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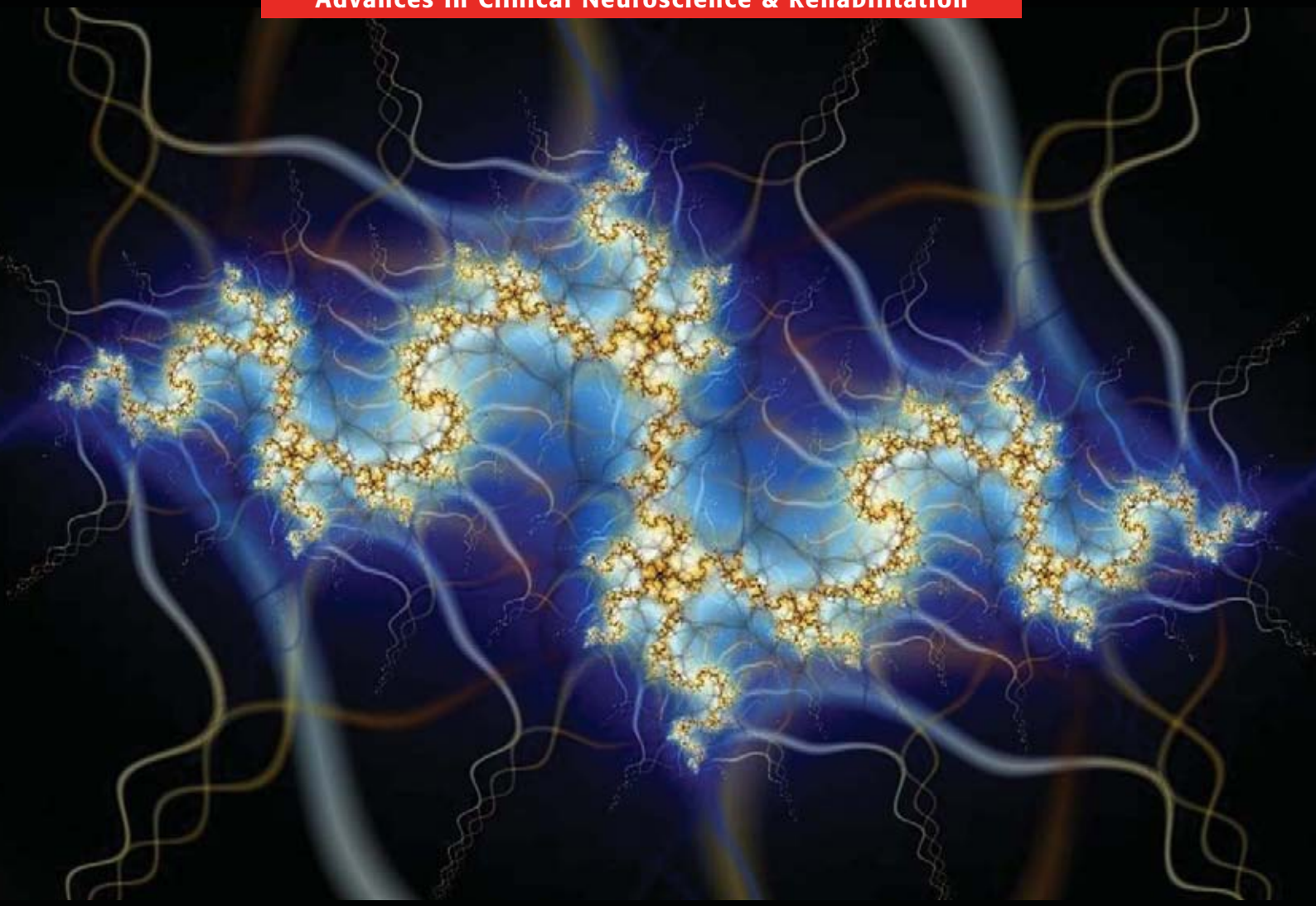

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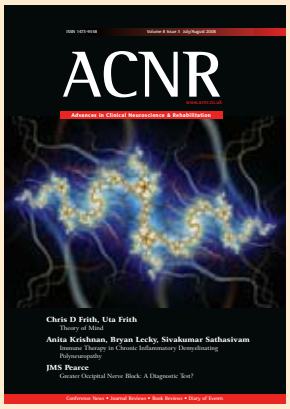

Cover picture
concept of the electrical impulse that neurons fire.
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Chris Frith and Uta Frith in their article on Theory of Mind discuss what is meant by this concept and its basis. In addition they discuss how it can be abnormal in certain conditions, most notably autism and schizophrenia, as well as its significance as a possible cornerstone of cultural evolution.

Anita Krishnan, Bryan Lecky and Sivakumar Sathasivam in their review article explore the evidence for the efficacy of different immunotherapies in CIDP in the short and long term. They conclude that whilst there are a number of proven therapies in the short term for the treatment of CIDP, the long term options are less well established. This is due to a lack of trial data, which may be difficult to acquire given the nature of the condition and the problem of optimising long term immunotherapy in such disorders.

"Among the peripheral nerves the greater occipital nerve has become a favourite target of needle wielders"; so writes J M S Pearce in his article for Controversies in Neurology. He argues that much of the evidence quoted in support of nerve blocks for occipital neuralgia or cervicogenic headache is unsound. As such much that is practiced has little basis according to his review of the clinical and anatomical literature.

In the final article in our series from India, Satish Khadilkar and Benny Rajesh discuss the spectrum of muscle disease encountered in this part of the world. Again, the diagnosis and optimal management of these patients is hampered by a combination of restrictions of access to diagnostic facilities and social and cultural behaviours. Nevertheless this informative article concludes what has been a wonderful series on aspects of neurology in India and we would like to thank all the authors for their contributions.

I have to confess that my knowledge of wheelchairs is very limited, but I suspect I am not alone in this. It is therefore most welcome to have a truly informative article on this by Rory O'Connor and Matthew Smith in our Rehabilitation article. In their review, these authors take us through the range of issues that ought to be considered when choosing a wheelchair and the types of such vehicle that exist. For those that rely on wheelchairs, it is clearly vital that they are given the best advice and ultimately have the chance to acquire the most suitable wheelchair for their needs. It is therefore comforting to know that such expert advice exists.

One of the most difficult areas of neuropathology is in cases of non-accidental injury and death, when the pathological findings often decide the outcome of the case. Nowhere is more apparent than in the tragic cases of "Shaken Baby Syndrome" (SBS). We are therefore grateful to have such a clear account from Thomas Jacques and Brian Harding from Great Ormond Street on this thankfully rare condition.

Our sponsored article features a discussion on Duodopa and whether it should be used ahead of deep brain stimulation in patients with advanced Parkinson's disease. Both parties argue their case with great coherence and leave you to decide what you think is best.

We have our usual book, conference, paper reviews and ABNT column, including a fascinating book review on the practice of Harvey Cushing and his case registry of over 2000 cases. We also have another new case on the website to learn from. So enjoy and do remember to feed back ways to improve ACNR.

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

Association of British Neurologist Trainees

Annual meetings

Soon the ABN will change its meetings format to one annual meeting per year, the inaugural one being in Liverpool in June 2009. This has been with some trepidation: delegates may find it harder to come to a 5 day meeting, with the negative manpower effect on departments. As trainees still carry the bulk of core emergency neurological services around the country, it might be particularly tricky for us to attend. Of course, we could attend part of the meeting, although essential cost structures have made this a more expensive option historically. We are continuing to try to make day attendance more cost-effective for all attendees, and in the light of reduced study leave budgets nationally and the absence of ring-fencing of MPET monies by the Department of Health (they continue to drag their feet on this recommendation of the Tooke Report), this is becoming increasingly relevant. One option might be to create "early-bird" registrations, with substantial discounts on day rates as well as whole meeting registration, but these plans have yet to be finalised. Nevertheless, the ABNT (and the ABN Officers) see the ABN meetings as core events in the neurology trainee's calendar, and we're continuing to apply pressure to encourage and facilitate attendance at these.

Teaching courses

There are now a number of teaching courses run either annually or biennially around the UK, and are increasingly popular with trainees. Whilst I don't believe that the increasing prevalence is secondary to a reduction in core training opportunities around the country, it is clear that, more than ever, junior neurologists are willing to spend money, invest their weekends, and travel long distances to attend them. Although the ABN has consolidated its scientific meetings into one annual event, there have been suggestions for some time that we might also provide teaching courses, especially for subjects that are not always provided locally in great depth, and that are not already covered by other, independent courses. The teaching of head injury is a relevant example: the national service framework for head injury was published a few years ago, and indicated that all patients with a head injury should be seen acutely by a clinical neuroscientist (of some description). In most areas, this is likely to be the local general neurologist. I certainly don't feel completely competent to assess and manage acute or sub-acute head injury, and know from informal discussions with colleagues that they feel the same. The ABN is in a perfect position to co-ordinate and run teaching courses in this area. Head injury isn't the only example of this – neuro-otology and neurogenetics have been covered recently in teaching sessions at ABN scientific meetings, to great success. If you have any suggestions or comments in this regard, please let me know, so that I can take this forward.

Calman days

The other logical place for "super-specialist" training, such as that described above, is on the "Calman" training days, which were organised as part of the new training arrangements for Specialist Registrars in 1998, following Sir Kenneth Calman's reforms of post-graduate medical training (the last time!). Quite what will happen to these under the new regime is not clear, but there is still a strong will from within the ABN to maintain this arrangement following the transition to MMC. While some programmes are highly successful, with strong attendance and local structures that facilitate time away from clinical duties to attend (London and Scotland are two very good examples of this), other regions are less fortunate (we have recently had a complaint from a trainee in the Wessex region). We are taking this to the Training and Education Committee of the ABN, who are keen to make these events as meaningful and effective as possible, so please get in touch if we need to include your region on our "name and shame" list.

Surveys

Finally, several years ago we ran a highly successful email questionnaire of training provision around the UK, produced in response to the withdrawal of RCP visits by PMETB. This identified many good things about the quality of our training, as well as some issues that required action. We are planning to repeat this in the near future, so keep your eyes open for that email!

Additionally, the ABNT Treasurer (Boyd Ghosh) is conducting a census of all ABNT members, to inform a piece of workforce planning, in an attempt to ensure there is sufficient consultant expansion to accommodate all the extra training opportunities that were created in 2007 and 2008. You should be receiving an email from your regional representative asking for this information, but please feel free to contact Boyd (bcpg1@cam.ac.uk) with your start and estimated completion dates, the region you work in, and any factors that might prolong your training.

Andrew Kelso is 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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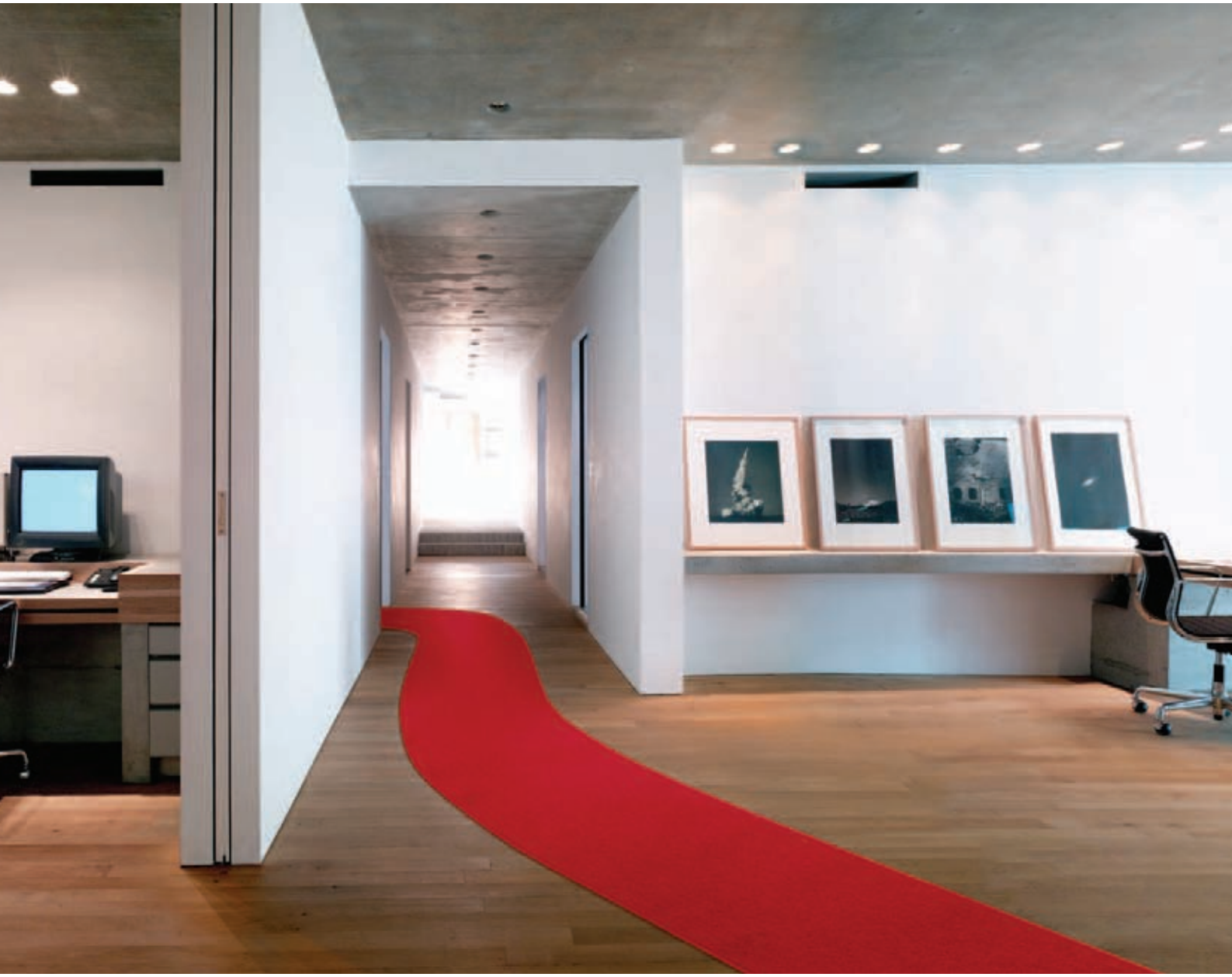

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Editorial board and contributors

Roger Barker is co-editor of ACNR, and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

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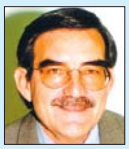
Professor Klaus Berek, Austria: Head of the Neurological Department of the KH Kufstein.



Professor Hermann Stefan, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nürnberg.

Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

Theory of Mind

Humans are, above all, intensely social creatures. We spend most of our time interacting with each other in groups and, through this group activity, we routinely achieve goals that could never be in the grasp of single individuals. These successful interactions depend upon a whole range of processes, collectively known as social cognition.[1] We share many of these processes with other social animals. The ability to recognise emotional expressions, the ability to keep track of the status of group members and of alliances within the group are important for successful social interactions because they help us to predict the behaviour of our fellows. However, there is one social process, Theory of Mind, that is highly developed in humans, but only found in the most rudimentary form in other animals.[2]

Terminology

We naturally explain people's behaviour on the basis of their minds: their knowledge, their beliefs and their desires. If for instance, John has taken his umbrella, but it is not actually raining, this does not present a conflict. We automatically assume that it is John's belief that it will rain – not whether it is actually raining – that determines whether he takes his umbrella. Understanding behaviour in this way is called having a 'Theory of Mind' (ToM), or 'an intentional stance.' The verb most frequently used to describe this ability is 'mentalising'. The concept was originally introduced into experimental psychology by Premack and Woodruff through their seminal paper: 'Does the Chimpanzee have a Theory of Mind?'.[3] This paper prompted the question whether young children have a ToM and in 1983 this was answered by means of a novel paradigm introduced to test children on their ability to attribute beliefs to others.[4] Shortly after, it was shown that autistic children have problems with such ToM tasks.[5] The terms mind-reading and mind-blindness are also often used as shorthand to refer to the effects of mentalising failure.

False Beliefs

The test which probes the child's ability to predict what a character will do on the basis of that character's own mental state, not the actual state of affairs, was as follows:[4]

Maxi eats half his chocolate bar and put the rest away in the kitchen cupboard. Then he goes away. Meanwhile Maxi's mother comes into the kitchen, opens the cupboard and sees the chocolate bar. She puts it in the fridge. When Maxi comes back into the kitchen, where will he look for his chocolate bar? The answer is 'in the cupboard, where he thinks it is'. This answer is obvious to most 5-year-olds, who can also explain exactly why Maxi now has a false belief. Autistic children, even of a higher mental age than five, were unable to reason like this and indicate that Maxi would look for his chocolate in the fridge, where it really is.

Cognitive mechanisms

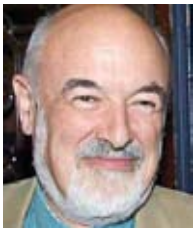
Only speculation is available at present. Perhaps our ability to mentalise depends upon the brain being able to decouple propositions from reality and set them in relation to an agent's attitude.[6] Perhaps the ability to mentalise is related to our capacity to mirror the actions and emotions of other people through the brain's mirror system.[7]

In children

The cognitive mechanism underlying the human ability to attribute mental states to self and others can be likened to a start-up kit that puts social learning on the fast track, so that even in their first year infants orient to information that is communicated to them by other people and pay preferential attention to other people's intentions. Thus, infants follow gaze, at first automatically, then deliberately and attract other people's attention by pointing and gazing themselves. In autism such a preference may not exist and social learning is very delayed. It has recently been shown that even 12-15 month old infants track social events by their gaze in a way that presupposes that they have implicit mentalising ability.[8] Long before they can talk, infants are surprised when, in the classic false belief scenario, Maxi looks in the wrong place (i.e. the fridge) for his chocolate.

In adults

Having a Theory of Mind routinely enables us to explain and predict what another person is going to do next, as in where will Maxi look. Our everyday speech is full of mental state attributions, such that we constantly seek psychological motives to our own and others' behaviour. ToM also enables us to monitor and manage our reputation and to manipulate other people's beliefs. Human communication is characterised by the pervasive importance of an attitude in which we cloak almost any message that we send or receive. Thus, intentionally conveyed information is hardly ever 'bare' information, but presented with the simultaneous use of persuasion, flattery, education, deception etc. In this sense human communication is



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Uta Frith, PhD is Emeritus Professor of Cognitive Development in the Institute of Cognitive Neuroscience at University College London and Research Foundation Professor at the Faculties of Humanities and Health Sciences, University of Aarhus. She identified the theory of mind problem associated with autism and is currently investigating the neural basis of social cognition.

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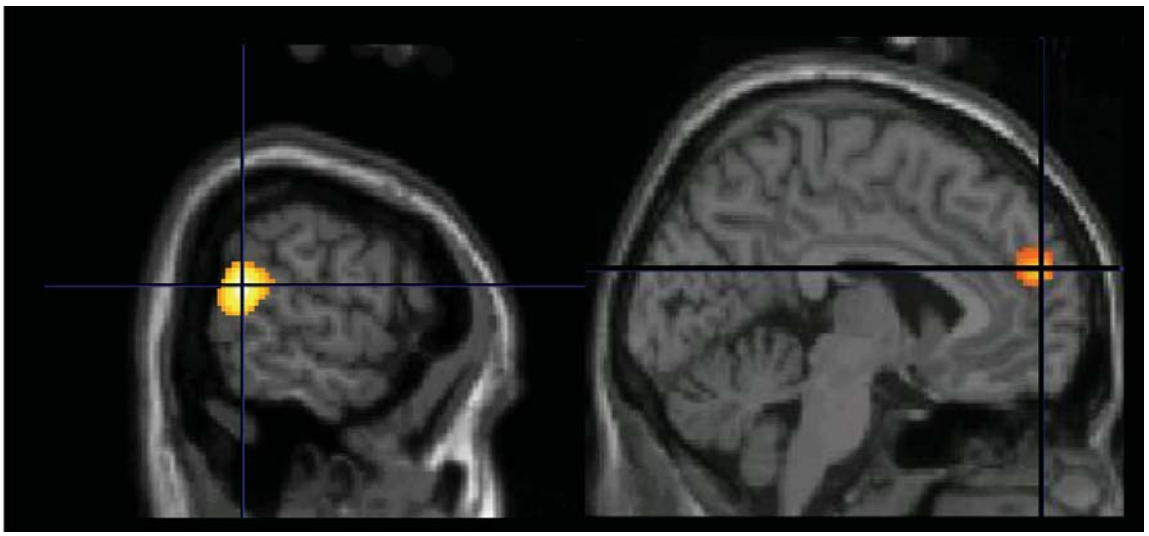

Two brain regions that are consistently activated during the performance of ToM tasks. Left panel: the temporo-pariental junction. Right panel: the paracingulate sulcus. Damage to these areas can cause impairments in the performance of ToM tasks.[12]

quite unlike information conveyed by machines. It has been claimed that ToM is a cornerstone of cultural evolution.[9] Thus, mind-reading plays a role in fostering co-operation and teaching. For instance, successful teaching seems to depend on the teacher's ability to monitor the learner's mental states, such as their prior beliefs and attitudes, as well as their increasing knowledge.

