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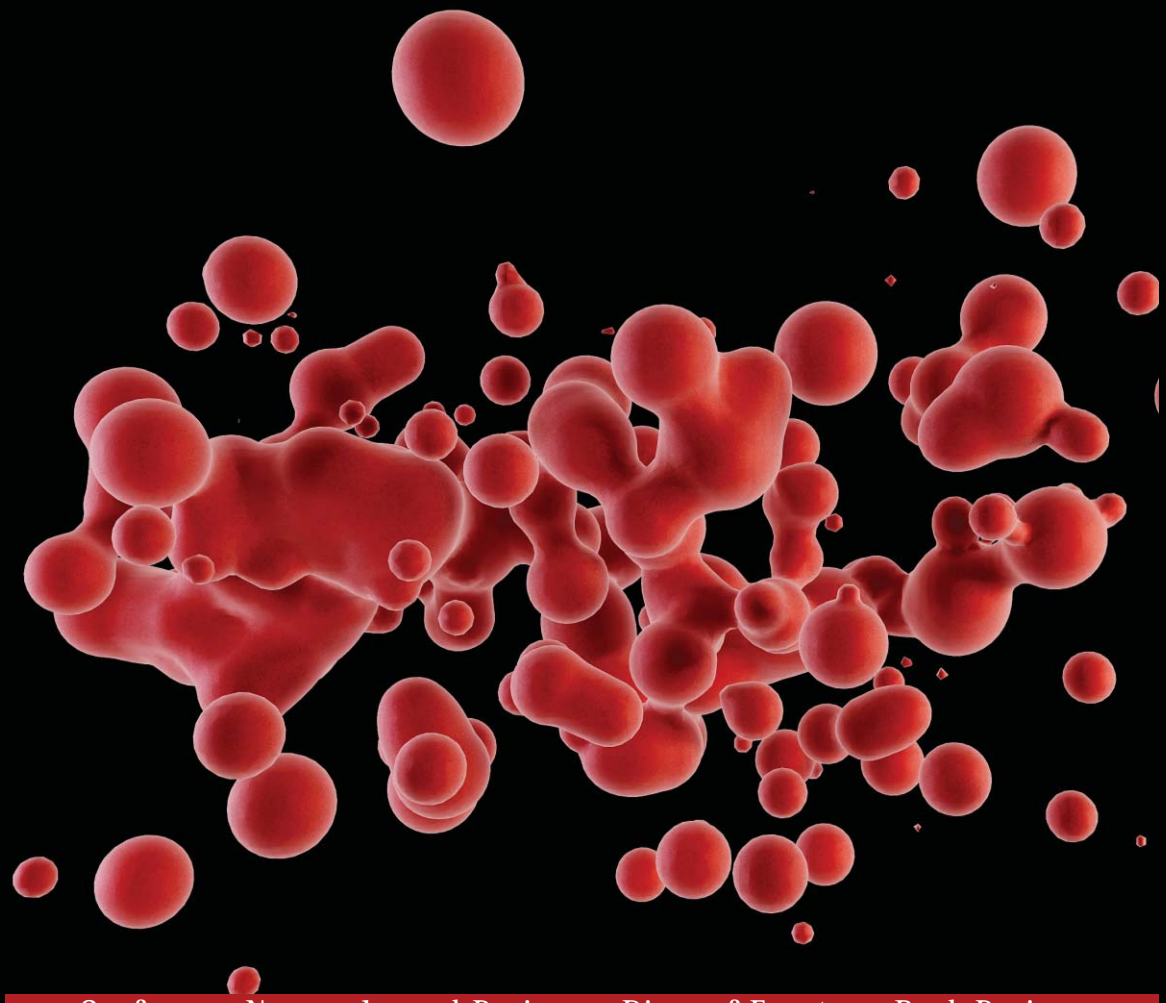
Advances in Clinical Neuroscience & Rehabilitation



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"This prospective study confirms marked dyskinesia reduction on continuous subcutaneous apomorphine therapy" (Relative to baseline) [1]

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Age and disease duration should not prevent the use of this valuable drug [2]

Apomorphine use can help elderly patients to maintain their independence [3]

References: 1 Katzenschlager et al, Movement Disorders, 2005, Vol 20, No. 2, pp 151-157. 2 Sharma et al, Int J Clin Pract, 2004, Vol 58, No. 11, pp 1028-1032
3 MacMahon, ACNR, 2003, Vol 3, Issue 3,pp 30-31

ABRIDGED PRESCRIBING INFORMATION
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Uses The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylaseinhibitor) and/or other dopamine agonists.

Dosage and administration Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5–10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg.

Contraindications Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia.

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Interactions Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents.

Precautions Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea and vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, 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 apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa when given concomtantly with apomorphine.

Side Effects Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration, and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually transient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Transient mild confusion and visual hallucinations have occurred during apomorphine therapy, and neuropsychiatric disturbances may be exacerbated by apomorphine. The use of apomorphine HCl in conjunction with levodopa treatment may cause Coombs' positive haemolytic anaemia. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Apomorphine is associated with somnolence. Breathing difficulties have been reported. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.*

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Version Number: APG.API.V5

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Microbleeds are small areas of haemorrhage which can be easily detected using gradient echo MRI scanning. David Werring, in his excellent review article, describes the possible pathogenesis of these abnormalities and also discusses their significance in different clinical settings – for example, do they predict the risk of haemorrhage in stroke patients receiving an antithrombotic agent? In addition the lesions can produce their own clinical syndrome such as cognitive dysfunction and given how frequently they are seen on MRI, it is clear that this is an area that will be of increasing significance in the future with our aging population.

The complexities of the immune system are so bewildering that it is a wonder we don't all have some form of autoimmune disease. In her review in the Immunology Primer series Vicki Robertson takes us through the history and function of regulatory T cells, or Tregs to immunologists! This carefully constructed article highlights how this field has recently developed and the extent to which abnormalities in this system have devastating consequences including MS.

The Neurosurgery series discusses spinal metastases and "despite there being class 1 evidence supporting the role of surgery in the context of spinal metastases, the management decision is often not clear cut". This is the conclusion that Catherine Gilkes and Tim Germon draw for us in their informed account of what is a very difficult area of neurological practice.

The patient who requires a long term tracheostomy often creates a great deal of anxiety for the patient, career, family and medical personnel involved with their care. However the development of multi-disciplinary tracheostomy teams has greatly eased these worries and Claire Scase takes us expertly through the assessment and process by which a patient with a tracheostomy can be successfully transferred and monitored in the community.

The development of unrelated medical problems in patients with persistent vegetative state (PVS) raises many issues on best management. In this issue of the ACNR, we have a sensitive and informed discussion of just such a situation in a young patient who developed Cushing's disease in the context of their PVS. Advice on the management of such cases is given and is a helpful guide to those who may find themselves in similar situations.

Neurology and literature feature heavily in this issue of the ACNR with Andrew Larner presenting the third in his series on headache. Alastair Wilkins (the ACNR case report coordinator) discusses the works of Proust and especially his great work "À la Recherche du Temps Perdu". This classic work has many fans and in his article Alastair explores why this book may be relevant to neurology in the 21st Century and in so doing raises question about whether the reading of such works of literature should be compulsory for all aspiring neurologists.

We also have the second in our series of patient perspectives, with David Pickin explaining what it was like to be given the diagnosis of Parkinson's diesease in his early 40s and how he has dealt with it for over 30 years.

We also have all our usual items, including a sobering report on the management of MS in India.

We hope you enjoy this new issue of the ACNR and if anyone would like to contribute to any of our regular journal, book or conference review series then do let us know.

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

Contents

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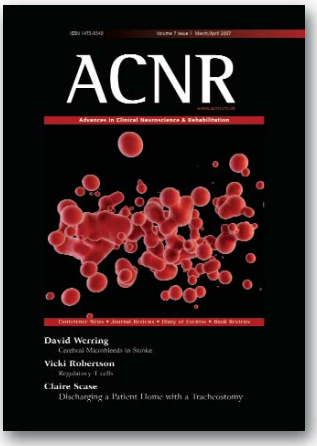

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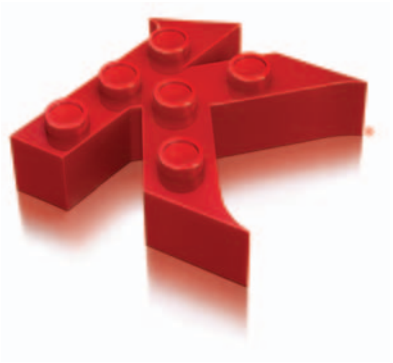

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Cerebral Microbleeds in Stroke

What are cerebral microbleeds?

Over the last decade, gradient echo MRI has disclosed small, dot-like low signal areas in patients with haemorrhagic and ischaemic stroke, hypertension, and in healthy elderly subjects.[1,2,3,4] These 'microbleeds' (or 'microhaemorrhages') are tiny focal collections of blood breakdown products adjacent to histologically abnormal small vessels,[5,6] resulting from blood leakage through the fragile vessel wall. Microbleeds probably persist for many years, making them a potentially unique marker for an individual's lifetime history of bleeding related to small vessel pathology.

Imaging method

Gradient-echo (also termed T2*-weighted) MRI is exquisitely sensitive to blood breakdown products (including haemosiderin, deoxyhaemoglobin and ferritin) which are paramagnetic and cause local dephasing of the MR signal ('susceptibility'). Cerebral microbleeds are thus well seen as small, round, dark dots of 2-5mm diameter (Figure 1), though the actual physical size of microbleeds is likely to be less than a millimetre. Care must be taken to distinguish microbleeds from blood vessels (in the subarachnoid space) or calcification of the basal ganglia (which is often symmetrical and is easily seen on CT scans).

What causes cerebral microbleeds?

Microbleeds are associated with lacunar infarcts and clinical syndromes, and with white matter lesions (including the confluent changes of leukoaraiosis),[3,7] suggesting that they result from small vessel damage. Their usual distribution, in the basal ganglia (including the putamen and thalamus), and the pons, in the territory of the small, deep perforating arteries, supports this idea. Moreover, in most studies microbleeds are more common in patients with hypertension.[1,8,9,10] and left ventricular hypertrophy on echocardiography correlates with their severity.[11] In a smaller group of patients (generally elderly, presenting with lobar haemorrhage) microbleeds are found at the cortico-subcortical junction in the territory of small and medium-sized leptomeningeal and cortical vessels; in this distribution, and in the appropriate clinical context, they are probably caused by cerebral amyloid angiopathy rather than hypertensive small vessel damage, though the conditions may co-exist.[4]

Recent experimental and human genetic studies of familial small vessel disease showed that mutations in the collagen IV gene predispose to small vessel damage and microbleeds,[12] but further studies are urgently needed to clarify the genetic contribution in the much more common sporadic patients. Microbleeds may be a useful intermediate phenotype for increasing the power of studies to detect genetic effects in small vessel stroke. One study has shown an independent inverse relationship between microbleed number and serum cholesterol, but a causal link is not established.[9]

Who gets cerebral microbleeds - and what is their significance?

(1) Healthy individuals with no history of stroke

Microbleeds are found in about 5% of the normal population in their fifth to eigth decades, increasing in prevalence with age to about 7-8% of patients over 70 having MRI for non-stroke indications.[7,13,14] The clinical significance of cerebral microbleeds in an otherwise healthy individual is unknown, but they may predict an increased future cerebrovascular risk.

(2) Primary Intracerebral haemorrhage

Primary intracerebral haemorrhage (PICH) accounts for about 20% of all strokes, and is usually caused by rupture of a small or medium-sized arterial wall (trauma, arteriovenous malformations or intracranial aneurysms are conventionally excluded from this diagnostic group). Cerebral microbleeds are found in between 54% and 71% of PICH,[7,10,15,16,17,18] and are especially common in Asian populations, which to date have been the most extensively studied.[19]

Cerebral amyloid angiopathy (CAA) is less common (though probably under-recognized) and causes recurrent, often non-disabling, PICH in a 'lobar' distribution, especially in elderly patients. CAA is due to amyloid deposition in small to medium leptomeningeal

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Figure 1 (below): (a) and (b) are axial T2*-weighted gradient-echo MR images; (c) is an axial CT scan from a 64-year-old woman who presented with sudden left sided sensory disturbance and mild weakness. She was taking warfarin for atrial fibrillation. The haematoma is located in the right temporo-parietal region (large white arrow, a). Note the microbleed (small, dark dot-like lesion, arrowed, b) in the right thalamus. Basal ganglia calcification is also present on the T2* MRI and confirmed on the CT scan (arrowheads, b and c).

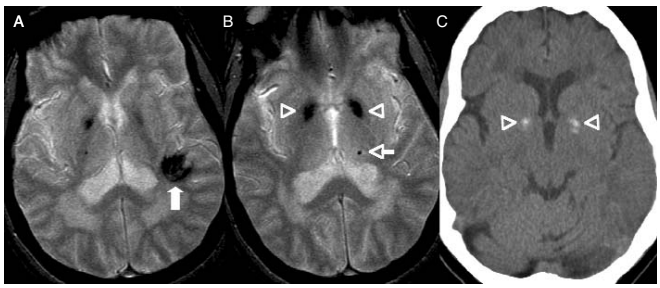
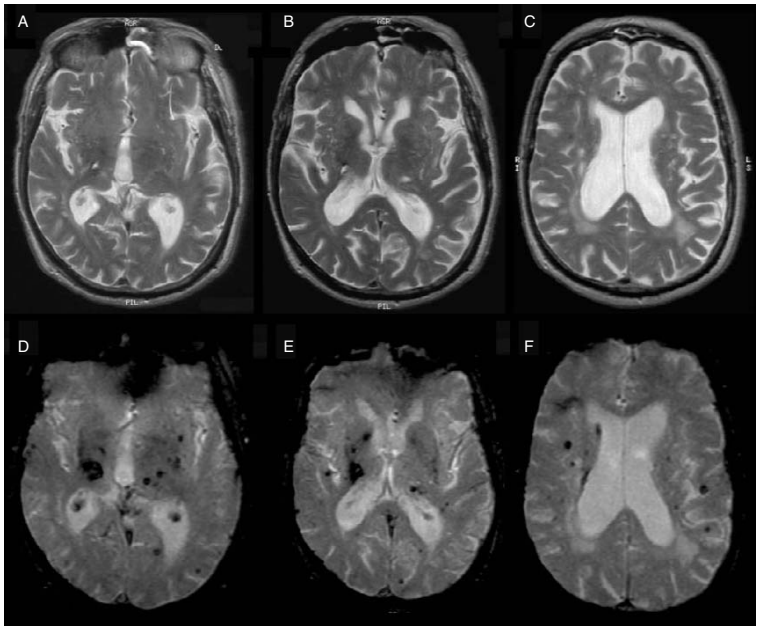


Figure 2 (right): Standard axial T2-weighted images (a to c) and Gradient-echo MRI (d to f) of a patient who continued to experience cerebrovascular events despite increasingly aggressive antithrombotic treatment. When the antithrombotic therapy was reduced in intensity the frequency of events also reduced. (Figure kindly provided by Dr R Jäger, Institute of Neurology).



and cortical vessels making them fragile and prone to bleeding. Greenberg[20] reported microbleeds in 80% of elderly patients with lobar haemorrhage compatible with presumed cerebral amyloid angiopathy.

The location of cerebral microbleeds may help to determine the underlying cause of intracerebral haemorrhage. An exclusively cortico-subcortical distribution suggests amyloid angiopathy, whilst deeper microbleeds in the basal ganglia, brainstem and cerebellum suggest hypertensive small vessel disease. Testing this hypothesis will be challenging, since the distribution of haemorrhages on MRI forms part of some current diagnostic criteria for amyloid angiopathy. Furthermore, hypertension and CAA may co-exist, especially in an elderly population. In practice, finding microbleeds in a patient presenting with intracerebral haemorrhage suggests a diffuse bleeding-prone angiopathy rather than an arteriovenous malformation or tumour. The probability of hypertensive arteriopathy versus amyloid angiopathy will depend on the clinical context, location of the symptomatic haemorrhage and microbleed distribution. Finding microbleeds and combining the information with other clinical and imaging data could therefore potentially avoid the need for invasive angiography in some patients, but this approach remains to be tested in clinical practice.

Limited data suggest that microbleed number may predict future bleeding risk after symptomatic intracranial haemorrhage.[21] Microbleeds are also associated with a larger volume of intracerebral haemorrhage.[22]

(3) Ischaemic stroke and antithrombotic treatments

Microbleeds are found in between 18% and 65% of patients with ischaemic stroke.[3,7,9,23,24] The wide variation reflects study population differences (hospital versus community; different proportions of stroke subtypes; and different demographic groups). Microbleeds are consistently more common in Asian patients and those with lacunar infarction compared with atherothrombotic or cardioembolic ischaemic stroke.

It was suggested that microbleeds may predict the risk of haemorrhagic transformation after acute cerebral infarction,[25] particularly after thrombolysis. However, a large multi-centre study found no significant difference in the rate of symptomatic intracranial haemorrhage in those with microbleeds compared to those without (8.3% in the microbleed group compared with 7.5% in the non-microbleed group).[26]

There have been few long-term prospective studies of patients with microbleeds in ischaemic stroke, but the limited available data suggest that microbleeds confer an increased risk of both haemorrhagic[23] and ischaemic events.[27]

Patients with ischaemic stroke are often treated with antithrombotic agents, and antithrombotic-associated intracerebral haemorrhage, the most feared complication, accounts for up to 14% of all PICH. Although leukoaraiosis and lacunar infarcts on CT scanning are associated with increased haemorrhagic risk,[28] the risk remains difficult to predict. Cross-sectional retrospective data reported that patients with aspirin-related intracerebral haemorrhage more often had microbleeds than matched patients taking aspirin without haemorrhage (90% vs 30% microbleed prevalence)[29] but whether microbleeds predict future bleeding risk urgently needs to be tested prospectively in a larger cohort of patients, including those on anticoagulants.

Microbleeds may help to guide antithrombotic treatments in patients with recurrent stroke or TIA events despite treatment. Figure 2 shows gradient-echo MRI in a patient who continued to experience recurrent transient focal neurological attacks despite increasingly aggressive antithrombotic treatment, culminating in anticoagulation. The finding of numerous microbleeds led to the antithrombotic treatment being discontinued, and the 'TIA's stopped. It is possible that some or all of the recurrent events could have been related to the formation of new microbleeds, but this hypothesis cannot be confirmed without longitudinal imaging.

