% of survivors left with significant neurological sequelae.

It has a varied neurological profile which, as well as the more familiar features of encephalitis, such as fever, headache, confusion, seizures, raised ICP and coma, may involve acute movement disorders with parkinsonism, orofacial dyskinesias, and choreoathetosis. The Japanese encephalitis virus can also attack anterior horn cells, leading to presentation with a polio-like ascending flaccid paralysis. Dengue is another mosquito borne flavivirus which can cross the blood-brain barrier to produce an encephalitic illness in a proportion of infected patients. Human enterovirus 71 (HEV71) was isolated from the stool of a child with encephalitis in California in 1969. After sporadic cases and small outbreaks of HEV71 infection worldwide in the 1970s and 1980s, there was a large and severe outbreak in Sarawak in 1997 with 34 deaths in 2628 reported cases. Neurological involvement included aseptic meningitis, encephalitis and acute flaccid paralysis. Since then there have been further outbreaks in Southeast Asia and Australia.

Although these illnesses have tended to be viewed in this country as exotic rarities, the ease and speed of international travel and the effects of climate change are making awareness of them increasingly relevant – a point illustrated by the appearance of West Nile fever in New York City.

Fungal infections of the CNS are mostly familiar to us in the UK as something seen on a relatively small scale in immunocompromised patients. However, as Dr William Hope, Infectious Diseases Physician and Senior Research Fellow, The University of Manchester, emphasised, they actually represent a major problem from a global perspective. *Cryptococcus neoformans* is a leading cause of AIDS-related deaths in sub-Saharan Africa and *aspergillus* is a major source of morbidity and mortality in immunocompromised patients, with an associated mortality of 40-50%. The expenditure on antifungal drugs worldwide is astronomical – billions of dollars – and rising. Dr Hope's presentation emphasised that the key to understanding the pathological process in cerebral aspergillosis is the recognition that *Aspergillus* is angiotropic and angioinvasive. He also reviewed the under-recognised but quite common condition of neonatal haematogenous candida meningoencephalitis, in which there is widespread involvement of the CNS with *Candida*.

The second theme of the meeting was the role of the immune system in the pathogenesis of encephalitis. Oxford has been a leading centre in the characterisation of voltage gated potassium channel antibody (VGKC) encephalitis and Professor Angela Vincent from the Weatherall Institute of Molecular Medicine reviewed the work of their group. VGKC antibody-associated limbic encephalitis occurs in both men and women. It is an adult-onset condition seen in people from 30 to over 70 years of age, with an acute or subacute onset of memory loss, seizures,



personality change and occasionally more florid psychotic features, with high signal in the hippocampi on MRI. Associated malignancies are uncommon and immunological treatments with intravenous immunoglobulins and steroids may produce significant clinical improvement. This antibody-mediated disorder seems to be an expanding phenotype. VGKC antibodies may be linked predominantly to seizures or atypical psychosis occurring in isolation, with some indication that immunosuppressive treatment may be helpful. A proportion of patients with adult onset temporal lobe seizures with hippocampal sclerosis may actually have a history of a previous encephalitic illness with evolving MRI changes, raising the possibility that untreated limbic encephalitis may be a causative factor in some cases. So what started out as something of a rarity may turn out to have much broader implications for epileptology and neuropsychiatry.

Dr Ian Hart, Consultant in Neurology and Neuroimmunology from the Walton Centre in

Liverpool, developed the theme of autoimmune encephalides, dealing with Hashimoto's encephalitis, Rasmussen's encephalitis and paraneoplastic encephalitis.

He emphasised that these relatively rare conditions should not be forgotten in the differential diagnosis, looking for serum antibodies is useful and can help make the diagnosis. They need to be thought of sooner rather than later, since immune treatments may be helpful in individual patients if they can be started early enough, before brain cell death and permanent disability has developed.

The meeting ended with a fascinating presentation from Professor Gavin Giovannoni from Barts and the London on encephalitis lethargica, which in contemporary neurology is defined as an acute or sub-acute encephalitis with at least three of the constellation of basal ganglia involvement, oculogyric crises, ophthalmoplegia, obsessive-compulsive behaviour, akinetic mutism, central respiratory irregularities and somnolence or inversion of the sleep-waking cycle. There is evidence of an inflammatory process in the basal ganglia, brainstem and hypothalamus. Encephalitis lethargica may be one of a spectrum of autoimmune CNS disorders, characterised by anti-basal ganglia antibodies associated with recent streptococcal infection.

The encouraging message from this seminar is that the future for encephalitis research in the UK looks bright, with the very active involvement of several different research groups of international standing. It is also encouraging that the Encephalitis Society is able to convene meetings like this one, to make sure that the practical benefits from this new knowledge will reach a wide audience as quickly as possible, helping improve the care of people with encephalitis both in this country and on a more global scale.

*Dr Steve White and Ava Easton,
Encephalitis Society, UK.*

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www.encephalitis.info
Tel. +44 (0)1653 692 583
Email. ava@encephalitis.info

Ava Easton is the Society's Development Manager and Dr Steve White is Consultant Neurophysiologist, St Mary's Hospital, London.

PREVIEW European Association for Neuro-Oncology

12-14 September, 2008; Barcelona, Spain.

The European Association of Neuro-Oncology (EANO) has been in existence for 15 years and over that time has grown and developed to include over 600 members from 40 countries. Members include scientists, neurologists, neurosurgeons, medical and radiation oncologists, neuropathologists, neuroradiologists, specialist neuro-oncology nurses, paediatricians and many other groups. Major EANO meetings are held every two years in Europe and jointly with the American Society for Neuro-Oncology and the Asian Society of Neuro-Oncology as part of the World Federation of Neuro-Oncology. In May 2005, EANO had the pleasure of hosting the Second Meeting of World Federation of Neuro-Oncology, with the participation of more than 1200 delegates from 35 different countries. In 2006, EANO held their VII meeting in Vienna, attracting 1,000 participants. In 2008, EANO VIII will be held in Barcelona. EANO is a full member of the Federation of European Cancer Societies (FECS) and has developed a section devoted to the education of neuro-oncology cancer nursing.

The aim of the association is to encourage the multidisciplinary exchange of knowledge and to implement cooperative studies in the field of neuro-oncology, including different experts involved in cancer research, treatment and care.

A special educational program is planned for young researchers from Central and Eastern Europe with the goal of promoting a high standard neuro-oncological qualification and favouring a more intense integration

with these countries. We have launched a new website to provide better communication between members and to allow a forum for discussion and ideas (www.eano.eu).

If you have an interest in neuro-oncology, we would be delighted to see you at the next EANO meeting, scheduled in Barcelona on 12th-14th September 2008. The congress will take place in the "Palau de Congressos de Catalunya", a modern, multipurpose building situated in a smart area of Barcelona. Barcelona is a modern multicultural city and the main exponent of the Catalan culture and heritage. The city is known worldwide for its architecture, cuisine, and most importantly, the way people from Barcelona enjoy life. We hope you will take at least a glimpse of all these wonders during the Congress.

Registration forms and the programme details are available via the website. We are looking for active members – please register as a member via our website (www.eano.eu) or email us at secretariat@eano.eu

We look forward to welcoming you in Barcelona.

Es veiem a Barcelona!

Nos vemos en Barcelona!

PREVIEW 18th Meeting of the European Neurological Society

7-11 June, 2008; Nice, France.

Neurology: Learning, knowledge, progress and the future

Teaching programme :

- 22 practical workshops
- Interactive case presentations
- Practical sessions in clinical neurophysiology
- 24 Teaching courses covering all important topics in Neurology

The eighteenth meeting of the European Neurological Society (ENS) will be held at the Nice Acropolis Congress Centre on June 7-11, 2008. This year we will celebrate the 20th anniversary of the first meeting of the ENS, which was also held in Nice, in June 1988.

From the very beginning we have pursued the original goals of our society, namely excellence in the teaching and scientific programmes, and support to young scientists. The number of participants of courses, symposia and free communications has dramatically increased since the beginning, but the spirit remains the same. The ENS bets on neurologists in training, with 300 of them invited to attend the meeting. Younger colleagues are especially interested in teaching courses. 37 courses will be available, including eight practical hands-on sessions and four teaching courses jointly organised with colleagues of the American Academy of Neurology. In addition, 22 workshops covering the different fields of clinical neurology will take place during the meeting.

The Presidential Symposium will be dedicated to current knowledge and practical management of coma and locked-in syndrome. On the following day a symposium will cover behavioural disorders and dementia with talks on physiopathological bases of behaviour, synucleinopathies (Parkinson's disease, Lewy body); mild cognitive impairment and Alzheimer disease; and tauopathies (Fronto-temporal, PSP, etc.). A symposium on autoimmune disorders of the nervous system will include talks on latest developments in multiple sclerosis; autoim-

mune diseases of the neuromuscular junction; pathogenesis and treatment of the Guillain Barré syndrome and immunopathogenesis of inflammatory myopathies.

On the last day of the meeting there will be a symposium on multiple sclerosis: when to start a treatment, and which treatment with the best experts in the field from Europe and USA. Finally there will be a symposium on imaging and management of transient ischaemic attack (TIA) confronting the diagnosis and risk assessment for TIA, yield of brain and vascular imaging (MRI, ultrasound etc.); feasibility and efficacy of ultra early evaluation and intervention after a TIA, and the concept of the TIA clinic.