In autism

Autism is primarily characterised by an impairment in social communication. This is not a global social impairment. The failure lies specifically in an inability to take account of others' beliefs, desires and feelings. This is shown, for instance, in their poor understanding of deception, irony and reputation building, but good transmission of verbatim information. This inability could be due to an ultimately genetic fault in a basic neurophysiological mechanism. For nearly three decades researchers have investigated the apparent inability of autistic children to mentalise, and their slow and fragile acquisition of the concept of mental states. It has been argued that intuitive mentalising, as already shown by infants by their second year, is never attained in autism, but that explicit rule-based mentalising can be learned.[10]

In other disorders

Many brain-based disorders impair social and communication function. For example, some types of schizophrenia involve a disturbance of mentalising. Unlike autism, this disturbance seems to point to an overactive attribution of mental states, extending these to a wide variety of other agents, including physical objects which may be experienced as senders of significant messages.[11] Theory of Mind difficulties can also be acquired through brain damage in frontal cortex or in the region of the temporo-parietal junction (TPJ).[12] Patients with fronto-temporal dementia are also prone to suffer from an inability to mentalise.[13]

The brain's mentalising network

Evidence from neuro-imaging studies shows that mentalising, elicited by a wide variety of tasks, engages a circumscribed network of brain regions. When brain activity is measured during the performance of tasks engaging ToM, two regions have been consistently identified: a medial prefrontal region (paracingulate cortex) and the TPJ in the superior temporal sulcus.[14,15] The medial frontal region is also engaged when subjects reflect upon their own mental states as well as those of others, with the more inferior orbital region responding especially to emotional states. TPJ, on the other hand, seems to have a special role in using perceptual cues to recognise the actions and intentions of biological agents. Identification of the precise role of these regions awaits the development of a mechanistic account of our remarkable ability to make inferences about the minds of others.

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Immune Therapy in Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronically progressive or relapsing and remitting, symmetrical, sensory and motor polyradiculopathy. It typically causes weakness of proximal and distal limb muscles and sensory loss in a stocking-and-glove distribution. Cytoalbuminologic dissociation is a characteristic finding in the cerebrospinal fluid (CSF). The peripheral nerve shows evidence of demyelination and remyelination, particularly in relapsing and remitting cases. However, in the long-term, axonal loss tends to occur, leading to irreversible damage.

The pathophysiology of CIDP is thought to be due to an autoimmune process involving both antibodies and T lymphocytes. There are several lines of evidence for this: (a) sera and CSF of patients with CIDP show markers of T cell activation and migration, and (b) active lesions in nerve biopsies contain endoneural infiltrates of T lymphocytes and macrophages.[1] Several rabbit and rodent models of experimental autoimmune neuritis with CIDP-like features have been developed with immunisation of peripheral nerve components such as myelin,[2] although the exact antigens in human CIDP remain undiscovered.

In addition to the core clinical picture of the symmetrical sensory and motor syndrome, several other subgroups of CIDP have been described (Table 1).[1,3,4] Whether these variants need specific treatment is as yet largely unknown, with the exception of pure motor neuropathy and multifocal motor neuropathy where intravenous immunoglobulin (IVIG), but not corticosteroids, are effective.[3,4]

Table 1: Variants of CIDP

Classical symmetrical sensorimotor CIDP
Pure motor demyelinating neuropathy
Sensory ataxic neuropathy
Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis-Sumner syndrome
Distal acquired demyelinating symmetric neuropathy (DADS)
Subacute sensorimotor demyelinating neuropathy
Multifocal motor neuropathy (MMN)

This review will concentrate on the short- and long-term therapeutic options for CIDP, the most common of which is the classical symmetrical sensorimotor subtype. The primary goals for current treatments are to control symptoms, improve functional ability and maintain long-term remission. Recommendations on treatment options in this paper take into consideration recent consensus guidelines established by the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society.[5,6] A detailed discussion of the adverse events associated with each treatment is beyond the scope of this article, but we will provide an overview of common and serious adverse events for the main treatment options.

Corticosteroids

In an unblinded randomised controlled trial with 28 patients, prednisolone was superior to no treatment as it improved neurological disability at three months.[7] Long-term efficacy of corticosteroids in CIDP is more difficult to assess as treatment regimens often include combinations of treatment modalities such as IVIG, plasma exchange (PE) and other immunosuppressive agents. Patient series have reported that around 90% of patients were doing well two or more years after the initial treatment.[8,9]

Recommendations

Corticosteroids should be used first-line for short-term therapy as there is evidence of efficacy from a small randomised controlled trial (class II evidence). However, there is no clear evidence on whether prednisolone should be used daily or on alternate days, or whether intermittent high-dose intravenous regimens are better than oral regimens.[10] The long-term use of corticosteroids is associated with many adverse events, including cushingoid features, infections, hypertension, diabetes, osteoporosis, psychiatric disorders, insomnia and white blood cell count elevation. Therefore, the dose of corticosteroids is usually tapered down slowly to the lowest possible that allows sustained clinical improvement. In addition, other immunosuppressive and immunomodulatory treatments may be added to achieve the lowest maintenance dose.

Intravenous immunoglobulin

Meta-analysis of four double-blind, placebo-controlled, cross-over trials of intravenous immunoglobulin (IVIG) versus placebo with a total of 113 CIDP patients have shown significant improvement in disability lasting two to six weeks.[11-15] More recently, a randomised, double-blind, placebo-controlled, response-conditional crossover trial of IVIG in 117 patients with CIDP showed both significant short-term (first 24 weeks) and long-term (extension phase of 24 weeks) benefit of IVIG over placebo.[16]

A randomised, double-blind crossover trial of IVIG versus corticosteroids of 32 patients did not show any short-term difference in improvement of neurological disability at two weeks.[17]

Recommendations

There is evidence from relatively large randomised controlled trials (class I evidence) for the efficacy of IVIG as first-line therapy for both short- and long-term use. The usual initiating dose of IVIG is 2g/kg/course and treatment usually needs to be repeated at intervals of several weeks to maintain improvement. However, doses of IVIG may be individually titrated to the lowest possible level for maintenance without altering treatment frequency.[18] If frequent high-dose IVIG is needed, the addition of corticosteroids or another immunosuppressive/immunomodulatory agent should be considered. Common adverse events associated with IVIG such as headache, nausea, diarrhoea, flushing, fever, shortness of breath, hypertension and rashes are usually transitory and related to the initial infusion. IVIG is generally well tolerated and easy to administer except in cases of immunoglobulin A deficiency, renal failure, vascular disease and cardiac insufficiency. Serious adverse events include acute renal failure, thrombogenesis and anaphylactic shock.

Plasma exchange (PE)

Two randomised double-blind sham-controlled trials in a total of 47 patients showed that PE provided short-term benefit in approximately two-thirds of patients.[19,20,21] However, a randomised crossover study that compared PE to IVIG demonstrated that they were equally effective in CIDP.[22]

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Recommendations
There is good randomised controlled trial evidence for the efficacy of PE as first-line short-term therapy in CIDP (class I evidence). Common and relatively minor adverse events include nausea, fever, urticaria, mild hypotension and hypocalcaemia. However, the difficulties associated with the use of PE, such as poor venous access and haemodynamic instability, make this a less attractive option than either corticosteroids or IVIG, especially in the long-term. Therefore, corticosteroids or another immunosuppressive / immunomodulatory agent should be started in conjunction with PE for maintenance therapy.

Interferons

Two small open labelled studies in CIDP, one of interferon-α 2a in 16 patients for six weeks,[23] and the other of interferon-β1a in 20 patients for six months,[24] revealed benefit in 56% and 85% of cases respectively. However, the only randomised double-blind placebo-controlled crossover trial of interferon-β1a for 12 weeks in 10 CIDP patients failed to detect any significant benefit.[25]

Recommendations
The very small number of patients in the only randomised controlled trial of interferon in CIDP makes the interpretation of the data very difficult. At best, there is class II evidence that interferons are not effective for short-term use in CIDP. However, interferons should be considered for short- or long-term use when the response to corticosteroids, IVIG or PE is inadequate. Common adverse events include fatigue, flu-like reaction, injection site reaction, headache, nausea, diarrhoea and depression. More serious adverse events include tremor and asthenia.

Other immunosuppressive and immunomodulatory drugs

A randomised parallel group open trial of azathioprine plus prednisolone versus prednisolone monotherapy with 27 patients for nine months showed no significant difference in disability scores.[26] There are no other published randomised controlled trials of other immunosuppressive drugs in CIDP, although results of a recently completed randomised placebo-controlled trial of methotrexate in CIDP is expected soon.[27]

There are several small case series or reports of the use of methotrexate, ciclosporin, cyclophosphamide, mycophenolate mofetil, etarnacept and rituximab in CIDP.[28] More recently, alemtuzumab has also been reported to be effective in CIDP.[29]

Recommendations
A relatively small trial has not demonstrated efficacy of azathioprine in CIDP (class II evidence). However, as azathioprine is generally well tolerated, it should be considered as a long-term immunosuppressant in CIDP when the response to corticosteroids, IVIG or PE is inadequate, as it can take several months for the drug to be effective. Common adverse events of azathioprine include hepatotoxicity, nausea, vomiting, rash, cytopenia and pancreatitis. In the long-term, malignancy is a potential complication, although the absolute risk is difficult to evaluate because it is hard to separate the effects of the drug from age-related increases in the background incidence of cancer.

More data from proper randomised controlled trials are needed for the other drugs which currently have class IV evidence before recommendations can be made on their use in CIDP.

Table 2: Use of main immunosuppressant/immunomodulatory treatments in CIDP

Drug	*Evidence class*[a]	*Recommendation*
Corticosteroids	*Class II*	*First-line therapy, best for short-term use*
Intravenous immunoglobulin	*Class I*	*First-line therapy for short- and long-term use*
Plasma exchange	*Class I*	*First-line therapy, best for short-term use*
Interferons	*Class II*	*To be considered for short- or long-term use in patients with inadequate response to corticosteroids, IVIG or PE*
Azathioprine	*Class II*	*To be considered for long-term use in patients with inadequate response to corticosteroids, IVIG or PE*
Methotrexate, ciclosporin, cyclophosphamide, mycophenolate mofetil, etarnacept, rituximab, alemtuzumab	*Class IV*	*More data needed before any recommendations can be made*

[a] *Evidence: Class I, controlled randomised trials available; class II, controlled trial without randomisation or randomised trial with small patient number; class III, uncontrolled trials; class IV, case series.*

Conclusions

There are huge gaps in our knowledge of immune therapy in CIDP. While there is reasonably good evidence for the short-term treatment of CIDP, long-term management is more difficult as a large amount of the evidence that we use in determining the choice of immunosuppressant or immunomodulatory treatment comes from clinical experience, observational studies and expert opinion (see Table 2 for a summary of recommendations). Treatment regimens among physicians from different parts of the world differ. The main reason for this is each physician's experience and familiarity with a particular treatment regimen. In addition, patients with different personal circumstances (e.g. pregnancy), disease subtypes and treatment responses warrant individualisation of treatment regimens.

There are many challenges to carrying out treatment trials in CIDP. One of the main problems is the number of different disease subtypes that exist. Indeed, most trials do not provide a breakdown of the subtypes of patients in a particular study. In addition, it can be difficult to design an immunosuppressant or immunomodulatory treatment trial in CIDP. Some treatments may take several months to be effective, making it expensive to conduct the studies and difficult to predict when these treatments reach their maximum effectiveness. Different study designs and the lack of long-term head-to-head treatment studies make it difficult to quantify the relative efficacies of different treatments in the condition.

It is important that in the future, better designed randomised controlled trials, especially for long-term treatments, be performed to inform us on best practice in CIDP.

Competing interests
Dr B Lecky and Dr S Sathasivam were involved in the recently completed randomised placebo-controlled trial of methotrexate in CIDP, which is yet to be published.[27]

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The primary goals for current treatments are to control symptoms, improve functional ability and maintain long-term remission

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Muscle Diseases in India

A wide spectrum of myopathies is routinely encountered in India. The clinical load of these patients is shared to a large extent by paediatricians and physicians and a proportion of these patients are then referred to the neurologists for further evaluation. This is not surprising as the number of neurologists servicing the large population of India is only just over a thousand.[1] Lack of availability of large scale laboratory facilities, especially in the fields of immunocytochemistry and genetic testing limits the molecular analysis of those myopathies seen in India and hence the available data may not be representative of the true situation. Also most of the prevalence data are based on hospital series and are not population based.

Muscular dystrophies

The most common muscular dystrophies are Duchenne muscular dystrophy (DMD) and limb girdle muscular dystrophy (LGMD). Of the 1950 patients studied by Das,[2] 27.4% were muscular dystrophies with 30% having DMD and 29.2% LGMD subtypes. In a tertiary neuromuscular center in Mumbai, DMD formed the main myopathy of childhood while limb girdle dystrophy was the most common diagnosis of adolescent and adulthood myopathies.

Duchenne Muscular Dystrophy: This is by far the most common muscular dystrophy. Though no ethnic variations have been observed, one hospital based study suggested a higher prevalence among certain Hindu communities.[3] The phenotype of DMD has been studied in detail by a number of investigators. The differential muscle wasting and hypertrophy giving the 'Valley sign' as described by Pradhan[4] can aid the diagnosis of DMD/BMD patients in cases without calf hypertrophy or late presentation. Due to the prevalent religious concepts and illiteracy, more than one case of dystrophinopathy in a family is not too uncommon in India. In general, familial cases with DMD seem to follow similar clinical courses but on occasions, striking intra-familial phenotypic variability has been see (Figure 1). For example, one family has been described in which three brothers were suffering from a dystrophinopathy; one with a DMD phenotype, the second with a BMD phenotype and the third cousin had only cramp-myalgia syndrome.[5]

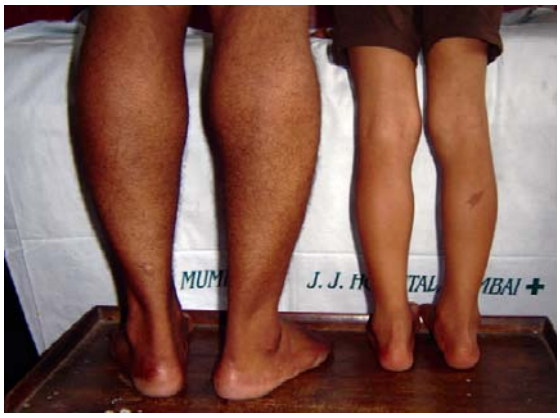

Figure 1: Index case with DMD and maternal uncle with BMD phenotype: Both had the same in frame mutation in exon 45-48.

Gene studies In dystrophinopathy: Multiplex PCR has been used to study the dystrophin gene in many centres in India and information is available from large centres in the north, west and south of the country. The deletion rates have been consistently around 70%[5-8], with the deletions being seen in the central and proximal hot spots of the dystrophin gene. In one study, the proximal deletions were essentially seen in the familial cases and sporadic patients tended to have deletions in the central hot spot.[5] An interesting phenomenon of double deletions has also been noted. These patients have two non-continguous hot spot deletions in the dystrophin gene. The significance is not clear as there are only few reports in the world literature.[5] Becker muscular dystrophy has been genetically analysed and the frame shift hypothesis seems to hold true in the majority of patients.

Rehabilitation: Due to a lack of awareness of muscle diseases, parents of affected children often do not know where to seek help. Illiteracy is also an issue which makes counselling difficult. The social structure in India is also not kind to the physically challenged with no availability of ramps for public modes of transport. Home rehabilitation programs,[9] designed for those patients who cannot come for regular visits, has proved to be more successful than clinic based programs, in Mumbai and other centers.

DMD-look-a-likes (Phenocopies): Information on the myopathies presenting in early life with a DMD phenotype is scarce. Case reports of a severe childhood autosomal recessive muscular dystrophy [SCARMD] phenotype with immunohistochemical characterisation are available.[10] A series of adhalinopathy children has also been reported from the south of India. An unusual family with severe autosomal recessive muscular dystrophy with mental retardation and chorea has been documented as well.[10]

Limb Girdle Muscular Dystrophy. LGMD is the most common muscle disease seen in the adult population. Sarcoglycanopathies and dysferlinopathies have been characterised.

Sarcoglycanopathies: The age at onset and tempo of the disease show a lot of variation. Proximal pelvic girdle involvement with later involvement of the shoulder girdle appears to be the most common phenotype. Due to severe involvement of the hip adductors and relative sparing of the hip abductors, the hip abduction sign has been observed.[11] Three series have been reported on this condition, with multiple sarcoglycan deficiencies most often being seen on the immunocytochemical studies.[11,12,13] In northern India, gamma sarcoglycan deficiency has been found to be more common.

Genetics of sarcoglycanopathies: There is as yet very little information available on the genetic aspects of sarcoglycanopathies. In a study from Mumbai, 16 patients were found to have abnormalities in the sarcoglycan genes. In this small study, the most common abnormalities were encountered in the gamma sarcoglycan gene, followed by alpha, delta and a single instance of a beta sarcoglycan gene defect. A noteworthy point was the prevalence of the 525delT deletion mutation amongst those with the gamma SGP abnormality. This mutation is seen in select Mediterranean populations and its appearance in Western India is curious. It may relate to the pattern of human migration or may simply reflect a hot spot region in the gene.

Dysferlinopathy: Data on dysferlinopathy is lacking with only one series of 14 patients having been reported.[14] Nine patients had a distal presentation with calf atrophy. 'Calf head on a trophy', an appearance resulting from focal

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The wide spectrum of myopathies seen in India is expected to be genetically characterised further in the coming years. Efforts need to be intensified for better rehbilitation of these chronic myopathies

muscle wasting[15] and the diamond sign[16] were described in those with dysferlinopathies by Pradhan, emphasising the focal and patchy wasting of various muscles. Large scale genetic data is not available and case reports have shown a variety of genetic abnormalities within the dysferlin gene.

Other muscular dystrophies: Facioscapulohumeral dystrophy (FSHD) is not uncommon but published data is scarce. In a series of 211 cases of muscular dystrophy, Srinivas[17] saw only five (2.3%) patients with FSHD and Das2 in only 8 (1.3%).The differential wasting in certain muscles with relatively preserved bulk or mild hypertrophy of the muscles around the shoulder girdle describes the 'poly hill sign' of Pradhan.[18] Myotonic dystrophy is less common in India. Gourie Devi[19] found myotonic dystrophies to form only 8% of all muscular dystrophies. Basu et al has studied the CTG repeats in these patients with myotonic dystrophy and found similarity in the molecular anatomy of 90% of the Indian patients with Caucasians. In the remaining 10%, the expansion of the CTG repeat was of a new haplotype suggesting a unique founder effect probably indigenous to the Indian population.[20]

Congenital myopathies: In a study from Bangalore, 100 cases of congenital myopathies (CM) were diagnosed over a period of 20 years and the spectrum of CM consisted of centronuclear myopathy (39), congenital fiber type disproportion (35), central core disease (9), multicore disease (7), myotubular myopathy (5), nemaline myopathy (4) and one case of congenital myopathy with tubular aggregates. In a north Indian study, 4 nemaline myopathy cases out of 15 were identified.[21]

Mitochondrial myopathy: Case series of mitochondrial myopathies have been published. In a large study from Hyderabad,[22] the most common clinical syndrome associated with ragged red fibres (RRFs) on muscle biopsy was progressive external ophthalmoplegia with or without other signs. Kearns-Sayre syndrome and myoclonic epilepsy with RRFs was seen less often.

Osteomalacic myopathy: Though it is less common at present in India, Irani[23] reported 15 female patients of whom eight had constantly worn the burkha when outdoors. Notably these patients were multiparous with prolonged periods of lactation. The striking features were bone pains and pelvic limb girdle weakness.

Inflammatory myopathies: All types of inflammatory myopathies are encountered,[24,25,26] although of interest is that inclusion body myositis is rare. Gayathri[27] reported five patients (four sporadic and one hereditary), and all had progressive muscle weakness with spared cranial nerve innervated muscles.

Conclusion

Thus a wide variety of myopathies are encountered in India and as the diagnostic facilities become more easily available, further useful information will come to light.

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With this paper, the series 'Neurology In India' comes to an end. In this six part series, we have dealt with major areas of neurological interest, which constitute the mainstay of work for the practicing Indian Neurologists. As can be appreciated from the papers, at one end, sub specialty work is catching on. Increasing numbers of neurologists are willing to spend time in their areas of interest. This trend has as yet not percolated to the research laboratories and clinical observations need support from collaborative work; often outside the country. On the other hand, the number of clinical neurologists in India is clearly inadequate to service the large population and hence only a small proportion of neurology patients reach the neurologists. In the next few years, we hope for and expect a significant rise in the neurology work force to study and service patients with neurological disorders encountered in this vast country.