Few studies have investigated microbleeds in patients with TIA, but one study found microbleeds in only 2% of TIA patients compared with 24% of ischaemic stroke patients matched for demographic and vascular risk factors and for MRI white matter abnormalities.[30]

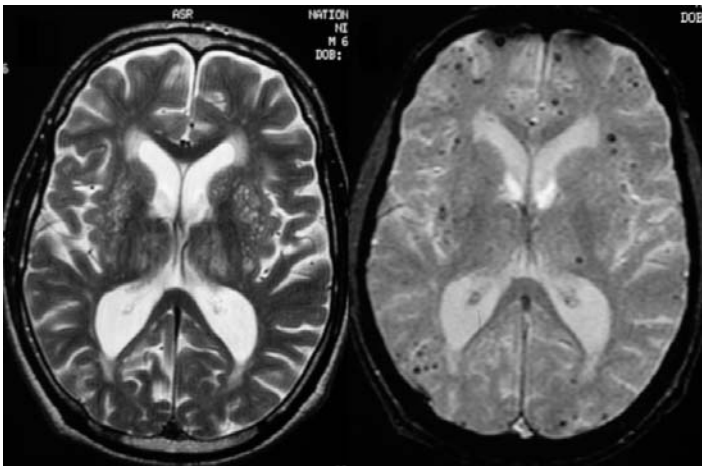


Figure 3: T2-weighted (a) and gradient-echo MRI (b) of a patient with frontal-executive dysfunction. Note the numerous microbleeds present, particularly in the frontal regions on the gradient-echo image (right hand panel), which are not visible on the T2-weighted image (left hand panel). The distribution is suggestive of cerebral amyloid angiopathy. Reproduced with permission from reference 33.

Table 1: prevalence of microbleeds in different groups of subjects / patients

Disease	*Proportion of patients with microbleeds (%)*	*Selected references*
Normal elderly	*4.5-8.5*	*7,13,14*
Ischaemic stroke	*18-65*	*3,7,9,23,24*
TIA	*2*	*30*
PICH	*54-71*	*7,10,15,16,17,18*
Cerebral amyloid angiopathy	*80*	*20*
CADASIL	*31-69*	*31*
Moya Moya	*15-44*	*32*

Table 2: aspects of stroke medicine where microbleeds may be clinically important

- *Guiding decisions about antithrombotic treatments and risk of intracranial haemorrhage*
- *Investigating the underlying cause of primary intracerebral haemorrhage*
- *Prognostic information after ischaemic or haemorrhagic stroke*
- *Investigating patients with unexplained cognitive disturbance, especially if they have vascular risk factors*
- *Screening and monitoring patients in clinical trials of antithrombotic or antihypertensive agents*
- *Intermediate phenotype for stroke genetic studies in small vessel disease*

Microbleeds therefore may be markers for a more severe small vessel vasculopathy than is revealed on conventional MRI, to the extent that there is an increased risk of ischaemic stroke. Furthermore, antithrombotics may be less hazardous in patients with transient syndromes than those with stroke.

Microbleeds have been detected in up to 69% of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a single-gene disorder of small vessels due to a mutation in the Notch-3 gene, and seem to occur largely outside areas of ischaemia.[31] Asymptomatic microbleeds were reported in 28% of patients with MoyaMoya disease at 1.5T field strength, increasing to 44% at 3T.[32]

Microbleeds probably persist for many years, making them a potentially unique marker for an individual's lifetime history of bleeding related to small vessel pathology

Do microbleeds cause symptoms?

Microbleeds have been considered to be asymptomatic,[3,4,7,10] but recent studies suggest that they may not be as clinically silent as was first thought. We investigated cognitive function in patients with cerebral microbleeds compared to a non-microbleed control group matched for age, white matter changes on MR, stroke subtype and associated large-vessel stroke.[33] Executive dysfunction was twice as common in microbleed patients (60% vs 30%) and was related to microbleed burden in the frontal lobes and basal ganglia, suggesting that cognitive impairment could result from disruption of strategic frontal-basal ganglia circuits. These findings may assist the assessment of stroke patients with cognitive impairment, and influence the use of antihypertensive and antiplatelet treatments. Figure 3 shows gradient echo and T2-weighted MRI in a patient with frontal-executive dysfunction.

Clinical experience suggests that small haemorrhages can cause distinct stroke syndromes: indeed, a recent case report describes a patient with abrupt onset of lateral gaze disturbance due to a cerebral microbleed in the medial lemniscus at the mid-pontine level.[34] Microbleeds may also cause partial seizures secondary to irritation of adjacent cerebral cortex, which respond to anticonvulsants.[35]

Conclusion

Microbleeds are a recently described imaging finding in patients with stroke, related to pathological damage to small vessels. Although knowledge has increased rapidly in the decade since their first description, many important questions remain. Perhaps the most urgent of these is whether microbleed imaging can help predict stroke patients' haemorrhagic risk when treated with antithrombotic agents. The general significance of microbleeds for haemorrhagic and ischaemic stroke risk, and for vascular cognitive impairment, also need to be further clarified. Clear imaging criteria for microbleeds need to be developed to allow multi-centre prospective studies to answer these questions.

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NEU3887

Raising Awareness of Multiple Sclerosis in India

Mumbai, Bangalore, Hyderabad & Delhi, India, 1-15 February 2007

Multiple sclerosis is not as common in India as in the UK, but it does exist. There are 4000 people with the disease on the MS Society of India's books, with an estimated 40,000 affected in the entire country. Understandably, they struggle to gain the attention of a health system overwhelmed by infectious diseases (including sadly a maternal HIV prevalence of 1%). As an example, consider the workload of the roughly 1000 neurologists serving the one billion population in India. Half see at least 30 patients every day, and 15% see more than 50 patients a day, with average consultation times for new patients being just 15 minutes.[1]

Sheela Chitnis' husband developed multiple sclerosis when they were newly-married. It took several years for the diagnosis to be made, during which they experienced all the stress and anguish of perplexing, unpredictable symptoms. This experience led her to found the MS Society of India in 1985 and eventually to attend the MS Life conference organised by the MS Society of the UK and N. Ireland last year. There she met Caron Furnival, and the two planned a delegation from the UK to raise awareness of multiple sclerosis in India. It nearly floundered through lack of financial backing, until Healthcare at Home very generously stepped in as the sole


Mumbai Neurologists at the meeting

sponsor. (This company provides home delivery and administration of many different injectables, including the interferons).

So it came about that a team of eight from the UK spent two gruelling and exhilarating weeks delivering lectures and workshops for as few as 40 to as many as 250 health professionals or people affected by multiple sclerosis, in Mumbai (Bombay), Bangalore, Hyderabad and Delhi.

We learnt that unenhanced MRI scans cost about 50US$ and are accessible for many for diagnostic purposes, although many baulked at the (unnecessary?) request of some neurologists for serial MRI scans. On the other hand, the interferons are theoretically available in India but at a price very few can afford. So neurologists are making imaginative use of cheaper alternatives: such as first-line therapy with mitoxantrone, or intermittent pulsed corticosteroids; reasonable strategies which would be impossible to test in countries where the interferons are more available. It would make sense for this uncontrolled prescribing to be subsumed within clinical trials, with appropriate financial support, so that the world-wide multiple sclerosis community can learn from them.

It was encouraging to learn that all the patients are offered support and counselling around adjustment issues. However mental health issues such as depression were often ignored, perhaps because of negative stigma associated with psychology or psychiatry. In contrast, spiritual issues were widely acknowledged to be important by patients and health professionals. So too the effect of the illness on the family. That, and the mainstream use of what we would call "alternative medicine" make for an enviably holistic approach to care of those with multiple sclerosis, from which we could learn much.

The group comprised three representatives from the MS Society (Alison Handford, Carron Furnival and their lead physio, Jane Petty), one from Healthcare at Home (Carrie Brown), a MS specialist nurse (Adrienne Cox), an occupational therapist (Denise Middleton), a clinical psychologist (Anita Rose). The neurologist slot was filled by two part timers: Alasdair Coles and Eli Silber for one week each, unable to cope with the pressure of the full timetable!

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1st UK Stroke Forum Conference

Harrogate, UK, 7-8 December 2006.

The Stroke Association hosted the first ever UK Stroke Forum conference at the Harrogate International Centre. The event combined The Stroke Association's Scientific Conference, the National Stroke Nursing Conference and The British Association of Stroke Physicians Conference as a multidisciplinary meeting bringing together over 1000 delegates. Those attending included healthcare professionals, researchers, people with stroke and their carers. The programme featured leading figures in stroke care, research and policy, presentations on the latest stroke research and the inaugural Princess Margaret Memorial Lecture.

The conference opened with an update on the work of the UK Stroke Research Network in the areas of prevention, acute care, rehabilitation, community care and translational research. The Clinical Study Groups, which offer support designing, writing and securing funding for studies as well as identifying studies for adoption as multi-centre trials across the Network, presented their portfolio of ongoing studies.

The second plenary session explored the translation of research findings into good practice. Professor Charles Warlow gave examples where this had happened (e.g. Stroke Units, aspirin) and highlighted barriers (cost, unimpressive findings, inertia and impracticality). He reported that patients' views on what is relevant and valuable to them can differ from statistical results and concluded that good and relevant research both encourages and reduces uncertainty.

As part of the same session Professor Pam Enderby highlighted that focused research triangulating qualitative, quantitative and other evidence is slowly reducing the gulf between researchers and practitioners and improving the translation of findings into practice. Dr Bernard Gibbon discussed the shift in nursing research from the profession-centred 'Carry On' role of nurses, to today's focus on evaluating interventions carried out by nurses in an inter-professional team to improve patient outcomes.

A range of issues in stroke were addressed in the parallel sessions, including imaging, the management of swallowing, communication, cognitive and visual problems. Sara Demain (University of Southampton) discussed how physiotherapists discharge people with stroke. She suggested that the goals and feelings of therapists, the nature of the therapeutic relationship and service constraints shaped the decision to discharge, whilst opportunities for patient participation were limited. Once discharged, people with stroke often experienced feelings of abandonment. Professor Sheila Payne spoke of the need to bridge the gap between stroke rehabilitation and palliative care.

Day two of the conference saw the inaugural Princess Margaret Memorial Lecture taking place with guest lecturer Professor Werner Hacke (University of Heidelberg, Germany). Professor Hacke shared interesting insights into the future of acute stroke care, drawing on international perspectives to set the scene for potential developments. The third plenary session followed, dedicated to the best five research presentations selected through the call for abstracts. These covered motor imagery, insulin and lesion volume, bilateral upper limb training, motivational interviewing and patterns of recovery. The latter was part of the CERISE project, which compared stroke recovery in rehabilitation centres in the UK, Belgium, Germany, and Switzerland. Professor Nadina Lincoln (University of Nottingham) reported significant variation in amount of therapy patients receive. Despite similar staff numbers, UK patients spent significantly less time in therapy and made a worse recovery in comparison to those in Germany and Switzerland.

The conference closed with a session exploring innovations in stroke care. Professor Garth Johnson discussed new technologies in rehabilitation and Professor Sally Byng presented a model to underpin the planning of integrated, comprehensive and sustainable services to meet long-term needs. Professor Martin Dennis focused on the challenge to health care professionals of designing innovative stroke services with limited resources. He concluded that success depends on our willingness to change the way we work to ensure that people have access to and benefit from effective, efficient and equitable services.

For me and the other members of the Stroke Association Rehabilitation Research Centre, the conference provided a platform for networking, sharing ideas, hearing about best practice and discussing challenges. With new contacts and ideas, we are looking forward to next year's event. Speaker presentations are available online at www.ukstrokeforum.org

Dr Dorit Hyndman, Senior Research Fellow at The Stroke Association Rehabilitation Research Centre, University of Southampton, UK.

PREVIEW: The Parkinson's Disease Non Motor Group and the 2nd Annual Meeting on Non Motor Symptoms of Parkinson's Disease

London, UK, 21 April 2007.

A range of non motor symptom (NMS), including dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia complicate the lives of people with Parkinson's disease (PD). However, even though the last 30 years have seen enormous advances in the management of the motor symptoms of PD, the NMS complex of PD has remained relatively unexplored. NMS of PD contribute significantly to morbidity and may lead to admission to a nursing home, more than quadrupling the cost of care of PD. Furthermore, recent evidence suggest that NMS such as olfaction, REM behaviour disorder, fatigue and depression may be markers of preclinical stage of PD and thus occur in early stage of PD. PDNMS are not well recognised in clinical practice and are recognised as a key unmet need in the NICE guideline for management of PD (Chapter 9).

The international Parkinson's disease non motor group (PDNMG: www.pdnmg.com) was set up by K Ray Chaudhuri after a group of dedicated neuroscientists met and felt that NMS of PD needs recognition, awareness and assessment tools. The unique feature of this group is its multidisciplinary origin bringing together neurologists, geriatricians, psychologists, sleep experts, nurse specialists, cognitive experts and last but not least, patient group representatives.

We would like to draw your attention to the second meeting of the Parkinson's Disease Non Motor Group (PDNMG) in London, April 21, 2007. We hope this will be an exceptional day with areas of Parkinson's disease management being discussed by an excellent panel of an international faculty of neuroscientists.

We are anticipating approximately 300 people and would be delighted if you could attend and make this second meeting a bigger success. The panel is exceptional, international and will provide an up-to-date summary of various aspects of non motor symptoms of PD that affect the day-to-day life people with Parkinson's, the carers and the treating healthcare professionals. The meeting will also address areas of the major unmet need in PD, as addressed by NICE. The day will then conclude with four illustrative cases being discussed in an interactive session.

This will be a whole day meeting on a Saturday and lunch, coffee and refreshments are provided.

The second meeting of the PDNMG is supported by the Parkinson's Disease Society UK and the Movement Disorder Society and made possible by an unrestricted educational grant from Boehringer Ingelheim, Solvay and Britannia Pharmaceuticals. Also the meeting is accredited with 6 CPD points.

PREVIEW: Rehabilitation Medicine Today and Tomorrow: Service models for specialist rehabilitation in hospitals and communities

London, UK, 22 May 2007.

The British Society of Rehabilitation Medicine is hosting its Spring Conference at the Royal College of Physicians, London, on Tuesday 22 May 2007. This will provide an overview of best practice in the provision of specialist medical and multidisciplinary rehabilitation for people with complex needs. Examples from both UK and international service models will demonstrate the role of rehabilitation medicine in a primary-care-led, community-orientated NHS.

The day will deliver updates on modern approaches to service delivery and will identify key criteria for the organisation of services. Questions to be addressed will include:

- How does rehabilitation medicine contribute to national strategies such as 'Our Health, Our Care, Our Say'?
- How much specialist rehabilitation can be delivered in and through community and primary care services?
- What is the role of hospital-based and super-specialist services?

Speakers from abroad will be asked to describe how they have responded to these issues, sometimes with very limited resources.

The Conference will open with a keynote lecture by Professor Dame Carol Black, National Director for Health and Work (and past President of the Royal College of Physicians, London) entitled 'Health, Work and Well-being: An Inter-departmental Government strategy'. This session will highlight the importance of work and occupation and the role of specialist vocational rehabilitation. Other sessions during the day will

- explore the role of specialist musculoskeletal rehabilitation services and the scope for delivery in the community
- provide overviews of UK service models with international comparisons highlighting challenges and opportunities for service development
- provide reviews of services delivered both by the NHS and by the voluntary sector, and discuss the role of specialist medical expertise in brain injury rehabilitation.

The day will conclude with a panel discussion addressing the question of cost effectiveness of specialist Rehabilitation Medicine, and its role in delivering current healthcare and social policies and a discussion on the future of rehabilitation medicine.

The conference also includes an opportunity for showcasing rehabilitation medicine service models of excellence in the form of posters, for which abstracts are invited.

The content of the day will be highly relevant to public health specialists, commissioners of specialist services and secondary care services, voluntary sector organisations, consultants in relevant medical specialties such as rehabilitation medicine, neurology, neurosurgery, trauma and orthopaedics and rheumatology. We look forward to welcoming you on the 22nd.

Professor Christopher Ward,
President,
British Society of Rehabilitation Medicine.

For further information visit:
www.bsrm.co.uk

PREVIEW

17th Meeting of the European Neurological Society

Rhodes, Greece, 16 – 20 June, 2007.

Neurology: Learning, knowledge, progress and the future

Teaching programme:
- Interactive case Presentations: What is your decision?
- Practical sessions in Clinical Neurophysiology
- 22 Teaching Courses covering all important topics in Neurology

The teaching programme of the ENS meeting at Rhodes includes five interactive sessions with case presentations, 22 teaching courses, 1 practical workshop and three practical breakfast sessions.

The interactive sessions on Saturday morning, June 16 encourage attendants to bring cases of interest to the meeting and to discuss clinical presentations by making decisions on diagnosis and treatment. The 21 half-day and one full-day teaching courses are spread out over the entire meeting from Saturday, June 16 to Wednesday, June 20 and aim at providing up-to-date clinical and related scientific information on a broad range of topics covering the main neurological diseases of the central and peripheral nervous systems, neuromuscular transmission and muscle. One teaching course will focus on submission of successful grant applications and the writing of scientific papers. The chairpersons and the faculty have been invited based on their known scientific and clinical expertise on the selected subjects. Three courses are given jointly with the American Academy of Neurology.

Five courses are designated as "integrated courses" and will be part of the scientific programme of the congress, preceded by poster viewing and followed by selected 15-minute oral presentations. One practical workshop on Botulinum Toxin treatment is presented on Sunday, June 17. Practical breakfast sessions on Clinical Neurophysiology will be given on Sunday, Monday, and Tuesday. It is the policy of the ENS teaching programme to interact with attendants as much as possible and instructions to the faculty emphasise the practical clinical relevance of presentations. In order to make the teaching programme as accessible as possible, the interactive sessions and practical breakfast sessions are provided free of charge, and the teaching courses at extremely low cost. Moreover, teaching courses are free of charge for young physicians attending the congress with the "Young Neurologists in Training" offer.

Prof C Krarup,
Executive Committee.

Visit the ENS 2007 website
www.ensinfo.com featuring:

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Regulatory T cells

EDITOR'S COMMENT: One of the most important papers of 2004 was that from David Hafler's group (Viglietta 2004 J.Exp.Med. 199: 971) showing that the basic immunological defect in multiple sclerosis is impaired function of a new type of cell: the "regulatory T cell". Post-doc scientist, Vicki Robertson, summarises what is known about this novel class of immune cells.