In addition to the symposia, the Scientific Programme includes five poster sessions and approximately 16 oral sessions of free communications. We will once again have poster walks to display the posters in a lively and interesting format. Experts will lead a review of selected posters promoting discussion with their authors. The selection of scientific papers is based on the review by three experts in the field. On average 800-900 free scientific papers are selected for presentation at the meeting. We are looking very much forward to these stimulating sessions.

Prof G Said, ENS Executive Committee.

Visit the ENS 2008 website www.ensinfo.com

- Continuously updated scientific programme
- Online registration as well as hotel & tour registration
- Option to compose your personal congress programme
- Details about the industrial exhibition and symposia arranged with the industry
- Information about NICE

EARLY REGISTRATION DEADLINE: 8th APRIL 2008



The ROYAL
SOCIETY of
MEDICINE

Academic Symposia

Sleep and the hospital doctor

Date: Monday 14 April 2008 | Examination of the factors and research underpinning the sleep requirements of hospital doctors in the context of shift working.

Key advances in the treatment of Post Traumatic Stress Disorder

Date: Tuesday 13 May 2008 | Evidence based view of the treatments currently used for PTSD

Frontiers in the degenerative dementias: pathogenesis, diagnosis and therapy

Date: Monday 9 June & Tuesday 10 June 2008 | A two day conference jointly organised by The Royal Society of Medicine and the New York Academy of Medicine

Call Miss Chandni Kohar on 02072902965 or book online www.rsm.ac.uk/diary

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7 April, 2008.



INTERNATIONAL LEAGUE
AGAINST EPILEPSY

UK CHAPTER

Annual Scientific Meeting

9-11th July 2008
Apex City Quay Hotel, Dundee

Topics include:

- **Genetics and its Relevance to Clinical Practice:**
ION Channel and Chromosomal Disorders;
Pharmacogenetics; Complex Inheritance in Epilepsy
- **ILAE UK Chapter and Epilepsy Research UK Basic Science Session:**
Submitted Topics
- **Epilepsy Neurosurgery Network Meeting:** Case Discussions
- **GABA and Epilepsy: From the Receptor to the Clinic:**
GABA Receptors: A Review; Depolarization and GABA;
GABAergic AEDs
- **Intracranial EEG Monitoring – Different Approaches:**
Review of EEG Basics; Marseilles Approach; Cleveland Approach
- **Non-Epileptic Attacks and Dissociative Seizures:**
Epidemiology; Clinical Observations; Conversational Analysis;
Management
- **Provision of Care:**
Managed Clinical Networks for Epilepsy; Measurement of Adherence;
Joint Decision Making in Epilepsy Management

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For more information please contact Denise Hickman-Rowe, Conference 2k Ltd, Capstan House, Western Road, Pevensy Bay, East Sussex BN24 6HG • Tel: 01323 740612 • denise@conference2k.com

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The EUROPEAN
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NEUROONCOLOGY



8th MEETING

2008



September 12-14

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PALAU DE CONGRESSOS DE CATALUNYA

Advance Programme - www.eano.eu

Contact: Marieke Hodel, Romana Koenig
Vienna Medical Academy, Alser Strasse 4, 1090 Vienna, Austria
T: +43 1 40513830, F: +43 1 4078274, E: eano2008@medacad.org

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 7 April, 2008

2008

March

2nd International Conference on Hypertension, Lipids, Diabetes and Stroke Prevention
6-8 March, 2008; Prague, Czech Republic
www.kenes.com/strokeprevention2008

Putting Rehabilitation into Practice – Advanced
6 March, 2008; Derby, UK
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk
T. 01332 254679

3rd Meeting of the UK Parkinson's Disease Non Motor Group
8 March, 2008; London, UK
E. yogini.naidu@uhl.nhs.uk, www.pdnmg.com

Cognitive Rehabilitation Workshop
10-11 March, 2008; Auckland, New Zealand
E. JanisHenry.jan@iphld.co.nz

Child and Adolescent Addiction: risks, consequences, treatments and management
10-11 March, 2008; London, UK
E. annehaylock@markallengroup.com

Head Injury Conference: The Claiming Culture
11 March, 2008; Derby, UK
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk
T. 01332 254679

Posture and Balance in Neurological Conditions - Lower Limb Qualified Staff
12-13 March, 2008; Derby, UK
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk
T. 01332 254679

Birmingham Movement Disorders Course
12-14 March, 2008; Birmingham, UK
T. 0121 507 4073, E. susan.pope@swbh.nhs.uk

Community Therapists Network Workshop – Building Your Business Case in Community Rehabilitation
13 March, 2008; Lutterworth, UK
www.communitytherapy.org.uk

International Neuroimmunology Symposium
14 March, 2008; Dublin, Ireland
T. +353 1 716 6700, E. mniest@ucd.ie, www.ucd.ie/mniest/Neuroimm_workshop.html

Mental Capacity Act Training
17 March, 2008; Derby, UK
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk
T. 01332 254679

Cognitive Rehabilitation Workshop
17-18 March, 2008; Auckland, New Zealand
E. JanisHenry.jan@iphld.co.nz

8th Advanced Prosthetic & Amputee Rehabilitation Course
17-19 March, 2008; London, UK
T. Sandy Weatherhead on 01992 638865

Aiming Higher. A one-day conference with a European perspective on the social impact of childhood acquired brain injury
19 March, 2008; Birmingham, UK
E. sharon@cbituk.org
www.cbituk.org
T. 01869 341075

Genomic Disorders
17-20 March, 2008; Cambridge, UK
<http://firstcontact.hinxton.wellcome.ac.uk>

ABN Spring Meeting
26-28 March, 2008; Dublin, Ireland
E. info@theabn.org

Computational Biology
26-29 March 2008; Cambridge, UK
<http://firstcontact.hinxton.wellcome.ac.uk>

The Science, Culture and Art of Neurorehabilitation, Tripartite Regional Meeting of Neurological Rehabilitation
27-29 March, 2008, Cebu City, Philippines
E. NeuroRehab@yahoo.com

Recognising Post Traumatic Stress
28 March, 2008; Derby, UK
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk
T. 01332 254679

Motor Neurone Disease Study day
28 March, 2008; Derby, UK
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk
T. 01332 254679

MS Life
29-30 March, 2008; Manchester, UK
www.msconvention.org.uk

Explain Pain with Lorimer Moseley
30 March, 2008; Worcester, UK
E. info@physiok.co.uk

Practical Neurology Study Days
31 March – 1 April, 2008, London, UK
T. 020 7242 9789,
E. 020 7831 0488,
E. courses@ich.ucl.ac.uk

April

Report Writing for Doctors and Consultants
2 April, 2008; Derby, UK
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk
T. 01332 254679

Witness Skills for Doctors and Consultants
3 April, 2008; Derby, UK
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk
T. 01332 254679

60th Annual Meeting of the American Academy of Neurology
5-12 April, 2008; Chicago, USA
T. +1 651 6952717,
E. memberservice@aan.com

The Psychosocial Burden of Epilepsy: Ameliorating the impact
6-8 April, 2008; Oxford, UK
E. Isabella@eruk.org.uk,
www.epilepsyresearch.org.uk

Sexuality and Acquired Brain Injury Workshop
7 April, 2008; London, UK
T/F. 0208 780 4530, E. psimonson@rhn.org.uk

The International Brain Injury Association's 7th World Congress on Brain Injury
9-12 April, 2008; Lisbon, Portugal
E. mjroberts@aol.com, or
T. 001 703 960-6500

World Parkinson's Disease Day conference
10 April, 2008; Cairo, Egypt
E. lizzie@epda.eu.com

The British Pain Society's 2008 Annual Scientific Meeting
15-18 April, 2008; Liverpool, UK
www.britishtainsociety.org/meet_futureasm.htm

Mobility On The Edge International seminar
16-18 April, 2008; Oswestry, UK
Karen Edwards,
E. karen.edwards@rjah.nhs.uk
T. 01691 404531

Nicotinic Receptors
23-26 April, 2008; Cambridge, UK
<http://firstcontact.hinxton.wellcome.ac.uk>

BISWG-Brain Injury and Mental Health - National Conference in Cardiff
24 April, 2008; Cardiff, UK
T/F. 0208 780 4530,
E. psimonson@rhn.org.uk

Physiotherapy Research Society Scientific Meeting
24 April, 2008; Manchester, UK
T. 01332 299017
E. pdziunka@yahoo.co.uk
W. www.prs-uk.org

2nd National Treating Schizophrenia
24-25 April, 2008; London, UK
E. annehaylock@markallengroup.com

3rd Essential Neuro MRI Study Day: Basic approach to reading MRI of Brain & Spine
26 April, 2008; Liverpool, UK
E. kath.tyler@thewaltoncentre.nhs.uk
T. 0151 529 5416/5552

Applied Bioinformatics & Public Health Microbiology
27- 29 April, 2008; Cambridge, UK
<http://firstcontact.hinxton.wellcome.ac.uk>