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Greater Occipital Nerve Block: A Diagnostic Test?

Often a neurosurgeon or orthopedic surgeon requests a diagnostic nerve block to determine, prior to attempting any surgical procedure, whether a specific cervical nerve root is the generator of the patient's symptoms.[1]

This statement from a contemporary textbook reflects the commonly held view that in pain management nerve blocks are diagnostic.

There is wide variability of headache syndromes treated by greater occipital nerve (GON) blockade.[1] The putative mechanisms by which they might relate to the GON are unclear. It seems a priori improbable that such diverse conditions as migraine (with its complex cerebral and brainstem mechanisms), cluster headache, occipital neuralgia, cervicogenic headache, whiplash syndrome,[2] and various tension type headaches, should either share a common aetiological mechanism or be responsive to the same treatment of a peripheral nerve.

Anatomy

The GON is composed of the medial fibres from the dorsal ramus of the second cervical nerve. The ventral ramus of C2 also contributes to the lesser occipital nerve and innervates deeper structures (periosteum of the occiput, vertebrae, etc.). In rats, a population of neurones of the dorsal horn at C2 shows convergent input from both dura and cervical skin and muscle territories, suggesting a functional continuum between the trigeminal nucleus caudalis and upper cervical segments involved in cranial nociception. GON stimulation in rats facilitates dural stimulation, implying a central mechanism at the second order neurone.[3] C2/C3 blockade is claimed to produce benefit of comparable order to GON blockade and both are said to be effective in the diagnosis and treatment of cervicogenic headache.[4]

The literature fails to incriminate specific anatomical structures as the source of cervicogenic pains. Very similar diagnoses invoke structures such as nerve roots, individual peripheral nerves, bony structures, and the non-specific cervicogenic pain/headache. For example:

"*Diagnostic anesthetic blockade for the evaluation of cervicogenic headache can be directed to several anatomic structures such as the greater occipital nerve (dorsal ramus C2), lesser occipital nerve, atlanto-occipital joint, atlantoaxial joint, C2 or C3 spinal nerve, third occipital nerve (dorsal ramus C3), zygapophyseal joint(s) or intervertebral discs based on the clinical characteristics of the pain and findings of the physical examination.*"[5]

The authors state fluoroscopic or interventional MRI-guided blockade may be necessary, to assure specific localisation of the pain source; yet they fail to present evidence that such measures do inculpate the actual source of pain. The opposing view (which I share) is that of Silverman:

"*there are no diagnostic imaging techniques of the cervical spine and associated structures that can determine the exact source of pain.*"[6]

Are nerve blocks diagnostic?

Neural blocks may be useful as an empirical way of treating diverse head and neck pains, but such a response is also often used as the criterion for diagnosis.[7,8] But such diagnoses, though clinically useful, are inexact and the procedure may be valid (if proven by properly designed trials) only as an empirical mode of controlling pain.

Blondi rightly notes that "*Occipital nerve blockade, … often results in a nonspecific regional blockade rather than a specific nerve blockade and might result in a misidentification of the occipital nerve as the source of pain.*" And he says: "*occipital neuralgia is believed to arise from trauma to or entrapment of the occipital nerve within the neck or scalp, but the pain may also arise from the C2 spinal root, C1–2, or C2–3 zygapophyseal joints or pathologic change within the posterior cranial fossa.*" If its source is the nerve roots, how can it be rationally considered to be a neuralgia of the occipital nerve?

Despite many published studies, the diagnostic utility of employing greater occipital nerve (GON) blockade in a variety of headaches and neck strains is unproven. Many trials contain small numbers. The physician administering the injection in many trials is not blinded to the treatment. Follow-up assessment is commonly at about four weeks, too brief a period may have detected significant differences in outcome. The local anaesthetic or steroid used, and the doses vary and are commonly chosen empirically. Controls are often omitted or poorly matched. And, interpretation is confounded by subjective criteria of pain relief and marked variation of techniques. There are therefore, several unresolved issues concerning both rationale, claimed benefits, and techniques.

Ashkenazi and co-workers report, "*The rationale of GON blockade for the treatment of headache is based on the anatomical connections between trigeminal and upper cervical sensory fibres at the level of the trigeminal nucleus caudalis.*"[9,10] But is this alone a diagnostic foundation or a mechanism sufficient to explain such diverse head pains?

The methodologies of some of the studies are limited by lack of a standardised treatment protocol or by a retrospective design. In migraine, for example, improvement has been reported after GON blockade, but also after prophylactic drugs, and injected botulinum A toxin.[11] There are claimed to be four major 'trigger points' along the course of several peripheral nerves that may cause migraine headaches, which are therefore also treated by injection.[12] Among the peripheral nerves the greater occipital nerve has become a favourite target of needle wielders.

Structures said to be involved in the pathogenesis of occipital headache include the aponeurotic attachments of the trapezius and semispinalis capitis muscles to the occipital bone, and entrapment of the GON within these aponeuroses, causing symptoms of 'occipital neuralgia'.[13] Whereas cervicogenic headache is a useful clin-

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In respect of diagnosis, the current evidence appraised suggests that the use of nerve blocks as the defining or pathogenetic criterion is both unsound and unreliable

Table 1: Variation of anatomical sites for greater occipital nerve.

Study	Vertical location of GON (cm)	Lateral location of GON (cm)
1. Mosser et al.	3cm below EOP	1.5cm from midline
2. Loukas et al.	2cm below EOP	2cm from EOP
3. Natsis et al.	The site where the semispinalis capitis is pierced by the GON	
4. Bovim et al.	no anatomical landmark given for injection	
5. Becser et al.	Along intermastoid line	0.5 to 2.8cm from midline
6. Tubbs et al.	2cm above intermastoid line	4cm lateral to EOP

EOP = external occipital protuberance.

ical description,[14] it is not a diagnosis that accurately inculpates the pathogenic structures involved, nor the mechanism of pain. The International Headache Society (IHS) proposed diagnostic criteria[15] for cervicogenic headache (11.2.1) are:

1. Pain referred from a source in the neck and perceived in one or more regions of the head and/or face.
2. Clinical, laboratory and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be, or generally accepted as, a valid cause of headache.
3. Evidence that the pain can be attributed to the neck disorder or lesion, based on either clinical signs that implicate a source of pain in the neck or abolition of headache following diagnostic nerve block.
4. Pain resolving within three months after successful treatment of causative disorder or lesion.

Interestingly, cervical spondylosis is NOT accepted as a valid cause. Taken in turn, these criteria don't confront these fundamental issues.

1. There is no hard evidence, only imprecise inference that the pain can be attributed to the neck disorder or lesion.
2. Disorders within the cervical spine or soft tissues of the neck, known to be, or generally accepted as, a valid cause of headache is an all-embracing and unproven generalisation that does not indicate the primary pathology.
3. Since there are no conclusive clinical signs that prove a source of pain in the neck, this is spurious; and, abolition of headache following nerve block is only suggestive, not diagnostic. Clinical signs or pain relief after nerve blocks do not constitute attributable proof of causation.
4. Pain resolving within three months after successful treatment of causative disorder or lesion, illogically and falsely assumes that response to treatment is proof of causation. Few trials extend to three months or beyond.

A further difficulty is that the techniques employed and for which success is claimed differ from one series to another.

Anatomical variability

An important but neglected factor is the anatomical variability (Table 1) of the greater occipital nerve.[16]

1. Mosser et al. dissected 20 cadaver heads to trace the normal course of the greater occipital nerve from the semispinalis muscle penetration to the superior nuchal line. Standardised measurements were performed on 14 specimens to determine the location of the emergence of the nerve using the midline and occipital protuberance as landmarks. The location of emergence was determined to be at a point centered approximately 3cm below the occipital protuberance and 1.5cm lateral to the midline.[12]
2. Loukas et al.[13] examined the course and distribution of GON and its relation to the aponeuroses of the trapezius and semispinalis capitis in 100 formalin-fixed adult cadavers. The greater occipital nerve was located at a mean distance of 3.8cm (range 1.5-7.5cm) lateral to a vertical line through the external occipital protuberance and the spinous processes of the cervical vertebrae. It was also located approximately 41% of the distance along the intermastoid line (medial to a mastoid process) and 22% of the distance between the external occipital protuberance and the mastoid process. The location of GON for anaesthesia or any other neurosurgical procedure has been established as one thumb's breadth lateral to the external occipital protuberance (2cm laterally) and approximately at the base of the thumb nail (2cm inferior)[13] This was the first study proposing landmarks in relation to anthropometric measurements.
3. Natsis and colleagues reported the course and the diameter of the GON in 40 cadavers.[17] In three cases, the GON split into two branches before piercing the trapezius muscle aponeurosis (TMA) and reunited after having passed the TMA, and it pierced the obliquus capitis inferior muscle in another three cases. The GON and the lesser occipital nerve reunited at the level of the occiput in 80% of the specimens. The nerve became wider towards the periphery. This may be relevant to entrapment of the nerve. In three cases, the GON split into two branches before piercing the TMA. Anaesthetic blockade of the GON for diagnosis and therapy was best aimed at the site where the semispinalis capitis is pierced by the GON.
4. An autopsy study by Bovim et al. on 20 cases without known headaches showed a marked variation in the relation between the GON and nuchal muscles.[16] The trapezius muscle was penetrated by the GON in 45% of cases, the semispinalis muscle of the head was penetrated in 90% of cases, and the inferior oblique muscle of head in 7.5% of cases. Macroscopic findings of possible compression were made in 11 cases (27.5%), *"indicating that nerve compression per se may be of minor importance since it seems to exist in the absence of headache."*
5. Becser, Bovim and Sjaastad reported topography shown by dissection and careful measurements of 10 embalmed cadavers.[18] A great variability in nerve topography was seen interindividually and intraindividually. The greater occipital nerve ascended between 5mm and 28mm from the midline along the intermastoid line. The minor occipital nerve was found between 32mm and 90mm from the midline along the same landmark. In most cases, both the GON and the minor occipital nerve pierced the aponeurosis after branching. Thirteen GONs and eight minor occipital nerves also were embedded in this tissue. Twelve of the 20 GONs formed a rich network around the occipital artery. Importantly they commented: *"anatomic structures with an imminent risk of causing entrapment were not observed. … results suggest that optimal locations for blockade techniques should be reconsidered."*
6. Tubbs and colleagues noted the surprising lack of surgical landmarks in the literature for avoiding the cutaneous nerves in this region. The GON was found to lie at a mean distance of 4cm lateral to the EOP. On all but three sides, a small medial branch was found that ran medially from the GON to the 3rd occipital nerve approximately 1cm superior to a horizontal line drawn through the EOP. The GON was found to pierce the semispinalis capitis muscle on average 2cm above the intermastoid line, and to divide into medial and lateral branches 0.5cm superior to the EOP.[19] This fits with the observation that it may be technically difficult to block the greater occipital nerve without also blocking the third occipital nerve and some of the fibres of the semispinalis…[20]

These considerable differences in proposed landmarks for the GON are reflected in the diversity of proposed and tried treatment sites. Cervical epidural steroid injections are used in patients with spondylosis,[21] but are largely ineffective.[22] Greater and lesser occipital nerve blockade may provide temporary, but substantial, pain relief in some cases of similar efficacy to blockade of the C2 and C3 nerves.[23] Blockade, neurolysis, nerve resection, rhizotomy, and decompressive techniques have all been employed, each with claims of success. Bogduk's team reported[24] the efficacy of percutaneous radiofrequency medial branch neurotomy in the treatment of chronic neck pain in 71% of patients, but the precise nature and anatomical basis of the symptoms are not thereby clarified. What is the basis in the unrelieved substantial 29%?

Lieppman (1980) described[25] 164 patients

with comparable symptoms in whom he diagnosed 'occipital neuralgia' and found a high cure rate after occipital subcutaneous injections of lidocaine; however, he also found a 50% cure rate in patients given occipital subcutaneous injections of saline. A significant contributory placebo effect is probable, as in all pain syndromes.

Discussion

Thus, there are problems in accepting GON and related neural sites subjected to blockades as a rational as opposed to empirical method:

1. Anatomical structures threatening neural entrapment are seldom observed.[16]
2. Nerve compression per se may be of minor importance since it can exist in the absence of headache.[16]
3. There are many and considerable anatomical variations in the nerve so that consistent surgical landmarks in this region are surprisingly lacking,[12,13,16-18] and the injected substance may not have affected the GON.
4. Clinical techniques of localising the nerve are variable and imprecise.[18,19] Tenderness and evoked pain on palpation are notoriously unreliable.

An apparent response to neural blockade is often used as one of several criteria for the diagnosis of cervicogenic and other headaches.[26,27] but such a diagnosis, though of arguable clinical value, is itself inexact and justifies the procedure only as an empirical mode of controlling pain. As Pollman and colleagues commented, "*cervicogenic headache should therefore be understood as a homogeneous but also unspecific pattern of reaction.*"[28] The placebo effect[29] of injections is often underestimated or neglected. To the scientist, a major problem is that placebos influence patient outcomes after any treatment, including surgery. The well-known extent of placebo effects in acute head pains was illustrated in Harden and coworkers' trial which concluded:

This profound reduction observed after administration of a placebo prevented accurate evaluation of the effects of [ketorolac]. The placebo response must be considered in the design of future trials using intramuscular medications in the acute intervention of headache crises. In addition, the use of a standard analgesic is necessary to demonstrate both assay sensitivity and magnitude of response to placebo.[30]

Placebo effects and spontaneous remissions can cause apparently good results that are falsely attributed to the efficacy of any treatment claims.[31] As one example, Peres et al. treated 14 cluster headache patients with greater occipital nerve block. Four patients (28.5%) had a good response, five (35.7%) a moderate, and five (35.7%) no response. The authors concluded GON blockade is a therapeutic option for the transitional treatment of cluster headache,[32] yet their results are entirely consistent with a placebo effect. It is suggested that the placebo response may contribute significantly to the apparent successes of nerve blocks, but does not necessarily account for the relief of pain in all cases. Placebo effect does not imply psychogenesis, but is a genuine, validated phenomenon, which may be organically founded in regionally specific changes in brain function; for example, dorsal-cortical increases and limbic-paralimbic decreases in glucose metabolism demonstrated in a trial of antidepressant vs placebo.[33]

Conclusion

The lack of specificity of greater occipital or other peripheral nerve, and cervical root blockade in the treatment of diverse headaches, (including migraine, cluster headache, cervicogenic and occipital pains), though achieving variable empirical therapeutic success, is a continuing cause of diagnostic confusion and wooly thinking. Although various structures in the neck probably contribute to several patterns of headaches and neck pains, they have not to-date been adequately defined. More rigorous studies are needed to identify the several anatomical structure and the physiological mechanisms that underlie these ill-defined symptoms. In respect of treatment, these considerations agree with the conclusions of Bogduk[34] that "*The available evidence from the small number of case series and retrospective studies published in the peer-reviewed literature is insufficient to conclude that either local injection therapy or surgery is an effective treatment for occipital neuralgia or cervicogenic headache.*"

In respect of diagnosis, the current evidence appraised suggests that the use of nerve blocks as the defining or pathogenetic criterion is both unsound and unreliable.

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Wheelchairs and Special Seating for Neurological Conditions

Since 1932 when Everest and Jennings built the first lightweight folding wheelchair (US patent no. 2095411), there has been a huge increase in the options available for wheelchair users. The range of existing wheelchair designs, features and accessories can be bewildering to patients and clinicians. The aim of this article is to detail the general types of wheelchairs available in the UK and a number of their important features. We believe that this will be useful to any clinician interested in maximising independence for a disabled patient, or perhaps dealing with clinical problems related to wheelchair or special seating use.

Manual wheelchairs

A self-propelled manual wheelchair can allow great flexibility to a wheelchair user with sufficient upper body stability and arm dexterity and strength (Figure 1). They are generally lighter, less bulky and more manoeuvrable than a powered chair. They are not limited by the need for recharging and with quick release wheels and swingaway footrests they can be transported in a car, train or aeroplane. They are also cheaper to buy and maintain than a powered chair. However self-propelling in a manual chair requires significant energy[1] and upper body strength and can be a cause of shoulder pain and injury. Only a small proportion of wheelchair users can self propel outdoors, where even small changes of incline, camber and surface, imperceptible to pedestrians, may obstruct people in manual chairs.

A manual wheelchair can be rigid or folding; the folding version obviously taking up less space in the home or vehicle when it is not being used. A folding chair is also more flexible and may be more stable over rough terrain, but flexibility increases the amount of energy required for propulsion. The simpler design of a rigid chair allows it to be lighter and stronger, which may offer the user more energy efficiency and allow the user to participate in sports activities (Figure 2).

For the user of a self-propelling wheelchair to push comfortably and efficiently, the chair must have the correct seat height and wheel diameter (Figure 3). For example, starting a push with the elbows extended will lose power and efficiency of propulsion, or if the user has to start a push with raised shoulders and flexed elbows, this is also inefficient and may unnecessarily strain muscles. The minimum seat height is that which allows the feet to sit comfortably on the footrests, when the footrests are positioned clear of the ground, castors and door thresholds. The seat angle can be customised on a rigid chair according to the user's preference – a seat angled backwards will bring the user's arms closer to the wheel rims. Once the seat position is correct, then wheel diameter should be chosen to allow the user to push in a comfortable manner.

Another customisable feature of a manual chair is the placement and angle of the wheels. The wheel axle constitutes the point of pivot of the chair which supports the user's weight and this can be moved forward or backward in relation to the seat in most modern chairs. If this is moved forwards, the centre of balance of the chair moves behind the axle and the chair will tip backwards more easily, lifting the front castors off the ground. This may be advantageous to an experienced user negotiating a step or kerb, but even a less experienced user should be able to tip the wheelchair back a little to negotiate rougher terrain, and it makes it easier to turn from side to side. Cambered wheels give greater lateral stability and may help a sportsperson to turn quickly or lean out of the chair, but for the casual user, they may present difficulty in getting through doors due to the increased width of the chair.

The handrims of a manual chair should also be of a suitable diameter[2] – a wider rim allows easier pushing but less speed. They should be easy to hold – grips can be added if a user lacks grasp strength – but should be smooth enough not to injure the hands on braking. Rims wear more quickly than other parts of a chair as they often strike doorways and are under constant friction and it is important that they are maintained to prevent hand injury. Many users also wear fingerless gloves to avoid friction burns. It is important also to ensure that the chair's user can work the handbrakes to allow safe transfers.

Powered wheelchairs

A powered wheelchair may be more suited to a person with significant trunk and upper limb impairments (Figure 4). For easily fatigued patients, powered mobility can help to preserve energy for other activities. A powered wheelchair also leaves a hand free to carry or perform other tasks; however they are limited by battery life and need more maintenance than a manual wheelchair.

There are many options available to the powered wheelchair user. For instance, front wheel drive will provide a better turning circle and may be better when moving onto an uneven surface. Rear wheel drive may feel more stable, but may cause the wheelchair to tip if going steeply uphill. Centre drive, 6 wheel, chairs combine many of the benefits of both. Larger wheels may make it easier to travel over rougher terrain, although may increase the wheelchair's width, and will carry more mud into the house.

Most powered wheelchairs are controlled by a joystick which should be within easy reach of the user's least impaired hand without compromising posture. For people unable to manage hand controls, the wheelchair may be driven using chin, head or breath controls. An ataxic user may prefer less sensitive controls, which may not register some unintended movements. The controls take time

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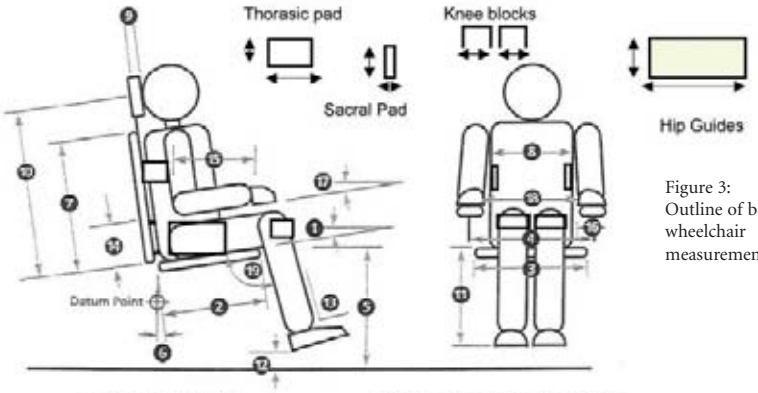
Figure 1: Basic manual folding wheelchair.

Figure 2: Rigid manual wheelchair suitable for sports.