In the late 1960s and 1970s it was proposed that T cells could act as suppressor cells to suppress the immune response by producing soluble factors.[1] The existence of a dedicated population of 'suppressor' T cells was the subject of significant controversy among immunologists for many years, and by the 1980s the mechanisms behind T cell suppression had failed to be characterised by both molecular and biochemical studies. The discovery of T helper 1 (Th1) and Th2 cells led immunologists to believe that suppression was achieved through counter-regulatory cytokines and not by a distinct subset of T cells; thus the field of suppressor T cells was widely discredited. In 1993, Green and Webb even went as far as describing suppressor cells as "the nearest thing we have to a dirty word in cellular immunology".[2]

Over 30 years ago a series of experiments completed by Nishizuka and Sakakura[3] corroborated the existence of regulatory cells (Tregs) as we know them today. These experiments demonstrated that mice thymectomised between day two and four of age developed organ specific autoimmune disease which could be prevented by 'adding back' syngeneic T cells obtained from adult thymus and spleen.[3] However, until recently it has been difficult to distinguish Tregs from effector cells due to the lack of a robust expression marker.[4] Current interest in Tregs was revived in 1995 by Sakaguchi et al[5] who characterised the cells responsible for the prevention of organ specific autoimmunity. Sakaguchi et al showed that these regulatory cells are CD4+ T cells which express the CD25 antigen (interleukin-2 receptor α-chain), the transcription factor forkhead box P3 (FoxP3), and protect against autoimmunity in murine models of gastritis and thyroiditis.[5]

Now Tregs are regarded as separate lineages of cells with specific differentiation patterns and distinct functions, which regulate peripheral self-tolerance by suppressing the activity and expansion of autoreactive T cells. Several different subsets of Tregs have been characterised and described in the literature but they can generally be divided into two groups: Naturally occurring/innate Tregs (expressing CD4+CD25+ and FoxP3) and adaptive/inducible Tregs (Th3 and Tr1 cells) (Figure 1).

Naturally occurring Tregs

Naturally occurring Tregs are the most widely studied population of regulatory cells and constitute 8-12% of the CD4+ T cell pool in mice and 2-5% of CD4+ T cells isolated from human peripheral blood. Naturally occurring Tregs express high levels of the CD25 antigen, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), glucocorticoid-inducible tumour necrosis factor receptor (GITR) and FoxP3.[6] Whilst FoxP3 is currently considered the best marker for Treg identification, low expression of FoxP3 has been detected in CD4+CD25- populations and in CD8+T cells. 'Knock in' experiments in mice have shown that FoxP3 is highly specific for Tregs and it was thought that low levels of FoxP3 detected in CD4+CD25- was likely to be due to contaminating FoxP3+ Tregs in these cell populations.[7] However, there have been recent data to suggest that FoxP3 is expressed transiently by activated non-suppressive CD4+CD25- T cells in humans[8] and there have been many reports of CD4+CD25+ Tregs being induced in the periphery in response to antigen from naïve CD4+CD25-cells. To date no distinguishing features, either phenotypic or functional, have been found between these cells or naturally occurring Tregs.[9]

Clonal deletion of self-reactive T cells in the thymus is a major mechanism of immunologic self-tolerance, although it is uncertain how much of T cell self-reactivity can be removed by thymic negative selection, especially T cells which have T cell receptors (TCRs) for self-antigens, expressed outside the thymus.[6] Tregs are generated in the thymus during negative selection[10] and have TCRs specific for self-antigens with an intermediate affinity so that they are not deleted. Shevach et al

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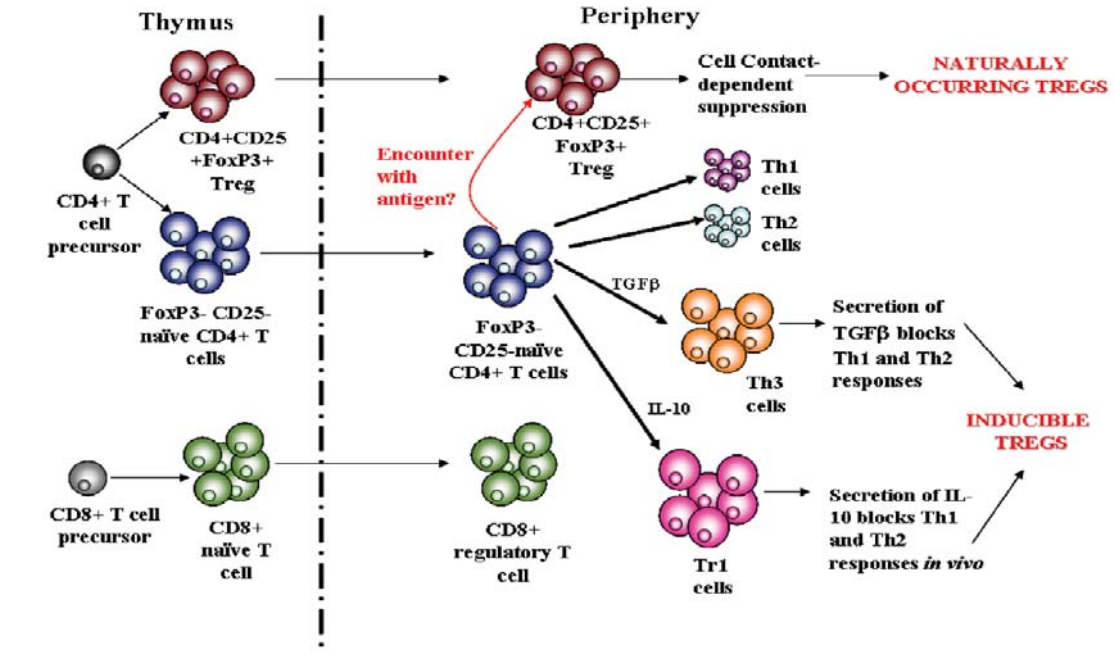

Figure 1: The development of regulatory T cells. Naturally occurring Tregs are produced in the thymus during negative selection, express CD25 and FoxP3 and mediate suppression via cell contact-dependent mechanism. CD4+CD25-FoxP3- can differentiate into Tregs in the periphery that are phenotypically and functionally identical to naturally occurring Tregs, possibly through encountering an antigen. CD4+ naïve T cells can differentiate into both Th1 and Th2 cells, however if stimulated with high levels of either TGFβ or IL-10 they differentiate into Th3 or Tr1 cells respectively which exert suppression via the secretion of cytokines. CD8+ T cells can also differentiate to have a regulatory function.

have proposed that Tregs go through a further process, which they term altered negative selection. This results in their TCR signal transduction process being permanently altered so that Tregs leave the thymus in a partially incapacitated state, and are precommitted to function as regulatory cells when they encounter their target antigen in the periphery.[6] The survival of Tregs in the periphery is dependent on them encountering their target antigen and on the presence of interleukin-2 (IL-2); IL-2 knock-out mice do not have Tregs.[11] In humans, only Tregs expressing high levels of CD25 are considered to be regulatory as intermediate levels of the CD25 antigen are expressed by activated T effector cells;[5] however, the functional role of CD25 in T cell mediated immunoregulation is, as yet, unknown.

Naturally occurring Tregs are anergic in vitro when stimulated via their TCR or with IL-2 alone; however, stimulated with a combination of anti-CD3 antibodies and IL-2, or IL-15 they proliferate vigorously, but this abolishes their suppressive properties.[12,13] In vivo Tregs are capable of clonal expansion and proliferate in an MHC class II-dependent manner in response to an antigen and lymphopaenia whilst retaining their suppressor function.[14,15] Naturally occurring Tregs mediate their suppression in a cell-contact dependent, cytokine-independent manner,[6] and suppression can be abrogated in vitro by the addition of high concentrations of IL-2 to the culture. Suppression is accompanied by cell cycle arrest and is mediated via the inhibition of IL-2 production by effector cells at the mRNA level, although the mechanisms behind this process have yet to be defined.[6] Suppression mediated by naturally occurring Tregs is, however, insensitive to IL-10 and TGF-β blockade, although there have been some recent reports to suggest that TGF-β may be required to sustain FoxP3 expression in human Tregs.[16] Cross-linking of CTLA-4 to CD80 and CD86 on the surface of activated T effector cells and antigen presenting cells (APCs), which results in Tregs secreting TGF-β, is thought to be one mechanism by which Tregs exert suppression.[17] Blocking CTLA-4 with antibodies abrogates Treg-mediated suppression.[6,18] In addition to suppression, activated human Tregs can directly kill activated CD4+ and CD8+ T cells, dendritic cells and activated B cells in a perforin-dependent but Fas/FasL-independent manner.[19,20]

Adaptive Tregs

Adaptive Tregs are generated in the periphery, and require IL-2 for their survival and are thought to suppress immune responses by releasing anti-inflammatory cytokines such as IL-10 and TGFβ. The two most commonly studied adaptive Tregs are Type 1 regulatory T cells (Tr1) and Th3 cells.

Tr1 cells

Tr1 cells resemble naturally occurring Tregs in many ways and are essential for the maintenance of peripheral tolerance. The role of Tr1 cells is in the regulation of immune responses in transplantation, allergy, and autoimmunity. Tr1 cells are inducible from naïve cells both in vivo and in vitro, and exposure to high levels of IL-10 is required for their generation.[21] Whilst having a low proliferative capacity, Tr1 cells can be expanded in the presence of IL-2 and IL-15 without the need for TCR activation.[22] Antigen specific Tr1 cells do need to be activated via their TCR as well as by IL-10, but once activated they can mediate bystander suppression against other antigens, probably regulated by the local production of IL-10 and TGF-β.[23] IL-10 downregulates the expression of costimulatory molecules and pro-inflammatory cytokines produced by APCs and directly inhibits IL-2 and TNF-α production by CD4+ T cells,[24] whilst TGF-β downregulates the function of APCs and inhibits cytokine production and proliferation of T cells.[25,26] Once fully differentiated Tr1 cells produce large amounts IL-10 themselves as well as TGF-β and IL-5. Tr1 cells can be easily distinguished from Th1 and Th2 cells as they produce interferon-γ (IFN-γ) at a level of at least one log lower than Th1 cells,[21] low amounts of IL-2, and IL-4 is undetectable.[21]

Tr1 cells are largely found in the gut where their primary role is thought to be the induction of tolerance to the large number of antigens that pass through an animal's intestine as part of their diet. Induction of Tr1 cells in the gut is as a result of priming by specialised APCs such as dendritic cells. Mice deficient in IL-10 suffer from inflammatory bowl disease, however adding back IL-10 into IL-10-deficient mice transiently cures this inflammation.[27] Unlike naturally occurring Tregs, Tr1 cells do not express high levels of CD25 or FoxP3 but do express high levels of the IL-15 receptor-α chain. Tr1 cells mediate their suppression through a cell contact-independent mechanism by the secretion of IL-10 and TGF-β to suppress both memory and naïve T cell responses, both in vitro and in vivo.[21,28] However, Tr1 cells can take on a cytotoxic function when induced by anti-CD3/CD46 resulting in apoptosis in target cells by the production of perforin and granzyme B in a CD18 dependent manner.[19] Tr1 cells have also been shown to suppress B cell immunoglobulin production and can modulate the antigen-presenting capacity of monocytes and dendritic cells.[29]

Th3 regulatory cells

Th3 regulatory cells were first discovered during experiments to investigate oral tolerance.[30] These cells are dependent on the costimulation of the TCR and TGF-β signalling for their development, and once differentiated secrete TGF-β, IL-4, IL-10 and provide help for IgA production.[31] Th3 cells are generated from gut associated lymphoid tissue in the presence of high levels of TGF-β, primarily after the ingestion of a foreign antigen. It has also been proposed that Th3 development can be induced by the presence of IL-10 with the simultaneous inhibition of IL-12 to downregulate the development and maturation of Th1 cells which can inhibit Th3 expansion.[31] Th3 cells express CTLA-4 on their cell surface and it is the stimulation of CTLA-4, which results in TGF-β secretion. Upon stimulation by TGF-β, Th3 cells also up regulate CD25 and FoxP3; however, unlike naturally occurring Tregs, the main mechanism of Th3 cell-mediated suppression is the production of TGF-β which suppresses the proliferation of both Th1 and Th2 cell subsets. Oral administration of myelin basic protein (MBP) in SJL/J mice has been shown to induce tolerance and Th3 cells taken from MBP tolerised mice inhibit the proliferation and cytokine secretion of MBP-specific Th1 cells and suppress the development of experimental autoimmune encephalitis (EAE); the rodent model of multiple sclerosis (MS).[31] Suppression of EAE by Th3 cells is abrogated by injection of anti-TGF-β antibodies.[30] Unfortunately, a trial of oral bovine myelin in the 1990s in humans with multiple sclerosis was negative; thankfully, the myelin was not sourced from British beef.

CD8+ Tregs

Recently, a CD8+ T cell population with suppressive properties has been identified. It is thought that these cells can have a suppressive effect on both activated CD4+ cells and B cells through an interaction that is dependent on target cells expressing the HLA class 1b Molecule, Qa-1. The human homologue of Qa-1 is HLA-E and it is proposed that Qa-1 restricted cells expand as part of the primary immune response to inhibit the expansion of autoreactive CD4+ cells and consequent autoimmunity.[32] Experiments in animals have suggested an important role for suppressor CD8+ cells in the protection against disease recurrence and exacerbation in MS.[32] Tr1-like CD8+ cells have also been described. The induction of these cells is IL-10-dependent and once differentiated these CD8+ T cells secrete high levels of IL-10, are anergic and have a suppressive function.[33,34]

Tregs and Autoimmune Disease

A breakdown in the homeostasis of the immune system is a hallmark feature of autoimmune disease. There has been wide interest in the role of Tregs in various autoimmune diseases. Clinically, loss of function mutations in the FoxP3 gene is strongly linked to immune dysregulation.[35] In mice this results in multiple organ autoimmunity and uncontrolled lymphoproliferation,[12] whilst in humans it triggers a syndrome of lymphoproliferation and myeloproliferation, autoimmunity and allergic dysregulation.[36]

In autoimmune diseases such as systemic lupus erythematosus (SLE), juvenile idiopathic arthritis (JIA), and Kawasaki disease, naturally occurring Treg numbers have been reported to be lower than in healthy individuals, and these lower Treg numbers correlate with either a higher disease activity or a poorer prognosis. It is hypothesised that a reduced number of Tregs results in a shift in balance between Tregs and pre-inflammatory T cells and so there is a breakdown in tolerance. No difference in Treg numbers has been observed in other autoimmune diseases such as spondyloarthritis, myasthenia gravis,

immune-mediated Type 1 arthritis or MS. However, Tregs have been shown to have impaired function, in in vitro assays, in myasthenia gravis[37] and in MS[38] compared with healthy controls, and there is evidence to suggest that Tregs from MS patients have reduced FoxP3 expression which correlates to reduced suppressive function.[39]

Th3 regulatory cells are also clearly important in protecting against autoimmunity. It has been shown that abrogation of TGF-β differentiation leads to autoimmune disease[40] and that TGF-β plays a part in natural resistance to EAE in rats.[41] Thus, Th3 cells are an important regulatory cell type through which TGF-β exerts suppression of immune responses to self.

Tr1 cells were first implicated in the modulation of T cell mediated disease when it was observed that patients with severe combined immunodeficiency (SCID) could be transplanted with HLA-mismatched allogeneic stem cells and did not develop GVHD. These patients had high levels of IL-10 in their plasma and had high numbers of donor derived T cells, which were producing the IL-10. High numbers of these donor derived cells correlated to a low incidence of GVHD after allogeneic HSC transplantation in cancer patients.[42]

While the immunosuppressive function of regulatory T cells prevents the development of autoimmune disease, it is not desirable during immune responses to infectious microorganisms. Current hypotheses suggest that upon encounter with infectious microorganisms the activity of regulatory T cells may be downregulated, either directly or indirectly, by other cells to facilitate elimination of the infection. Experimental evidence from mouse models suggests that some pathogens may have evolved to manipulate regulatory T cells to immunosuppress the host and so potentiate their own survival. For example, regulatory T cell activity has been reported to increase in several infectious contexts, such as retroviral infections and various parasitic infections including Leishmania and malaria.[43,44]

Tregs are also pose a problem in the context of tumour immunity. CD8+ cells have shown to be potent mediators of anti-tumour immunity, however they require CD4+ T cell help for CD8+ T cell activation, function and survival, but Tregs suppress the anti-tumour properties of CD8+ cells by invoking immunological tolerance to self antigens.[45]

Summary

Tregs are essential components of the immune system and self-tolerance. A dysregulated Treg response can lead to a severe or even fatal immunopathology. It is clear that all types of Tregs are inter-dependent on one another to achieve regulation, maintain self-tolerance, and prevent autoimmunity. It is likely that naturally occurring Tregs are recruited at the beginning of an immune response to control the degree of response, but that adaptive Tregs, which are induced after repeated antigen stimulation, act later to diminish the immune response and re-establish homeostasis. To date, all the evidence suggests that Tregs have the potential to be used therapeutically as targets to enhance tumour immunotherapy or to manage autoimmune disease and aid transplantation tolerance.[15]

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A Sixteen-Year-Old in PVS Who Develops Cushing's Disease: Medical and Ethical Issues

Introduction

We present the medical and ethical concerns we encountered when a young adolescent in permanent vegetative state (PVS) developed Cushing's disease.

History and Examination

A previously healthy boy of 16 years presented with two tonic clonic seizures due to an arteriovenous malformation (AVM). He underwent embolisation, which was complicated by catastrophic postoperative bleeding resulting in severe brain injury. On transfer to the neurological rehabilitation unit three months later he appeared to have no awareness of himself or his environment. His tracheostomy had been removed just prior to his transfer and he was maintaining normal respiration and circulation. He was fed through a percutaneous endoscopic gastrostomy tube. He exhibited minimal spontaneous movements in his limbs. Tone was generally increased with flexion contractures in upper limbs, extensor posturing in lower limbs and his feet were fixed in equinovarus. He had sleep-wake cycles with non-purposeful roving eye movements, chewing movements and reflex response to noxious stimuli. His Wessex Head Injury Matrix (WHIM) score was 1/7.

Rehabilitation goals

The main aims of his rehabilitation were, firstly, to establish whether there was any evidence of recovery that might result in him improving from a vegetative state to a higher level of awareness, with the attendant possibility of communication; secondly, to establish a clear nursing and postural management plan, including managing issues related to growth. Thirdly, it was important to provide his family with appropriate emotional and psychological support.

Diagnosis of PVS

In order to confirm the diagnosis of PVS, it was necessary to review his treatment and cognitive state. His clinical condition did not improve over the following nine months in our unit. For the diagnosis of vegetative state, he underwent formal and systematic assessment of the three major sensory systems (auditory, visual and somatic) and the motor system.[2,8] The awareness assessment consisted of ten sessions over a 14-day period, at varying times of the day and lasting approximately 40 minutes. This process was repeated two months later after a multimodal sensory stimulation programme. He showed a generalised startle response to loud noise, occasional slow but inconsistent localisation of sound by turning his head and no response to verbal commands. He had normal pupillary responses, spontaneous eye movements, spontaneous blinking but no consistent tracking and no response to visual threat. There was reflex flexion to pain in the legs but no response to pain in the arms or face. Some grunting noises were made, but not with any consistency or meaning. His level of awareness was therefore rated at level two on the Rancho Los Amigos Scale, which is a cognitive functioning scale[7] (Table 1).

In view of the significance of a diagnosis of PVS, a second opinion[5] was sought from an experienced clinician from another institution. He independently confirmed our clinical findings.