May

13th European Congress of Clinical Neurophysiology
5-8 May, 2008; Istanbul, Turkey
www.eccn2008.org/

9th European Congress of Neuropathology
8-10 May, 2008; Athens, Greece
E. i.m.huang@amc.uva.nl, T. 30-2-107-257-693,
F. 30-2-107-257-532

6th Workshop of the International Society for Musculoskeletal and Neuronal Interactions
8-11 May, 2008; Cologne, Germany
E. info@mes-berlin.com Mrs Yvonne Beetz,
T. 00 49-3-070-078-950
F. 49-3-07-007-895-111

V Scientific Symposium of Polish Society for Neurological Rehabilitation
9-10 May, 2008; Tarnowskie Gory, Poland
W. www.repty.pl

AAC:Basic Principles & Practical Solutions
16 May, 2008; London, UK
T. 0208 780 4500 x5140
E. institute@rhn.org.uk

1st Asian Oceania Conference of Physical and Rehabilitation Medicine
16-19 May, 2008; Nanjing, China
Danny Yan
T. 86 10 62 180 141
F. 86 10 62 174 061
E. info@aocprm2008.com

5th International Symposium on Neuroprotection and Neurorepair:Cerebral Ischemia and Stroke
17-20 May, 2008; Magdeburg, Germany
T. +49(391)67-13088
E. georg.reiser@medizin.uni-magdeburg.de
W. www.neurorepair-2008.de/

BSRM Spring Meeting
19-20 May, 2008; Birmingham, UK
E. admin@bsrm.co.uk
T. 01992 638865

3rd National Neuroscience Nursing Conference: back to basics
20 May, 2008; London, UK
E. annehaylock@markallengroup.com

BISWG Annual General Meeting and Study Day: 'Money Matters 2'
21 May, 2008; Birmingham, UK
T/F. 0208 780 4530
E. psimonson@rhn.org.uk

Plasticity, Learning, and Development
30-31 May, 2008; London, UK
E. rosalyn.lawrence@ucl.ac.uk

Brain Injury and the Law-Scotland Event
30 May, 2008; Dunfermline, UK
T. 0131 537 6857
E. fenparry@blueyonder.co.uk/mhairi.mckay@lpc.scot.nhs.uk

Magstim/ Institute of Cognitive Neuroscience Second TMS Summer School
30 – 31 May, 2008; London, UK
www.magstim.com
T. 01994 240798
E. nick.lewis@magstim.com

June

2nd Migrating Course on Epilepsy
1-8 June, 2008; Trakai, Lithuania
E. MildaEndziniene.endziniene@gmail.com or
PetraNovotny.petra@epilepsy-academy.org

Signalling to Chromatin
4-8 June 2008; Cambridge, UK
<http://firstcontact.hinxton.wellcome.ac.uk>

18th Meeting of the European Neurological Society
7-11 June, 2008; Nice, France
T. +41 61 686 77 11
F. +41 61 686 77 88
E. info@akm.ch
W. www.ensinfo.com

6th International Society for Stem Cell Research Annual Meeting
11-14 June, 2008; Philadelphia, USA
E. isscr@isscr.org

Genomics of Malaria Epidemiology
15-18 June, 2008; Cambridge, UK
<http://firstcontact.hinxton.wellcome.ac.uk>

9th Eilat Conference on New Antiepileptic Drugs (EILAT IX)
15-19 June, 2008; Sitges, Spain
F. +972 3 5175155
E. eilatix@targetconf.com
W. www.eilat-aeds.com

Study Day on MND
17 June, 2008; Birmingham, UK
E. pam.aston@mndassociation.org

Cognitive Rehabilitation Workshop
20-21 June, 2008; London, UK
E. enquiries@braintreelearning.co.uk
W. www.braintreelearning.co.uk

International Congress of Parkinson's Disease and Movement Disorders
22-26 June, 2008; Chicago, IL, USA
T. +1 414 2762145
E. info@movementdisorders.org

12th Congress of the Movement Disorder Society
22-26 June, 2008; Chicago, USA
E. congress@movementdisorders.org

July

Fourth International Neuroanthocytosis Symposium: Bridging clinical and basic aspects
1-2 July, 2008; London/Oxford, UK
E. glenn@naadvocacy.org
T. 020 7937 2938

SRR Summer Meeting
2-3 July, 2008; Preston, UK
W. www.srr.org.uk, E. dforshaw@uclan.ac.uk

Inflammatory Neuropathy Consortium (INC) Meeting of the Peripheral Nerve Society (PNS)
4-5 July, 2008; Paris, France
W. <http://pns.ucsd.edu/INC.htm>

ILAE UK Chapter Annual Scientific Meeting
9-11 July, 2008; Dundee, UK
E. denise@conference2k.com
T. 01323 740612, F. 01691 670302
W. www.ilae-uk.org.uk

Techniques & Applications of Molecular Biology
14- 17 July, 2008; Coventry, UK
T. 024 7652 3540
E. Charlotte.Moonan@warwick.ac.uk

Parkinson's Academy/PD Section, British Geriatrics Society Specialist Registrar Masterclass
28 July – 1 August, 2008; Truro, Cornwall
E. RedPublishingLtd,redoffice@btinternet.com

August

NeuSIG Satellite to the Glasgow 2008 World Congress on Pain
13-15 August, 2008; London, UK
W. www.kenes.com/neuropathic2008/

12th World Congress on Pain
17-22 August, 2008; Glasgow, UK
T. 001 206 547 6409
E. iaspdesk@iasp-pain.org

12th European Federation of Neurological Societies Congress
23-26 August, 2008; Madrid, Spain
F. 00 43 1 88 92 581
E. headoffice@efns.org

Interactome Networks
27-30 August, 2008; Cambridge, UK
<http://firstcontact.hinxton.wellcome.ac.uk>

2nd Baltic Sea Summer School on Epilepsy
31 August-1 September, 2008; Denmark
E. petra@epilepsy-academy.org.

September

Genetics of Epilepsy
September, 2008;
ILAE-VIREPA distance learning course
E. office@epilepsy-academy.org,
www.epilepsy-academy.org

**Eighteenth Meeting of the
European Neurological Society**








June 7–11, 2008

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20th Anniversary of the first ENS Meeting in Nice
Neurology: Learning, knowledge, progress and the future

Key symposia:

-  Coma and locked-in syndrome
-  Behavioural disorders and dementia
-  Autoimmune disorders of the nervous system
-  Multiple sclerosis: when to start a treatment and which treatment
-  Transient ischemic attacks: diagnosis and management

The congress programme includes interactive case presentations, 23 teaching courses, workshops organised by the ENS subcommittees and selected scientific sessions in the form of oral sessions, poster sessions (guided poster walks) and satellite symposia.

Abstract Submission Deadline: January 31, 2008

Early Registration Deadline: April 8, 2008

For further information please contact:

Administrative Secretariat:

18th ENS 2008, c/o AKM Congress Service

P.O. Box, CH-4005 Basel / Switzerland

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www.ensinfo.com

EDITOR'S CHOICE

Stem cells become front page news again! Why?

One of the most sought after solutions in medicine is the development of an ethically neutral, readily available and reliable source of cells by which repair could be effected by their use, and disease pathogenesis possibly studied by growing them in the lab. To date, the big problems have either been difficult ethical and theological issues associated with pluripotential embryonic stem (ES) cells derived from blastocysts from IVF programmes or the limited capacity to generate sufficient numbers of appropriate cells with other ethically more acceptable cells such as adult stem cells from bone marrow or brain. It is therefore of great interest that two groups have independently generated embryonic stem like cells with all their attendant pluripotentiality using reprogrammed skin fibroblasts – papers that have spurred numerous reports in the newspaper and scientific journals alike. These two papers in *Cell* and *Science* have both shown that adult human fibroblasts can be transduced with four factors to make pluripotent stem cells. Takahashi et al found that Oct4, Sox2, Klf4 and c-Myc were needed to produce pluripotential ES like cells which show all the characteristics of true embryonic stem cells in terms of their behaviour in culture, profile of molecular markers using gene arrays and behaviour in vivo. In contrast Yu et al used Oct4, Sox2, Nanog and Lin28 to produce similar results. These are exciting findings because if they can be refined to avoid the need for viral vectors (and especially the risk of tumours with the c-myc transfection), then one truly has the potential to repair damaged systems, including brains, in patients using their own cells. In addition, one could start to study disease pathogenesis in these individuals using these very same cells to model disease. Of course this work is predicated on the grounds that:

1. Cell repair therapies work and that any such human induced pluripotential stem cells (iPS) are not going to be affected by the same disease process in the short term whilst also allowing
2. The cells to accurately reflect disease states which have wider relevance to the modelling of disease beyond that of the individual affected by it.

Nevertheless the capacity to generate iPS cells using human fibroblasts is a tour de force although what the moral status of such a cell is in terms of its potentiality for human life is still debatable. Indeed the ethics of embryonic stem cell research will continue to vex many working in the field at the same time as the scientific advances take us into the realm of therapeutic reality. – **RAB**

Yu J, Vodyanik MA, Smuga-Otto K et al.

Induced pluripotent stem cell lines derived from human somatic cells.

SCIENCE

2007;318:1917-20.