1 Seat plane angle
2 Effective seat depth
3 Seat width
4 Effective seat width
5 Seat surface height at front end
6 Backrest angle
7 Backrest height
8 Backrest width
9 Headrest in front of backrest
10 Headrest height above seat
11 Footrest to seat
12 Footrest clearance
13 Footrest to leg angle
14 Armrest height
15 Armrest length
16 Armrest width
17 Armrest angle
18 Distance between armrests
19 Leg to seat surface angle

Figure 3: Outline of basic wheelchair measurements.

Figure 4: Powered wheelchair with joystick for right-hand control.

Figure 6: Individually moulded seat insert ready to fit onto wheelchair chassis.

Figure 5: Adjustable modular seating system.

Figure 7: Gyroscopically-controlled standing wheelchair.

and practice for a user to perfect and should be reviewed in conjunction with a knowledgeable wheelchair engineer.

Cushions

The purpose of a cushion is to allow the wheelchair user to travel in comfort and safety, with good pressure distribution and postural support.[3] It is vital that the cushion does not allow pressure areas to develop, especially if the user has muscle atrophy, sensory loss or tends to slide on the cushion. A good cushion should support spinal alignment, and if a spinal deformity is present, should prevent worsening of the deformity. The size of the cushion will influence other factors including seat height and footrest position.

There are four main types of cushion. Foam cushions can adapt their shape to spread pressure across the surface and can be layered to provide different degrees of softness and memory in different places. Foam cushions are relatively cheap and easily modified, but tend to wear quickly and need to be replaced frequently to prevent pressure on the skin.

Gel cushions spread and mould to pressure placed upon them and therefore provide excellent pressure distribution. It is also possible to provide moulded gel inserts, for example to keep adducted knees apart. They are however much heavier than foam cushions and less able to absorb impact as they are already moulded to the user's shape.

An air cushion sits the user on rows of connected rubber balloons. Air is distributed between neighbouring balloons and pressure is evenly balanced. They are therefore superior to gel and foam cushions at relieving pressure.[4] They are better at absorbing impacts but are very dependant on the user or carer to ensure they are correctly inflated. Some air cushions may even allow the user to inflate different areas of the cushion to different pressures which may be useful when managing a pressure sore. They are fairly robust but can leak or puncture and require frequent maintenance to be effective.

Urethane honeycomb cushions consist of a network of cells which together absorb and distribute pressure. The easy airflow keeps skin cool and dry which can protect against skin breakdown. They are light and good at absorbing impacts and are machine washable but as they are a more recent product, there is less experience of their use. The cover material has a great impact on the pressure relieving properties of a cushion: if it does not stretch in both directions, the potential benefits of more sophisticated cushions will be lost.

Seats and backs

Whether used in a manual or powered wheelchair, the seat should be of the correct dimensions and configuration to improve posture, minimise pressure areas and maximise function. There is evidence that good posture improves cardiopulmonary function, respiratory function, upper limb function and mental performance.[5] It is possible that adaptive seating may help to reduce scoliosis for the duration of use[6] although evidence for this is scanty.

The seat width should be wide enough to allow seating without pressure points even in a heavy coat, but also as narrow as possible to maximise manoeuvrability and to prevent slumping to one side. The base of the seat should accommodate the correct cushion and not impede its function. An inadequately deep seat base (see Figure 3) may decrease trunk stability and worsen posture. A very deep seat will catch behind the user's knees rotating the pelvis into sacral sitting which may risk spinal deformity and pressure damage to the popliteal fossae. Tipping the base of the seat backwards may aid sitting into the chair which makes the user feel more stable. However, posterior tilt may increase shear forces on the sacral area and hinder safe transfers.

It is important that the wheelchair has the correct back support, particularly for a user with less strength and trunk stability. A back can have a number of adjustable pads to provide support where required (Figure 5) or individually tailored, moulded back supports can be fabricated to the user's shape which can wrap around laterally (Figure 6). A hip (not waist) or chest belt may help a user who tends to slide to stay in position, although care must be taken if the person would not be able to extricate themselves if they slip into a dangerous position or if they have seizures and

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Prescribing Information

(Please refer to the full Summary of Product Characteristics before prescribing).

Presentation 'ReQuip XL' Tablets, PL 10592/0293, 5, 6, each containing ropinirole hydrochloride equivalent to either 2, 4 or 8 mg ropinirole. Available in 2, 4 and 8 mg packs of 28 prolonged-release tablets – packs cost £31.36, £62.72 & £105.28 respectively. **Indications** Treatment of idiopathic Parkinson's disease in patients already taking ropinirole immediate release tablets and in whom adequate symptomatic control has been established. May be used alone (without L-dopa) or in addition to L-dopa to control "on-off" fluctuations which might permit a reduction in the total daily dose of levodopa. Substitution of ropinirole prolonged-release tablets should supervised by appropriate specialists in Parkinson's disease. **Dosage** *Adults:* Once daily and at a similar time each day with or without food. Patients should be considered for switching to ropinirole prolonged-release tablets only after they have achieved sufficient symptomatic control on ropinirole immediate release tablets. 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After switching to ReQuip XL prolonged-release tablets, patients will initially require more frequent and careful monitoring in order to adjust the dose if necessary. If sufficient symptomatic control is not maintained after switching to a dose of less than 8 mg once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg at weekly or longer intervals up to a dose of 8 mg once daily of ropinirole prolonged-release tablets. If sufficient symptomatic control is not achieved or maintained at a dose of 8 mg or greater once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg at two-weekly or longer intervals. Individual dose titration against efficacy and tolerability is recommended. Patients should be maintained on the lowest dose of ropinirole prolonged-release tablets that achieves symptomatic control. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually depending on clinical response. When switching from another dopamine agonist follow manufacturer's guidance on discontinuation before initiating the patient on ropinirole immediate-release tablets. Only once sufficient symptomatic control is achieved can patients be switched to ropinirole prolonged-release tablets. If treatment is interrupted for one day or more, re-initiation by dose titration on ropinirole immediate-release tablets should be considered. Discontinue ropinirole gradually by reducing the daily dose over one week. *Renal or hepatic impairment:* No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. *Elderly:* Clearance of ropinirole is decreased in patients over 65 years of age – titrate dose in normal manner. *Children:* Studies have not been carried out in patients under 18 years of age – do not give to children. **Contra-indications** Hypersensitivity to ropinirole or to any excipients, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Special warnings and precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with a history or presence of major psychotic disorders should only be treated with dopamine agonists if potential benefits outweigh the risks. Pathological gambling, increased libido and hypersexuality reported in patients treated with dopamine agonists for Parkinson's disease, including ropinirole. Ropinirole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. 4 mg only – contains sunset yellow (E110) which may cause allergic reactions. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's disease but, as is common practice, care should be taken when adding a new drug to a treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma concentrations of ropinirole have been observed with high doses of oestrogens. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. Smoking induces CYP1A2 metabolism therefore if a patient stops or starts smoking during treatment with ropinirole, dose adjustment may be required. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Effects on ability to drive and use machines** Patients should be warned about the possibility of dizziness (including vertigo). Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Adverse reactions** *Psychiatric disorders; common:* confusion, hallucinations, *uncommon:* psychotic reactions including delusion, paranoia, delirium. Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. *Nervous System Disorders; very common:* somnolence, dyskinesia, syncope, *common:* dizziness (including vertigo), *uncommon:* extreme somnolence, sudden onset of sleep. *Vascular disorders; common/uncommon:* hypotension, postural hypotension. *Gastrointestinal disorders; very common:* nausea, *common:* abdominal pain, vomiting, dyspepsia, constipation. *General disorders and administrative site conditions; common:* peripheral oedema. *Hepatobiliary disorders;* very rare: hepatic enzymes increased. **Overdosage** Symptoms of overdose likely to be related to dopaminergic activity. **Legal category** POM. **Marketing Authorisation Holder** SmithKline Beecham plc t/a GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT. **Further information is available from:** Customer Contact Centre, GlaxoSmithKline, Stockley Park West, Uxbridge, Middlesex UB11 1BT; Freephone 0800 221 441. **Prescribing information last revised:** May 2008. **REQUIP®** is a trademark of the GlaxoSmithKline group of companies.

Adverse events should be reported. Reporting forms and information can be found at **www.yellowcard.gov.uk**. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.

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there is a risk of asphyxiation or injury.[7]

The back should be high enough to provide support if necessary, but some users find a high back restricts their ability to rotate freely in the chair and to socialise. Reclining the back increases support and may aid positioning but may encourage sliding and make it difficult for the user to reach or lean forward to propel themselves up an incline.[8]

Tilt and recline

Tilt and recline systems are a useful option for people with very limited trunk stability and strength or who have spinal deformities or muscle contracture and need a mechanism to shift their weight to ease pressure. With a tilt-in-space system (chassis of wheelchair in Figure 5), the back, seat and footplates tilt backwards as one unit, maintaining the angle between seat and backrest. This may be useful for someone with significant lower limb spasticity who is unable to straighten their legs in a recline system. A recline system simply moves the backrest, and usually elevates the footplates to allow the user to rest in a recumbent position. Recline facilities may provide a greater degree of pressure redistribution than tilt systems although the user will tend to slump when returning to the upright position if they are unable to reposition themselves, suffering significant shear forces.[9] Tilt systems may be more efficient to self propel.[10] Both systems decrease the pressure running vertically through the spine and decrease pressure on the sacrum and ischial tuberosities, transferring it along the backrest.[11] It is important that these systems incorporate good back and head support when tilting or reclining and most users who need this facility need lateral back support, perhaps with a contoured back cushion. In powered chairs, tilt and recline functions may be operated by the user, from a multifunction joystick control.

Other features

There are many other customisable options when a user chooses a wheelchair, including swingaway footrests, angled footrests, position and type of brakes, suspension systems, anti-tipping devices, armrests, clothing guards and a range of accessories including cup holders, storage for clothes, shopping or walking aids, trays and weather shields. A wheelchair may become an important part of the user's image and it is important that it gives the desired impression. Some users may want a chair that facilitates eye level communication to aid conversation and participation, emphasising ability rather than their disability (Figure 7). Other users may want to emphasise certain features of the wheelchair as an aesthetic statement and certain features may be crucial to one person and unimportant to another. Many users will require more than one wheelchair for different situations, for instance, an attendant propelled wheelchair as a backup for when a powered chair is impractical or undergoing maintenance. It is therefore vital that the person who will be using the wheelchair is as informed and involved as possible in any decision making associated with obtaining or modifying it in order that their function and participation are maximally enabled.

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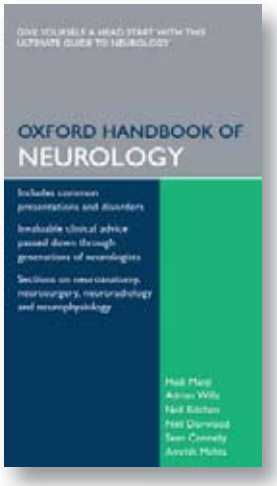
Oxford Handbook of Neurology



White coat pockets were once a target for publishers, but in an era of e-medicine and naked-below-the-elbow dress codes is there still a need for these cute tomes, or anywhere to put them? After using and scrutinising this book we think it has a great future; it does exactly what it says on the tin and with minor tweaking it could easily become the book we all use to inform and record registrar training.

The book has seven sections entitled Neurological history and examination, Neuroanatomy, Common clinical presentations, Neurological disorders, Neurosurgery, Clinical neurophysiology and Neuroradiology; an ambitious coverage but one reflecting the range of authorial interests. The text is not referenced, which diminishes its authority in areas with a strong evidence base, but it reads well.

We began by consulting it regularly regarding cases we had seen. The sections on acute myasthenia and acoustic neuroma with communicating hydrocephalus were thorough but concise and the details about actually how to do a tensilon test were useful. MND was covered comprehensively with notes on clinical features, investigation and management. The section on bedside cognitive testing section included both the Mini-Mental State Examination and the Camels in Holland version. In general clinics the tables containing the starting doses and common side effects of drugs for epilepsy, migraine, trigeminal neuralgia and spasticity were handy and the tables about seizures and syncope, short-lasting unilateral headache, and the paraneoplastic conditions and their antibodies were informative and easy on the eye. Neurosarcoid gets a (brief) mention, head injury gets ten CT images and as a primer in neurosurgery and neurophysiology it is worth having around.

Reading it cover to cover gave us some different insights. With time we became unsure whether it was a pragmatic guide to dumpety-dump clinical neurology, or a minified unreferenced version of an authoritative text. Coverage seemed uneven at times. Early on there are 20 pages of very familiar anatomical illustrations but with no insights into the diagnostic thinking required to spot the common mononeuropathies, the posterior cord plexus lesion, or the infarcted lateral medulla. Despite the importance of the consultation it gets only one page. Ten different patterns of chronic neuropathies are described but bulbar and respiratory failure in neurological disease are not discussed or indexed. There is a refreshing emphasis on inherited disorders but the degree of detail seemed disproportionate at times although we now long to make the diagnosis of Gelsolin familial amyloid neuropathy (Finnish) so we can tell our colleagues it is the stuff of handbooks, not obscure journals.

However the choice of section headings and their contents works well with minimal duplication and omission; the differential diagnosis of acute vertigo on page p58 excludes BPPV, although it is discussed in depth on p 254. The appendices were useful. Kurtzke, Barthel, Hoehn & Yahr, and Rankin make up the first. Clinical pearls follows; a nice idea but we were left wanting more. Then the eponyms appendix, which helped with Duane's, disappointed with Lewis Sumner, but put us straight about Villaret, Monakow, and Foix-Alajouanine. Some useful website addresses make up the fourth appendix.

So we recommend it to you. With some tick boxes and more room to record patient details it could become a neurological trainee's tacnometer, a combined logbook and pocket reference which no SpR will be allowed not to mention at their RITA, and its future will be deservedly ensured.

Reviewed by: Rob Powell and Tom Hughes, University Hospital of Wales, Cardiff, UK.

Authors: H Manji, S Connelly, N Dorward, N Kitchen, A Mehta, A Wills
Published by: Oxford University Press, 2006 • **Price:** £29.95
ISBN: 9780198509738

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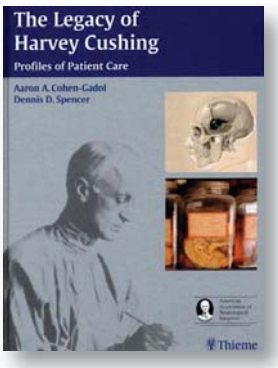
The Legacy of Harvey Cushing – Profiles of patient care



Harvey Cushing's Brain Tumor Registry was an immense collection of more than 2200 patient case studies from Johns Hopkins Hospital, Baltimore and later, the Peter Bent Brigham Hospital in Boston. The meticulous recording of clinical information, annotated with exceptional photographic records, provided the earliest and most enduring archive of neurosurgical case histories.

Cohen-Gadol and Spencer dissect the collection, now held in Yale University, in a clear and cohesive fashion. The Legacy of Harvey Cushing enables this important historical work to be available to all neurosurgeons. The book, which includes a detailed introduction about the history of the collection itself, is divided into chapters based on disease type, including pituitary tumours, meningiomas, malignant tumours, posterior fossa tumours, spinal tumours and cerebral aneurysms. Each of these chapters also includes an introduction written by a variety of currently practicing neurosurgeons. These foster an understanding of both past and current practices and enable the reader to gain insight into the remarkable talents of Harvey Cushing.

Through the vignettes of each patient, the authors translate Cushing's meticulous notations on disease and provide a unique level of detail about the individual patient. The patient case histories detail the presenting symptoms and signs. They are supplemented with clinical and operative notes, radiology and pathology reports, patient correspondence and notes on further clinical events and, where relevant, autopsy reports. It is, however, the powerful photographic images that captivate the reader. These catalogue the devastating impact of neurological diseases in a way that could not be achieved today due to both the current ability to diagnose disease earlier and restrictions now placed on such photographic documentation.

This book contains several hundred photographs. The power of these is reminiscent of Frank Hurley's photographs detailing Shackleton's Endurance expedition. Many of the patients have advanced disease. The cachetic appearances of a patient with a pineal tumour are akin to those showing prisoners of war from by-gone conflicts. The free text and final collection of photographs provide a better understanding of Harvey Cushing, who is often considered to be the father of modern neurosurgery. To tackle the enormous Cushing collection and compile this list of case histories is a tremendous task.

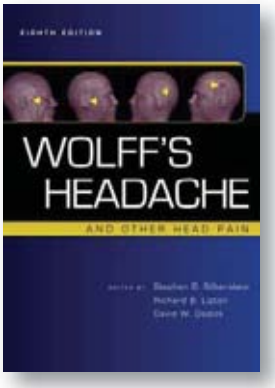
This book enables the neurosurgeon to understand the impact of the man that reduced mortality for his patients to below 10%. Given the advanced state of disease at presentation and the lack of an operating microscope in the pre-antibiotic era this achievement was remarkable.

In summary, this new book is a remarkable catalogue of neurological disease exploring the impact upon the patient and the evolution of surgical and non-surgical treatments. Furthermore, the cases suggest the possible origins of collaboration of different medical specialties. This type of collaboration survives today in the form of weekly tumour conferences. This book is a recommended addition to the collection of any medical historian. It is also an incredibly powerful read for anyone pursuing a career in the care of the patients with neurological disease. The clinical vignettes provide insight into disease for everyone, from those who care directly for patients and observe the ravages of those diseases first hand, to those who rarely engage the patient and look for cures through a microscope or elsewhere. The patients, stoic in their diseased state, captured in dramatically clear black and white photos, provide an extraordinary reminder of what inspires us to be neurological surgeons. This unique book will have an enduring impact on all of those who take the time to read, observe and study Cushing's pioneering work.

Reviewed by:
Neil Malhotra (Visiting Neurosurgical Resident from Pennsylvania) and Peter C Whitfield (Consultant Neurosurgeon), Plymouth, UK.

Authors: Aaron A Cohen-Gadol, Dennis D Skinner • **Published by:** Thieme New York : Stuttgart • **Price:** $129.95 • **ISBN:** 978-1-588890-389-1

Wolff's Headache and Other Head Pain (8th edition)



Harold Wolff died in the year I was born, having just completed the revision for the second edition of his textbook. The fact that his book lives on, now in its eighth edition, is testimony to its value, described in the blurb as "the definitive reference text in the field".

The core of the book is structured around the second edition of the International Headache Society classification (ICHD2) of primary and secondary headache disorders. As one would expect there is a wealth of information, related to both pathophysiology and clinical management of these disorders. "Migraine treatment", for example, runs to 88 pages (without the references), so this is for those readers wanting a comprehensive account rather than a quick refresher. The clinician who can recall all 6 pages tabulating causes of ocular, orbital or periorbital pain in the "quiet eye" has a better memory than I do.

As one might anticipate, it is hard to identify omissions, although I cannot recollect any mention of ophthalmoplegic migraine and its possible reclassification as a focal demyelinating neuropathy. Errors of commission, on the other hand, are plentiful. Does Oxford University Press permit authors to proof read their chapters (I presume the answer is no, since one misspells his own name, p601) or employ professional proof readers? Typographic errors are sufficiently frequent to be intrusive. Nonetheless, this book is excellent value for money at £60, a must for all those professing an interest in headache and worth dipping into by all neurologists seeing headache patients (i.e. all neurologists).

Reviewed by:
AJ Larner, WCNN, Liverpool, UK.

Authors: Silberstein SD, Lipton RB, Dodick DW (eds.). • **Published by:** Oxford University Press, 2008 • **Price:** £60.00 • **ISBN:** 978-0-19-532656-7

New Developments in 'Shaken Baby Syndrome'

Inflicted head injury is one of the commonest causes of explained death in infancy.[1] Following a number of high profile cases including an Appeal Court judgement, there has been increasing legal and medical controversy surrounding the diagnosis of inflicted head injury in children and in particular the triad of pathological findings that define the 'Shaken Baby Syndrome' (SBS).[2,3] We will discuss the basis for this diagnosis and some of the hypotheses that are offered to explain the pathophysiology of this syndrome.

Inflicted head injury in infancy

Inflicted head injury in infancy is associated with a distinct pattern of injury characterised by a triad of retinal haemorrhage, sub-dural haemorrhage and an encephalopathy in the absence of any other explanation[1,4] (Table 1). Each of these features has specific characteristics that suggest the diagnosis but it is the combination of the features in the absence of an adequate explanation that carries the most diagnostic significance.

Table 1: The triad of inflicted head injury in infancy

1. Retinal haemorrhage
2. Thin film sub-dural haemorrhage
3. Encephalopathy

In fatal cases, the retinal haemorrhage is typically extensive, bilateral and affects multiple layers of the retina.[5] The nature of the sub-dural haemorrhage differs from those typically seen in adults. In infants, including those with fatal injuries, the sub-dural blood tends to be a low volume 'thin film' and is frequently bilateral.[6] In fact, it is unusual for the sub-dural haemorrhage to exert mass effect and its diagnostic significance is as an indicator of the mechanism of injury rather than the direct cause of death.