His medication was reviewed to consider the potential for sedative side-effects.[5] He was on baclofen and carbamazepine. The baclofen was stopped to judge any change in his level of arousal, with no positive effect. The dosage of carbamazepine was extremely low and felt unlikely to be contributory.

A brain CT scan at six months confirmed the presence of widespread ischaemia in both hemispheres (see figure).

In summary he was found to have intact primary sensory pathways and primary motor output but no evidence of sustained, reproducible, purposeful or voluntary behavioural responses to normal or noxious visual, auditory or tactile stimuli, no language comprehension or expression. He only had reflex motor responsiveness with no evidence of co-ordinated motor activities. As his neurological status remained unchanged for one year after catastrophic brain injury, the diagnosis of PVS was made.[1,2,5]

Presentation and diagnosis of Cushing's Syndrome

At the time the patient was being assessed for PVS one year after his haemorrhage he was found to have hypertension with no obvious cause, unexplained weight gain and rapidly progressive purple striae on his arms, trunk and thighs. He was also noted to be severely osteopenic on an ankle x-ray.

Four 24-hour urine collections showed elevated uri-

Figure

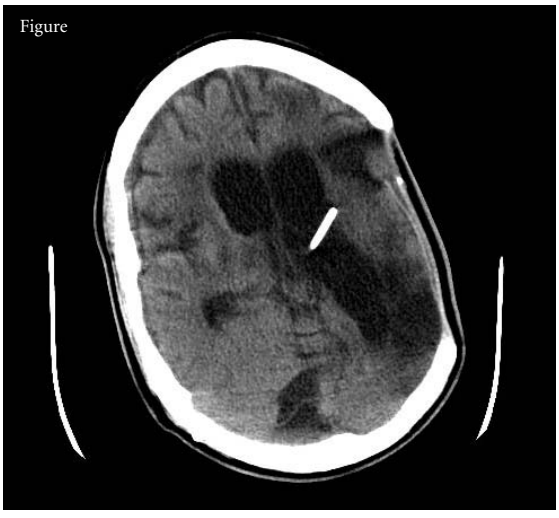

Table 1: Rancho Los Amigos Scale Level 2: Generalised Response: Total Assistance

1	*Demonstrates generalised reflex response to painful stimuli.*
2	*Responds to repeated auditory stimuli with increased or decreased activity.*
3	*Responds to repeat external stimuli with generalised physiological changes , gross body movement with or without purposeful vocalisation.*
4	*Responses noted above may be same regardless of type and location of stimulation.*
5	*Responses may be significantly delayed.*

Original Scale co-authored by Chris Hagen, PhD, Danese Malkmus, MA, Patricia Durham, MA Communication Disorders Service, Rancho Los Amigos Hospital, 1972. Revised 11/15/1974 by Danese Malkmus, MA and Kathryn Stenderup, OTR.

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Table 2: Dexamethasone Suppression Test

The patient failed to suppress cortisol levels on the low dose dexamethasone suppression test. On the high dose test there was satisfactory cortisol suppression and a fall in ACTH. These results indicated Cushing's syndrome, most likely secondary to a pituitary microadenoma (Cushing's disease).

Low-dose Dexamethasone Suppression Test	***Day 1***	***Day 2***	***Day 3***
Cortisol	*365 nmol/L*	*172 nmol/L*	*245 nmol/L*
High-dose Dexamethasone Suppression Test	***Day 1***	***Day 2***	***Day 3***
Cortisol	*385 nmol/L*	*12 nmol/L*	*12 nmol/L*
ACTH	*11 ng/L*	*< 5 ng/L*	*< 5 ng/L*

nary free cortisol. A low- and high-dose dexamethasone suppression test indicated Cushing's syndrome, probably secondary to a pituitary microadenoma[9] (Table 2).

Management of the dual diagnosis

It was now necessary to consider not only the implications of PVS but also Cushing's syndrome which would very likely shorten his life if left untreated. Moreover, with the diagnosis of PVS the possibility of withdrawal of artificial nutrition and hydration (ANH) was considered.[1,2,5] The situation was further complicated by the fact that the patient was still a child in law, but having reached the age of 16 years, his parents had no legal power to give or withhold consent to treatment.[6] Nevertheless it was felt essential to fully involve his parents in the decision-making process. After full reflection and consideration it was decided not to pursue withdrawal of ANH.

Management of Cushing's syndrome would normally include invasive procedures to localise the source – in this case, most likely a pituitary adenoma, followed by definitive surgery where possible.[9,10] Palliative treatment with medical treatment (e.g. aminoglutethimide or ketaconazole) or adrenal resection is an option in otherwise untreatable cases. Medical treatment is associated with significant side-effects. Expert input was provided by a paediatric endocrinologist. Usual management of pituitary adenoma would involve high resolution brain MRI with contrast, followed, if necessary, by inferior petrosal sinus sampling in a specialist centre. This would require general anaesthesia to enable him to lie still. Subsequently, pituitary surgery and/or radiotherapy would be required.

After discussion between the family, the medical and the rehabilitation teams it was felt inappropriate to employ invasive investigations and it was decided instead to use simply symptomatic treatment. It was also agreed not to resuscitate him in the event of cardio-respiratory arrest, or to transfer him to an acute hospital for management of intercurrent illness. However, transfer to an acute hospital for technical help such as PEG tube problems was felt to be appropriate.

Advice was sought from the trust's solicitors as to the need for High Court involvement. This was felt unnecessary as all parties involved were in full agreement with the management plan.

Subsequently the patient was transferred to a long stay community facility to receive ongoing care, where he remains, having developed no adverse sequelae from his Cushing's syndrome. The treatment plan was agreed with his new clinical team prior to transfer, with regular monitoring of blood pressure and blood sugar. Up to the present time he has not developed diabetes, but if he does so the plan is to treat only symptomatic diabetes, such as dehydration and infection. His parents remain satisfied with the approach we, and his new clinical team, have taken.

Discussion

We have presented the medical and ethical dilemmas encountered in a 16-year-old boy with concurrent PVS and Cushing's syndrome.

Accurate diagnosis of PVS is crucial. A structured, systematic clinical assessment[2] of awareness is required because errors in diagnosis have occurred.[3,4] It is important to establish the mechanism of brain injury, aided by neuroimaging: however, the diagnosis remains essentially clinical. Observational tools such as the WHIM can be used to assess and monitor cognitive recovery after severe head injury.[11] Exclusion of reversible causes such as sedative medication is important. Patients in persistent vegetative state should be observed for twelve months after a traumatic brain injury and six months after other causes before it is judged to be permanent (PVS). When the diagnosis of PVS is being considered, the patient should be examined by at least two doctors, both of whom are experienced in assessing disorders of consciousness.[5]

Cushing's syndrome was diagnosed concurrently with the confirmation of PVS, raising additional management issues. Untreated Cushing's syndrome has a poor prognosis and will very likely shorten the patient's life due to impaired immunity, increased vulnerability to hypertension and cardiovascular disease, diabetes, propensity to skin breakdown with poor wound healing and pressure sores, osteoporosis, peptic ulceration and gastrointestinal haemorrhage. Symptomatic treatment such as bisphosphonates to ameliorate osteoporosis in Cushing's syndrome[12] are effective but the effect is modest because normally treatment is directed towards dealing with the Cushing's.[13]

The combination of PVS and Cushing's disease is previously unreported. It raises the possibility that unrecognised Cushing's syndrome may have contributed to the catastrophic intracranial haemorrhage.

Diagnosis of PVS has important implications, especially in conjunction with an additional life-threatening diagnosis. With the family's agreement, we felt intervention to investigate or treat the Cushing's syndrome was inappropriate beyond employing simple symptomatic measures.

In summary, the approach we took with early involvement of an endocrine specialist in our face-to-face meetings with the family and multi-disciplinary team was very effective in achieving a satisfactory resolution to a very difficult, and distressing situation. This had the significant advantage of obviating recourse to legal proceedings and is an approach we would commend to others confronted with complex issues of dual diagnosis.

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References:

1. Galetta SL, et al. *Arch Intern Med*, 2002; 162: 2161–2169.
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3. TYSABRI SmPC, Biogen Idec Ltd.

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Surgical Management of Metastatic Disease of the Spine

The incidence of metastatic spine disease is increasing with rising cancer incidence and improved treatment. 5-10% of patients with cancer develop spinal metastases and 10% of these develop cord compression.[1] Treatment options for metastatic spinal disease include radiotherapy, surgery, hormone therapy and chemotherapy.

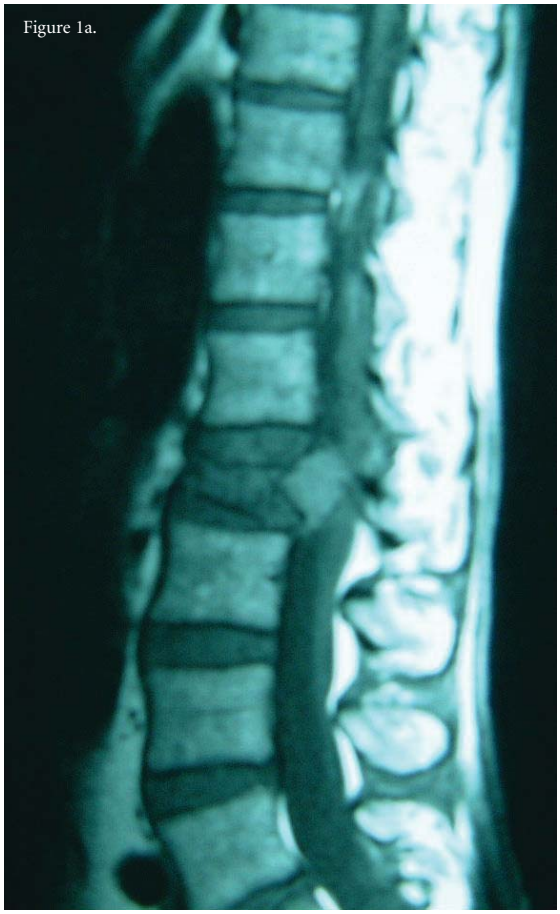
The objectives of management are to treat the patient's pain and disability. To best do this, the nature of the patient's spinal problem must be thoroughly assessed. Once this assessment has been made, potential surgical solutions can be considered. These need to be evaluated in the context of the individual patient's circumstances: how fit are they, what is the likely course of their disease and what other options for intervention are available? These complex decisions are best made within a multi-disciplinary team.

Pathology

Primary tumours of the prostate, lung and breast most commonly metastasise to the spine, accounting for about 50% of epidural compression cases. Other common primary cancers include lymphoma, melanoma, renal cell carcinoma, sarcoma and multiple myeloma.[2] The most frequently affected part of the vertebra is the body (see Figures 1a and 1c), followed by the pedicles and posterior elements. More than 90% of spinal metastases are extradural, 5% are intradural and <1% intramedullary.[3]

Metastatic tumour growing into the spinal canal can cause spinal cord damage by direct compression resulting in oedema, venous congestion and demyelination. With prolonged compression, secondary vascular injury occurs with capillary or venous occlusion and/or infiltration followed by infarction of the spinal cord. The metastatic infiltration of bone can cause pain with or without frank instability. Destruction of the vertebral body can lead to a pathological fracture and progressive kyphotic deformity. Such deformity further threatens a spinal cord that may already be compromised by tumour within the spinal canal (see Figure 1c). Radiculopathy may ensue as a result of exiting nerve roots being compressed.

Figure 1a.



Presentation

History

Patients at increased risk of spinal metastases are those with known malignancy and those aged over 50. Spinal pain is the main presenting symptom in 85% of spinal tumours. However, back pain is a common complaint and malignant disease will only be responsible for a minority of all back pain.

Red flag features of pain that increase the likelihood of serious spinal disease are:-

- Gradual onset, progressive, constant, night-time or recumbency pain and axial pain exacerbated by movement in all planes.[4]

The pain may be accompanied by a progressive neurological deficit, deformity or unexplained constitutional symptoms. These symptoms are important to elicit as they may have a bearing on subsequent decision making.

Examination

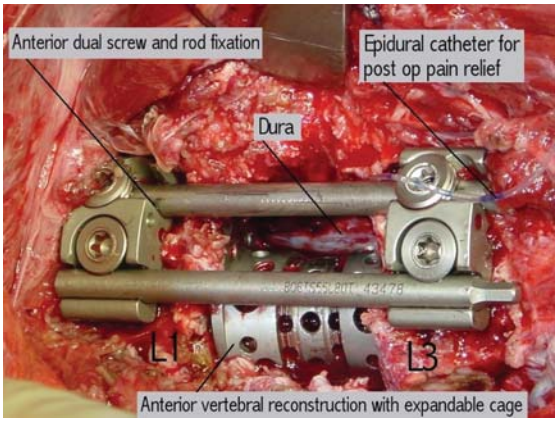
The neurological findings depend on the site and level of the lesion. As most spinal metastases begin in the vertebral body, anterior cord compression involving the corticospinal tracts causing spastic paraparesis, is the most common initial neurological deficit. It is important to establish whether the patient can walk. Examination of the supine patient may reveal good lower limb power but the patient may be unable to weight bear. Whilst the patient is upright, check for any visible kyphotic deformity secondary to vertebral body collapse or localised bony tenderness. Sensory and sphincter disturbances tend to present later.

Investigations

Laboratory tests are helpful in assessing the patient's fitness for surgery but infrequently aid the diagnostic process, haematological malignancy being the notable exception. However, if metastatic spinal disease is suspected, FOB, PSA, CEA and urine and serum electrophoresis may be helpful in determining the primary lesion. A raised transaminase in the LFTs raises the suspicion of liver metastases.

An MRI scan is crucial to aid diagnosis and delineate the extent of the spinal disease. The initial scan may focus on the part of the spine from where the patient's symptoms seem to

Figure 1b.



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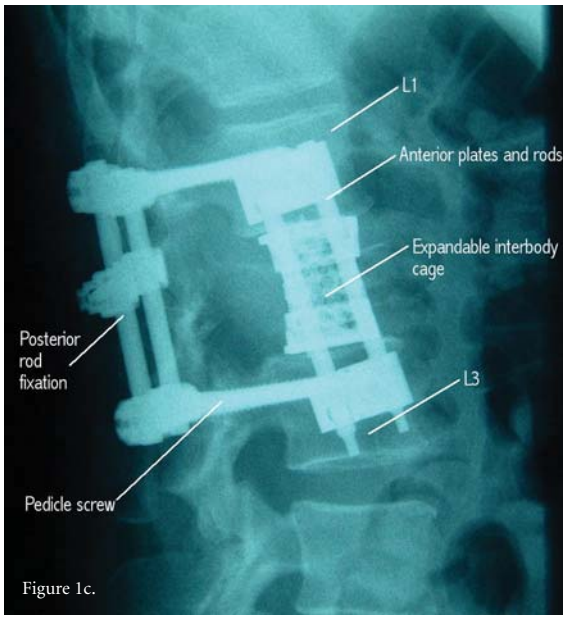

Figure 1c.

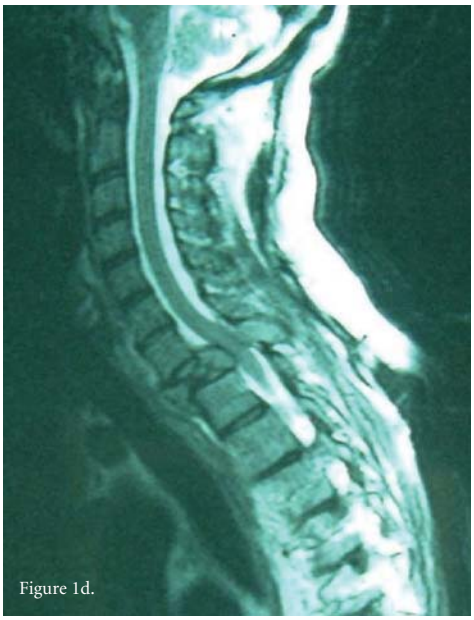
Figure 1d.

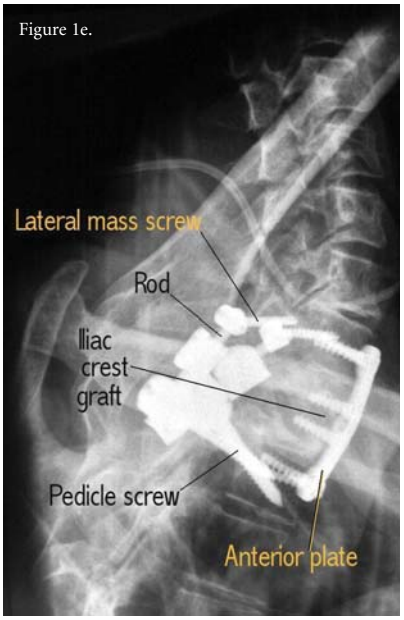

Figure 1e.

be arising. However, if metastatic disease is discovered, the whole spine must be imaged. If the MRI cannot be tolerated or is contraindicated, a myelogram can be used to establish the level of compression. Although the T2 weighted image is generally the most sensitive sequence to detect pathological change, the T1 sequence is often best to identify metastases. If contrast is given, the metastases may be rendered isointense and thus not seen on a T1 + gadolinium image. Similarly, the increased T2 signal of pathological tissue may be isointense with the fatty bone marrow masking the appearance of metastases on a T2 sequence. A fat suppressed T2 scan is therefore often useful.

Plain x-rays often serve as the initial screening test as they are readily available. They are poor at detecting lytic metastases, since up to 50% of the bone must be destroyed. However, they are the best modality for assessing and monitoring deformity and for identifying sclerotic lesions.

CT scanning may be helpful to determine the amount of bony destruction that has occurred, and for the assessment of potential bony fixation points if reconstruction is being considered.

Bone scans are sensitive for detecting early stage bone pathology. However they lack specificity and are largely restricted to assessing the extra-axial skeleton and cases where diagnostic doubt prevails.

Management Options

The therapeutic objectives in the management of metastatic disease of the spine are to:-

1. Maintain and restore neurological function
2. Treat pain

Surgery can obtain these therapeutic objectives by:

1. Decompression of neural elements
2. Restoration and maintenance of the alignment and integrity of the spinal column

Surgical strategies

Instrumentation and fusion

Traditionally a decompressive laminectomy was the surgical option in metastatic spinal disease. This may satisfy some of the therapeutic objectives by indirectly decompressing the cord or cauda equina but deformity will develop without surgical stabilisation, increasing pain and neurological deficit. The use of instrumentation allows realignment and stabilisation of the spine and consequently a more aggressive decompression and tumour resection (see Figure 1b, 1c and 1e). Those patients with neurology secondary to deformity will not improve without realignment.[5]

Instrumentation includes:

1. Fixation using rods and screws. In the cervical spine, screws are placed in the lateral masses. In the thoracolumbar spine pedicle screws are normally used.
2. Vertebral body reconstruction. This may be with a metal cage, cement, ceramic spacer or iliac crest graft.