Takahashi K, Tanabe K, Ohnuki M et al.

Induction of pluripotent stem cells from adult human fibroblasts by defined factors.

CELL

2007 131(5):861-72.

BRAIN REPAIR

The relationship between injury and repair in the brain is complicated. Take, for example, the bizarre observation that regeneration of retinal ganglion cells following an optic nerve crush injury can be improved by injuring the lens of the eye. (Who said two wrongs don't make a right?) The standard thinking had been that the lens injury attracted macrophages into the eye, which went on to secrete neurotrophic factors, specifically the rather grandly-named oncomodulin. In the latest issue of *Brain*, a team from Ulm, Germany, show otherwise. They injured the optic nerve and lenses of rats and then, five days later, dissected out the retina to study retinal cell behaviour in culture. Their first discovery was that lens injury upregulated the neurotrophin CNTF in the retina; and, secondly, that this was not in macrophages but in retinal astrocytes. They went on to show that the same CNTF secretion could be induced in uninjured retinas by

the application of lens proteins; in other words, that CNTF release was not just due to injury or an inflammatory response. This is intriguing: perhaps astrocytes recognise lens proteins through Toll-like receptors, or other innate immunity mechanisms? Antibodies to CNTF (but not anti-oncomodulin) blocked the regeneration of retinal ganglion cells induced by lens injury. And, crucially, dibutyryl-cAMP (which raises intraocular cAMP) amplified this regeneration. So, is the implication that everyone with an optic nerve injury should have a scalpel through their lens? Perhaps not. But there are real implications for treatment: the CNTF-production facility of astrocytes could be exploited to promote optic nerve repair by applying non-toxic lens proteins and drugs to boost cAMP. Given that this might be the difference between useful sight and not, this is no small discovery. – **AJC**

Müller A, Hauk TG, Fischer D.

Astrocyte-derived CNTF switches mature RGCs to a regenerative state following inflammatory stimulation.

BRAIN

2007 Dec;130(Pt 12):3308-20.

NEUROLOGY JOURNALS: Oooops!

It is rare to get frank self-criticism in the editorial of a journal. But Stephen Hauser has gone out of his way to apologise for a press-release from the *Annals of Neurology*. This all arose because of a growing feeling that epidemiological research gets too much, or inappropriate, press attention. So Hauser set up a little internal research to decide how the *Annals* promoted such research. In 2006, 84 of the 280 published manuscripts were epidemiological. Five of the 20 top-cited publications were epidemiological. And, of the 7 press releases for 2006, six were epidemiological. So, it does seem they are giving disproportionate attention to this sort of research. And, when they reviewed their press release for one of these studies [Scarmeas N et al *Mediterranean diet and risk for Alzheimer's disease* *Ann Neurol* 2006 Jun;59(6):912-21], they felt the journal had to take some of the blame for media distortions of the investigators' careful conclusions. Surely, never a problem for *ACNR*! – **AJC**

Johnston SC, Hauser SL.

Epidemiology in the Annals: part of the problem or the solution?

ANNALS OF NEUROLOGY

2007;62(4):A8-9.

EPILEPSY: Moving from epilepsy treatment to prevention

There are certain lesions which we know have a high risk of being complicated by epilepsy: major cerebral trauma, parenchymal CNS infection and intracerebral haemorrhage. So far all we can do is to wait and see if seizures occur and then treat them as best we can. How much better to identify those patients in whom epileptogenesis is taking place and treating them with drugs to abort the process. In this study, rats were given a lateral fluid-percussion brain injury, the laboratory rodent equivalent of assault with a baseball bat. They then had repeated MRI scans from hours after injury up to one year. All animals, whether having suffered traumatic brain injury or not, were exposed for just one hour to the epileptogenic agent pentylenetetrazole (PTZ) at one year after injury, using previously recognised subconvulsant doses and then underwent video-EEG-telemetry. At the end of this process, their brains were examined for mossy fibre reorganisation in the hippocampus, a common marker of epileptogenesis. The injury on its own was not enough to produce epileptic activity in any of the control animals but subconvulsant doses of PTZ caused electrographic abnormalities in all animals, controls and injured. There was no association between MRI evidence of cortical damage and the increased seizure susceptibility. The latency to onset of spikes was significantly shorter, and the number of spikes and epileptiform discharges significantly greater, in animals with traumatic brain injury. MRI showed an early (hours) fall in diffusion tensor signal from the ipsilateral hippocampus of injured animals and which then rose progressively compared to control animals, peaking at three months. T2 weighted signal in the ipsilateral hippocampus rose compared to controls progressively from about 3 months. Injured animals had mossy fibre sprouting into the inner molecular layer of the hippocampus and this was positively correlated with EEG measures of seizure susceptibility. This study identifies changes which may be markers of evolving seizure susceptibility. The questions to be addressed include their applicability to humans and whether any treat-

ments can influence this development and help to prevent late post-traumatic seizures, rather than simply trying to treat them (regrettably often unsuccessfully) after they have started. – *MRAM*

Kharatishvili, Immonen R, Grohn O, Pitkanen A.

Quantitative diffusion MRI of hippocampus as a surrogate marker for post-traumatic epileptogenesis.

BRAIN

2007;130:3155-68.

BRAIN INJURY: Trauma, drugs and alcohol

Because of the circumstances in which traumatic brain injuries are sustained, issues around drugs and alcohol often emerge during a patient's rehabilitation. This study looks at drug and alcohol use pre- and post-traumatic brain injury in an attempt to establish factors associated with heavy post-injury substance abuse. The basic method involved patients recalling (which is surely a problem in the brain-injured population) their pre-morbid levels of usage, and then re-assessing them at 1 and 2 years post-injury. There are no differences in baseline (pre-morbid) levels of substance use between patients and demographically matched controls. Perhaps, not surprisingly, the authors show that young, male, heavy drinkers are most likely to return to alcohol. Drug and alcohol use tends to diminish at 1 year but rises to levels approaching pre-morbid use at 2 years. What was encouraging, but somewhat understated in the discussion, was that very few people actually increased their drug and alcohol consumption following a brain injury. From this the authors conclude that there is a need for more active intervention to reduce alcohol and drug use following brain injury. While, as a principle, this would seem admirable, it would be interesting to see research demonstrating the effectiveness of such an intervention in this population. It is also, perhaps, worth considering if it is not overly paternalistic to try and modify peoples' lifetime basic behaviours and attitudes just because they happen to have had a brain injury. The social environment is a strong factor in guiding attitudes to recreational substances, generally, and it is interesting that the authors highlight the advice given in the States to completely abstain from alcohol permanently following a head injury conflicts with that given in Australia, where patients are advised that a return to drinking after a year has passed is permissible. – *LB*

Ponsford J, Whelan-Goodinson R, Bahar-Fuchs A.

Alcohol and drug use following traumatic brain injury – a prospective study.

BRAIN INJURY

2007;21:1385-92.

HEADACHE: Migraine and sinuses

*** RECOMMENDED

We all meet patients who vehemently deny migraine but have regular "sinus" headaches. Sometimes these even get worse perimenstrually, and often have other migrainous features. So this article is interesting. It examined the rate of radiological sinus disease in migraineurs and those with "sinus headache". It is a step in untangling the knot of people with migraine and sinus changes, a step towards getting them onto the right treatment. The impetus for the study is that previous work suggests that most patients with "sinus headache" fulfil the International Headache Society (IHS) criteria for migraine. This makes it difficult to know what is causing their symptoms. There are few studies on this question, and on whether CT scan findings distinguish the groups. Thirty-five patients presenting with sinus headache were prospectively scanned for sinus disease. Using validated methodology (Lund-Mackay score, [L-M score]), these scans were assessed for sinus abnormalities. A control group of migraineurs had their scans analysed in the same way. Of the sinus headache group, 74 % had migraine by IHS criteria. There was no difference in CT scan L-M scores between the two groups (2.07 in the migraine group and 2.66 in the "sinus" cohort). Five of the migraine group had significant sinus disease radiologically. The authors conclude that the majority of "sinus headache" patients satisfy IHS criteria for migraine, and are surprised that many of these have sinus disease radiologically. Because a number of migraine patients also have sinus disease they suggest we should be looking harder for sinus disease in migraineurs. I would view the situation somewhat differently. This small but useful study shows that radiological findings don't correlate well with the clinical diagnosis. There are false positives and negatives, and further it's hard to estimate the level of incidental sinus disease in the background population. This adds to the need for caution in interpretation of radiological changes of sinus disease. The

distinction between migraine and sinus headache is sometimes opaque, and radiological disease is not enough to diagnose causality. As its not always the cause of the symptoms, we need to remain careful to avoid sending the wrong patients down medical and surgical sinus treatment paths, when what they need is good migraine prophylaxis. – *HAL*

Mehle ME, Kremer PS.

Sinus CT findings in "sinus headache" migraineurs.

HEADACHE

2008;48:67-71.