The pattern of injury seen within the brain also differs from than that seen in older individuals. While a number of typical features of trauma may be seen in infants with inflicted head injury such as gliding contusions of the white matter (which are typically parasagittal contusions associated with acceleration-deceleration injuries), in most cases the pattern of injury is predominantly that of cerebral oedema and hypoxic-ischaemic damage.[7] The widespread pattern of diffuse traumatic axonal injury that is typical of severe closed head injuries in adults is more unusual in inflicted head injury in infants and traumatic axonal injury is often limited to the cortico-spinal tracts around the junction between the cervical spinal cord and medulla.

While a number of clinical syndromes have been associated with abusive head injury in children,[8] in fatal cases a commonly reported clinical history is that of a previously well infant that undergoes a sudden collapse in the care of a lone adult without corroborative witnesses. In a number of well-documented cases, the carer has confessed to a loss of temper followed by shaking the child with varying degrees of vigour.[9]

While in many cases the pathological findings are limited to the triad described above, in a proportion of cases there is additional evidence of non-accidental injury lending further support to the view that the injuries seen in the triad are due to inflicted trauma.[6]

Why does head injury in infants show a distinct pathology?

Two factors are likely to explain the pattern of head injury seen in infants. The first is that the infant head and neck have unique mechanical properties that influence their response to trauma (Figure 1). The second is that the nature of the injury is likely to be different in older children and adults.

In infants, the head is relatively heavy and the neck musculature relatively weak. In some cases, there is evidence of traumatic axonal injury at the cervico-medullary junction and this would support the view that the cervico-medullary junction is vulnerable in infants.

The cranial sutures have not fused at birth, which means that the cranial cavity is not the closed box system of the adult and therefore changes in intracranial pressure will behave less predictably. In addition, following an injury one would expect the bones to mould with respect to each other, increasing the torsion on underlying structures, including the dural veins and sinuses. In addition, the base of skull is smoother in infancy affecting injury to the basal structures (e.g. contusions, cranial nerve injuries).

Finally, at birth the brain is poorly myelinated, leading to a more fluid consistency and to a reduced difference in inertia between the grey and white matter. These factors can clearly alter the response of the brain to acceleration-deceleration injuries and may explain the relative rarity of typical traumatic axonal injury in infancy outside the cervico-medullary junction.

The second contributor to the pattern of pathology in infancy is that the nature of the traumatic insult differs. Transcripts of perpetrator's confessions support the assertion that shaking of a child with the head unsupported leads to the typical pattern of injury.[9] In contrast shaking is

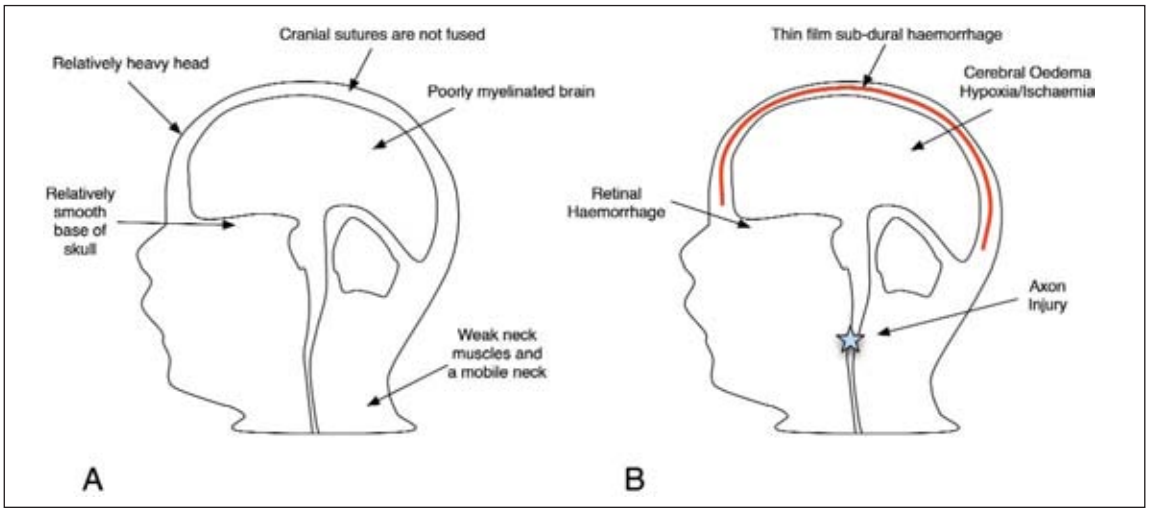


Figure 1: A. The infant brain has unique mechanical features that underlie the pattern of injury seen in inflicted head injury. The figure highlights potential sources of vulnerability. B. The typical pattern of injury in inflicted head injury in infancy.

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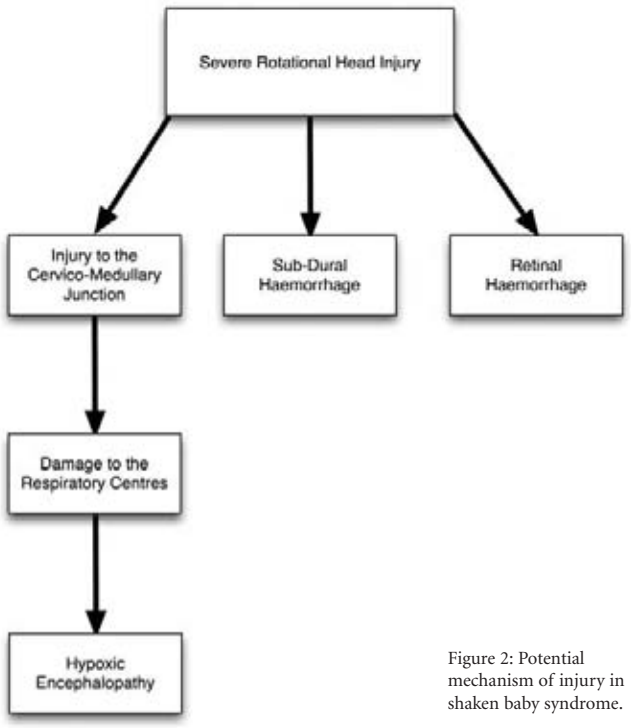

Figure 2: Potential mechanism of injury in shaken baby syndrome.

an unusual cause of death in older children where road traffic accidents and other impact injuries predominate. Controversy surrounds whether shaking is sufficient alone or if shaking in combination with an impact is necessary (e.g. 10). However, in many cases there is no evidence of an impact and, more importantly, the pattern of injury is not that seen in impact injuries.

A plausible hypothesis is that shaking an infant leads to stretching of the cervico-medullary junction due to the particular mechanical vulnerability at this site in infants. This injury causes a respiratory disturbance or apnoea through damage to the respiratory centres and their connections. Finally, the respiratory failure causes a global hypoxic injury to the brain. In such a model, the concurrent retinal and sub-dural haemorrhages are simply indicators of a severe rotational injury (Figure 2).

Controversy in the shaken baby syndrome

Some authors have proposed that the pattern of injury labelled Shaken Baby Syndrome may be caused by non-violent mechanisms.[3] For example, as an extension of the observation that hypoxic / ischaemic brain injury is common in the triad, some authors have asked can hypoxia or ischaemia cause all the features of shaken baby syndrome? We believe this is unlikely as there is no well-documented clinical evidence of the syndrome arising in the presence of a defined hypoxic / ischaemic insult. Furthermore, such a hypothesis fails to explain the evidence of confessions, the cases in which there are extra-cranial injuries and the cases in which there is other evidence of traumatic head injury (e.g. gliding contusions, skull fractures etc or even traumatic axonal injury in the medulla).

In one small cohort of paediatric autopsies, fresh intra-dural haemorrhage was a relatively frequent finding at post-mortem in fetal, perinatal and infant autopsies in the absence of evidence of trauma.[11] However, macroscopic sub-dural haemorrhage is the important finding in SBS, not microscopic intra-dural haemorrhage. Indeed, the authors did not see macroscopic thin film sub-dural haemorrhage (with or without the rest of the triad) in their non-trauma infant cohort. Furthermore, the cohort contained only nine infants, the remainder of the cases being made up with perinatal and fetal cases. In addition, the retina was not examined in these cases. While the cohort included frequent evidence of hypoxic-ischaemic injury, the authors did not show a statistically significant correlation between hypoxia and intra-dural haemorrhage.

A further explanation proposed for the sub-dural bleeding is that it arises during birth or that a sub-dural haematoma that formed at birth has re-bled. If re-bleeding from these haematomas were the cause of death, one would predict that it would need to generate a space-occupying lesion with mass effect. Such a space-occupying mass is not seen in the triad and therefore it seems unlikely that re-bleeding is a mechanism of death. Furthermore, in a careful longitudinal study, congenital sub-dural haematomas had a different distribution to that seen in SBS and importantly they resolve by the age of four weeks.[12]

An alternative hypothesis that has been proposed is that paroxysms of coughing, possibly associated with feeding difficulties or choking, may generate a massive rise in intracranial venous pressure that leads to sub-dural and retinal haemorrhage and may be associated with venous infarction.[13] However, there is no well-documented direct evidence that this occurs and it does not explain the cases in which there is direct evidence of trauma. The hypothesis has been based on a mathematical model that estimates the rise in venous pressure during a paroxysm of coughing. In this model, rapid rises in venous pressure are predicted and the authors have argued that there are areas of vulnerability in the veins bridging the sub-dural space that may rupture in the face of a sudden rise in venous pressure. However, the site of bleeding in SBS is not known with any certainty and the pressure needed to rupture the veins in human infants is not known. As with all biomechanical models, the hypothesis generated would have to be validated with good clinical data.

Conclusions

A general issue at the heart of the debate around SBS is that the quality of scientific evidence that informs it has serious limitations. Central to this is the clinical evidence. However, even in the carefully documented cohort of Geddes, there are only 37 cases.[6,7] Cases with corroborative evidence of trauma (e.g. fractures) are persuasive of the association with inflicted injury but the events are not witnessed and therefore the evidence from legal confession is also an important part of the case for a traumatic mechanism. A number of experimental approaches have been undertaken such as biomechanical models, animal models and cadaveric studies but each of these has been beset with controversy and difficulties in validating the unique mechanics of the infant head and neck. Future studies must include unbiased cohorts of post-mortem studies with standardised protocols of suspicious cases and importantly of non-suspicious cases. It is unfortunate that recent changes in regulation in the UK have made these sorts of studies increasingly difficult. The understandable and justifiable emphasis on parental consent for tissue research taken together with the increasing pressures on the coronial system are likely to introduce significant bias into future cohort studies in the UK.

Acknowledgements

We are grateful to Prof. Tony Risdon for his helpful comments on the manuscript.

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2008

July

Posture & Balance in Neurological Conditions - Lower Limb Qualified staff
3-4 July, 2008; Derby, UK
NCORE -
Tel: 01332 254679 or
www.ncore.org.u

Autism Today:
7-8 July, 2008; London, UK
E. annehaylock@markallengroup.com

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

Masterclass "Stress in MS"
15 July, 2008; Newcastle, UK
E: michelle.constable@mstrust.org.uk

11th International Conference on Alzheimer's Disease
26-31 July, 2008; Chicago, IL, USA
Joretta Rahim,
E. icad@alz.org,
T. 001 312 335 5790,
Fax. 001 866 699 1235

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

Glenside Hospital Open Day
30 July, 2008; Salisbury, UK
E. marketing@glensidemanor.co.uk

August

BISWG South West Regional Meeting
5 August, 2008; Exeter, UK
E. jackie.burt@plymouth.gov.uk,
www.biswg.co.uk

Biologising Pain with Lorimer Moseley
12 August, 2008; Nottingham, UK
E. info@physiouk.co.uk

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

Nociceptors - New Biology
Official Satellite Meeting of the 12th World Congress on Pain
15 - 16 August, 2008; Edinburgh,
www.edinburghneuro
science.ed.ac.uk/nociceptorsymposium2008

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

Measuring Behaviour 2008
26-29 August, 2008; Maastricht, The Netherlands
E. mb2008@noldus.nl,
www.noldus.com/mb2008/

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

2nd Baltic Sea Summer School on Epilepsy
31 August – 4 September, 2008;
Copenhagen, Denmark
www.epilepsy-academy.org
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

EEG in the diagnosis and management of epilepsy
September, 2008; ILAE–VIREPA
distance learning course
E. office@epilepsy-academy.org,
www.epilepsy–academy.org

Neuroimaging
September, 2008; ILAE–VIREPA
distance learning course
E. office@epilepsy-academy.org,
www.epilepsy–academy.org

Clinical Pharmacology and Pharmacotherapy
September, 2008; ILAE–VIREPA
distance learning course
E. office@epilepsy-academy.org,
www.epilepsy–academy.org

Federation of the European Societies of Neuropsychology
2-5 September, 2008; Edinburgh, UK
T. 01332 254679,
www.ncore.org.uk

Genomic Perspectives to Host Pathogen Interactions
3-6 September, 2008; Cambridge, UK
http://firstcontact.hinxton.wellcome.ac.uk

6th International Conference on Frontotemporal Dementia
3-5 September, 2008; Rotterdam,
The Netherlands
E. office@FTD2008.org,
www.ftd2008.org/site/

Making the Evidence Work for your Patients and their Families
4-5 September, 2008; Southampton, UK
T. +44 (023) 8079 8669
F. +44 (023) 8079 4340
E. neurorehab2008@soton.ac.uk,
www.neurorehab2008.soton.ac.uk

European Headache and Migraine Trust International Congress 2008
4-7 September 2008, London, UK
E. enquiries@ehmticongress2008.com,
www.ehmticongress2008.com
T. +44 (0) 20 8979 8300

Festschrift for Professor David Milner "The Neuropsychology of Perception and Action"
6 September, 2008; Durham, UK
E. l.h.de-wit@durham.ac.uk

Understanding Neuroscience: an innovative approach for mental health practitioners
8-9 September, 2008; London, UK
E. annehaylock@markallengroup.com

Brain and Behaviour: exploring how neuro-science can support clinical treatment in child and adolescent mental health
8-9 September, 2008; London, UK
E. annehaylock@markallengroup.com

BISWG South Wales Regional Meeting
9 September, 2008; Cardiff, UK
E. kate.coles@hughjames.com,
www.biswg.co.uk

BSS hosting the 19th Congress of the European Sleep Research Society
9-13 September, 2008; Glasgow
E. enquiries@sleeping.org.uk

11th Annual Advanced Rehabilitation Event
10, 11 & 12 Sept, 2008; Derby, UK
NCORE
T. 01332 254679 or
www.ncore.org.uk

ABN Autumn Scientific Meeting
10-12 September, 2008; Aviemore, UK
E. Karen.reeves@theabn.org

Genome Informatics
10-14 September, 2008; Cambridge, UK
http://firstcontact.hinxton.wellcome.ac.uk

VIIIth Congress of the EANO
12-14 September, 2008; Barcelona, Spain
T. +43 1 4051383 0,
F. +43 1 4078274,
E. eano2008@medacad.org

Evolution of Brain, Behaviour & Intelligence
12-14 September, 2007; Hinxton, UK
T. 01223 495000, E. wtmeet-
ings@wtconference.org.uk,
http://firstcontact.hinxton.wellcome.ac.uk/

Enabling People with Long-Term Conditions: How Telecare, Electronic and Computer-based Technologies can help
16 September, 2008; London, UK
F. 020 7760 7193,
T. 020 7921 0002,
www.innervate.co.uk

"Mind in the Brain" (a Festschrift in honour of Professor Chris Frith, FRS)
17-18 September, 2008; London, UK
E. Rosalyn Lawrence
rosalyn.lawrence@ucl.ac.uk

AANEM Annual Scientific Meeting
17-20 September, 2008; Providence, Rhode Island, USA
T. + (507) 288 0100,
F. + (507) 288-1225,
E. aanem@aanem.org

ECTRIMS/LACTRIMS/RIMS
17-20 September, 2008; Montreal, Canada
T. 001 212 476 0469,
F. 001 212 476 0485,
E. msmontreal@nmss.org,
www.nationalMSsociety.org

2nd International Symposium On Pheochromocytoma
17-21 September, 2008; Cambridge, UK
E. isp2008@hamptonmedical.com

7th Mediterranean Congress of Physical Medicine & Rehabilitation Medicine
18-21 September, 2008; Potorose, Slovenia
E. marincek.crt@mail.ir-rs.si

Understanding and Dealing with Behaviour Problems
19-20 September, 2008; London, UK
E. enquiries@braintreetraining.co.uk,
www.braintreetraining.co.uk

Congress of Neurological Surgeons Annual Meeting
20-25 September, 2008; Orlando, USA.
Congress of Neurological Surgeons
T. +847 240 2500,
F. +847 240 0804,
E. info@1CNS.org,
www.neurosurgeon.org

10th International Symposium On Thrombolysis And Acute Stroke Therapy
21-23 September, 2008; Budapest, Hungary
E. tast2008@kenes.com,
www.kenes.com/tast2008

8th European Congress on Epilepsy
21-25 September, 2008; Berlin, Germany
E. berlin@epilepsycongress.org,
www.epilepsyberlin2008.org

10th National Conference - Parkinson's Disease: responding to mental health issues in Parkinson's
23 September, 2008; Birmingham, UK
MA Healthcare Ltd
T. 01722 716007
F. 0207 733 8174
www.mahealthcareevents.co.uk,
E. annehaylock@markallengroup.com

18th Ion Channel Meeting
23-26 September, 2007; Presqu ile de Giens, France
E. arnaud.monteil@igf.cnrs.fr,
http://congres.igh.cnrs.fr/canaux-ioniques/

Exploring Gait as it Relates to Posture & Balance for qualified staff
24 September, 2008; Derby, UK
NCORE
T. 01332 254679 or
www.ncore.org.uk

New Venue
5th World Congress for NeuroRehabilitation
Brasilia, Brazil
24-27 September, 2008;
www.wcnr-brasilia2008.com

6th World Stroke Congress
24-27 September, 2008; Vienna, Austria
E: stroke2008@kenes.com,
www.kenes.com/stroke2008

International E-coli Alliance
24-28 September, 2008; Cambridge, UK
http://firstcontact.hinxton.wellcome.ac.uk

2nd Seminar on Clinical Neurology
27-28 September, 2008; Rhodes, Greece
Mrs. Ifigenia Tambaki,
T. 302 310 253 465 7,
E. info@airmarit-erasmus.gr

Understanding the pelvis and its function in the neurological patient (Bobath trainer)
29, 30 September & 1 October, 2008; Derby, UK
NCORE
T. 01332 254679 or
www.ncore.org.uk

Anxiety and Depression: diagnosis and management, A National Conference on Child and Adolescent Mental Health
29-30 September, 2008; London, UK
E. annehaylock@markallengroup.com

October

Integrative Approaches to Brain Complexity
1-5 October, 2008; Hinxton, UK
E. meetings@cshl.edu

BISWG 8th Annual Brain Injury Legal Seminar
2 October, 2008; London, UK
E. lbellgard.rhn.org.uk,
www.biswg.co.uk

MOTOR NEURONE DISEASE ASSOCIATION

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2nd International Congress on Gait & Mental Function

February 1-3, 2008, Amsterdam, The Netherlands

The 2nd International Congress on Gait & Mental Function was an outstanding success, demonstrating the importance of scientific study and collaboration in a rapidly expanding field that envelops the complex interplay between gait and mental dysfunction. Gait and balance are traditionally seen as largely automatic motor functions. The conference challenged this conventional perspective by highlighting the many interactions between mental functions and walking or balancing. In only the second time this congress has been held, close to 600 delegates came together from over 46 countries across the world to engage in three days of intensive clinical and scientific interactions.

The conference was opened with a dance choreographed by the Movement Network, performed by young dancers who mimicked specific psychogenic gait disorders, thereby highlighting the prominent influence of cognition on gait and balance. This was followed by a lively opening lecture by Dr John Morley, whose preference for active participation and confidence building by dancing with his elderly patients will certainly be remembered. Dr Morley stressed during his lecture that exercise is clearly the best evidenced treatment in the elderly, with the least adverse effects.

The breakfast symposium with the Chelsea Football Club medical team was one of the highlights of the conference and an eye-opener into modern age rehabilitation medicine, seen from the perspective of elite sports. The team stressed that the ultimate goal of rehabilitation after each physical injury should be to return to football stronger, both physically and mentally, than ever before. Setting targets for rehabilitation with each individual player and visualising these targets were important tools that would easily lend themselves well for application in everyday clinical practice. Moreover, the team underscored that in movement science, one should also look at factors such as nutrition, footwear, attentiveness, and speed of eye movements, as practiced routinely in the Chelsea laboratory.