Implants have a finite life span, and will eventually fail. Since this is palliative surgery, the life expectancy of the instrumentation may well be longer than that of the patient. With increased longevity, measures must be taken to achieve bony union, to avoid instrument failure. The extent of instrumentation depends on the extent of metastasis, condition of the bone and the extent of the deformity.

Surgical Approach

Most spinal pathology can be managed using an anterior or a posterior approach. Sometimes a combined anterior and posterior approach is required (Figure 1b, 1c and 1e). The factors to consider are 1) the part of the spine affected, 2) the anatomy of the cord compression, 3) any deformity and 4) the general condition of the patient. In the thoracolumbar spine, posterior instrumentation involves the insertion of pedicle screws providing good bone purchase and allowing the correction of deformity. Whilst vertebral body reconstruction can be performed from a posterior approach,[6] it is easier if the vertebral body is accessed anteriorly. However, anterior fixation is not as reliable as pedicle screw fixation, particularly in patients with poor bone quality. In addition, the patient's respiratory function may preclude a thoracotomy or retroperitoneal approach to the vertebral body.

Extent of resection

Surgery for metastatic disease cannot be curative. The main aim is to provide a direct decompression of the spinal cord, removing as much tumour as feasible to reduce the risk of local recurrence, particularly when a chemo and radioresistant tumour is being treated, such as renal cell carcinoma.

Adjuvant therapy

All but emergency cases should be discussed in the context of a multidisciplinary team. A decision to proceed with initial radiation therapy should be made in the knowledge that this will increase the risk of wound infection by as much as a factor of three[7] should the patient come to surgery. Surgery should not be undertaken during the post-chemotherapy period of immune and haemopoietic compromise.

Embolisation

Metastatic tumours of thyroid and renal cell origin are notoriously vascular. Preoperative embolisation reduces the intraoperative blood loss.

Surgery versus radiotherapy

The relative roles of surgery and radiotherapy have been the subject of much debate. There is now class 1 evidence that appropriate surgery, followed by radiotherapy, is the treatment of choice in selected patients with symptomatic spinal metastases. Patchell et al[8] included 101 'acceptable surgical candidates' with a single level of metastatic epidural spinal cord compression, at least one associated sign or symptom including pain and at least three months life expectancy. Patients with very radiosensitive tumours and those that had been paraplegic for at least 48 hours were excluded. All patients were given dexamethasone and were randomised to radiotherapy or surgery followed by radiotherapy. The two groups were evenly matched in terms of primary tumour types, neurology, tumour loca-

tions and spinal instability. The most common primary tumours were lung (26 patients) and prostate (19 patients). The thoracic spine (88 patients) was the commonest site of disease. The vertebral body was involved in 61 patients. No lumbar lesions were included. 32 patients were unable to walk and 39 patients were incontinent preoperatively. Surgery with radiotherapy resulted in better neurological function, better pain control and increased longevity compared with radiotherapy alone. The post treatment ambulation rate was 84% in the surgery group and 57% in the radiation group. Of those unable to walk preoperatively, 62% regained the ability to walk following surgery compared with 19% of the radiation group. Those patients receiving surgery remained ambulant for longer, in most cases for the remainder of their lives. The major disadvantages of surgery are that the patient must be fit enough to tolerate it and their life expectancy must be sufficient to justify the extent of the proposed surgery.

Factors contributing to the decision making process include:

Attitude of patient
This is ultimately the most important factor. The risks and benefits of surgery and conservative treatment must be discussed frankly with the patient. Having been fully informed, most individuals are able to make their own decision as to which treatment strategy they would prefer.

Neurological status
If the neurology is rapidly progressing, a complete irreversible cord lesion may supervene before radiotherapy has any effect. Surgery is the most expedient means of decompressing the neural elements. Whilst it is well documented that the preoperative Frankel grade is a strong predictor of functional outcome,[7] our experience is that surgical decompression and reconstruction of the spinal column is very effective in restoring spinal cord function despite the severity of the lesion. In our series of 14 immobile patients (Frankel grades A, B and C) treated surgically for spinal cord compression, 12 became mobile (Frankel grades D and E) and two remained unchanged.[9] In a retrospective review of patients receiving surgery for solitary spinal lesions, Sundaresan et al.[10] included 19 patients with Frankel grade B (incomplete spinal cord lesion with preserved sensation only). All improved post operatively, 18 to a functional/mobile Frankel grade (Frankel D or E).

However surgical stabilisation is an excellent treatment for painful spinal metastases in the absence of neurology or nerve root compression.

Tumour type
Characteristics of the primary tumour influence treatment decisions. Radiation is recommended as first line in highly radiosensitive tumours e.g. lymphomas, leukaemia, multiple myeloma and germ cell tumours where there is no significant malalignment. Life expectancy varies with tumour type. Once metastases are detected, the median survival for breast carcinoma is 18-24 months,[11] whereas the median survival for metastatic lung disease and melanoma[12] is six months. Surgical treatment is considered and discussed with the patient in the context of their estimated life expectancy.

Extent of metastases
Multiple spinal metastases do not preclude surgery; however, the more extensive the bony involvement, the more difficult the surgery.

General medical condition of the patient
Is the patient in a general condition that safely allows surgery? This is a subjective clinical decision and depends on the surgical procedure proposed. For example, a patient with metastatic lung cancer may not tolerate an anterior vertebral column reconstruction via a thoracotomy or retroperitoneal approach, but may be fit enough for an entirely posterior approach. Deranged LFTs not only raise the suspicion of metastases but also have implications for surgery. Consequent clotting abnormalities increase intra-operative blood loss and low albumin compromises post-operative recovery and wound healing.[13]

Spinal location
The location of the metastatic cord compression determines the approach e.g. in the cervical spine, an anterior approach and column reconstruction is most effective with low morbidity (see box). In the thoracic spine, nerve roots can be sacrificed facilitating decompression of the vertebral bodies and anterior reconstruction via a posterolateral/transpedicular route.[6]

Deformity
When cord compression is a consequence of kyphosis, the only way to achieve decompression is to restore and maintain alignment.[5] It is not clear from the Patchell trial[8] whether patients with kyphotic deformity were randomised to treatment or not. However, it is clear that radiotherapy alone will not decompress the cord in this group of patients. Any patients that are treated with radiotherapy alone should be monitored for the development of kpyhotic deformity.

Bone quality
The adjacent bone must be of sufficient quality to allow successful instrumentation.

Scoring systems
Various scoring systems have been proposed to aid objective management decisions e.g. those of De Wald,[14] Harrington[15] and Tokuhashi et al.[16] These criteria and scoring systems are useful for cohorts and research but their utility in making decisions for individual patients is questionable. In reality, all of the factors discussed must be considered by a multidisciplinary team and with the patient.

Summary
Despite there being class 1 evidence supporting the role of surgery in the context of spinal metastases, the management decision is often not clear cut. Many different factors, such as life expectancy, fitness for surgery, symptoms, deformity, site and extent of metastases, must be taken into account and discussed with the patient and amongst the multi-disciplinary team. The accompanying case history and figures illustrate this decision making process. (see Box 1).

Key points
- *There have been considerable advances in spinal surgery for metastatic disease*
- *A randomised controlled trial[8] has shown clear benefits of surgery*
- *All patients with symptomatic metastatic spinal disease should be discussed with an appropriately trained spinal surgeon*
- *Surgery is the only means of decompressing the spinal cord when compression is secondary to deformity*

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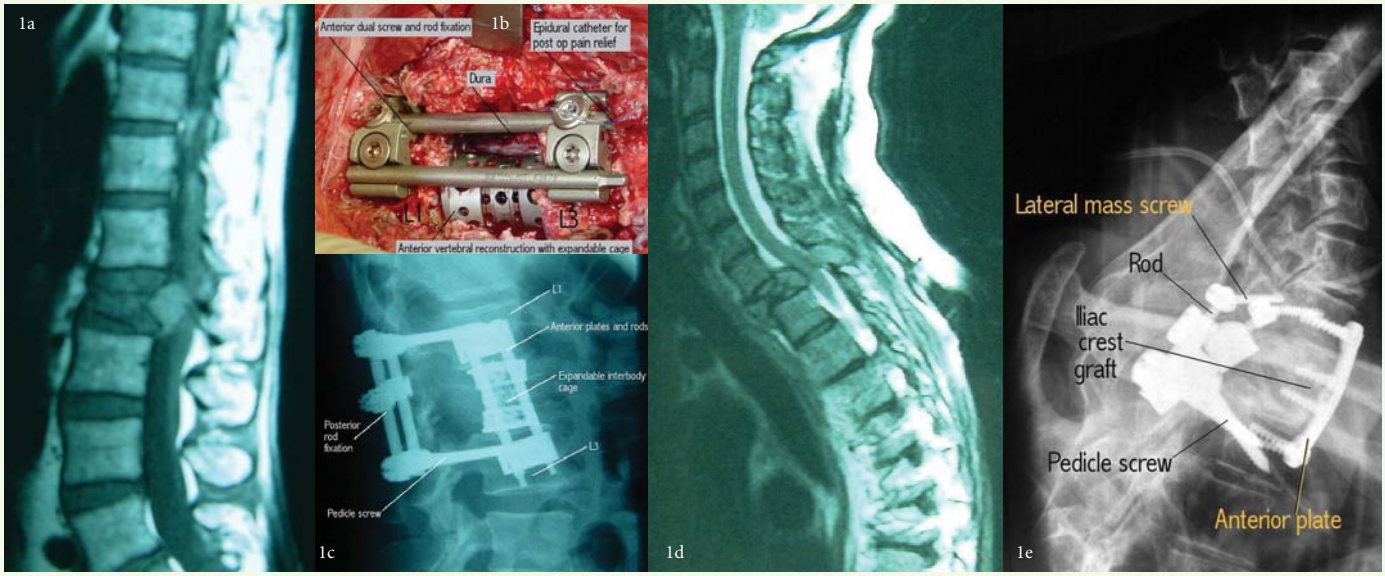
Abbreviations

FOB	Faecal occult blood
PSA	Prostate specific antigen
CEA	Carcinoembryonic antigen
LFTs	Liver function tests



BOX 1 - Case history

This 67-year-old gentleman presented in 2001 with bilateral sciatica and reduced mobility secondary to an isolated plasmocytoma at L2 (Figure 1a). A L2 vertebrectomy and anterior and posterior instrumentation were performed (Figure 1b, intraoperative photograph and 1c post operative lateral XR). He underwent post-operative radiotherapy and was soon pain free and mobile.

He represented in June 2002, paraplegic and incontinent of urine secondary to a T1 metastasis and associated pathological fracture (Figure 1d). An emergency posterior decompression was performed and the patient was placed in traction to reduce the deformity at C7/T1. Subsequently a T1 corpectomy was performed. The T1 body was replaced by an iliac crest graft, held in place by an anterior plate and stabilised with posterior fixation (Figure 1e, post operative lateral XR). Further adjuvant treatment was given including radiotherapy, chemotherapy and autologous stem cell transplantation. The patient's neurology completely resolved and he has remained in remission until 2006.

Discharging a Patient Home with a Tracheostomy

Introduction

The majority of patients who require a tracheostomy during their treatment in hospital are decannulated prior to discharge home. However, there are occasions when the patient will continue to require their tracheostomy tube either as a long-term option or even permanently. As a result, tracheostomies are becoming increasingly common in the community setting.[1] The wide range of tracheostomy tubes and accessories available and the advances in specialist knowledge are contributing to the individual's living successfully at home as a neck breather.

It is important to clarify why an individual has a long-term tracheostomy as this will determine their management and care requirements. Examples will include:

- to deliver mechanical ventilation
- to bypass an upper airway obstruction (e.g. tumour or vocal cord palsy)
- to protect the airway from aspiration
- to access and remove chest secretions

Before the discharge process can begin, the medical stability of the individual must be established. The tracheostomy site should be healed and there should be no signs of infection.[2]

The community team

The focus of the discharge planning will be effective communication between the hospital-based and community team. Early identification of a patient who will not be decannulated before discharge will be pivotal to the discharge process. Once this has been established, referral to the patient's general practitioner and community team will begin a complex process of events.

The community team should be encouraged to attend the ward to meet with the staff and patient. This will provide the opportunity to discuss the patient's clinical condition and care needs. The community nurses will provide the patient and their family with support and guidance in the routine management of the tube and first line management in the event of a critical incident.[3] This will include basic life support with a tracheostomy. However, these are not skills commonly acquired during nurse training[4] and the community nurse's experience may vary enormously within the team. It will be important that they are adequately prepared in order to fulfil this role.[5] The hospital based staff must support this need with training and information. The following considerations should be presented to the community team:

Why has the patient got a tracheostomy?

If the tracheostomy is providing a primary airway (there is compromised airflow above the level of the tube) this will have considerations for the community team. If the tube were to block with secretions or accidentally fall out, the priority will be to reinsert another tube without delay. The tracheostomy tube should be double lumen with a removable inner cannula. Should the tube block with secretions, the cannula can be removed, cleaned and reinserted therefore promoting tube patency and avoiding the need for an emergency tube change (Figure 1).

A cuffed tracheostomy tube will be required to provide protection from aspiration for the patient with swallowing difficulties. In this situation, the cuff should be checked regularly using a cuff pressure manometer to ensure it is inflated correctly (Figure 2).

Who will be caring for the tracheostomy?

To care for a tracheostomy at home requires advanced technical skills.[4] Ideally, the individual will be able to carry out their own care, providing them with a sense of self-control and reducing the dependency on others.[6] An education programme[7] to include suctioning, humidification, wound care and inner cannula care should be provided. These practical aspects require physical ability and dexterity to perform competently. The individual should be able to identify and manage complications and apply their knowledge and skills to the changing needs of their tracheostomy. They should be motivated to carry out their care consistently and reliably. Any cognitive impairment or anticipated decline should cause the healthcare team concern as to the individual's suitability to self-care. In this instance a

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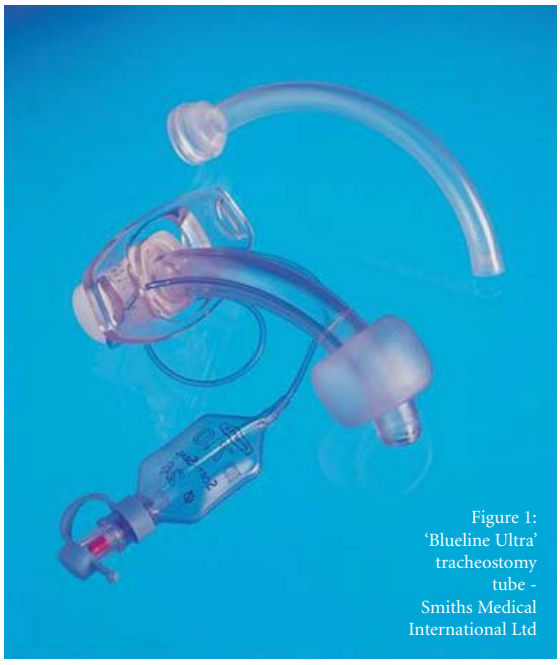

Figure 1: 'Blueline Ultra' tracheostomy tube - Smiths Medical International Ltd

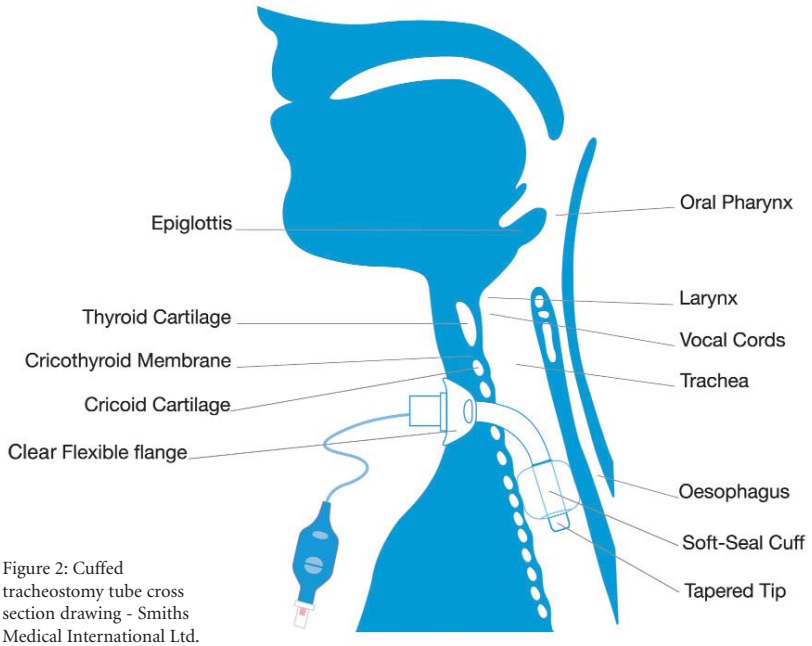

Figure 2: Cuffed tracheostomy tube cross section drawing - Smiths Medical International Ltd.

'key carer' should be identified to provide the tracheostomy care. However, the healthcare team should not assume that this is a role a family member is willing or indeed capable of undertaking. A tracheostomy can cause a substantial amount of caregiver strain and this should be considered when deciding on a treatment plan.[8] Caregivers will be required to learn skills to apply to the care of the tracheostomy which can be daunting and overwhelming. Depending on the level of supervision the individual requires, the family member may become exhausted. Stressors the carer may experience will include knowledge deficit, worry over the individual's health, level of responsibility and restricted social activities.[9] The healthcare team should consider these issues and discuss the possibility of respite services to prevent the carer becoming unable to cope.

What equipment and supplies are required?

The care of a tracheostomy demands specialised equipment and supplies to maintain a safe and functioning airway. A portable suction unit and nebulizer must be issued to the patient before discharge. The patient who does not require regular suction or nebulizers should be equipped in the event of deterioration in their clinical condition (e.g. increased secretion production as a result of a cold).

Disposable supplies of tracheostomy products will be required. This will include tracheostomy tubes, dressings, Velcro collars and heat moisture exchangers (HME). The community team will require details of items to order in preparation for the discharge. The equipment and supplies will be extensive and costly for the community team to purchase. It is recommended that the discharging ward provide at least one week of supplies for the patient to take home with them. This will overcome any delays experienced with the ordering process and ensure a smooth transition from the hospital to home setting.

Continuing Care

The community team should be advised as to the ongoing management plan for the patient to include further treatment and review of the tracheostomy. They should be made aware of the patient's prognosis or any predicted deterioration in their health.

As discussed, the indication for a long-term or permanent tracheostomy will vary between individuals. It will be important to continue to monitor the patient as to the suitability of their tube type when considering their changing clinical needs and indeed whether they still require their tracheostomy.

Contact telephone numbers should be provided to include district nurse, access to ENT medical team, ENT Ward and tracheostomy nurse (if available). This will provide the patient with support and a treatment plan in the event of a difficulty arising with their tracheostomy.