HEADACHE: Migraine incidence

There is little definitive data on the incidence of migraine in the community. This study quantified incidence and comorbidity in a large cohort using the General Practice Research Database. 51,688 patients with a first time diagnosis of migraine were found, between 1994 and 2001. The migraine incidence rate was 3.69% cases per 1000 person-years and was 2.5 times more common in women. Compared to age-matched controls, most common chronic diseases were slightly more prevalent in migraineurs. Patients using triptans had higher health care utilization than other migraineurs. Possibly these patients were those who developed chronic daily and analgesia overuse headaches. However, this finding is open to so many interpretations that it is hard to draw any definite conclusions from it. The study provides solid incidence data on the most common neurological ailment we see. – *HAL*

Becker C, Brobert GP, Almqvist PM, Johansson S, Jick SS, Meier CR.

Migraine incidence, comorbidity and health resource utilization in the UK.

CEPHALGIA

2008;28:57-64.

EPILEPSY: Does your mother's epilepsy or education matter most?

The authors assessed 71 children of mothers with epilepsy (CME), identified prospectively from an epilepsy and pregnancy register. The children underwent an Indian adaptation of the Wechsler IQ test and a specially designed language test in the local Malayalam language at around the age of six and were compared to controls, matched for age and educational status. They developed a score for AED exposure, comprising tenths of a standard daily dose (each tenth scored ten points) of each drug and this allowed them to have a measure of total drug load, independent of which drug was being taken, as well as looking at different AED and monotherapy versus polytherapy. Their mothers had mild epilepsy compared to a standard neurology outpatient cohort, with over half having either no seizures or just one seizure during their pregnancy.

The mean FSIQ of CME was 87.7 compared to 93 (P=0.02) for controls. There was an especially dramatic difference in language function between the two groups. In a multiple regression analysis, the strongest predictor of IQ was maternal education, with medication having a weaker association and seizure type or severity no association at all. There was no difference between monotherapy and polytherapy, but numbers were small. For 50 CME exposed to an AED score <90, mean FSIQ was 94.6 (SD 13.4) and mean language score 77.3 (SD 13.9) compared to FSIQ 71.3 (SD 30.8) and language score 64.1 (SD 21.3) for children exposed to an AED score >90.

If maternal education is the key determinant, the study begs the question of what factors underlie this? Is it their epilepsy, their drugs or other factors? The study does raise the optimistic possibility that poorly educated mothers with epilepsy could be identified and they and their children targeted for educational support. – *MRAM*

Thomas SV, Sukumaran S, Lukose N, Geore A, Sarma P.

Intellectual function and language functions in children of mothers with epilepsy.

EPILEPSIA

2007;48:2234-40.

BRAIN INJURY: Calling time on prognosis

*** RECOMMENDED

One of the most challenging elements to dealing with the families and friends of those who have suffered severe brain injury is being able to have a sensible discussion about the longer term prognosis without either being too vague or too definitive (and, inevitably being proved wrong). There are many indicators, in the acute stage, which have varying degrees of usefulness. Glasgow coma scale on admission, duration of post-traumatic amnesia and initial brain scan findings can all provide clues as to what the longer term outlook

is likely to be for an individual being admitted to the neuro-intensive care unit. Uncertainty, however, is accepted in this environment. Six months later, in an outpatients' clinic, the situation has changed, somewhat. "Will he get any better?" The authors of this study have used the Glasgow Outcome Scale Extended (GOSE) to track the outcomes for 214 brain-injured patients admitted to an intensive care unit with a GCS of <9 over a year in order to assess improvements between 6 months and 1 year. The GOSE is a rather crude measure with eight categories ranging from death to 'upper good recovery'. Although there are many studies looking at outcomes of head injury with this broad categorical approach, the paper in question provides new information in terms of the specific changes occurring after 6 months, a point at which many would consider further functional recovery unlikely.

Perhaps unsurprisingly, patients admitted with more severe brain injuries (GCS <5) showed little change between 6 months and a year, whereas the less severe group (GCS >6) showed a number of improvements. None of the patients recruited deteriorated, in terms of this scale, between 6 months and a year. Although very small in number, half of the patients in a "persistent vegetative state" at 6 months had moved into improved functional categories at 1 year, which does somewhat question the validity of this element in the GOSE. Although this study supports the notion that recovery from brain injury is an ongoing process, it would have been more revealing to look at meaningful outcome measures, rather than broad categories. – **LB**

Corral L, Ventura JL, Herrero JI, Monfort JL, Juncadella M, Gabarrós A, Bartolomé C, Javierre CF, García-Huete L.

Improvement in GOS and GOSE scores 6 and 12 months after severe traumatic brain injury.

BRAIN INJURY

2007;21:1225-31.

EPILEPSY: How much does it cost?

This study reviews all those which estimate the costs of epilepsy. Whether you feel this kind of data should be in a journal which, for any clinical or basic science paper, would apply quite rigorous scientific standards, is an interesting question. But fortunately those who hold the purse strings do not apply scientific rigour and so these data are useful to anyone putting a case forward for service development. So long as you see it as game and are happy to play quasi-scientific numbers with the powers that be, then you can enjoy the process and not get too frustrated at its stupidity. So to help you bend the rules in your favour here are some figures for epilepsy. The authors divided the studies into three groups. The first were epidemiological, from which they concluded that in the EU the prevalence of epilepsy is 5.8-7.4/1,000 in men and 4.0-5.3/1,000 in women. Highest prevalences were in children and adults and lower in the elderly but this group is susceptible to poor case ascertainment. The second type of study was a cost-of-illness study. There was a very wide variation from €2,000 per case per year in Estonia to €11,500 per year in Switzerland, the UK coming in at around €9,000 per year. These figures mostly reflect the cost of living in these countries. This amounted to a total cost of €15.5bn across the EU in 2004. Indirect costs were 55% and direct health care costs €2.8bn (18%) half of which was outpatient care. Drug costs were €400m (only 3% of total costs). The remaining costs were social services costs. The breakdown of total costs was sick leave 51%, adaptations 14%, social services 13%, outpatient care 8%, hospitalisation 6%, premature mortality 4%, drugs 3%, devices and procedures 0.3%. As always the financial arguments used in health care do not take account of the massive social costs of the condition and until the NHS talks to the DSS all the financial arguments we use to make a case for improved medical care are only taking account of 18% of the financial cost, let alone the personal and social burden of this illness. – **MRAM**

Pugliatti M, Beghi E, Forsgren L, Ekman M, Sobocki P.

Estimating the cost of epilepsy in Europe: A review with economic modelling.

EPILEPSIA

2007;48:2224-333.

Dopamine, the basal ganglia and cognition

There is a long history of studies involving cognition and the role of dopamine on this and its differential effects in the basal ganglia and cortex. In a series of papers this has been further explored in an attempt to define more explicitly how the system works and what are the major determinants of any variability within it. Our own work in Parkinson's disease has clearly shown that a functional polymorphism in the COMT gene can influence working memory through an alteration in the fronto parietal cortical system linked to the striatum. Whilst the exact focus of action for the effect of the polymorphism is unknown (ie striatum or cortex) the latter seems more likely given the major effect COMT activity has on synaptic dopamine levels in the cortex compared to the striatum. We have recently extended these studies to show that this polymorphism in COMT not only influences performance in Tower of London in early Parkinson's disease and activation of the above network but also impacts on the ability to form an attentional set. These studies though have only looked at PD and COMT polymorphisms using specific tasks and functional MRI. Others have now directly looked at other aspects of this relationship and shown:

- Cortical dopamine release during task specific actions. Mark Hallett and his team have shown that they can measure dopamine release in the pre SMA and globus pallidum internal segment in healthy controls and that there is a motor learning related interaction between dopamine release in the left globus pallidum and pre SMA.
- Others have now shown that functional polymorphisms in dopamine receptors have an impact on cognitive performance especially D2 and D4 receptors and
- Finally that the basal ganglia seem to be responsible for allowing only relevant information into working memory and as such act as some form of selective filter.

Therefore we start to see emerging a tightly coupled cortical basal ganglia network where dopamine acts as the key determinant such that variations in it (through functional polymorphisms in genes known to impact on dopamine function) can influence our capacity to perform motor and cognitive tasks such as attentional sets and working memory. It is now necessary to dissect out exactly how this process occurs and what impact this has, if any, on our ability to perform everyday actions and functions. – **RAB**

Williams-Gray CH, Hampshire A, Barker RA, Owen AM.

Attentional control in Parkinson's disease is dependent on COMT val158met genotype.

BRAIN

2008, Epub Jan 4th

McNab F, Klingberg T.

Prefrontal cortex and basal ganglia control access to working memory.

NATURE NEUROSCIENCE

2008;11:103-7.

Garraux G, Peigneux P, Carson RE, Hallett M.

Task-related interaction between basal ganglia and cortical dopamine release.

JOURNAL OF NEUROSCIENCE

2007;27:14434-41.

Kramer UM, Cunillera T, Camara E et al.

The impact of Catechol-O-Methyltransferase and dopamine D4 receptor genotypes on neurophysiological markers of performance monitoring.

JOURNAL OF NEUROSCIENCE

2007;27:14190-8.

Cohen MX, Krohn-Grimberge A, Elger CE, Weber B.

Dopamine gene predicts the brain's response to dopaminergic drug.

EUROPEAN JOURNAL OF NEUROSCIENCE

2007; 26:3652-60.