Dr Mark Carpenter of Vancouver, Canada, highlighted our rapidly expanding knowledge on balance and posture in relation to fear of falling, clearly showing that body stiffening, as a result of increased anxiety, may be counterproductive in elderly subjects, thereby increasing the chance of falling and fractures. He also elegantly demonstrated how standing at an elevated surface (thus producing experimentally an increase in the level of postural threat) may lead to increased monitoring of somatosensory information, thereby leading to amplification of sensory gain with resultant changes in postural responses.

Diffusion Tensor Imaging was noted as a promising tool to disentangle the heterogeneity in white matter lesions by Dr Caterina Rosano. Dr Rose Anne Kenny pointed out the often forgotten impact of neurocardiogenic instability, being associated both with cognitive decline and with orthostatic syncope, resulting in falls. The results presented from trials on pacemaker treatment in cases of cardio inhibitory carotid sinus syndrome were largely new to the audience.

A highlight of the congress was presented by Dr Giselle Petzinger, who introduced her latest results on exercise and disease-modification in rats with experimental parkinsonism. The results of her studies emphasise the potential of exercise to induce adaptive plastic changes in the rodent brain, and the first evidence is emerging to suggest that exercise may also have functional beneficial effects in human patients with Parkinson's disease.

In a provocative lecture, Prof Eric Scherder took the audience on a virtual tour through the brain, highlighting the similarities in anatomic lesions for cognition and motor function, as observed in patients affected by Alzheimer's disease.

During the workshops, the attendants engaged in lively debate on the pros and cons of, among others, ambulatory gait and balance monitoring, cognitive testing, and neuroimaging. For example, one workshop discussed the merits of "paper and pencil" versus computerised testing of cognition (presented by Prof Jeffry Hausdorff and Prof Roy Kessels), concluding that there is still place for both methods, and that choices have to be made based on application (clinical use versus scientific use), the domain to be tested attention and reaction time (best computerised), insight, abstract reasoning and valuation (best paper and pencil). The number of computerised tests is rapidly increasing, so choices should be re-evaluated from time to time. The interactive video session of usual and unusual presentations of gait or balance impairments (presented by Prof Tony Lang and Dr Evzen Ruzicka) was received with great enthusiasm, with standing room only in the audience.

The Congress closed with a remarkable lecture by Dr Kenneth Rockwood, a geriatrician from Halifax, Canada. In his lecture, he emphasized the need for further development and refinement of individually based outcome measures for cognition and mobility, as valid and responsive tools for clinical trials.

The conference will be followed by the 3rd International Congress on Gait and Mental Function to be held in Washington DC, February 26-28, 2010.

Website: www.kenes.com/gait

Bastiaan R. Bloem, MD, PhD &
Marcel Olde Rikkert, MD, PhD,
conference chairs,
Department of Neurology and Geriatrics,
Radboud University Nijmegen Medical Centre,
The Netherlands.

Claims Management Rehabilitation Conference

12 February, 2008; London, UK.

The first Claims Management Rehabilitation Conference took place on the 12th February this year at One Great George Street. The day was chaired by Robin de Wilde QC, Chairman of the Ogden Working Party, Secretary of BICMA and former Chairman of the Professional Negligence Bar Association and Fellow at the Royal Society of Medicine. Speaking at the conference, Susan Scott Parker OBE, founder and chief executive of the Employers' Forum on Disability, warned that employers are 'losing good people' through misunderstanding of the Disability Discrimination Act.

She said that DDA compliance is not static; it requires flexibility and an ongoing commitment to meeting the changing needs of staff. These people could end up being forced to make avoidable claims because they are unable to return to, or stay at, their workplace. Susan also said she thought that 'the rehabilitation community fail to provide services to employers that are adequate and efficient.' Her comments coincide with the health secretary Alan Johnson's suggested overhaul of the sick note system to focus on what workers are able to do, rather than what they are not, to help people back to work.

The second speaker of the day, Norman Cottingten, President of BICMA and Chairman of The Injury Care Clinics, spoke of the origins and application of the Rehabilitation Code. Norman covered the Code's beginnings as the Early Assessment Agreement through to the 1997 launch and publication of the Rehabilitation Code in 1999 and the subsequent establishment of the charity Case Management Society UK (CMSUK). Commenting on the current Personal Injury Protocol, which contains the Rehabilitation Code, Norman commented, "Rehabilitation is here to stay, and the courts will not look at whether it was cost-effective, but at whether it was reasonable in all the circumstances". An insurer who declines an opportunity to participate in the process will often find that the solicitor will proceed independently with the cost to be recovered within the claim. This will extract the insurer from the decision making process, meaning that the claim will likely be the subject of litigation. All of this will make the process more protracted and expensive.

Christopher Mercer followed this with a detailed look into the role of physical therapy and investigations in the management of back and neck pain. He explained the risks associated with the overuse of x-rays and CT scans and shocked delegates with the fact that there is a one in 2000 likelihood of developing fatal cancer from one CT abdomen scan. Obviously this risk becomes preferable if it helps to enable treatment of the patient but, Christopher explained, often clinicians revert to x-rays and CTs when a clinical examination could have given them the same information.

Other speakers included Melanie Summers, Managing Director of AIG Medical & Rehabilitation; Tony Goff, chairman of Motor Accident Solicitors' Society; Liz Haunch Independent Case Management Consultancy; Heather Batey, a head injury specialist; David Bingham, CEO of IPRS UK; and Claire Ginders Remploy, and trustee of the Vocational Rehabilitation Association.

The conference proved a great success, with more than 170 delegates attending and excellent opportunities for debate and networking. The headline sponsor was AIG Medical & Rehabilitation; silver sponsors were HCML; Reach Personal Injury Services; TICCS The Injury Care Clinics; and Nuffield Diagnostics.

Laura Callicott,
Events Manager, Barker Brooks Media.

For more information,
visit www.legal-medical.co.uk/rehabilitation2008
For further media information,
please contact Susan Reid or Jane Burgess on 01423 851150
or email susan.reid@barkerbrooks.co.uk
or jane.burgess@barkerbrooks.co.uk

Highlights from the 4th Annual Clinical Neurology and Neurophysiology Update Symposium

February 18-19, 2008. Tel Aviv, Israel.

Co-sponsored by the Department of Neurology and Neuroscience of Weill Cornell Medical College, New York, the Adams Super Center for Brain Studies, Tel Aviv University, and the Joseph Sagol Neuroscience Center at Chaim Sheba Medical Center, Tel Hashomer, Tel Aviv, Israel, this year's conference took place not far from the Mediterranean seashore in sunny but windy, downtown Tel Aviv. The busy two day scientific program covered neuromuscular diseases, neuroimmunology, ageing, neurodegenerative diseases, and dementia. Twenty-seven speakers from Israel, the United States, and Germany presented their work to nearly 200 attendees and discussed significant advances in their field.

Neuromuscular diseases

Despite a paucity of adequate, critically performed, controlled trials for most therapeutic modalities in myasthenia gravis, a majority of patients are successfully treated despite a lack of therapeutic uniformity (Zohar Argov, Hebrew University, Jerusalem). Regarding immune mediated neuropathies, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and paraproteinaemic neuropathy, intravenous immunoglobulin or corticosteroids remain the first choice of treatment, but again evidence-based second choices are found wanting (Yitzhak Wirguin, Saroka Medical Center, Be'er Sheva, Israel).

Creutzfeldt-Jakob disease

Joav Chapman (Sheba Medical Center, Tel Aviv, Israel), one of the symposium directors, discussed Creutzfeldt-Jakob disease (CJD), a disease caused by the conversion of a normal protein into the self-propagating prion protein. He noted that genetic forms are all linked to mutations in the prion precursor protein PrP and that the most common genetic form is found in Israel. Currently little data exists on effective treatment but prophylactic treatment of PrP mutation carriers will likely be the first step forward.

Isak Prohovnik, (Mount Sinai School of Medicine, New York, USA) discussed recent advances in neuroimaging of human prion diseases. It has long been known that high T2 signal in the basic ganglia is common in these diseases. Recent literature, mainly in sporadic, variant and familial CJD, has established such hyperintense signals, in basal ganglia, thalamus and cortex, as sensitive and specific markers. Diffusion-weighted MRI (DWI) appears to provide the most promising imaging modality, and may reveal fundamental features of pathophysiology early on, raising the possibility of developing DWI as a surrogate marker of disease progression and treatment response.

Stroke in systemic inflammatory disorders

Steven R Levine (Mt. Sinai School of Medicine, New York) covered the various systemic inflammatory disorders which cause cerebrovascular disease, including systemic lupus erythematosus, the antiphospholipid syndrome, and the vasculitides. Key concepts included (a) involvement of which sized vessel(s) – large, medium, or small? (b) different diseases having predilection for different sized vessels. (c) is the clinical syndrome due to an inflammatory vasculopathy? (d) is there good evidence of an underlying systemic illness or is it a primary, isolated CNS process? (e) are there other potential causes for the cerebrovascular disease? Mechanisms of autoimmune cerebrovascular injury discussed encompassed inflammation, fibrin deposition,

necrosis, anaphylactic, cytotoxic/cell activation, immune complex, cell-mediated, cytokine mediated, genetically mediated, infectious, and environmental/chemical mediated vasculitis. Differential diagnoses, emerging new imaging technologies, and management and treatment closed the session.

Immunology of neurological disorders

An informative talk by Philipp von Landenberg (Institute for Clinical Chemistry and Laboratory Medicine, Johannes Gutenberg University, Mainz, Germany) focused on the data regarding the involvement of toll-like receptors (TLR) in inflammatory neurological disorders. Particularly in experimental allergic encephalitis (EAE) models and in multiple sclerosis, expression and signaling via TLR 2 and 4 seems to have some impact. Data regarding ischaemic neurological disease, with the antiphospholipid antibody syndrome (APS) presented as an example, showed the specific upregulation of TLR8 mRNA, with augmented expression and secretion of TNFa and IL1b in monocytes. Using monocytes in an in vitro system, this increase in cytokine secretion can be further enhanced by adding the specific ssRNA-ligand for TLR8, and may be subsequently neutralised by adding an inhibitory DNA-oligonucleotide. These findings provide a first indication that endogenous stimulation of TLR8 in APS patients and consequent elevation of inflammatory cytokines might lead to increased thrombotic risk, as well as to specific changes in the CNS.

White matter imaging

Using magnetic resonance diffusion tensor imaging as a tool for characterising and visualising white matter in normal subjects as well as in pathological conditions, striking illustrations, including the pyramidal tract, optic radiations, and arcuate fasciculus, as well as the smaller uncinate, cingulum, and anterior commissure, and even the carpal tunnel were demonstrated (Yaniv Assaf, Tel Aviv University, Israel).

Dementia

David M Blass (Johns Hopkins University School of Medicine, Baltimore, USA) discussed the management of depression and behavioral abnormalities in dementia. He noted that psychiatric disturbances are highly prevalent in dementia patients and may persist for long periods of time. Psychiatric symptoms may have a variety of causes and therefore require careful evaluation, preferably using a structured approach. These symptoms cause significant patient and caregiver suffering, and are associated with nursing home placement. Treatment for these disturbances must be multifaceted and include medications, behavioral interventions, and caregiver education.

Ageing, motor decline, and Alzheimer's disease were covered by another of the symposium directors, Aron S Buchman (Rush University, Chicago, and Sheba Medical Center, Tel Aviv). He noted that age-related motor decline is common even among persons without overt disease but its biology is poorly understood. The prevalence of traditional neurological diseases (e.g. cerebrovascular disease, Parkinson's disease, amyotrophic lateral sclerosis and Alzheimer's disease) or geriatric syndromes (e.g., frailty and sarcopenia) do not account for the ubiquitous occurrence of impaired motor function in older persons without overt disease. Recent work suggests that the presence of subclinical common brain pathology, as well as degenerative changes in neural elements from the spinal cord and muscle, may contribute to age-related motor decline. Next year's symposium is already in the planning stage. We hope to see you there!

Next meeting planned for Feb. 16 and 17, 2009 in Tel Aviv, Israel. Planned topics include stroke, autoimmune diseases, neuromuscular diseases and EMG, epilepsy and EEG, movement disorders, botulinum toxin in neurology, and infectious diseases of the nervous system.
Visit our website at
www.neurophysiology-symposium.com/
for updates

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International Leksell Gamma Knife Society Meeting

18-22 May, 2008; Quebec, Canada

At the 14th International Leksell Gamma Knife Society Meeting, over 500 participants including neurosurgeons, radiation oncologists and other medical specialists using Leksell Gamma Knife for treatment of tumours and other brain disorders convened at the historic Château Frontenac Hotel in Quebec, Canada. During the meeting, 260 oral and poster presentations covered treatment of malignant and benign brain tumours, functional neurosurgery, imaging & biology as well as physics & technology. On Wednesday, May 21, the prestigious Pioneers in Radiosurgery Award was presented to John Flickinger, MD, Professor of Radiation Oncology and Neurological Surgery at the University of Pittsburgh for his early pioneering work on prediction of complications following Gamma Knife surgery.

The Leksell Gamma Knife Society was established in 1989 to provide a forum for Gamma Knife users to share information, experiences, clinical techniques and advanced scientific research in their quest to non-invasively treat an expanding number of brain disorders. The meetings, which are held biannually, result in a large number of clinical publications, in recent years published as a supplement to Journal of Neurosurgery. The Society plays an important role in increasing the visibility and acceptance of Gamma Knife surgery in the worldwide medical community, among healthcare providers and among patients. The open sharing of results and experiences allows all Gamma Knife users to maintain leadership in the field of intracranial radiosurgery, based on the most recent clinical advancements.

The 14th meeting in Quebec was held with the theme, 'Je me Souviens' ('I Remember'), which is the motto of Quebec. The theme connects the celebration of Quebec's 400 year long history with the 40 year long history of Gamma Knife surgery.

Pioneers in Radiosurgery Award

John Flickinger, MD, is Professor of Radiation Oncology and Neurological Surgery at the University of Pittsburgh, and recipient of this year's Leksell Gamma Knife Society Pioneers in Radiosurgery Award. Bestowed upon researchers who have consistently pioneered new approaches and methods that enhance the results of Gamma Knife surgery, Dr Flickinger pioneered the 'integrated logistic formula' for prediction of complications in his landmark paper of 1989. He has since conducted numerous studies on dose effects of Gamma Knife surgery in a diverse group of pathologies.

Previous recipients of the Pioneers in Radiosurgery Award include Steven Rasmussen, MD, and Richard Marsland, R.N. of Butler Hospital, Rhode Island; and Christer Lindquist, MD, of Cromwell Hospital, London, UK. They were awarded for their work in the treatment of Obsessive Compulsive Disorder using Gamma Knife surgery.

Leksell Gamma Knife Perfexion

During the Society meeting, a special lecture was held by Professor Jean Regis, from University Hospital La Timone in Marseille, France. Professor Regis and his team has now treated over 800 patients with Leksell Gamma Knife Perfexion, a new, completely revised and fully robotised Gamma Knife and the most advanced technology for radiosurgery available on the market. The presentation by Professor Regis highlighted the unique dose shaping capabilities of Leksell Gamma Knife Perfexion, treating a broader range of targets, much faster and more efficiently than ever before.

Now in clinical use in over 30 locations worldwide, Leksell Gamma Knife Perfexion combines the proven precision of the revolutionary Leksell Gamma Knife with a 300 percent expansion in clinical reach to treat a wider range of targets faster and more efficiently than ever before. The system's unique geometric and dosimetric design simultaneously administers hundreds of beams of low-intensity radiation that converge to deliver a single, therapeutic dose of radiation with pinpoint accuracy to the most difficult targets. Integrated treatment planning and delivery streamlines the radiosurgery process to treat even multiple brain lesions in a single, automated procedure.

Meeting the needs of both neurosurgeons and radiation oncologists, nearly 50,000 patients undergo Gamma Knife surgery every year on the several hundred Leksell Gamma Knife systems installed worldwide. The unique procedure has earned an outstanding scientific track record with thousands of peer-reviewed articles on treatment efficacy, improved quality of life for patients and cost efficiency..

For further information contact Peter Ejemyr, E. peter.ejemyr@elekta.com

The Duodopa Debate

The effective treatment of motor complications is a challenge for all clinicians caring for patients with advanced Parkinson's disease (PD). During the XVIIth World Congress on Parkinson's Disease and Related Disorders (9-13 December 2007, Amsterdam, the Netherlands), delegates to a stand-alone meeting met to debate the place in therapy of Duodopa (co-careldopa) intestinal gel. This recently available treatment is indicated in the UK for patients with advanced levodopa-responsive PD with severe motor fluctuations and dyskinesia that do not respond to other medical treatments.

The Faculty

Chairman: Professor Andrew Lees, Consultant Neurologist, London

"This house believes that Duodopa should be used prior to deep brain stimulation in advanced Parkinson's disease patients"

For the motion

- Professor Anthony Schapira, Consultant Neurologist, London
- Dr David Stewart, Consultant Physician, Medicine for the Elderly, Glasgow
- Dr K Ray Chaudhuri, Consultant Neurologist, London

Against the motion

- Dr Donald Grosset, Consultant Neurologist, Glasgow
- Dr Doug MacMahon, Consultant Physician, Medicine for the Elderly, Redruth
- Dr Paul Worth, Consultant Neurologist, Norwich

For the motion

It is true that, compared with oral PD medication, deep-brain stimulation (DBS) improves motor control and reduces dyskinesia in advanced PD.[1] However, the treatment has important limitations. Older people form the majority of the PD population, but DBS may not be appropriate in this age group because, although DBS reduces motor complications in both older (mean age 69 years) and in younger (mean age 57) patients, postoperative quality of life improves only in younger people.[2]

DBS is generally well tolerated, but it is associated with important adverse effects. A recent wide-ranging, 10-year, retrospective meta-analysis of outcomes in 10,339 patients reported 6,573 device-related adverse events, including infection (16%), explantation (15%), lead fracture (14.7%) erosion (14%), battery failure (2.1%) and intracranial haemorrhage (2%). This study also drew attention to a risk of serious psychiatric adverse events, including completed suicide in 11 patients.[3]

Such retrospective analyses are open to reporting bias, but prospective studies also demonstrate a significant association between DBS and cognitive and psychiatric adverse events. These include significant declines in verbal memory,[4] cognitive problems,[5] and suicide or attempted suicide.[6] There are many potential reasons why DBS might affect cognitive function; a recent study concluded that DBS selectively interferes with the normal ability to slow down when faced with decision conflict; indeed patients speed up their decision making when faced with high-conflict conditions. This impulsivity differs from that seen in association with dopamine agonists, which impair the ability to learn from negative experiences.[7]

Duodopa infusion is therefore an alternative to DBS for advanced PD patients with severe motor fluctuations and dyskinesia. Compared to conventional oral levodopa, Duodopa provides smoother levodopa plasma levels,[8] resulting in an average increase in 'on' time without severe dyskinesia, greater overall improvement in Unified Parkinson's Disease Rating Scale (UPDRS) total scores and statistically significant improvements in quality of life.[8]

Levodopa was introduced into clinical practice over 40 years ago, and there are 25 years' experience of levodopa infusion in patients with advanced PD. Treatment with Duodopa involves surgery for placement of the percutaneous endoscopic gastrostomy (PEG) tube but, unlike DBS, this is a common procedure that is reversible. Long-term costs are of course important and Duodopa infusion is more expensive than DBS. It is, however, important to bear in mind the continuing costs of oral PD medication following DBS. Treatment with Duodopa can potentially abolish the need for oral treatment and, since it is a treatment in evolution, we can expect to see improvements in the use of the product as clinical experience grows.

DBS is undoubtedly an excellent treatment for some patients with advanced PD, but it is essential to give patients an informed choice from among all appropriate treatments. In short, as doctors, we should consider and offer Duodopa to our patients, both in preference to and as an alternative to surgery.

Against the motion

Like levodopa, targeted brain lesioning has a long history. Earlier procedures such as pallidotomy, although destructive, involved tiny areas of targeted ablation. DBS as currently performed is not a lesion, but a non-destructive, programmable, technologically advanced intervention that specifically targets the site of the primary problem in advanced PD. Over 30,000 patients worldwide have undergone DBS. Its beneficial results are sustained in the long-term whether stimulation is targeted to the subthalamic nucleus (STN) or the global pallidus internus (GPI), and there is added improvement in symptoms when DBS is combined with oral medication.[9]

There is some long-term experience with Duodopa in a small series of 28 patients, albeit with a total infusion time of 87 patient years (median 44 months, range 2-83 months). The authors reported that mean daily levodopa was reduced by a median of 1% and at the end of the study 12 patients were taking oral anti-parkinsonian drugs. Like any surgery, including DBS, Duodopa is associated with adverse effects and the need for further intervention, including in this series transient postoperative infections in six patients, 162 X-ray and fluoroscopic examinations, and 35 gastroscopic changes or catheter adjustments. After a median of 33 months (range 13-67), six patients had returned to oral therapy: two reported decreasing effect (both developed symptoms of multiple system atrophy), three encountered problems in handling the infusion system after developing dementia, and one experienced no improvement in symptoms.[10]

DBS is not appropriate for all patients with advanced PD, but neither is Duodopa. DBS smoothes out, but does not cure, motor fluctuations, and bilateral surgery is often required. Surgery improves tremor, ridigity, bradykinesia and dyskinesia, but it does not eliminate these symptoms. It will not improve symptoms that are unresponsive to anti-parkinson medication. Many, but not all, patients need less oral anti-parkinsonian medication, but they do need to attend frequent programming visits during the first six months after surgery, with subsequent follow-up visits and multiple adjustments in the stimulator and medication.[11]

In the UK, the costs of DBS surgery itself, follow-up visits and probable continuing need for medication amounts to £25,000-£30,000 over five years[12]. This sum is, however, equivalent to the cost of the first year's treatment with Duodopa, taking into account initial placement of the PEG, follow-up visits and the cost of the drug itself[13]. This debate concerns the order of treatment, rather than a choice between Duodopa and surgery. DBS is worth considering before Duodopa on grounds of its cost implications as well as its proven effectiveness in treating the motor symptoms of advanced PD.