Tracheostomy tubes need to be changed according to the manufactures guidelines. This can vary between monthly (double lumen PVC tubes) or long term tube materials (silicone, silver). The ongoing management of this should be established prior to discharge. Each individual will require an assessment to determine the most appropriate setting for their tube to be changed. Firstly their clinical conditions should be considered. A large tumour distorting the trachea may cause difficulty with a tube change. Excess secretions and a high aspiration risk may complicate the procedure. Previous tube changes should be examined. Has there been difficulty either removing or inserting a tube? This can be caused as a result of hypergranulation of the stoma edges or the tract itself.[10] If there is an anticipated complication or difficulty associated with the tube change, the procedure should be performed in the hospital setting. This will ensure access to experienced practitioners and facilities in the event of a difficulty arising.

Living with a tracheostomy

The tracheostomy may affect lifestyle in terms of activities and choices, but it is possible to successfully adapt without unnecessary restrictions.

The patient and their carers should receive clear guidance on living with a tracheostomy. This will include adapting their skills to the community setting and being aware of hazards in the environment which will be detrimental to their wellbeing. The patient will be vulnerable if exposed to risks such as water entering the tracheostomy tube and toxic substances including aerosols, smoke, or fine animal hair causing airway damage or infection.

The individual or carer should have access to emergency tracheostomy equipment (suction unit with tubing and catheters and portable nebulizer) and supplies at all times. This will ensure there is no delay in delivering the tracheostomy care in any environment or situation. It is recommended that a tracheostomy bag or case (Figure 3) containing such items should be available to include:

Spare tracheostomy tube of current size
Spare tracheostomy tube one size smaller (in event of being unable to insert tube)
Spare inner cannulas
Precut tracheostomy dressing
Velcro collar or tracheostomy tapes
Heat moisture exchange (Swedish Nose, Buchanan Bib)
Syringe (if tracheostomy tube is cuffed)
Cuff pressure manometer (if tracheostomy tube is cuffed)
Lubricating jelly

Figure 3:
Kapitex Healthcare Ltd
'Trachi-Case'.

Conclusion

The discharge of a patient with a tracheostomy is clearly a complex and multifaceted process. The healthcare team are presented with issues unique to a neck breather and the management of this will be instrumental in determining the success of the discharge, the health of the individual and ultimately avoid readmission to hospital.

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Gambling

Gambling may be defined as any game of chance involving financial stakes and an element of risk. Such games are common in our society, either using ones own money (e.g. the National Lottery, betting on horse or dog racing, visiting a casino or on-line gambling) or, better, other people's money (e.g. banking, insurance, the Stock Market). Gambling as a form of risk-taking and decision-making, is of interest to neuropsychologists and may be characterised as an executive function task,[1] amenable to testing with instruments such as the Iowa Gambling Task (IGT)[2] and the Cambridge Gamble Task.[3] The neuroanatomical substrates of such decision making are believed to encompass the prefrontal cortex and the amygdala.

Gambling may be defined as pathological when greater risks are taken and potential losses are correspondingly greater. DSM categorises pathological gambling as an impulse control disorder. A famous 'sufferer' from this 'addiction' was the author Fyodor Dostoevsky, who wrote a novella, *The Gambler* (1866), on the subject (in just 26 days). Pathological gambling may also be a reflection of brain disease and its treatment.

A number of reports of pathological gambling in patients with Parkinson's disease have appeared, the common factor apparently being treatment with various dopamine agonists.[4,5] Whether the small numbers of patients reported in these case series simply reflect the population prevalence of gambling behaviour, irrespective of treatment, or whether the numbers of PD patients with 'problematic gambling' are in fact much higher (e.g. 10% of patients prescribed dopamine agonists in the west of Scotland[6]) remains to be clarified. Certainly cases may be seen outwith dedicated PD treatment centres: I have seen two such patients in district general hospital clinics, both with debts exceeding £10000, who were able to conceal their activities from family members for long periods of time.[7] IGT performance may be impaired early in PD suggesting ventromedial prefrontal cortical dysfunction.[8]

If gambling is an executive function, then one might anticipate that frontal lobe pathology would be associated with impaired performance on tests of gambling.[3] This is the case in patients with frontal variant frontotemporal dementia (fvFTD) who have been shown to display risky decision-making, even in early disease and without evidence of behavioural disinhibition or impulsiveness.[9] FTD presenting with pathological gambling has been reported.[10] Risk-taking behaviour in fvFTD may be ameliorated by methylphenidate.[11] In contrast to fvFTD, successful gambling may be preserved in other focal frontotemporal lobar degeneration syndromes. A patient with semantic dementia seen in this clinic,[12] who is now essentially mute, continues to bet on the horses with, according to his wife with whom he shares half his winnings, no tailing off in his success rate; the bookies have noticed he says little but believe he has had a stroke.

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Awards and Appointments

Professor Gavin Giovannoni and Professor David Baker have moved from the Institute of Neurology, Queen Square, to take up joint appointments at the Institute of Cell and Molecular Science, Queen Mary University London.

Gavin Giovannoni has taken up the Chair of Neurology, with a joint appointment at Barts and The London NHS Trust. Gavin did his undergraduate medical training at the University of the Witwatersrand, South Africa. He moved to the Institute of Neurology, Queen Square, London in 1993 after completing his specialist training in neurology. He was awarded a PhD from the University of London in 1998. David Baker has a personal chair in neuroimmunology. He received his BSc in Zoology from Bedford College, University of London in 1983. He trained in immunology at The Hunterian Institute, University of London and received his PhD in 1987 for studies on control of immune responses in delayed hypersensitivities of the skin.

Professor Gavin Giovannoni Professor David Baker

David Baker developed a novel relapsing-remitting model of MS in the late 1980s, which closely mimics the clinical disease course of MS. Using this model he has discovered a particularly effective immune tolerance strategy to treat antigen-specific autoimmunity, which he hopes will translate into clinical practice.

Their research programme includes MS-related neurodegeneration, MS biomarker discovery, neutralising anti-interferon beta antibodies as model of human autoimmunity, immune tolerance strategies and antibody mediated autoimmune disorders of the central nervous system. They currently hold a programme grant from the US National MS Society and the MS Society of Great Britain and Northern Ireland to investigate novel neuroprotective and neurorestorative therapies in patients with MS.

We would like to publish more awards and appointments in future issues of ACNR. If you know of someone who should be considered for this feature, please send details to **Rachael@acnr.co.uk**

'Neurological Literature' - Headache (Part 3)

Andrew Larner is the editor of our Book Review Section. He is a Consultant Neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool, with a particular interest in dementia and cognitive disorders. He is also an Honorary Apothecaries' Lecturer in the History of Medicine at the University of Liverpool.

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> *English, which can express the thoughts of Hamlet and the tragedy of Lear, has no words for the shiver and the headache. … let a sufferer try to describe a pain in his head to a doctor and language at once runs dry.*[1]

This famous declaration by Virginia Woolf (1882-1941) in her essay *On Being Ill*, first published in 1930, will strike a chord with many neurologists who have sat listening to patients attempting to convey their headache symptoms: "It's difficult to describe" is a common refrain.

Nonetheless, many authors have felt able to use headache in their works, sometimes as a literary device, sometimes with a fuller account of symptoms. David Perkin has identified accounts of headache and migraine in works by George Eliot, Jane Austen, Tolstoy, Trollope, Saki, Arnold Bennett, Thomas Mann, Charlotte Bronte, and Victor Hugo,[2,3] and other examples have been reported by JMS Pearce[4] and in two earlier articles in this journal.[5,6] These pieces have not exhausted the fund of literary descriptions of headache; some further observations are offered here.

The spectrum of authors who have incorporated headache in their work is noteworthy, perhaps reflecting the ubiquity of headache disorders. The master dramatist who was able to "express the thoughts of Hamlet and the tragedy of Lear", William Shakespeare (1564-1616), may also be included: he has Juliet's nurse in *Romeo and Juliet* (1595-6), acting as a go-between for the "star-cross'd lovers", say (Act II, scene V: 49-50):

> *Lord! How my head aches; what a head have I!*
> *It beats as it would fall in twenty pieces.*

This, of course, is entirely incidental to the plot. However, headache, as one feature of a temporal lobe tumour along with epilepsy, is central to the action of Allan Cubitt's play *The Pool of Bethesda*, in which the central character, a surgeon, has psychic seizures in which he "talks" to William Hogarth as the latter paints the mural of Christ healing the lame man at the pool of Bethesda, still visible at St Bartholomew's Hospital, London.[7]

Fyodor Dostoyevsky (1821-1881) is known for his descriptions of epilepsy, a condition from which he suffered,[8] and it has also been claimed that he described hemifacial spasm.[9] Hence it is perhaps not surprising that headache should also appear in his work. For example, in the short story *Bobok* (1873):

> *Something strange is happening to me. My character is changing and my head aches. I am beginning to see and hear some very strange things.*

Namely the voices of those buried in the graveyard. Headache also occurs in *The Idiot* (as noted by Perkin[2]) and in Dostoyevsky's master work, the *Brothers Karamazov* (1881: books III, V, VI, IX and XI). Of these, Marfa Ignatyevna's headache following consumption of her herbal remedy for lumbago, which cures Grigory Vassilyevitch (book V), might be "headache induced by acute substance use or exposure", and Madame Hohlakov's presentiment of a nocturnal sick headache following excitement (book IX) might be migraine.

In a previous article,[5] a passage was quoted from one of the novels of Arthur Ransome (1884-1967), *We didn't mean to go to sea* (1937), describing a headache which may well have been childhood migraine. As with other such passages, it may prompt the question as to whether the author was writing from personal experience. Examining the published selection of Ransome's correspondence, his posthumously published autobiography, and the definitive biography of his life, headache is mentioned on various occasions. Features which emerge from these accounts of his headache include its recurrent nature, extreme severity preventing work, apparently accompanied by a desire to move about, and probable periods of remission, leading to the suggestion that he may have suffered from cluster headache or some form of trigeminal autonomic cephalalgia, although no definitive reference to unilaterality of headache was found.[10]

Diaries, as contemporaneous records, may also be of interest. That of the Reverend Francis Kilvert (1840-1879) is well known as a resource of social history for the period 1870-9, but of relevance to this article it seems he was also a sufferer from headaches and facial pains:[11]

> *Drunk too much port after dinner … last night and a splitting headache all today in revenge. … Everything in a daze and dazzle and I could hardly see to read (20th February 1870)*

Aside from episodes with obvious triggers, Kilvert also suffered from "face ache", which he sometimes calls "neuralgia", associated with sleep disturbance and restlessness:

> *Tossing about with face ache till 3 o'clock this morning (27th February 1871)*

> *Neuralgia very troublesome all the week, no sleep at nights (27th April 1878)*

Again the details vouchsafed by the author are insufficient to permit a confident retrospective diagnosis (if that is not a tautology!), but it would seem to lie between cluster headache and trigeminal neuralgia.

Grim though the experience of headache may be, it may also be a subject for wit. Oscar Wilde (1854-1900) has this exchange in Act Two of *The Importance of Being Earnest* (1899):

> *CECILY: Miss Prism has just been complaining of a slight headache. I think it would do her so much good to have a short stroll with you in the Park, Dr Chasuble.*
> *MISS PRISM: Cecily, I have not mentioned anything about a headache.*
> *CECILY: No, dear Miss Prism, I know that, but I felt instinctively that you had a headache.*

After a little further conversation. Miss Prism remarks "*I find I have a headache after all, and a walk might do it good*". Either Cecily has preternatural diagnostic skills which would be the envy of most neurologists, or Miss Prism is highly suggestible.

The difficulty in finding efficacious treatment for headache may also be reflected in jests, extreme acts, or "sick jokes". St Stephen, the first Christian martyr, was killed by stoning (Acts of the Apostles 7:58-59); because of the manner of his death, in the Middle Ages he was invoked against headaches.[12] Fasting, one of the cornerstones of Christian observance in the Middle Ages, might also be tried: William Tyndale (1494-1536), first translator of most of the Bible into English before he was burned at the stake for his troubles, noted in *The Parable of Wicked Mammon*, published in Antwerp in 1528, that "*Some fast … for the head ache*".[13] Charles Dickens, in *A Tale of Two Cities* (1859; Book III, chapter IV, "Calm in Storm"), describes La Guillotine thus: "It was the popular theme for jests; it was the best cure for headaches ..". Perhaps NICE should submit it to a cost-effectiveness analysis.

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How Proust Can Make You a Better Neurologist

It was a Proustian moment, of course, the sunlight filtering through the blinds at the start of an afternoon clinic, bathing the room in an uneasy, watery half-light, as the Professor, elegant and aloof, strode into the room, took his chair and surveyed the list of patients without even a glance at the assemblage of registrars and visiting dignitaries. Dr X, to my left, erstwhile attending neurologist to the Queen of Y, shuffled uneasily, gazing intently at his new mentor, studying the lines on his face in order to gauge the spirit of the next four hours, cooped up in this consultation room with its cork-lined walls. He recalled last week's clinic with its emphasis on nosology, the subtle messages he had obtained from the Professor to study a particular chapter of his text book and the embarrassment he had suffered for thinking Brown-Séquard to be two people.

But he was, as indeed we all were, in luck. The Professor, now smiling to himself, took out a document from the pile of manuscripts without which he never travelled, and reread the first few lines, before handing it to me with the words: "I thought you might be interested in this". I smiled, and between us we shared a moment of understanding that signified our common interest in taking neurology to a higher level; in exploring the endless possibilities which broken minds open up to our understanding. After all, we were co-authors of a recent article in a respectable journal on the link between neurology and literature.

This moment of connection between two like-minded people underlies the bond of friendship and respect, but I, in my role of student, had never once thought of its reciprocation, until this time when I started to read the document which he had handed to me in such a way. It was an obituary of a recently deceased 'pioneer' of modern neurology, who had practiced in a room not twenty yards from where I now stood and whose portrait still hangs in the gloomy hostility of the lecture theatre: William Walton Gooddy M.D.Lond., FRCP, consulting physician to the National Hospital for Nervous Diseases and University College Hospital, London. Gooddy was a man who, so the obituary claimed, differed from the usual neurologists of his time by being 'amusing and charming, lacking the austere asceticism and obsession regarded as prerequisites for success'. I read on as the Professor turned his attention to the list of patients before him and the prospect of being late for his five o'clock meeting, again, but my thoughts were arrested by the sentence that I have looked back on since and re-examined over and over again: 'His first words to me on starting neurology were that I should take a week off to read *À la Recherche du Temps Perdu* as this would be far more useful in my career than Big Brain, the standard textbook of neurology.'

Of course, I knew a little about the book, noted for its length in particular, but had not previously given serious thoughts to reading it, tending to agree with Bellow's verdict on writing that as he grows older everything he reads tends to be not short enough. But from that moment I started to wonder why he should have given that advice to a neurologist in training. What could there be within those 3000 pages which would inform a budding neurologist concerning the mysteries of the brain? How could a work of fiction help to understand the consequences of neurological injury?

And so I read the book, which, over its closely printed pages, became not only an amusement or a way to pass a few hours of leisure time, but an experience of time itself. Only today, walking through the hospital grounds on a cool autumn morning, did my gaze fall upon a tree, denuded of half its leaves, and I recollected that I had sat under its blossom laden boughs and read a few pages of the *Bal des têtes.* Just as the protagonist associates physical cues with memories, undoubtedly Proust expected the reader to use the book as a temporal guide for the months spent pondering its pages. Indeed the association of memories, famously illustrated by the smell of tea-soaked madeleines, is of much interest to the neurologist who has an interest in cognition.

> *'And as soon as I had recognized the taste of the piece of madeleine … which my aunt used to give me (although I did not yet know and must long postpone the discovery of why this memory made me so happy) immediately the old grey house upon the street, where her room was, rose up like a stage set to attach itself to the little pavilion opening on to the garden which had been built out behind it for my parents (the isolated segment which until that moment had been all that I could see); and with the house the town, from morning to night and in all weathers, the Square where I used to be sent before lunch, the streets along which I used to run errands, the country roads we took when it was fine. And as in the game wherein the Japanese amuse themselves by filling a porcelain bowl with water and steeping in it little pieces of paper which until then are without character or form, but, the moment they become wet, stretch and twist and take on colour and distinctive shape, become flowers or houses or people, solid and recognizable, so in that moment all the flowers in our garden and in M. Swann's park, and the water-lilies on the Vivonne and the good folk of the village and their little dwellings and the parish church and the whole of Combray and its surroundings, taking shape and solidity, sprang into being, town and gardens alike, from my cup of tea.'*

The 'petites madeleines' phenomenon has entered medical parlance (albeit transiently and perhaps erroneously) to

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describe patients recovering from amnesia. Maybe those patients are the ones who seek most vehemently to recapture 'Lost Time'. But much more than this, Proust explores not only the way memories are rekindled in us, but why we recall particular events; how each one of us remembers the identical person or event in a different way; and even how dreams compound and interfere with memories. If Proust were to sit in our consulting rooms (for his multifarious complaints) what kind of history would he give to us? Undoubtedly a highly detailed one, but he would probably point out to us that a hundred people suffering from the same symptoms would present a hundred different histories. It is up to the doctor to interpret these.

And what of doctors? Proust presents several in his novel, most notably Dr Cottard. Cottard was, in all probability, based upon Jules Cotard, a contemporary of Charcot in Paris. Proust's father (Adrien) was a distinguished physician who trained with Cotard at the Ecole de Médecine and the young Proust would have met many medical people. Yet Proust had an uneasy relationship with the medical profession. His own illness, reflected by the infirmity of the protagonist of *À la Recherche du Temps Perdu,* consisted of severe asthma and a multitude of other complaints. The prevailing view at the time, thought also to be held by Adrien Proust, was that asthma was a nervous habit that could be treated by isolating victims in sanitaria for nervous diseases. The theory that conditions such as asthma were psychosomatic flourished in those times. Perhaps it is little wonder then that he had a deep mistrust of some within the profession. Nevertheless, Proust's writing is highly influenced by medical terminology and analogy. The protagonist of *À la Recherche du Temps Perdu* suffers from 'neurasthenia' and is never far from his bed. His infirmity leads him to observe objects and occurrences in the minutest detail; and, more importantly, reflect on all those experiences he has had in his life. Many of these reflections centre around his illness or the illness of others. His metaphors are often medical and there is little doubt that Proust was fascinated with medicine; the novel using themes of sub-conscious thought and dreams to explain emotions. One might say Proust 'medicalises' human suffering and experience (for instance he describes Swann's love for Odette in terms of 'malade', 'convalescent' and 'chirurgien'). To a certain extent, this may reflect the contemporary movement in France, led by Charcot (who is mentioned in the work), to illuminate the function of the mind and rationalise the disciplines of neurology and psychiatry.