Journal reviewers

Heather Angus-Leppan, Royal Free & Barnet Hospitals;
Chrystalina Antoniadou, Cambridge Centre for Brain Repair;
Roger Barker, Cambridge Centre for Brain Repair;
Lloyd Bradley, Colman Centre for Specialist Neurological
 Rehabilitation Services in Norwich;

Alasdair Coles, Cambridge University;
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Wendy Phillips, Addenbrooke's Hospital, Cambridge;
Robert Redfern, Morriston Hospital, Swansea;
Ailie Turton, University of Bristol.

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

Understanding Neurology – A Problem Orientated Approach

In the veritable forest of publications to bring neurology to students, and vice versa, another sapling springs forth. Whether it will survive and find a niche time & sales will tell but I doubt it will be the last on the subject. The authors have wrestled with an old problem. Clinically orientated neurological information is relevant and interesting, fun to learn, easy to retain, and makes you look good at the bedside. But it is based on preclinical neurological information which for some poor souls can be less fascinating, seldom fun to learn, hard to retain, and producing it could make you look either sad or a swot. This offering of a “problem-orientated approach to the commonly presenting complaints seen by neurologists” is an admirable effort to get the balance right.

Thirteen contributors, a dozen working in Glasgow and one representative from the not-so-soft South (Essex) take us through familiar territory with 11 pages on history taking (of which half concerns cognitive neurology). This is supplemented throughout the book by excellent subsections on “focused” history taking which serve to highlight the immense and undiminished diagnostic potential of this clinical art which, though seemingly less appealing to those who feel diagnosis can be achieved by just ordering a scan or two, survives (and even excels through the unlikely persona of Hugh Laurie as Dr Greg House; Channel 5US – don’t miss!). Indeed one doesn’t have to wait long for the first brain scan (five pages in). Furthermore, the second chapter - neurological investigation, runs to 35 pages perhaps underpinning sentiments expressed that “the advent, easy availability, and low risk of cross sectional imaging have undoubtedly diluted clinical skills...the current danger is that of over –investigation and that clinical skills are reduced such that investigations are targeted to the wrong site or incidental imaging findings are mistaken as relevant.” And don’t neurologists, increasingly invited to extinguish the fireworks ignited by ill-advised colleagues doing ill-advised tests (“just to be on the safe side / reassure the patient” / insert your own pet hate phrase) know it! Perhaps a section on the pitfalls of investigation, “When scanning is a bad idea”, may come one day. The radiological images in this book are appropriately illustrative with a valiant effort to explain how MR actually works, still a mystery to me. Again a “pitfalls” or “incidentaloma” section would, I think, be very informative. I was surprised to read in the spinal cord section of this chapter that the spinal cord ends at L2/L3. I have always thought & taught it to be a space higher, as do later authors in this book.

The neurophysiology section is informative in a qualitative if not quantitative way.

A few more problem-orientated “peripheral” cases to illustrate the values (& pitfalls) of these tests would enable normative data to be included and bring what can appear a rather dry subject to its appropriately vibrant status.

And so to “The Problems” which constitute $\frac{3}{4}$ of the book and this bit I liked a lot.

Divided into five subsections with disorders of consciousness including acute confusional states, (with inevitable overlap with), cognition, special senses (vision, dizziness & vertigo, with inevitable overlap with), a seminal chapter on “motility” (incoordination, weakness, movement disorders), and finally “sensation”

(headache, neck pain & back ache, numbness & tingling).

Cognition features a lot in this book which is no bad thing given the high prevalence, imperfect understanding not wholly confined to juniors, and undeniably neurological nature of dementia. As in all sections the end of chapter cases help make it relevant and demonstrate how knowing stuff helps. An additional nod to the problem-orientated nature of life in the clinic would include a bit more on helpful clinical pointers that differentiate those worried well with “short term memory” problems that are not dementing, but attend neurology clinics in ever increasing numbers, from those who are.

The sections on vision and vestibular disorders are awash with illustrative cases and more digestible and enjoyable for that. A few quibbles if I may: do patients with parietic eye muscles really tilt their heads “away” from the direction of the parietic muscle to minimize diplopia?; an explanation of why only the first division of V is affected in cavernous sinus lesions despite two diagrams showing that both first & second divisions can be found there would be informative. These are minor, if important, points.

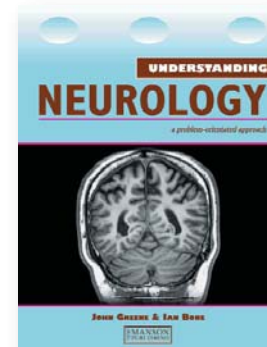
The “dizziness & vertigo” and “motility” sections both make the obvious but crucial point that many patients referred to neurology with neurological symptoms have diseases outside the nervous system. This cannot be overemphasised in our era of subspecialisation. Again a few quibbles detract somewhat from what are in many ways well written sections. Hip flexion appears in the L1, 2 myotome and also L4; knee flexion appears as an L5 root phenomenon and an S1 phenomenon two pages later; and whilst many would argue the value of the incorrectly named “supinator” jerk I’m not sure it is yet timely to exclude it completely from “Reflexes routinely tested,” especially if the finger jerk (admittedly more useful but surely less widely known at junior level) is included. A later table of reflexes & roots would seem to concur. Also (sorry to go on but..) a table listing what distinguishes UMN & LMN problems that proceeds - power, tone, reflexes, plantar responses, bulk - would jar with many of my more particular colleagues (and to be honest, me too).

The well written movement disorder section included some functional images which always provide visual relief if not pleasure. I now know that Froment (assuming it’s the same docteur) has two signs, the other one being accentuation of muscle tone with contralateral limb activity. Done it for years & never knew it had an eponym – ah, the joy of learning!

The final two sections on spinal symptoms and numbness & tingling show how just much useful information can be crammed into 24 pages – with pictures and tables (one even duplicated in case you missed it five pages previously!) included.

Perhaps one should accept that whilst demystifying neurology remains an urgent necessity amongst trainees, the development, acquisition and retention of such skills cannot exist without a solid grounding of neurological knowledge, which informs knowing what questions to ask, and why. This book strives with some success to achieve this educational balance. A touch of editorial rigour would go a long way, too.

Andrew Larner, WCNN, Liverpool, UK.



Authors: John Greene and Ian Bone

Published by: Manson Publishing

ISBN: 978-1-84076-061-3

Price: £24.95

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

Dizziness – A Practical Approach to Diagnosis and Management

“There can be few physicians so dedicated to their art that they do not experience a slight decline in spirits on learning that their patient’s complaint is of giddiness.” Bryan Matthews’ famous quote (Practical Neurology, 3rd edition. Oxford: Blackwell, 1975: 76), recently paraphrased in these pages by John Bowen (ACNR 2007; 7(2): 19), is familiar to many neurologists. But what is it that causes the spirits to sink? The complex neuroanatomy of the vestibular systems? A feeling that ENT surgeons rather than neurologists should be dealing with the problem of dizziness (they often send patients our way, so perhaps feel the converse)? The concurrence of psychiatric symptoms which may perhaps “drive” the complaint of chronic dizziness, as in chronic headache?

This well-produced volume in the Cambridge Clinical Guides series is a symptom-oriented text accompanied by a CD-ROM with 45 clips by two well-known neuro-otologists whose target audience includes any doctor called upon to assess dizziness, hence primary care physicians and A&E doctors as well as neurologists and ENT surgeons. They hope to make clinicians more optimistic when approaching these problems.

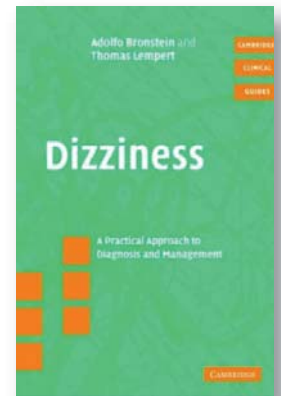
Introductory chapters on anatomy, symptoms and examination are followed by specific symptoms: acute single episode vertigo, recurrent vertigo, positional vertigo, chronic dizziness, falls in the elderly, concluding with notes on vestibular rehabilitation. The importance of clinical history taking and examination, especially of eye movements, is emphasized throughout. The fact that “vestibular function tests” generally address only one-fifth of the vestibular system (2) may explain the common scenario (Clin Otolaryngol 2007;36:217-8) of the dizzy

patient referred from ENT to neurology to exclude a central cause because “vestibular function tests are normal” yet whose history and examination suggest a peripheral origin for symptoms. Migrainous vertigo seems underdiagnosed as a cause of recurrent vertigo and Meniere’s overdiagnosed (30). The intimate connection of vestibular and psychological symptoms (anxiety, panic, depression, somatisation) is addressed (117-24). The concepts of vertebrobasilar insufficiency (10) and cervical (28,185) or head extension (153-4) vertigo are debunked, and the lack of utility (low specificity) of the hyperventilation test pointed out (123,169). Betahistine does not feature in the list of “10 common vestibular suppressants and antiemetics” (209-12), despite the frequency with which it is used in the patients reaching my clinic.