Proceedings of a Solvay Healthcare meeting held during the XVIIth World Congress on Parkinson's Disease and Related Disorders, December 2007

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Professor Andrew Lees: Chairman's Summary

"The more options available to deal with the motor problems of advanced PD, the better. Duodopa and DBS are both important, and my concern is not which to use, but that patients may not be considered for either therapy. I hope that this debate will help to highlight the potential roles of both Duodopa and DBS in people with advanced PD."

Questions from the Audience

Q "I am concerned about the timing of surgery, given the comparatively brief follow-up to date and the very narrow two year window of opportunity for referral."

Answer 1:

"In my experience, two years usually allows sufficient time in which to make a decision about surgery. I would not recommend earlier referral until there is strong evidence of a good and sustained effect from the intervention." (Dr Grosset)

Answer 2:

"Patients who are relatively young – for example, in their 50s – do ask about DBS when they are still well controlled on oral therapy, and at present surgery is inappropriate in such patients. When patients develop advanced PD and oral therapy no longer controls their motor symptoms, the issues then concern when to perform surgery, its limited availability in the UK and the risk of cognitive problems associated with DBS." (Professor Schapira)

Q "Most PD patients will develop motor complications if they live long enough, so why is it not appropriate to refer them for surgery before they experience these symptoms?"

Answer:

"It is very difficult to refer a patient, who is well controlled on oral medication, for a procedure that that is associated with a finite, albeit low, risk of significant morbidity and mortality. For this reason, surgery is at present only appropriate in patients with advanced PD. Furthermore, there are some data indicating that stimulation of the STN and GPI is no better than maximised oral therapy. DBS is a good therapy and a major advance, but we should carefully consider the sequencing of treatment and offer an alternative – that is, we should insert Duodopa into our and our patients' paradigm." (Professor Schapira)

Q "I believe that we should remember the significant risk of irreversible complications with DBS. Duodopa complications are relatively rare and the therapy derives from an alteration in the pharmacokinetics of a familiar drug. Based on current evidence, we should follow the standard therapeutic model in which a medical therapy like Duodopa is used before surgery."

Answer:

"There are other important issues such as operator dependence. Gastroenterologists regularly perform gastrostomies, and so it should be straightforward to find a skilled and experienced surgeon to reproduce the results with Duodopa seen in the literature. This contrasts with DBS, and I question whether it is possible to generalise results reported from expert centres to the average neurosurgical unit." (Dr Stewart).

DBS in PD: a mnemonic for PD patients[11]

Does not cure
Bilateral DBS is often required to improve gait, although sometimes unilateral DBS has a marked effect on walking
Smoothes out on/off fluctuations

Improves tremor, stiffness (rigidity), bradykinesia and dyskinesia in most cases, but may not completely eliminate them
Never improves symptoms that are unresponsive to your best 'on'. For example, if gait or balance does not improve with best medication response, it is very unlikely to improve with surgery

Programming visits are likely to occur many times during the first six months and then follow-up visits as frequently as every six months. There will be multiple adjustments to the stimulator and in the medication
Decreases medication use in many, but not all patients

Comparison of Duodopa and deep-brain stimulation

Duodopa infusion	Deep-brain stimulation
Improves motor control	Improves motor control
Reduces dyskinesias	Reduces dyskinesias
Well tolerated with good side-effect profile	Mostly well tolerated, but some serious morbidity/mortality
Widely available technique	Limited availability confined to Tertiary specialist neurosurgical centres
PEG reversible	Lesion not reversible
Long-term economics?	Long-term economics?

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Discussions from this meeting were recorded and written up by Sue Lyon, medical freelance writer

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The Parkinson's Disease Nurse Specialist Association

The Parkinson's Disease Nurse Specialist Association, [PDNSA] is a professional organisation with membership throughout the UK and overseas.

The objective of the Association is to act as a national resource and network for nurses and other healthcare professionals to share knowledge, expertise and best practice about Parkinson's disease and its management locally, nationally and internationally. It represents a body of healthcare professionals with an interest in Parkinson's and works in collaboration with the Department of Health, the Parkinson's disease society, The Royal College of Nursing, The British geriatric Society and the British and Irish Neurologists Movement disorders group.

Full membership of the PDNSA is available to Parkinson's Disease Nurse Specialists who are employed primarily in the practice of Parkinson's disease in primary and secondary care in the United Kingdom. Associate membership is open to any person who wishes to join the Association and is not eligible for full membership. Overseas Membership is open to any person who wishes to join the PDNSA and is not resident in the UK. Overseas members assume the same status as associate members. Honorary membership is awarded to individuals who have made a considerable contribution to the advancement of Parkinson's Disease Nurse Specialists. The PDNSA Committee are responsible for awarding honorary membership.

Membership entitles you to;

- 'Transmitter' our newsletter, which is published three times per year. This is an excellent forum to share best practice, experience, and inform others of current issues and developments.
- Any relevant documents published with support from the PDNSA.
- Reduced rate at our annual conference.

Professor Sir George Castledine has recently become the associations president and will be the keynote speaker at our annual conference which this year is being held on Monday 6th October and Tuesday 7th October. It is being held at the Scarman centre at Warwick University, the programme will be available very soon. The conference covers both clinical and professional issues and is an excellent opportunity for networking. We welcome new members.

To find out more about the association visit www.pdnsa.net

EDITOR'S CHOICE

Transplants, Lewy bodies and Parkinson's disease – a new link?

The use of fetal ventral mesencephalic dopaminergic cell therapies for Parkinson's disease has been a contentious treatment since its first use in the late 1980s. Its proponents point to the success of individual patients who have remained on low doses of medication for many years after their transplant. Their opponents refer to the two double-blind placebo controlled trials, published in 2001 and 2003, which showed no significant clinical benefit over sham surgery. Thus the field is in a state of indecision. A series of articles in a recent issue of *Nature Medicine* further complicates the situation as these papers report alpha synuclein pathology in these transplants.

The rationale for using ventral mesencephalic transplants in Parkinson's disease is to replace the dopaminergic cell loss that characterises this disease. By using the developing dopaminergic cells of the fetal midbrain, derived from elective terminations of pregnancies (abortions), the expectation is that they survive and mature into fully functional adult dopaminergic neurons and replace the function of the patient's own nigral dopamine cells that have been lost in the disease process. To date this approach has been seen to work, insomuch as dopamine cells so transplanted have survived long term and some individuals have shown marked improvement with evidence for dopamine release from the transplants and restoration of normal cortical motor activation. However the results are inconsistent. These new papers now also highlight that the pathology of PD may occur in the transplants. In two of these, the authors report on alpha synuclein positive elements within the transplant despite the fact that these dopamine cells are only 10-15 years old. Whether this pathology affects the functional efficacy of the transplant is unknown, as the patients reported in these papers did not derive a huge benefit from the transplant. Thus, it is not known whether these pathological abnormalities have implications for the cell transplant approach to Parkinson's disease, especially given that the remaining paper reports that the graft is free of PD pathology. So these papers certainly do not spell an end to fetal ventral mesencephalic allografting for PD. Perhaps of greater interest is what this says about the pathogenesis of Parkinson's disease, as it would imply that the diseased brain can induce pathology in normal dopaminergic cells. In other words, either the glia in the PD brain or some trans-synaptic communication from diseased neurons to grafted neurons, can induce alpha synuclein aggregation in 'non-PD' dopaminergic nigral neurons. Thus, the disease may be self propagated within the CNS once some critical pathological event has occured. It is this which is the most important message of these papers, rather than anything to do with cell transplants and their future use in patients with Parkinson's disease. – ***RAB***

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NATURE MEDICINE
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EPILEPSY: Should patients with bad brains be considered for epilepsy surgery

Bad brains as evidenced by low IQ mean a poor prognosis for epilepsy surgery, or so the received wisdom goes. In the Swedish National Epilepsy Surgery Register, 448 patients were operated from 1990 to the date of publication and of these 18 had IQ < 50 and 54 had IQ 50-69. When low IQ groups were compared to higher IQ groups it was clear that the median seizure frequency correlated inversely with IQ; patients with IQ <50 had a median seizure frequency of more than 100 per month compared with 10/month in the temporal lobe cohort and 30/month in the cohort with IQ > 70. The ratio of temporal lobe versus extratemporal resections was similar in all the groups. Seizure-freedom at two years was achieved in 80% of those with IQ>70, 36% of those with IQ 50-70 and 22% of those with IQ<50, another 22% achieving >75% seizure reduction and a further 35% > 50% seizure reduction. The likelihood of seizure freedom was predicted by histopathological lesion type in all groups, with lesions doing better than cortical malformations or gliosis. IQ was an independent predictor of seizure outcome. Three of five patients in the lowest IQ group who had a lesion underlying their epilepsy became seizure-free. This means that only one of the remaining 13 became seizure free. So in the lowest IQ group, unless there is a clear lesion underlying the epilepsy, it is hard to give an unreserved recommendation for surgery. We clearly need more data on quality of life benefits of lesser degrees of seizure reduction in this cohort, as well as longer term follow-up, as lesser levels of seizure reduction may (or may not) be useful. This is clearly a retrospective study in which only the best candidates were offered surgery and it does not give enormous ground for optimism. – ***MRAM***

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BRAIN
2008;313:535-42.

GUILLAIN BARRE: a new treatment?

Despite all our cleverness with ITUs and IVIG, people still die from Guilllain-Barre and its variants. One such is the Miller Fisher syndrome: ophthalmoloplegia, ataxia and areflexia. We could do with a better treatment. And Hugh Willison and colleagues from Glasgow and the Netherlands may have come up with just that. The key step in their study was getting hold of a monoclonal antibody against the ganglioside GQ1b. This mimics the antibody produced in vivo during the disease. Using this antibody both in vivo and in an in vitro model (mouse hemi-diaphragm), they had shown that this antibody disrupts pre-synaptic neuromuscular junction signalling. Crucially, this only occurs through activation of complement and formation of the membrane attack complex. Enter eculizumab. This humanised monoclonal antibody prevents formation of the C5 components and thus disables the complement pathway. Very happily, it is already a licensed therapy: for that curious illness paroxysmal nocturnal haemoglobinuria, in which there is complement-mediated haemolysis. Does it work to suppress experimental Miller Fisher? In short, yes. An impressive array of data, from histology, immuno-histochemistry, electrophysiology and electron microscopy, confirms that pre-treatment with eculizumab successfully prevents the damage done by anti-GQ1b antibodies. Unfortunately, the experimental monoclonal caused damage so rapidly, it was not possible to test the more real-life situation of treating with eculizumab after the disease has started. Against all the odds, it seems there is a real prospect of a new agent for the treatment of Guillain-Barre syndrome… provided the relevant drug company (for your stockbroker: Alexion Pharmaceticals) can be persuaded to invest in the necessary trials. – ***AJC***

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STROKE: Robots can help recovery of hand function

It is recognised that task specific training with lots of repetition is important for optimising motor recovery following stroke. The problem in many stroke services with resources is how to deliver intensive practice. The provision of robots to assist therapy may provide a solution in the future. A

number of groups have developed robotic based systems for helping people to practice goal directed arm movements, concentrating mainly on the elbow. Early phase studies have produced promising improvements in performance, however without a functioning hand there is little point in moving the arm. Perhaps because of its greater complexity the hand has been neglected in rehabilitation robotics. Now in a paper by Takahashi et al. it appears advances have been made to address this omission. In Brain they report a behavioural evaluation with investigation of the specificity of the robot assisted therapy effects on brain reorganisation. The actuated device developed and evaluated by Takahashi et al. helps the hand in grasp and release movements by assisting flexion and extension of the fingers, thumb and wrist. Patients use the device in conjunction with some virtual reality games or with real objects to perform grasp and release actions. The robot-assisted therapy programme emphasises movement repetition as well as attention, speed, force, precision and timing. Task difficulty is also adjustable to avoid ceiling and floor performances. Thirteen patients with chronic stroke resulting in moderate weakness in the right hand were recruited for evaluation using the robotic system and programme. After two baseline assessments (over two weeks) the participants followed the therapy programme for 15 days. However seven of the participants were given assistance from the robot for all 15 days while the remaining six, although strapped into the apparatus, were only given assistance from the robot after the first 7.5 days of treatment. The groups were allocated by a pseudo random method. Outcome was measured after the first 7.5 days, after 15 days and at a follow up one month later. FMRI scans were carried out during the baseline period and after the completion of the 15 day course of treatment. During the scans the participants performed a target grasp and release action and a control (unpractised) task involving pronation and supination of the forearm. Of course the sample was a small select group, but nevertheless the results were impressive: significant gains on both a hand function and an impairment level assessment were found at the end of treatment and these benefits were still present at follow up. The participants who received robotic assistance in all sessions made greater gains than those who received robotic assistance in only half of sessions. The grasp task performed during fMRI showed increased sensorimotor cortex activation across the period of therapy, while the non-practiced task, supination/pronation did not. Takahasi et al have shown that their robotic system and therapy program based on motor learning theories can improve hand function and that the assistance of the robot to perform the practice is helpful in achieving this. Given the equity of the intensity of practice this finding may be considered surprising. Shouldn't those who had to do the tasks more independently have done better than those who received assistance everyday? The authors suggest that by providing assistance the movements produced are wider in range of motion, more normally coordinated, and thus provide a larger and more organised afferent signal to brain sensorimotor areas, which could be important for recovery. While this may be the case, the fMRI results emphasise another principle that can be applied to rehabilitation in general and not just to robot assisted therapy: task specific practice is important for the recovery. **– *AJT***

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BRAIN
2008;131:425-37.

MULTIPLE SCLEROSIS: Pathologists awry

Since people have been studying the plaques of multiple sclerosis for over one hundred years, you would have thought their basic histology would be sorted by now. But, if anything, we are more in disarray today than we ever were. For the recent literature contains apparently irreconcilable results. In 2000 Hans Lassman, Claudia Lucchinetti and others published an oft-quoted study, in which they classified plaques into four types… and, importantly, insisted that only one type appeared in each patient. So multiple sclerosis is heterogeneous between patients, but homogenous within an individual. Now Esteher Breij, Lars Bo and colleagues from Amsterdam have completely contradicted this work. They studied 131 lesions from 39 patients with definite multiple sclerosis, from the Dutch Brain Bank. They showed homogenous pathology of active demyelination amongst all patients, with deposition of complement and macrophage-associated immunoglobulin in all cases. There may be a simple explanation for the controversy. Breij studied post-mortem material from patients with established multiple sclerosis, present for a median of 22 years. In contrast, Claudia Lucchinetti had examined 81 cases of acute multiple sclerosis, 49 from biopsy samples. As all clinicians know, the need for a brain biopsy suggests the patients had very atypical multiple sclerosis, at least at presentation. So perhaps there is no real debate and the described differences are just those between early, fulminant disease and established multiple sclerosis. **– *AJC***

Breij EC, Brink BP, Veerhuis R, van den Berg C, Vloet R, Yan R, Dijkstra CD, van der Valk P, Bö L.
Homogeneity of active demyelinating lesions in established multiple sclerosis.
ANNALS OF NEUROLOGY
2008 Jan;63(1):16-25.

BRAIN REPAIR: how stress alters fate

What happens to neural precursor cells (NPCs) when they are exposed to oxidative stress or at least manipulation of local redox states - a state that is probably altered in most neurological conditions? The answers, from this Nature Cell Biology paper, from a series of in vitro and in vivo studies are:

1. that E17.5 mouse cortical NPC have reduced proliferation as measured by Ki67 or BrdU.
2. astroglial differentiation is promoted at the expense of neurons, with the opposite occurring in reducing conditions. There is no change in oligodendrocyte differentiation nor in the proportion of monopotent or bipotent NPCs, suggesting there is a switch in the differentiation process rather than a selective growth of different types of NPCs.
3. there is increased expression of Sirt1- a class III NAD dependent histone deacetylase - without there being any change in neural transcription factors. This mediates the shift in differentiation as blocking it using siRNA, or increasing its activation using resveratrol, has the anticipated effects on the differentiation profile in oxidatively stressed NPCs.
4. The downstream mechanism by which Sirt1 exerts this effect involves a co-operative action with the transcription factor hes1. They then act together on the promoter region of Mash1, which is an important transcription factor in normal neuronal differentiation. This effect on Mash1 also involves the TLE1 containing co-repressor complex.
5. To look at the in vivo relevance of this work, the authors then go to show that Sirt1 and Mash1 are expressed in one of the major sites of neurogenesis in the adult brain- namely the subventricular zone. They also demonstrate that their expression are altered by the oxidative state in these P2 mouse brains with a change in the differentiation profile as predicted from the in vitro studies.
6. Finally the expression of Sirt1 in Experimental Allergic Encephalomyelitis (EAE) was investigated. EAE is an animal model of autoimmune demyelination often used to model MS. In this model it was shown that areas of inflammation with astrogliois had marked Sirt1 upregulation in GFAP positive cells, which could be further increased with the Sirt1 activator resveratrol.

Therefore this group has revealed a clear pathway by which the differentiation fate of NPCs can be changed by the local redox state, although how this plays out in disease is unknown- outside of their interesting observations in EAE. Whatever its exact significance, it does show that relatively subtle local changes in the brain may impact on its innate ability to repair itself. **– *RAB***

Prozorovski T, Schulze-Topphoff U, Glumm R, Baumgart J, Schröter F, Ninnemann O, Siegert E, Bendix I, Brüstle O, Nitsch R, Zipp F, Aktas O.
Sirt1 contributes critically to the redox-dependent fate of neural progenitors.
NATURE CELL BIOLOGY
2008;10:385-94.

Two clinical neurologists elected Fellows of the Academy of Medical Sciences

Professor Masud Husain (pictured left) (Institute of Neurology and The National Hospital for Neurology & Neurosurgery, London) and Professor Peter Rothwell (pictured right) (University of Oxford) are among forty newly elected Fellows of the Academy of Medical Sciences. Fellows are selected primarily for their exceptional contribution to the advancement of medical science either in the form of original discovery or of sustained contributions to scholarship, or for the application of existing scientific knowledge or understanding in an innovative way, so as to bring about advances in human health and welfare.

They attended an Admission Ceremony on the 24th of June which included talks from Professor Sir John Bell FRS PMedSci, Professor Stephen O'Rahilly FRS FMedSci and five new Fellows. The celebration was held at the Royal Society, 6 Carlton House Terrace, London.

For more information contact:
Web. www.ion.ucl.ac.uk

Two Michael J Fox awards for UCL Parkinson's research

Two teams at the UCL Institute of Neurology (Department of Molecular Neuroscience) have received grants from the Michael J Fox Foundation for Parkinson's Research. The Foundation's Rapid Response Innovation Awards are given in support of high-risk, high-reward projects aimed at tackling some of the major obstacles to developing therapies for Parkinson's disease. Grants are made on a rolling basis, with decisions taken within six weeks of the submission of applications. Eighteen such awards, to institutions all over the world, have just been announced, including two at UCL.

Professor John Hardy

Drs Henry Houlden and Coro Paisan-Ruiz applied for funds for a study on 'The Glucosylceramide Pathway in Parkinson's Disease and Other Synucleinopathies: Genetic Defects, Neuropathological Characterisation and Cell Culture Models'. The application from Dr Patrick Alfryn Lewis and Professor John Hardy was entitled 'A Novel Cell Model for LRRK2 Parkinson's Disease'.

Parkinson's disease affects about 120,000 people (one in 500) in the UK. It is hoped that both UCL studies will yield results that will soon have an impact on the treatment of the condition.

For more information contact:
Web. www.ion.ucl.ac.uk

Autism Centre honours pioneer

The National Autistic Society's Centre for Social and Communication Disorders was renamed The NAS Lorna Wing Centre for Autism on the 13th of May, in recognition of Consultant Psychiatrist Dr Lorna Wing's pioneering contribution to the study and understanding of autism.