The death of the protagonist's grandmother is of major significance in the novel. She becomes unwell before suffering from a stroke and consults a variety of medical practitioners. She consults a doctor called duBoulbon (predicted by Charcot to be the next great name in Neurology). He diagnoses neurosis and expounds his theories on human illness (no doubt reflecting some of Proust's ideas). duBoulbon also states, when explaining the grandmother's diagnosis, that 'everything that we think of as great has come to us from neurotics'. Thus, he introduces a link between creative sensitivity and illness. In a way, Proust is telling us that he would never have written *À la Recherche du Temps Perdu* were it not for his own suffering. Could this explain some of his hostility towards physicians and their desire to cure all illness?

The paucity of and often bizarre nature of treatments in Proust's day linked to the pompous and dictatorial manner of doctors ('the symptoms you show will simply disappear at my command') underlies much of the medical text in *À la Recherche du Temps Perdu*. Proust goes further than expounding medical impotence and lays the root of illness at the door of the medical profession: 'for each illness that doctors cure with medicine, they provoke ten in healthy people by inoculating them with the virus that is a thousand times more powerful than any microbe: the idea that one is ill'. Perhaps this is a little harsh. It may be that Proust was presenting an alternative to the vogue for turning all illness into psychosomatism.

So Proust describes illnesses from the patient's point of view and presents his own theories. We learn about the relationship between illness and creativity, and about recollection of events and the influence we all put on seemingly random aspects of a history. Maybe understanding these concepts will make us better neurologists.

And so I return to Dr Gooddy. What made him put such relevance on Proust magnum opus? If we are to examine his own published output there are clues. Not least an article published on Saturday 31 May 1958 in *The Lancet* entitled 'Time and the Nervous system: the brain as a clock'. Within the elegantly written piece he introduces the concept of 'temporal neurology', arguing that the erstwhile emphasis on neurology has been a dissection of spatial aspects of disease. Presenting theories on chronometric mechanisms he uses examples of nervous and non-nervous physiological clocks which underpin our existence. Gooddy takes neurology into the fourth dimension and uses the clock theories to explain why 'when memory fails, we find a defect of recall and arrangement of time past'. And in that sentence I begin to understand what he means when recommending the novel to neurologists in training. Neurology is a temporal discipline, not just about locating lesions within the 'space' of the nervous system. Indeed chronobiology is now a burgeoning discipline. Gooddy predicts 'we should be able to describe physiological chronometric mechanisms'. Whole conferences are now devoted to circadian rhythms, hox genes and neuroendocrine regulation of time.

In current times of molecular biology and the human genome does anyone have enough time to sit down and read novels as part of a medical curriculum? Perhaps Dr X would tell me that we can explain so much in terms of genetic regulation and spatial patterning that there is no longer a need for 'amateur' musings by latter-day philosophers. Science has negated philosophy; passing of time is another philosophical concept that has been explored and explained. I begin to argue that Proust tells us what it is to experience time, but instead I smile and let my mind wander and think back to a passage in *À la Recherche du Temps Perdu* which is able to elucidate in such elegant terms all those things which I have been battling to understand:

> *The places that we have known belong now only to the little world of space on which we map them for our own convenience. None of them was ever more than a thin slice, held between the contiguous impressions that composed our life at that time; remembrance of a particular form is but regret for a particular moment; and houses, roads, avenues are as fugitive, alas, as the years.*

References

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Lucchelli F, Muggia S, Spinnler H. *The 'Petites Madeleines' phenomenon in two amnesic patients: sudden recovery of forgotten memories.* Brain, 1995:118;167-83.

Pearn J, Gardner-Thorpe C. *Jules Cotard (1840-1889).* Neurology, 2002:58;1400-3.

Sharma OP. *Marcel Proust (1871-1922): reassessment of his asthma and other maladies.* Eur Resp J 2000:15;958-60.

Living with Parkinson's Disease for 30 Years


David Pickin

My name is David Pickin, I live in North Bedfordshire and this is the account of my illness over the past thirty years from memory.

It all started when I was nearly forty. I was a regular runner of varying distances. Whilst taking exercise I started to run with my right arm elevated. As this hadn't happened before I became concerned. My wife noticed me doing this; I told her that it was due to me carrying a heavy briefcase each day. Later I began to have a tremor in my right arm so I consulted my GP. After seeing him, he suggested that I visit a Neurologist at our local Hospital.

I was 43 when he diagnosed me with an illness he called 'Parkinosis'. He prescribed me with a drug called Artane. After taking this drug I found that I started to walk oddly, however I was prepared to put up with this, as my tremor had significantly decreased. I was playing rugby at this time in my life and trained daily. Whilst I was on this drug I continued to run, and completed 2 half, and one full marathons.

My Employment was at a Defence Engineering Company. This was a very stressful post, as I was a Quality Control Manager in charge of many departments. At home I carried out many tasks including gardening and bringing up a daughter. I led a normal active busy life but needed support from the family at times.

I continued to visit the Neurologist every six months. At these times he used to talk to me about other drugs that I could perhaps try, and of course he warned me about their possible side effects.

After more time spent with him, and continuing to take Artane, he concluded that I did have Parkinson's disease. The diagnosis of this came, as a great shock to me, however I decided that life had to go on, and I had to make the best of it.

In my fifties activities I used to do easily, I found harder, for example dressing myself, writing, and standing for long periods. At Fifty-seven, I had a very nasty car accident, (which incidentally was not my fault), this crash really affected my confidence, and following the accident I seemed to become shakier and not so nimble on my feet, however I continued to drive. Later my Neurologist as a consequence prescribed me with a new drug called Madapar. At the age of 58 I retired early from my job.

In subsequent visits to my Neurologist I spoke to him about how I was losing confidence in myself, and how the illness was continuing to affect me. He invited me to take part in some clinical trials. I said I would be happy to oblige, as no doubt the trials could possibly help me, but could also in the long run, benefit others. I had concerns about these trials, and ultimately the results, however I informed the Neurologist that I was prepared to participate and see how things went. I was around 65 when I started the trials. My wife had now retired, and therefore I made the decision, due to several factors, including speed of my reactions, that I could no longer continue driving.

These trials started off with a full medical, physical and psychological assessment. At this trial the Neurologist there told me that they wished to try some drugs that had not been prescribed before. It was also mentioned that I might be given a placebo. I was informed that I was a suitable candidate to take part, which of course delighted me.

I continued to go back to my local hospital for regular tests. I was pleased to inform my Neurologist that I felt much better, and I realised that I was taking something extra and not the 'placebo'.

I found for the first time in many years that I could, with little difficulty, start to fully dress myself. Exercising became easier as well, and it was not long before I was able to start training and running again, and I continue daily to reach a distance of two miles. Continuing on these drugs now known as Azelect, this has increased my confidence in many areas.

I found for the first time in many years that I could, with little difficulty, start to fully dress myself. Exercising became easier as well, and it was not long before I was able to start training and running again

I have started to do things again which I used to enjoy but put on hold. I have had two separate holidays to Russia and South Africa, which involved a lot of physical excursion, I have some help at the Airports, but most of the holiday is under my own control. I would never have imagined that I would be able to contemplate these trips before the trials. I concluded taking part in the trials in late 2002.

In the last six months I have started to use a patch called Rotigotine. This works well with the other drugs I am currently taking.

When I look back at the years of having Parkinson's disease, I can't pretend that I have had no side effects to the drugs I have taken. My walking has become affected, I have had falls, my eyelids have closed often, and I have suffered from upset stomachs, but thankfully at the moment the drugs I am taking seem to be suiting me much better, so I do hope that the way I am feeling at the moment continues. I am now in my early seventies and have just booked a holiday for a fortnight in Norway!

David Pickin,
13th February 2007.

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by March 22nd, 2007

2007

March

Myelination, Demyelination and Multiple Sclerosis 2007
2 March, 2007; London, UK
W. www.abcam.com/myelin2007

1st Congress on Epilepsy, Mind & Brain
2-4 March, 2007; Prague, Czech Republic
W. www.kenes.com/epilepsy

Multiple Sclerosis Trust Annual Meeting for Specialist Nurses
6-7 March, 2007; York, UK
W. www.mstrust.org.uk
T. 01462 476704, E. Education@mstrust.org.uk

International Congress on Neurology and Rehabilitation (ICNR)
9-11 March, 2007; New Delhi, India
E. icnr2007@gmail.com
W. www.iamst.com

NEW
22nd Corso di base in EEG clinica, 9th EUREPA Course,
11-16 March, 2007; Gargnano, Italy
E. raffaele.canger@ao.sanpaolo.it
W.http://www.studioaes.it

23rd Annual Pacific Rim Conference on Disabilities
12-13 March, 2007; Waikiki, Hawaii
E. prinfo@hawaii.edu
W. www.pacrim.hawaii.edu

4th Annual Meeting of the Global College of Neuroprotection & Neuroregeneration
14-16 March, 2007; Garmisch-Partenkirchen, Germany
W. www.gcnpnr.org
E. info@gcnpnr.org
T. +44 115 969 2016, F. +44 115 969 2017

8th International Conference AD/PD 2007
14-18 March, 2007; Salzburg, Austria
W. www.kenes.com/adpd/

RSM "Growth factors and psychiatric disorders"
23 March, 2007; London, UK
T 0207 290 2965
E. primrose.ante-bennett@rsm.ac.uk

NEW
EEG Intensiv-Kurs
24-29 March, 2007; Erlangen, Germany
E. saeftel@eumecom.de or
hermann.stefan@neuro.imed.uni-erlangen.de

1st International Congress on Epilepsy, Mind & Brain
29-31 March, 2007; Prague, Czech Republic
T. +41 22 908 0488
F. +41 22 732 2850
E. epilepsy@kenes.com

April

International Symposium on 'Brain Ageing and Dementia in Developing Countries'
10-13 April, 2007; Nairobi, Kenya
Samantha Tannahill, c/o Prof RN Kalaria
T. +44 191 256 3206
F. +44 191 256 3011
E. advascular@ncl.ac.uk
W. http://advascular.ncl.ac.uk

Certificate Course in Neurological Rehabilitation
10-27 April, 2007; Newcastle upon Tyne, UK
E: traceymole@wfnr.co.uk

ABN Spring Scientific Meeting
11-13 April, 2007; Cambridge, UK
Info: info@theabn.org

1st London Colloquium on Status Epilepticus
12-15 April, 2007; London, UK
T. 01323 740 612 / 01691 650 290
F. 01691 670 302.

Alzheimer's Disease: Update on Research, Treatment, and Care
12-13 April, 2007; San Diego, California, USA
W. htttp://cme.ucsd.edu

NEW
BNS Spring Meeting 2007
18-19 April, 2007; Nottingham, UK
Georgina Jackson
E. Georgina.Jackson@nottingham.ac.uk
T. 0115 82 30416

Understanding and treating insight problems after brain injury
20-21 April, 2007; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

NEW
Non Motor Symptom Complex Of Parkinson's Disease
21 April, 2007; London, UK
E. yogini.naidu@uhl.nhs.uk or
chaudhuriray@hotmail.com

The Challenges of Commissioning for Brain Injury Services-A National Conference
25 April, 2007; London, UK
Patti Simonson
T. 0208 780 4530
F. 0208 780 4530
E. psimonson@rhn.org.uk

NEW
BISWG South Wales and the West Country Regional Meeting
26 April, 2007; Cardiff, Wales
Kate Coles
T. 02920 224871
E. kate.coles@hughjames.com

Synaptic Plasticity in Pain
27 April, 2007; London, UK
W. http://www.abcam.com/pain07

5th Staffordshire Conference On Clinical Biomechanics
27 - 28 April, 2007; Stoke-on-Trent, UK
Cheryl Blewitt
E. c.l.blewitt@staffs.ac.uk
T. 01782 294341

59th Annual Meeting of the American Academy of Neurology
28 April-5 May, 2007; Boston, USA
W. www.aan.com

American Academy of Neuroscience Nursing (AANN) Annual Meeting
29 April – 2 May, 2007; Orlando, USA
E. info@aann.org

May

Management of Parkinson's disease - Joint conference of the Royal College of Physicians and the Parkinson's Disease Society
3 May, 2007; London, UK
RCP Conference Dept
T. 0207 935 1174 ext 252/300/436
E. conferences@rcplondon.ac.uk

Visual Perceptual Dysfunction and brain injury, Part 2
9 - 11May, 2007; London, UK
W. www.braintreetraining.co.uk
E. enquiries@braintreetraining.co.uk

Brain Development 2007
10 May, 2007; London, UK
W. www.abcam.com/brain2007

EFNS Academy for Young Neurologists 8th Course
10-13 May, 2007; Staré Splavy, Czech Republic
E. efns@fnkv.cz or pragueoffice@efns.org
T/F. +420 2 6716 35 63

NEW
UCL Short Course Epilepsy
14 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

NEW
International Conference on Diagnosis & Treatment in Pediatric Neurology
14-17 May, 2007; Warsaw, Poland
E. neuroped2008@firstclass.com.pl
W. http://www.neuroped2008.pl

NEW
UCL Short Course Neuro-ophthalmology
15 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

NEW
UCL Short Course Movement Disorders
16 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

NEW
UCL Short Course Statistical Parametric Mapping
17, 18. & 19 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

Primary Care Neurology Society 2007 Conference
17 May, 2007; Birmingham, UK
W. www.p-cns.org.uk

NEW
UCL Short Course Neuromuscular Disease
21 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

NEW
UCL Short Course Stroke
22 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

Multiple Sclerosis Trust Masterclass for MS Specialist Nurses
22 May, 2007; London, UK
W. www.mstrust.org.uk
T. 01462 476704
E. Education@mstrust.org.uk

NEW
UCL Short Course Neuropathology
23 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

NEW
BISWG Annual General Meeting
23 May, 2007; Birmingham, UK
Patti Simonson
T./F. 0208 780 4530
E. psimonson@rhn.org.uk

NEW
UCL Short Course Neuropsychiatry
24 May, 2007; London, UK
Jean Reynolds
T. 020 7829 8740
F. 020 7278 5069
E. J.Reynolds@ion.ucl.ac.uk
W. www.ion.ucl.ac.uk

2nd Biennial Vocational Outcomes in Traumatic Brain Injury Conference
24-26 May, 2007; Vancouver, BC Canada
E. sljproductions@telus.net
W. www.tbicvancouver.com

Seventeenth Meeting of the
European Neurological Society

June 16-20, 2007 – Rhodes/Greece

Neurologists in training offer
Deadline January 18, 2007

Young neurologists programme 2007

Following the great demand in 2006, ENS is pleased to offer once again a limited number of grants providing free accommodation from Saturday to Wednesday, including registration and admission to teaching courses at the ENS 2007 meeting in Rhodes to European Neurologists in training, born on or after January 1, 1972. This programme is **not** dependent on submitting an abstract.

Applications should provide a letter from chairman of their department to certify that they are in training as well as a copy of their passport.

The applicants must also select the 3 courses they want to attend. Application is only available **online** at www.akm.ch/ens2007.

Attendance to courses is compulsory and no-shows will be excluded from this offer in the future and will be charged for their attendance.

Deadline for applications: **18 January 2007**. Applications without passport copy or arriving after this date will not be considered.

Good qualitiy accommodation has been reserved this year and will be on a double room occupancy basis. We invite applicants to mention on their registration form the name of another young neurologist they would wish to share the room with.

For further information please check our regularly updated website: **www.ensinfo.com**

Please apply online on **www.ensinfo.com** – ENS 2007 the online application will be available from October onwards.

Separately to this offer, young colleagues who have an abstract accepted for presentation at the ENS meeting may also apply for a travel grant. Please see further details on the congress website.

Visit the ENS 2007 website featuring:

- Continuously updated scientific programme
- **Online abstract submission (deadline February 7, 2007)**
- Online registration as well as hotel & tour reservations
- Option to compose your personal congress programme
- Details about the industrial exhibition
- Information on the congress venue and the island of Rhodes

www.ensinfo.com

For further information please contact:

Administrative Secretariat: 17th ENS 2007, c/o AKM Congress Service
P.O. Box, CH-4005 Basel / Switzerland
Phone +41 61 686 77 11 Fax +41 61 686 77 88 E-mail info@akm.ch

BRAIN AWARENESS WEEK

12-18 MARCH 2007

A global celebration of the latest brain science

Brain Awareness Week is an annual celebration dedicated to raising public awareness of brain research. Coordinated by the European Dana Alliance for the Brain, and the Dana Alliance for Brain Initiatives in the US, Brain Awareness Week has become a major international collaboration.

You can become involved in Brain Awareness Week by organising an activity. By registering as a partner, and then posting your event, your organisation will be listed on our worldwide Brain Awareness Week calendar of events, and you will receive information on running and publicising your programmes.

Please join us in this major international campaign

To organise an event or get involved:
Contact EDAB on 020 7019 4914 or by email at enquiries@edab.net

www.edab.net

The *Movement* Disorder Society
The International Society for Parkinson's Disease and Other Movement Disorders

Parkinson's Disease Society

PARKINSON'S DISEASE NON-MOTOR GROUP
www.pdnmg.com

Second Meeting of the

UK PD Non Motor Group

Non Motor Symptom Complex of Parkinson's Disease

Saturday 21st April 2007, Royal Society Of Medicine, London

Speakers include:

E Wolters (Holland)
AHV Schapira (UK)
A David (UK)
P Barone (Italy)
DJ Brooks (UK)
P Jenner (UK)
R Brown (UK)
F Stocchi (Italy)
B Van Hilten (Holland)
W Oertel (Germany)
P Odin (Germany)
P Odin (Germany)
G MacPhee (UK)
D MacMahon (UK)
A Forbes (UK)
V Voon (Canada)
P Piccini (UK)
K Breen (UK)
K Ray Chaudhuri (UK)

6 CPD points will be awarded to delegates for attendance

KRC and UK PDNMG acknowledges this meeting has been funded by an unrestricted educational grant from Boehringer Ingelheim Ltd, Solvay and Britannia Pharmaceuticals.

A small registration fee of £50 will be charged. Lunch, coffee and refreshments will be provided.

Contact points: yogini.naidu@uhl.nhs.uk or chaudhuriray@hotmail.com
For more info about registration please visit www.pdnmg.com

Royal College of Physicians
Setting higher medical standards

Parkinson's Disease Society

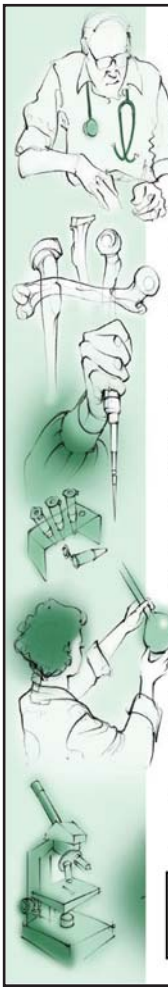
MANAGEMENT OF PARKINSON'S DISEASE

Thursday 3 May 2007

at the Royal College of Physicians,
11 St Andrews Place, Regent's Park, London NW1

With the ageing of the population, the prevalence of Parkinson's disease is set to increase dramatically in the next 20 years. Research in this important condition has led to many significant developments in the last few years. This conference, organised by the Royal College of Physicians and the Parkinson's Disease Society will summarise recent developments in relation to the recently introduced NICE guidelines for the diagnosis and management of Parkinson's disease.