This is a pragmatic text, steeped with the authors’ experience. I have few quibbles: it would have been desirable in the index of videoclips (xii-xiii) to cross reference the text where they are discussed. I foresee circumstances in which the recommendation a propos chronic dizziness to “send a few too many patients for neurological consultation” (171) might be misconstrued by an enthusiastic ENT SpR or GP trainee with rather significant consequences for local neurology outpatient clinics. A 70% hit rate for the aetiology of peripheral neuropathy (181) seems optimistic.

Short of having Adolfo Bronstein universally available to sort out dizzy people, this book is a very acceptable addition to a neurologist’s armamentarium for dealing with a common clinical problem.

AJ Larner, WCNN, Liverpool



Authors: Adolfo M Bronstein and Thomas Lempert
Published by: Cambridge University Press
ISBN: 0-521-83791-X
Price: £35.00

Neurological Disorders in Famous Artists (Part 2)

The visual arts seem to predominate in this second volume of neurological disorders in famous artists from the Karger Frontiers of Neurology and Neuroscience series. The effects of both neglect and of aphasia on visual artistic output are examined (Blanke), the former mostly after right hemisphere stroke (Bazner & Hennerici x2), for example in the painter Lovis Corinth and the film-makers Visconti and Fellini (Dieguez et al), the latter after left hemisphere stroke, for example in the painter Reutersward (Colombo-Thuillard & Assal). The high quality illustrations support the various authors’ theses. A possible depiction of sleep paralysis in a painting by Fussli (Baumann et al) is also presented.

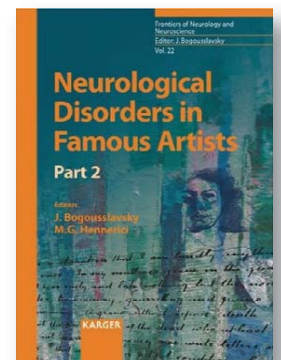
There are several chapters of straight pathography: Proust (Bogousslavsky) did not clearly have any neurological ailment although his asthma was regarded as a “nervous” disease, not least by his medical father, and he consulted Babinski amongst many others; Heine (Auf der Horst), a victim of syphilis; Baudelaire (Dieguez & Bogousslavsky) developed aphasia with recurrent utterances. Musicians are in a distinct minority: von Bulow (Wohrle & Haas) is best known for being cuckolded by Wagner but had additional problems, not least occipital neuralgia and strokes. The evidence for and against Mozart having had Tourette syndrome is carefully weighed and found wanting (Kammer).

The emergence of artistic behaviour following brain

injury (Pollak et al), mostly frontotemporal dementia but also in selected cases of epilepsy, Parkinson’s disease, and following subarachnoid haemorrhage, is truly fascinating. The problem of de Kooning’s late work, produced when he was suffering from Alzheimer’s disease, is reported solved (Espinell) through the development of no less than an entirely new intellectual discipline, “ArtScience”, requiring specific thinking and observation methods, all devised (single-handedly) by the author. Myself a dullard, subscribing to the Gordon Holmes approach (“Observe and describe, that’s all”), methinks this author doth protest too much! The place of synaesthesia in creativity is discussed (Mulvenna): is it a chance concurrence or over-represented in artists? Surprisingly in this context, Kevin Dann’s book, Bright colors falsely seen: synaesthesia and the search for transcendental knowledge (New Haven and London: Yale University Press, 1998) is not referenced. The discussion prompts a distinction between “creative cognition” (= having ideas) and creative output (= trying to communicate them).

As with the first volume (reviewed ACNR 2005; 5(5): 37) one can enthusiastically recommend this volume. Although not cheap, many neurologists with broader interests will be keen to have a copy.

AJ Larner, WCNN, Liverpool, UK.



Edited by: J Bogousslavsky, MG Hennerici
Published by: Karger, 2007
ISBN: 978-3-8055-8265-0
Price: €88.00

£140 Million Managed Equipment Service Commences

University Hospitals of Leicester NHS Trust and Asteral have announced a £140 million (at today's prices), 18.9 year Managed Equipment Service (MES) contract. This is the largest stand alone MES contract in Europe to date.

Under the terms of the agreement, Asteral will install, commission, maintain and manage the latest equipment across the Trust's multiple sites for the lifetime of the contract. It will also provide project management, training and related support services across each site.

Helen Seth, Deputy Director of Operations at the University Hospitals of Leicester NHS Trust, states, "This is an innovative approach



to the procurement, management and replacement of over 210 items of clinical equipment that will deliver real benefits to the patients served across the health-care community of Leicester, Leicestershire and Rutland using our hospitals."

Asteral's MES model delivers a fully integrated approach to procurement, management and maintenance of medical equipment. Asteral is completely independent of the equipment supply compa-

nies. In partnership with the Trust it uses its scientific and medical engineering expertise to ensure the optimum combination of equipment is selected to meet each Hospital's needs.

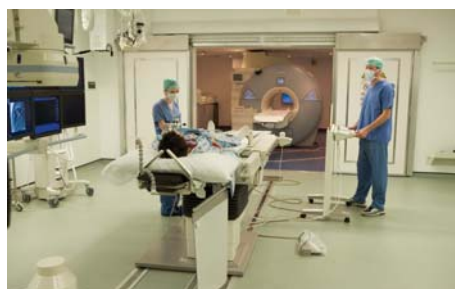
Further information can be found at www.asteral.com

Great Ormond Street Hospital opens innovative new MR & CT Imaging Centre

Great Ormond Street Hospital has officially opened its state-of-the-art MR & CT Imaging Centre. The new facility has been developed to provide a high quality diagnostic imaging and interventional treatment service whilst ensuring comfort for its young patients.

The Siemens portfolio at Great Ormond Street Hospital includes an independent MAGNETOM Avanto Cardiac MR unit; a MAGNETOM Avanto MR combined with an 'Artis dBC' Cardiac Angio suite incorporating Myabi patient transfer table and a SOMATOM Definition Dual Source CT Scanner. A 'Symbia T2' SPECT/CT Nuclear Medicine Scanner is also due to be installed shortly. All equipment is connected to a Siemens PACS and Medcon Cardiac system for fast image archiving and recall.

"Great Ormond Street Hospital is a recognised centre of excellence for paediatric diagnosis and treatment," said Peter Harrison, Director of Imaging & Oncology Systems at Siemens. "We are delighted to have been involved in the provision of new equipment and in devising a unique and bespoke MRI and angiography solution. Collectively the new equipment will extend the provision of care offered to patients and work towards improv-



Unique MR & Cardiac Angiography suite connected by Myabi table in situ and operational at Great Ormond Street Hospital's new MR & CT Imaging Centre.

ing clinical outcomes well into the future."

The official opening event was held on 17th January 2008 and involved key hospital stakeholders. Dr Jane Collins, Chief Executive of Great Ormond Street Hospital addressed the guests and assisted Oliver Barlin, a 9-year-old patient, to unveil the commemorative plaque marking the opening of the new MR & CT Imaging Centre.

For more information contact: Siemens
T. +44 (0)1276 696000,
E. medmarketing.med.gb@siemens.com
W. www.siemens.co.uk/medical

Artis zeego provides imaging excellence and unrivalled flexibility for interventional environments



Artis zeego®, the newly launched multi-axis C-arm for interventional imaging, has been installed at the Institute for Clinical Radiology at the University of Munich Hospital. The rotation technology enables the physician to view vessels more easily from various sides, especially when evaluating tumours or vascular diseases.

Peter Harrison, Director of Imaging & Oncology Systems at Siemens, claims that "The zeego heralds the introduction of automotive industry precision robotics in angiography systems. The flexibility of the mechanics affords clinicians unprecedented flexibility and vessel visibility. The system also significantly increases image volume coverage and simplifies workflow during intervention,"

The engineering and development of this new angiography system has transferred from industrial robotics. The Artis zeego has 8 pivot points extending imaging capabilities through virtually unrestricted C-arm positioning, giving unprecedented flexibility in catheter labs and operating rooms. The extra positioning flexibility allows for advanced cross-sectional imaging not achievable with traditional C-arm systems and also enables off-centre rotational angiography for all areas of the body. The Artis zeego is part of the Siemens Artis zee family of interventional cardiology and radiology systems.

For more information contact: Siemens
T. +44 (0)1276 696000,
E. medmarketing.med.gb@siemens.com
W. www.siemens.com/artis-zee.

'Just doodle it!'

What do Joanna Lumley, Ricky Gervais and Suzanne Shaw all have in common? The answer, National Doodle Day 2008 of course! The nation's doodlers are being encouraged to join these celebrities and put pen to paper and join the fifth National Doodle Day on March 7.

The event raises vital funds for Epilepsy Action and The Neurofibromatosis Association and with the support of Lloyds Pharmacy and BIC stationary. Both companies have generously donated large prizes for a number of this

year's competitions.

With a theme of 'Just doodle it' it appears as though many celebrities have done just that. We have already received doodles from an array of celebrities from Sir Ian McKellen to Sally Gunnell and from Sir Bobby Charlton to Nick Park!

To celebrate, people can take part in the competition by picking up individual entry cards at branches of Lloydspharmacy for a £1



donation. Judging will be carried out by Maureen Lipman, the Doodle Day patron.

Paul Tranter, Epilepsy Action's fundraising manager, said: "We're now on our fifth National Doodle Day, we're hoping that lots of people are going to get involved and let their creativity flow."