Set up by Dr Lorna Wing in 1991, the centre was the first in the country to provide a complete diagnostic, assessment and advice service for children, adolescents and adults. The NAS Lorna Wing Centre for Autism now specialises in the diagnosis of individuals with complex needs and in training professionals in methods of diagnosis. As the mother of a daughter with autism, Lorna Wing was a founder member of The National Autistic Society in 1962 and has published widely on all aspects of autism spectrum disorders both in the UK and worldwide.

Jane Asher (left) and Dr Lorna Wing.

Attendees at the ribbon cutting were Dr Lorna Wing and NAS president and actress Jane Asher (pictured left).

For further information contact:
The National Autistic Society,
Tel. 020 7903 3546,
Email. matthew.stocks@nas.org.uk
Web. www.autism.org.uk

SonoSite receives international design award

SonoSite, Inc., the world leader and specialist in point-of-care, hand-carried ultrasound, has received a prestigious International Forum (iF) design award for its new S-Nerve™ ultrasound tool, in the Health+Care category. An international jury evaluated 2,771 entries based on design, functionality, aesthetics, innovation, workmanship and choice of materials.

The S-Nerve tool, part of SonoSite's recently introduced S Series™ product line, has been custom-designed with breakthrough image quality, speed and simplicity to support the visualisation needs of regional anaesthetists. It was designed with input from leading practitioners who expressed a substantive need for a compact, high-performance tool, to function exclusively for guidance of regional nerve blocks and central line placement.

The S-Nerve device, like other products in SonoSite's S Series line, is a radically new concept in ultrasound and offers the option of a 'zero' footprint by being mounted on a wall, the ceiling or on a pole by the patient's bedside. Dr Ian Harper, Consultant in Anaesthesia at Wansbeck Hospital in Northumberland, UK, commented: "The vertical orientation and mounting of the machine is a logistical improvement. Whoever designed this product got it exactly right."

The S-Nerve ultrasound tool will be on display with other award-winning products at the International Congress Center in Hannover, Germany, until August 31, 2008.

For more information contact:
Tel. +44 (0)1462 444 800,
Fax. +44 (0)1462 444 801,
Email. europe@sonosite.com www.sonosite.com

Young researchers recognised at Magstim TMS Summer School 2008

Magstim has announced the winners of both the Magstim Young Investigator Award 2008 and the Summer School Poster Session during the first day of the Magstim Transcranial Magnetic Stimulation (TMS) Summer School 2008, held in London on 30th – 31st May. Both awards recognise the scientific research of those working with magnetic stimulation within the fields of Neuroscience and Neurology.

Dr Marco Davare, University College London (UCL), Institute of Neurology, Sobell Dept of Motor Neuroscience and Movement Disorders has been awarded the Magstim Young Investigator Award 2008 for his work studying how the brain controls skilled hand movements.

PhD student Niamh Kennedy, Queen's University Belfast, School of Psychology was awarded the Poster Prize for her Poster on the effect of simultaneous contractions of ipsilateral muscles on changes in corticospinal excitability induced by paired associative stimulation (PAS).

For more information contact:
Catherine Stormont,
Tel.+44 (0)1489 557672,
Email. catherines@alto-marketing.com

From left to right: Magstim Young Investigator Award winner Dr Marco Davare with Professor Vince Walsh, Dr Heidi Johansen-Berg, and Poster Prize winner Niamh Kennedy.

ReQuip XL® - a new once daily formulation for the treatment of Parkinson's disease

GlaxoSmithKline (GSK) have launched a new treatment for Parkinson's disease (PD) in the UK. ReQuip XL® (ropinirole prolonged-release tablets) is the UK's first and only once-daily non-ergot oral dopamine agonist available for the treatment of PD, providing continuous delivery of ropinirole from a single daily dose.

Ropinirole prolonged-release is approved for the treatment of idiopathic Parkinson's disease (Monotherapy and Adjunct Therapy) in patients already taking ropinirole immediate release tablets and in whom adequate symptomatic control has been established.

Although a number of therapies are available for the treatment of PD, interim results from a recent pan-European survey of 1,026 people conducted by the European Parkinson's Disease Association (EPDA) suggest that there is still a significant unmet need for the treatment of PD.

The clinical trials programme has demonstrated that ropinirole prolonged-release tablets are an effective agent, generally well-tolerated in the treatment of both early- and advanced stage PD.

GSK has developed the ReQuip Patient

Support Service (RPSS) to offer patients free guidance and support should they decide with their healthcare professional to switch from ropinirole 3x-daily to ropinirole prolonged-release. The RPSS is designed to complement the care provided by their NHS health professionals. The service comprises proactive telephone calls over a three-month period from trained health professionals (including nurses) to patients starting ropinirole prolonged-release tablets, to help ensure a smooth transition from ropinirole 3x-daily to ropinirole prolonged-release.

For further information contact
GlaxoSmithKline UK on
Tel. 020 8990 2144.

The new A1 series from Nikon

Even the most rapid biological processes can now be captured at ultra high resolution as a result of the launch of a new range of confocal laser scanner systems by Nikon Instruments. Two models are available; the fully automated A1 and the high specification A1R. The A1 utilises conventional paired galvanometers producing high resolution images (up to 4096 x 4096 pixels), whilst the A1R incorporates a unique hybrid scanner system (offering frame rates of 30fps, 512 x 512 pixels). This facilitates ultra-high-speed imaging with unsurpassed image quality. Furthermore, the hybrid scanner enables simultaneous photo-activation and imaging, critical for unveiling cell dynamics and interactions.

The new systems are a natural complement to the recently launched Ti inverted microscope, particularly when coupled with Nikon's patented Perfect Focus System, essential for eliminating focus drift. Together they set a new standard for advanced time-lapse studies of rapid cellular interactions to literally bring biological imaging to life.

For more information please contact
Nikon Instruments Europe, Tel. 0208 247 1718,
Email. info@nikoninstruments.eu
Web. www.nikoninstruments.eu

Best practice recommendations for young people with cerebral palsy in transition

The experience of young disabled people with cerebral palsy and other long-term neurological conditions, moving from children's to adult health services can often be traumatic, and in many health settings there is a gap in service provision. To address this 'gap', best practice recommendations entitled 'Young People with Cerebral Palsy in Transition from Paediatric to Adult Health Services: Best Practice Recommendations have been launched this month aimed at all health professionals who are involved in the transition of care of the young person with cerebral palsy.

Mr Richard Parnell, Head of Research at the national disability organisation, Scope said: "Transfer of care and support from the paediatric service to the adult health service is a major step in these young people's lives and it needs to be holistic, taking into consideration all transition issues, not just health. Scope welcomes this document and hopes that health professionals will review transition service provision in their own hospitals".

Further information contact: Ipsen Ltd,
Tel. 01753 627609
Email. access.coordinator@ipsen.com

Zeiss launches 13-megapixel monochrome camera

Carl Zeiss has launched a high resolution, monochrome digital camera optimised to meet the demands of fluorescence microscopy and live cell imaging. The 13-megapixel AxioCam HRm R3 will capture up to 48 images per second.

The new camera produces high resolution images up to 4,164 x 3,120 pixels. The new design features high sensitivity and low noise with a dynamic range of 2,500 resolvable grey scales and 14-bit digitisation. A special NIR mode ensures increased sensitivity in the near infrared.

Two switchable read-out speeds of 12.5 and 25 MHz satisfy the contrasting requirements of very high resolution and high speed with up to 12 images per second at maximum sensor resolution available at 25 MHz. Together with systems comprising Zeiss microscopes and AxioVision software, the sensitivity and high dynamic range enable users to take multidimensional images of even the weakest fluorescence signals emerging from dynamic events.

The AxioCam HRm also offers automated recording of high-resolution colour images via RGB filters mounted in the turret of the microscope in combination with the multi-channel fluorescence module. A colour version of the camera with up to 39 megapixel resolution is also available.

FireWire connection enables compressionless storage of images direct to the computer hard drive. Fast sequences are captured using the digital high-speed recorder module of the Zeiss AxioVision software, which also permits 3D visualisation of image stacks and sequences as well as qualitative and quantitative analyses.

For more information Tel. 01707 871 200, Email. micro@zeiss.co.uk

Olympus sponsors neurotechniques collection

Olympus Microscopy has partnered with the Nature Publishing Group to present the Neurotechniques Collection. This compilation of articles will draw together some of the ground-breaking research that has recently been published in Nature Reviews Neuroscience and Nature Methods. Sponsored by Olympus, this collection will be available free in print and online.

Olympus has a long track record of working with the scientific community. As a proven innovator, Olympus enables scientists to advance their research. Advances in genetics and molecular and cellular biology, together with the development of increasingly sophisticated imaging techniques such as those from Olympus, have allowed neuroscientists to view and manipulate the nervous system in unprecedented ways. The Neurotechniques Collection brings together both original research and relevant, timely reviews that have been published in Nature Reviews Neuroscience and Nature Methods in the last two years. There is also a compilation of Research Highlights written by the editors describing some of the most important advances in this primary research area.

Freely available in a printed supplement, the Neurotechniques Collection will also be accessible as a Web Focus at www.nature.com/focus/neurotechniques and on the Nature Reviews Neuroscience homepage - www.nature.com/nrn/index.html.

For a free copy, please contact Olympus, Email. microscopy@olympus-europa.com

Meiji Techno new range of digital cameras

Meiji Techno has announced the latest in CMOS digital camera technology: With scientific grade, defect free sensors, these high quality cameras are designed to be a cost-effective versatile solution for documentation of microscopy imaging where high resolution is required. The DK Series cameras have great sensitivity and very low noise figures. The included software features include auto and manual white balance, full exposure control and ROI (region-of-interest). The DK Series delivers outstanding image quality for a wide variety of production or scientific applications.

The cameras offer an extended range of user-convenient benefits including a high Speed USB2.0 interface that eliminates having to install cards or other hardware. They use low noise image sensors that deliver crisp colour quality for the most demanding bright-field and darkfield microscopy applications.

Full color sub-windowing allows for rapid focus and scanning of samples. The cameras have Selectable 8 & 10 bit pixel Data modes. Each pixel contains 30 bits of color image information resulting in 1024 intensity values per colour.

The industry standard TWAIN interface results in rapid image capture for archiving and documentation, high throughput applications, demanding research environments and teaching facilities. Drivers and plugins allow support for MatLab R2006, LabView and Image Pro platforms. The DK Series requires no power supply. The camera takes its power from the USB bus, meaning with a laptop, images can be generated in the field.

Visit www.meijitechno.com for more information.

Leksell Gamma Knife® Perfexion™ receives regulatory approval in Japan

The Japanese Ministry for Health, Labor and Welfare, MHLW, has given approval for Leksell Gamma Knife® Perfexion™, the world-leading clinical solution for non-invasive radiosurgical treatments of tumours, vascular malformations and other brain disorders. Elekta, the international medical technology group and developer of Gamma Knife® surgery, will now be able to deliver and install this advanced technology at new and existing customer sites in Japan. Gamma Knife surgery has become the world's most widely used radiosurgery treatment due to its extraordinary accuracy, reduction of excess radiation dose to the body, extensive history and clinical documentation. Unlike other systems, invoking compromises in order to be able to treat the whole body, Leksell Gamma Knife is specifically designed to optimise treatment to the head and neck area – a fact appreciated by neurosurgeons and patients alike.

For further information contact Peter Ejemyr, Email. peter.ejemyr@elekta.com

Alder Hey Hospital installs Artis Zee

The Royal Liverpool Children's NHS Trust, Alder Hey, has installed a biplane flat detector angiocardiography system from Siemens. The Artis zee will carry out general interventional radiology, cardiac and neurological investigations and therapy, supporting the work at one of the largest and busiest children's hospitals in Europe. The Artis zee is flexible in design, ideal for interventional procedures. Its versatile functionality means that vital neurological work can now be carried out at the hospital. Before the installation, patients had to be transferred to The Walton Centre for Neurology and Neurosurgery in Liverpool.

The adaptable system permits examinations at any gantry position whilst ensuring that images are always angled for the best possible visibility. Floor mounted and ceiling mounted C-arms give the radiographer the optimum level of freedom in which to work, including a second isocentric working position that permits free head access to the patient or anaesthesia equipment. The large flat detector provides high contrast resolution to improve accuracy in image-guided procedures at a significantly reduced radiation dose. The system installed at Alder Hey Hospital has been equipped with syngo DynaCT, an application that will be used at Alder Hey for neurological interventions. This will provide CT-like imaging of the head, neck and spine through the Artis system in order to enhance diagnosis and treatment.

Left to right: Dr. Andrew Healey, Consultant Paediatric Interventional Radiologist, Nurses; Lesley Spellman, Sergey Bratukhin and Margaret Gleave; Irene Abbott, Operating Department Assistant, Lilian Taylor, Radiographer.

For more information contact Mike Bell, Tel. 01276 696317, Email. mike.bell@siemens.com

New guidance for paediatric physiotherapists on the use of botulinum toxin

Evidence-based guidance has been produced for paediatric physiotherapists involved in the management of children with neurological conditions, where botulinum toxin may be an adjunctive treatment.

Entitled 'Evidence-based guidance for physiotherapists: the use of botulinum toxin in children with neurological conditions' the guidance has been developed by a UK Working Party of Physiotherapists, with the support of the Association of Paediatric Chartered Physiotherapists (APCP)*. The document addresses the need for specific advice on physiotherapy intervention following botulinum toxin treatment.

Commenting on the launch of the guidance, Lesley Katchburian, Clinical Specialist Physiotherapist at Great Ormond Street Hospital, London and Chair of the Working Party said, "Although the use of Botulinum Toxin A in paediatrics has become more widespread over the last ten years, there is no physiotherapy specific standardised pathway or consensus of practice for providing botulinum toxin injection services for children. The provision of services and practice varies widely throughout the UK. Paediatric physiotherapists have expressed a need for APCP guidance regarding their role in this area of spasticity management".

The guidance reviews current practice and makes recommendations in terms of patient selection, assessment, goal setting and outcome measures, the implementation of a post-injection management programme, communication and audit.

APCP members can request a copy of the guidance on the organisation's website www.apcp.org.uk. Non-members can request a copy of the publication at a cost of £5.00 plus postage and packaging by emailing Sharon Dyer (APCP Administrator) at Email. electrodoc@btinternet.com

Carl Zeiss launches next-generation Confocal Microscope

Carl Zeiss has launched the LSM 710 system. The new microscope boasts a more than doubling in sensitivity and unequalled signal-to-noise performance that will enable users to examine fluorescently-labelled biological systems, including thick living tissue samples, in more detail than ever before.

The performance is due to the LSM 710's new illumination and detection systems. Zeiss' unique QUASAR filter-free spectral detection unit is more sensitive and flexible than any detector previously released on the market and may be configured with 2, 3 or 34 channels. The 34 channel QUASAR allows rapid simultaneous spectral collection of images with a resolution of 9nm over the entire wavelength range. In addition, there is a sequential acquisition mode available that increases spectral resolution to 3nm (available on 2, 3 and 34 channel systems. Significantly, a spectral recycling loop increases the efficiency of the spectral splitting of the fluorescence emissions to almost 100%

The definite focus module maintains a constant focal plane throughout experiments to ensure that images are always in focus. The new microscope also incorporates PTC (pigtailed chain) laser capability, enabling plug-and-play use of to 8 lasers. In addition, the innovative main beam splitter, TwinGate, supports up to 50 laser line combinations, features individually exchangeable filters and offers unparalleled suppression of the excitation laser light for brilliant, high-contrast images. Up to 10 different fluorescent dyes may be resolved and imaged simultaneously, opening up new possibilities for researching multi-labelled cell systems.

For more information Tel. 01707 871 200, Email. micro@zeiss.co.uk

To include your news item in this section contact Rachael Hansford on Rachael@acnr.co.uk

COPAXONE® (glatiramer acetate)

PRE-FILLED SYRINGE
PRESCRIBING INFORMATION

Presentation - Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** - Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients who have had at least two relapses in the preceding two years before initiation of therapy. **Dosage and administration** - 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. Children (<18 years) Not recommended. Elderly No specific data. Impaired renal function No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** - Known allergy to glatiramer acetate or mannitol (excipient). Pregnancy. **Special warnings and precautions** - Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** - No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** - Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** - Injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, lipoatrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 41% of patients receiving Copaxone compared to 20% of patients receiving placebo. >1%: Nausea, anxiety, rash, sweating, chills, face oedema, syncope, vomiting, lymphadenopathy, oedema, nervousness, tremor, herpes simplex, skin benign neoplasm, eye disorder, vaginal moniliasis. Rarely: Anaphylactoid reactions, convulsions, shifts in white blood cell counts, elevated liver enzymes (with no evidence of clinical significance) and skin necrosis at injection sites. Please refer to the SPC for a full list of adverse events. **Overdose** - Monitor, treat symptomatically. **Pharmaceutical Precautions** - Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. **Legal Category** - POM. **Package Quantity and Basic NHS Cost** - 28 pre-filled syringes of Copaxone: £545.59. **Product Licence Number** - 10921/0023. **Further Information** - Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB **Date of Preparation** - September 2007.

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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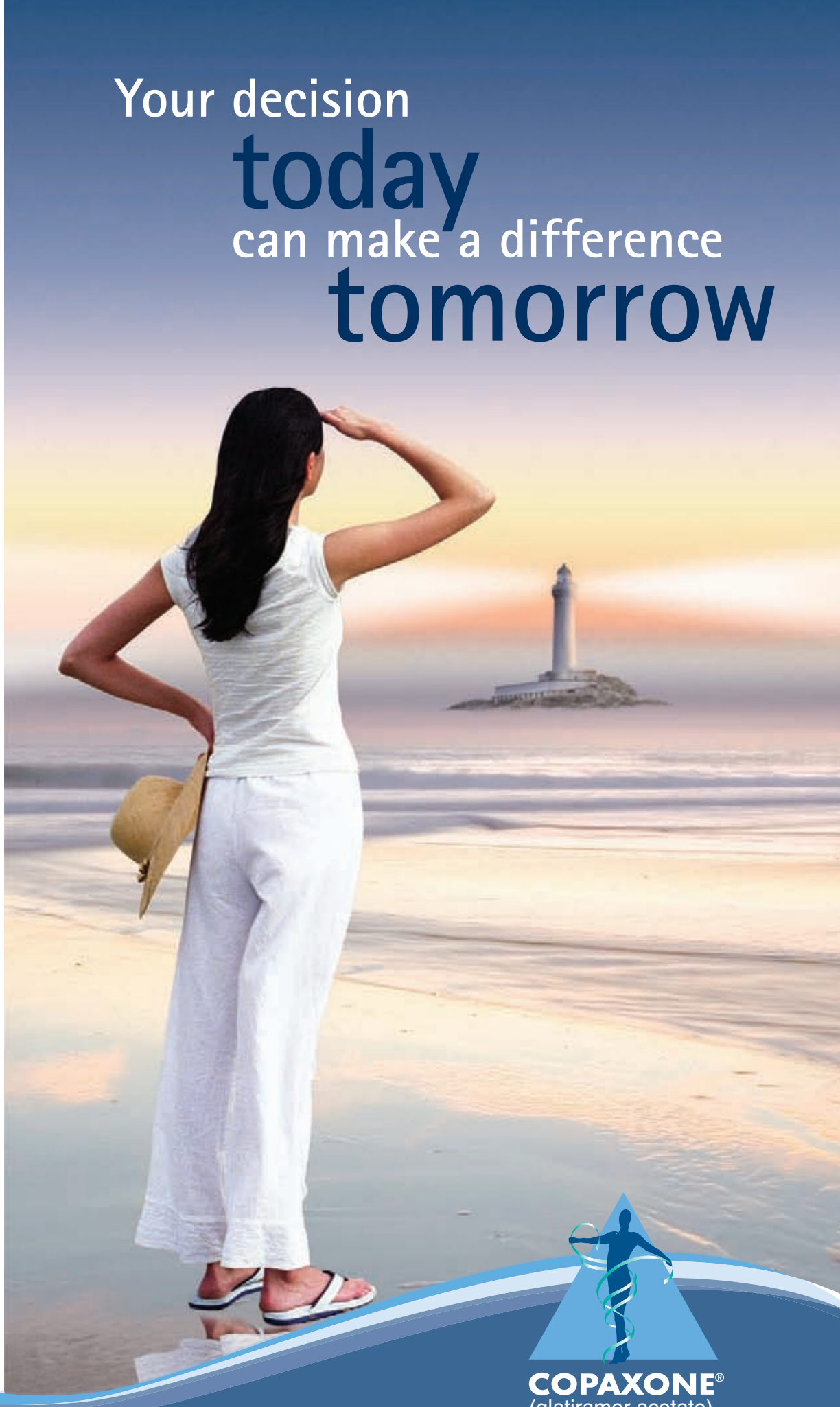

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Date of preparation: October 2007 Code: C0807/428a