For further information visit www.nationaldoodleday.org.uk or
T. +44 (0)113 210 8800.

Hand-carried ultrasound benefits ICU and surgical patients



(L to R) Tim Clarke, Rudi Brits and Stephen Holgate with their MicroMaxx ultrasound system.

Intensive care consultants and anaesthetists at the East Lancashire NHS Hospitals Trust, UK, rely on SonoSite hand-carried ultrasound systems for placing central lines, and for performing nerve blocks during upper and lower limb surgery at the Royal Blackburn and Burnley hospitals.

"We use our MicroMaxx® ultrasound system

on a daily basis for interscalene, femoral and sciatic nerve blocks, as well as for vascular access," said Dr Rudi Brits, Consultant in Intensive Care and Anaesthesia at the Royal Blackburn Hospital. "Being able to visualise the nerve as well as the anaesthetic during the injection has a number of advantages and in time we hope to see greater success rates, reduced risk of complications and less requirement for anaesthetic."

"The MicroMaxx system is very compact and easy to carry around, and its clear image resolution also makes it a really good teaching aid," Dr Brits continued. "Several of our staff are attending ultrasound training courses and can just pick up the system whenever a block is being performed, so they are constantly learning."

For more information,
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F. +44 (0)1462 444 801
E. europe@sonosite.com
W. www.sonosite.com

Overcoming challenging delivery of MRI magnets New access road built especially for the bulky and heavy delivery

London's National Hospital for Neurology and Neurosurgery has recently taken delivery of three large MRI magnets for machines from the Total Imaging Matrix (Tim™) family, as part of the ongoing project to complete the building of the hospital's new imaging centre.

Gary Cook, London Sales Manager at Siemens states, "The delivery of large MRI magnets can sometimes present problems due to their weight and dimensions, especially to older hospital sites that have unknown ground-work or underground vaults. However, by working in partnership with hos-



pital estate managers, construction companies and project managers all situations can be overcome. The end of an equipment sale is just the start of the delivery and installation process."

Further technology will be delivered to London's National Hospital new imaging department in due course. This includes a biplane neurology system, CT scanner and another MRI scanner.

For more information contact: Siemens
T. +44 (0)1276 696000,
E. medmarketing.med.gb@siemens.com

W. www.siemens.co.uk/medical

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To receive your discount, simply quote promotion code ACNR when you purchase a book. It's that easy!

Answering questions for life in the 21st century

Siemens debuts its MR & CT innovations to satisfy UK clinical and cost expectations



Gunter Dombrowe, Managing Director of Siemens Medical, welcomes guests to the launch evening at the Science Museum in London.

The latest innovations in the field of CT and MRI imaging have been formally launched in the UK by Siemens at the Science Museum in London.

A high-field 3T MRI system, the MAGNETOM Verio and an adaptable single source CT, the SOMATOM Definition AS, have both been designed to offer advanced imaging functionality for routine and specialised clinical procedures at a much more viable capital cost for the UK health marketplace.

With the NHS and private diagnostic centres demanding higher throughput rates and a return on investment, the new systems meet clinical and cost expectations.

The MAGNETOM Verio is a 3T field strength MRI and can be used in neurology and functional neuro evaluation, orthopaedic and cartilage assessment, breast, vascular and cardiac imaging. It has a wider than normal open bore (70cm) and features Tim™ (Total imaging matrix) in one powerful system. This offers advanced imaging capabilities with the patient's comfort in mind. Furthermore, it is an affordable capital purchase and efficient to operate.

The SOMATOM Definition AS and Definition AS+ break with the normal conventions of CT as the world's first adaptive scanners. This simply means they can adapt to any patient or clinical need in routine diagnostic work and complex examinations including cardiology, neurology and oncology.

For more information contact: Siemens
T. +44 (0)1276 696000,
E. medmarketing.med.gb@siemens.com
W. www.siemens.co.uk/medical

The SOMATOM Definition AS on show.



Partnerships in Care opens its first facility in Scotland

Partnerships in Care (PiC), the UK's leading independent provider of specialist mental health care and related services, is pleased to announce the purchase of its first hospital in Scotland, The Ayr Clinic in Ayrshire.

The Ayr Clinic is a 24 bed low secure, purpose built psychiatric unit providing secure in-patient care and treatment for men and women suffering from mental illness, personality disorder or a mild learning disability.

On completion of the purchase, Myles

Paterson, Regional Executive Director for Partnerships in Care in Scotland said, "We look forward to working in partnership with The Scottish Forensic Network and the local health boards to extend our first class mental health services to new purchasers, enhancing the quality of existing services and building on the good relationships that have already been established."

Andreana Adamson, Chair of the Forensic Network in Scotland, welcomes the arrival of

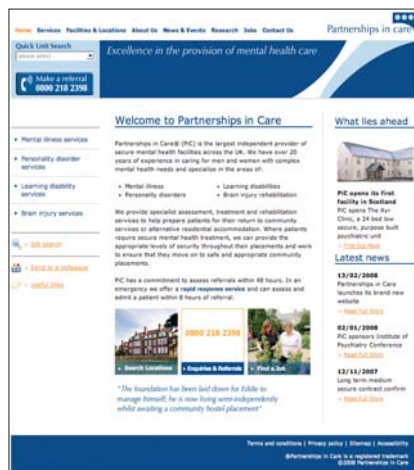


PiC to Scotland: "PiC has a well respected reputation in the field. Clinicians are experienced in referring patients to the services PiC offer in specialist forensic services, particularly in their units in the North of England."

For more information:

T. +44 (0) 20 8327 1818

E. LHamblin@partnershipsincare.co.uk



Partnerships in Care launches its brand new website

Partnerships in Care (PiC), the UK's leading independent provider of specialist mental health care and related services, is pleased to announce today the launch of its brand new company website at www.partnershipsincare.co.uk

The new site provides commissioners, healthcare professionals and other audiences interested in PiC with:

- increased functionality, including easier and more intuitive site navigation
- more in-depth information on the local services we provide
- further assistance for referrals
- an online job application process

The launch ties in with PiC's latest hospital acquisition, The Ayr Clinic in Scotland, announced separately today.

Fred Sinclair-Brown, Group Chief Executive of Partnerships in Care said: "We now have 23 hospitals providing services to over 180 primary care trusts, commissioning consortia and social services. We are excited to launch a new website that reflects the size and depth of our organisation and hope the new website provides customers and other interested parties with easy access to all the information they need."

For more information:

T. +44 (0)20 8327 1818,

E. LHamblin@partnershipsincare.co.uk

Awards and Appointments



Cheque presented to president of MND Association

President of the Motor Neurone Disease (MND) Association, Lembit Opik MP, was presented with a cheque for £5,000 from The Hospital Saturday Fund (HSF), the charitable trust associated with HSF health plan. The cheque was presented to Lembit at the House of Commons and is to be invested in research into MND.

After receiving the cheque Lembit said: "The HSF has always been a life saver and today they've put their money behind this noble intent by giving

a hugely generous £5,000 to the cause of curing MND.

"Every penny of the money given by HSF will be matched by the Government. So, in effect, this is a £10,000 contribution to the search for a cure.

"On behalf of all those living with MND, and those who won't suffer it one day in the not-too-distant future, I thank HSF, their staff and their vision of a world free of MND. It's a vision we all share."

The Encephalitis Society proudly welcomes their first president

Actors Martin Kemp, Patron of the Encephalitis Society and Mathew Bose, Ambassador for the Encephalitis Society welcomed the first President of the Encephalitis Society, Professor Barbara Wilson, OBE. The event took place on 17 October 2007 during a cruise along the river Thames in London.

The Encephalitis Society is the only resource of its kind in the world providing direct support, information and education to people affected by encephalitis and the professionals involved in their care. On behalf of the Society, Martin Kemp welcomed Professor Barbara Wilson, OBE,

'I am delighted to welcome Professor Wilson and look forward to working with her in our quest to support people affected by encephalitis and to raise awareness of this very grave syndrome,' Professor Wilson has been a long standing clinical advisor to



Ava Easton, Development Manager, Encephalitis Society, Martin Kemp and Professor Barbara Wilson, OBE.

the Society and on her forthcoming retirement from the Medical Research Council, accepted the position of President of the Society. Professor Wilson is a clinical neuropsychologist and international expert on memory problems following acquired brain injury: 'It is a great honour to be invited to accept this position with the Encephalitis Society,' said Professor Wilson. 'In my own field of brain injury rehabilitation, the patients most frequently referred for cognitive rehabilitation are those with traumatic brain injury but after that the diagnostic group most seen are survivors of encephalitis. The professionalism and innovation shown by the Society in their quest to support and inform is quite breathtaking.'

For further information contact: The Encephalitis Society, 7b Saville Street, Malton, YO17 7LL, Tel. +44 (0)1653 692 583, E. ava@encephalitis.info W. www.encephalitis.info

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Information about adverse event reporting can be found at www.yellowcard.gov.uk.

Adverse events should also be reported to Teva Pharmaceuticals Ltd on telephone number: 01296 719768.

Reference: Ford C. et al. Multiple Sclerosis 2006; 12: 309-320.

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