The programme and booking forms are available on-line:
www.rcplondon.ac.uk/conferences or from:
Conference Department,
Royal College of Physicians
Tel: 020 7935 1174 Ext. 436/252/300
Fax: 020 7224 0719
Email: conferences@rcplondon.ac.uk



Autistic spectrum disorders and co morbid conditions

Tuesday 8 May 2007- London

- Known genetic & medical causes
- Language and cognitive impairment in Autism
- Anxiety and mood disorders & their treatment in Autism
- Spectrum Disorder

Speakers Include:

- Professor Patrick Bolton, Institute of Psychiatry, London
- Professor Nick Bouras, President, Section of Psychiatry
- Professor Emily Simonoff, Institute of Psychiatry, London

Autism and Asperger Syndrome

Thursday 10 May 2007- Bristol

- The Autism spectrum
- Language and communication
- Early bird programmes
- Education strategies
- What do parents want?

Speakers Include:

- Professor Chris Gillberg Department of Child and Adolescent Psychiatry, University of Göteborg, Sweden
- Mike Collins, South West Region Representative, National Autistic Society
- Dr Melanie Merricks, CAMHS, Bristol

For more information or a booking form, please contact Sinem Gocmen on 0207 290 3844 or book online at www.rsm.ac.uk/diary

The Royal Society of Medicine

EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

11th CONGRESS OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

BRUSSELS, BELGIUM, AUGUST 25-28, 2007

President of EFNS Management Committee: **Jacques L. De Reuck**, Belgium
Chairperson of the Congress Programme Committee: **Gian Luigi Lenzi**, Italy
Chairperson of the Local Arrangements Committee: **Jean Schoenen**, Belgium

DEADLINE FOR SUBMISSION OF ABSTRACTS: FEBRUARY 15, 2007

The Congress Programme includes Teaching Courses, Focused Workshops, Special Sessions, Short Communications as well as the following Main Topics:

- RTMS and neuroplasticity
- Scientific basis of headache
- Frontiers in movement disorders
- The "more-than-6-hours" stroke
- Neuromuscular diseases
- Multiple sclerosis (MS) treatment: how and when?
- New disease modifying treatment approaches in Alzheimer's disease
- Status epilepticus: toward European treatment guidelines

www.efns.org/efns2007

EDITOR'S CHOICE

Is the Lewy body important in the death of neurons?

The relationship between alpha synuclein, Lewy body formation and neurodegenerative processes has always proven slightly elusive. Indeed the normal function of alpha synuclein has always remained somewhat mysterious but is thought to have something to do with normal synaptic function. In the mid 1990's it was discovered that mutations in alpha synuclein could cause parkinsonism and shortly afterwards it was shown that the Lewy body (the pathological hallmark of Parkinson's disease) contained alpha synuclein. This implied that alpha synuclein could have something to do with Parkinson's disease and by inference Parkinson's disease dementia and dementia with Lewy bodies (DLB). In a recent paper in the Journal of Neuroscience, Michael Kramer and Walter Schulz-Schaeffer have investigated this and suggest that it is not the Lewy body formation that is responsible for the neurodegeneration but the presynaptic aggregation of alpha synuclein. They used a technique called paraffin embedded tissue (PET) blot [not to be confused with PET imaging] and a protein aggregation filtration assay so that they could sensitively and accurately detect alpha synuclein aggregates in various tissue sources. They found that they could detect using this technique large amounts of alpha synuclein aggregates in patients with dementia with Lewy body and that this correlated more with the cognitive impairment than Lewy body formation which was relatively limited and not related to any measures of cognitive decline. This suggests that Lewy body formation may be a protective mechanism and not a direct pathogenic pathway and that the aggregation of alpha synuclein presynaptically may be the critical event in triggering neuronal dysfunction leading to neuronal death. It would therefore be this that causes neuronal death in DLB and also presumably in Parkinson's disease. This raises many interesting questions not least of which is what is the role of the Lewy body and in particular should we be targeting therapies to get rid of such structures or would such an approach prove to be more disastrous than helpful. - ***RAB***

Kramer ML, Schulz-Schaeffer WJ (2007).
Presynpatic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies.
JOURNAL OF NEUROSCIENCE
2007;27:1405-10.

STROKE: Stenting is not inferior to endarterectomy

This is, bless its cotton socks, a preliminary positive non-inferiority trial. For all that, I suspect its conclusions may not be correct. In the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial, 1183 people within 180 days of a TIA or ischaemic stroke, and with severe symptomatic carotid stenosis, were randomised to stenting or surgery. The headline result is that there is no difference in the early outcome at 30 days. Whilst this may be true statistically, endarterectomy outperformed stenting (non-significantly) on nearly every outcome (for instance the primary outcome measure of recurrent stroke was 4·0% in the carotid-artery stenting group and 2·9% in the carotid endarterectomy-group). I am not entirely sure why the Lancet published this… because the conclusion has to be wait and see what the 6-24 month data shows, but my suspicion is that endarterectomy will win the day. - ***AJC***

SPACE Collaborative Group.
30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial.
LANCET
2006 Oct 7;368(9543):1239-47.

MEMORY: working memory dysfunction in subclinical hypothyroidism

Hypothyroidism is often quoted as a cause of reversible dementia, but how many practitioners have ever seen a case? Nonetheless, the possibility that thyroid dysfunction may influence cognitive function remains, and is added to by this study from China. Patients with subclinical hypothyroidism (SCH; = low TSH with normal T3, T4, free T3 and free T4) performed a digit n-back task, a test of working memory, as well as the Wechsler Memory Scale (WMS) as did euthyroid, hyperthyroid, and hypothyroid patients. The former test was also performed whilst undergoing fMRI. The task load of the digit n-back task may be increased: n = 0 is a straight identification task, whereas n = 1 (recall the digit before the current one) and n = 2 (recall the second digit before the current one) require more "online manipulation", such that subjects with hypothyroidism may disengage from the task if it becomes too difficult. SCH patients proved less accurate than euthyroid and hyperthyroid patients at the 2-back task, but better than hypothyroid patients, whilst the WMS showed no significant differences across the groups, suggesting that working memory is impaired in SCH and hypothyroidism but not other memory functions. fMRI activation of a common frontoparietal network known to underpin performance of the n-back task was not seen in SCH subjects, in whom frontal activation was abnormal, suggesting impairment of executive function. Interestingly, a subgroup of the SCH subjects who were retested after 6 months treatment with thyroxine showed recovery in both task performance and fMRI parameters. Hence this study shows impairment of working memory in SCH with clues to the neural substrate for this dysfunction, and also provides some tentative evidence for the use of thyroxine in SCH. - ***AJL***

Zhu DF, Wang ZX, Zhang DR, Pan ZL, He S, Hu XP, Chen XC, Zhou JN.
fMRI revealed neural substrate for reversible working memory dysfunction in subclinical hypothyroidism.
BRAIN
2006;129(11):2923-30.

STROKE: Therapy time in stroke units: what are we doing with it?

★★★ **RECOMMENDED**

Intensive task specific exercise has a significant positive effect on the functional recovery of stroke patients. The evidence for this is very strong. However, stroke rehabilitation units in the UK are not organized to optimise the amount of therapy given to patients. Indeed, a recent investigation of therapy time allocated to therapeutic activities in four stroke units in different European countries showed the UK unit was for the most times poorest. Physiotherapists and occupational therapists spent only 46% and 33% of their time doing therapeutic activity with patients in the UK unit. This compared with 54%, 66% and 62% for physiotherapists in the Swiss, German and Belgian Units and 45%, 63% and 50% for occupational therapists. More time was spent on patient related co-ordination activities (e.g., administration, ward rounds) in the UK unit. The units involved in the study all have a long tradition of stroke rehabilitation. The survey was carried out by asking therapists to document their activities in 15-minute periods for two weeks. Diaries from 95 physiotherapists and 51 occupational therapists were collected and a total of 20,421 periods of 15 minutes encoded. The lack of time spent in therapeutic activity in the British unit was not due to lower staffing levels. The reason is more likely to be due to differences in priorities of the unit managers. This study is part of a larger European project, Collaborative Evaluation of Rehabilitation in Stroke across Europe (CERISE) comparing the outcome after stroke between SRUs and it remains to be seen whether outcome is any worse in the UK unit than the others, or indeed if the increased time spent communicating with the rest of the team in the UK unit leads to better discharge management and patient satisfaction. However, given the evidence for the benefits of task specific training, it would seem wise to explore ways in which we can increase opportunities for patients to practice. Perhaps some therapy could be given in groups. The survey also showed that most treatments were delivered on a one to one basis (91.2% of physiotherapy treatments and 86% Occupational therapy). Its time for a culture change in British stroke rehabilitation. – ***AJT***

Putman K, De Wit L, Schupp W, Ilse B, Berman P, Connell L, Dejaeger E, De Meyer A-M, De Weerdt W, Feys H, Walter J, Lincoln N, Louckx F, Anneleen M, Birgit S, Bozena Smith B, Leys M.
Use of time by physiotherapists and occupational therapists in a stroke rehabilitation unit: A comparison between four European rehabilitation centres.
DISABILITY AND REHABILITATION
2006;28:1417-24.

MULTIPLE SCLEROSIS: Treated by carbon monoxide poisoning?

In this paper, Soares' group in Portugal examine the role of hemeoxygenase–1 and carbon monoxide as treatments of EAE. This all arises from the finding of raised levels of hemeoxygenase–1 (HMOX1/HO-1) in the CNS during the course of MS and EAE, where it is the rate-limiting enzyme in the catabolism of heme. They showed first that HO-1 knock-outs get much worse disease than normal animals, and induction of HO-1, by cobalt protoporphyrin IX, reduced the severity of EAE –both when given prophylactically and therapeutically- in healthy animals. Based on their experience in other

inflammatory conditions, where exogenous CO mimics the effect of HO-1 induction, they then gave animals CO (250 ppm in air) before attempting to induce EAE and fewer animals succumbed. Nice pathology showed that HO-1 induction reduced the amount of inflammatory cells and foci in the brains of EAE animals. And there were fewer infiltrating T cells expressing IFN-gamma, but no change to those expressing IL-10, so all good anti-inflammatory stuff. On the other hand, there was no change in the number of regulatory T cells [see ACNR this issue - page 10] in the animal's brains. It turns out that HO-1 exerts its effects on T cells by reducing the reactivation of T cells that are already primed (as they would be in someone with multiple sclerosis) by reducing the expression of the key Class II molecule on CNS antigen-presenting cells. One of the first experiments that now needs to be done is to type, in multiple sclerosis patients, the (GT)n micro satellite polymorphism in the human HMOX1 promoter, which is already associated with susceptibility to a variety of other inflammatory disease. But, of course, the authors' main suggestion is that we should administer CO to patients with multiple sclerosis…… which would be a brave thing to do for after 3 hours of CO at 250ppm, most people will experience nausea, chest tightness and memory loss; at 800ppm people can develop seizures and become comatose within 45 minutes; and at 1600 ppm, death can occur within the hour. - ***AJC***

Chora AA, Fontoura P, Cunha A, Pais TF, Cardoso S, Ho PP, Lee LY, Sobel RA, Steinman L, Soares MP.
Heme oxygenase-1 and carbon monoxide suppress autoimmune neuroinflammation.
JOURNAL OF CLINICAL INVESTIGATION
2007 Feb 1;117(2):438-47.

REHABILITATION: Hand splints, a stretch of the imagination?

Recovery of arm and hand movement after stroke can take many weeks. While the arm is immobile muscle stiffness and contractures frequently develop which can lead to pain and discomfort and inevitably compromises emergent recovery of movement. In severe cases the stiffness can make every day activities such as dressing, washing and hand care difficult. The most common occupational therapy intervention to address this problem is to provide splints to prevent or correct contractures in the wrist and long finger flexors. Until a few years ago, there were no high quality trials to support or refute the effectiveness of wearing hand splints in stroke patients. Then a group of therapists in Sydney reported a randomized controlled trial comparing the effect of splinting plus stretch exercises, versus stretch exercises alone, in which no effect of splinting was apparent. They used splints that held the wrist in slight extension with the fingers with the metacarpophalangeal joints in flexion and interphalangeal joints extended. This 'neutral position' is most often used since it is comfortable but keeps length in the extensor tendons. However because the aim of splinting is to influence muscle extensibility, some therapists believe that sustained positioning of muscles close to the end of range is more likely to provide a greater effect on contracture. So now the same Australian group have reported another excellent trial but this time they compared three conditions. One group of 21 patients wore 'extension' splints, that held the wrist and finger in a comfortable end-of-range position >45° wrist extension and with the metacarpophalangeal and interphalangeal joints all extended. The second group of 20 patients wore neutral position splints and a third group of 21 patients did not wear splints at all. The splints were worn at night for between 9 and 12 hours on average for four weeks and none of the patients received stretching exercises over the period of study. An assessor who was blinded to the treatment group measured wrist extension range with the metacarpophalangeal and interphalangeal joints in the extended position with a standardised torque applied. There was no significant difference between the three groups; neither splint was effective in increasing the extensibility of the wrist and long finger flexor muscles. These results are contrary to current thinking, based on animal studies, that muscle length adapts to sustained stretch. The splints were worn all night and that is as long at a stretch as most therapists would advise, therefore the dose is as long a stretch as the maximum that would usually be considered practical. In the light of these new results it is time for occupational therapists to consider whether the time-consuming practice of making and fitting hand splints to prevent muscle contracture during acute rehabilitation after stroke should be discontinued and instead more effective solutions should be sought - ***AJT***

Lannin NA, Cusick A, McCluskey A, Herbert RD.
Effects of Splinting on Wrist Contracture After Stroke: A Randomized Controlled Trial.
STROKE
2007; 38:111-6.

A Day in the Life…

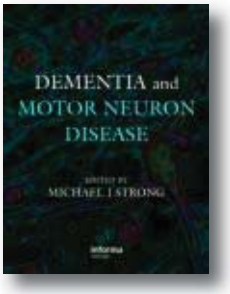
…is a simple and fun way for European neuroscientists to get involved in communicating what you do to the public. Using a disposable camera to document your day, we want to show the public and young people in particular what the everyday lives of neuroscientists entail: highlighting the important research work as well as showing the human side to a career in neuroscience.

The project is run by The Manchester Science Group **www.manchesterscience.blogspot.com** and sponsored by the European Dana Alliance for the Brain.

To take part, email your postal address to: **mansci@googlemail.com** with **A DAY IN THE LIFE** in the subject line and you will receive a disposable camera pack and instructions.

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

Dementia and Motor Neuron Disease



Edited by: Michael J Strong
Published by: Informa Healthcare 2006
ISBN: 0415391660
Price: £80.00

Traditional teaching was that motor neurone disease (MND) or amyotrophic lateral sclerosis (ALS) was a disorder exclusively of the motor system and that patients were cognitively preserved and hence all too horribly aware of their progressive neurological predicament. Occasional reports of MND with dementia (the first possibly by Alzheimer, in 1891; p 133) and of frontotemporal dementia (FTD) complicated by MND have now been succeeded by more systematic studies suggesting that overlap is common and that this may be a spectrum or multisystem disorder with purely motor and purely cognitive boundaries but with extensive overlap, shared pathophysiology and neuropathology.

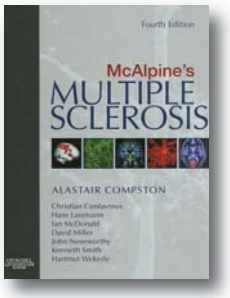
This book is based on papers presented at the First International Research Workshop on Frontotemporal Dementia in ALS held in London, Ontario, in 2005. Whereas workshop proceedings can often be somewhat arid for non-participants, the chapters in this volume do engage, in part because a work on the convergence of these two fields is timely. Individual chapters cover clinical and cognitive features of MND and FTD, neuroimaging findings and neuropathology, including a welcome piece on primary lateral scerosis (8), with chapters devoted to disease in Japanese (7,15) and Guamanian (14) populations. To be sure, the multiplication of terminology (e.g. Tables 2.1 and 5.1, p 10 and 63) which may bewilder non-initiates, and which has to some extent inhibited taxonomy, has yet to be resolved, but the neuropathological division into disorders with tau positive inclusions (e.g. Pick's disease, FTDP-17) and disorders with ubiquitin inclusions (FTD-U) may help (Table 12.1, p 148). On the other hand, genetically defined FTDP-17 with tau gene mutations may encompasss cases clinically defined as FTD, progressive supranuclear palsy, corticobasal degeneration, and Alzheimer's disease; furthermore P (= parkinsonism) may be absent. The role of tau in disease pathophysiology is discussed but generally there is little on mechanisms (e.g. apoptosis, ubiquitin-proteasome system).

This is a well-produced volume with high quality illustrations (odd, though, that throughout the book pathological images are without scale bars or magnifications, excepting some in chapter 12). From a clinical standpoint, it would have been interesting to learn how entities such as Mills syndrome (progressive hemiparesis) and pure hippocampal sclerosis (mentioned only in passing, p 170) fit into the spectrum. Unluckily for the editor, the recent discovery of progranulin mutations causing some cases of FTDP-17 already dates the book, although the dynactin mutation associated with familial ALS/FTD is mentioned (p 49). John Hardy, doyen of the genetics of neurodegenerative disease, suffers an unfortunate meltdown in his clinical knowledge at p 202 when he confuses dementia with bone cysts (Nasu-Hakola disease) with the syndrome of inclusion body myositis, Paget's disease, and frontal dementia (IBMPFD), suggesting VCP mutations occur in the former, rather than the latter. Easily done!

Nonetheless, minor reservations aside, neurologists with an interest in either MND or dementia may profit from reading this book.

S Sathasivam, AJ Larner, WCNN, Liverpool, UK.

Mc Alpine's Multiple Sclerosis - 4th Edition



Authors: Alastair Compston (Editor), Ian R McDonald, John Noseworthy, Hans Lassmann, David H Miller, Kenneth J Smith, Hartmut Wekerle, Christian Confavreux
Publisher: Churchill Livingstone
Price: £145 Amazon UK and Elsevier Book store online

McAlpine's Multiple Sclerosis has been the most authoritative text book on MS since the publication of its first edition in 1985. It was edited by Nigel Compston, father of the current editor. But its origins go back to 1955, to Douglas McAlpine's, *Multiple Sclerosis*. The book has had remarkable success and has remained the comprehensive gold standard reference text for MS.

The current edition (2005) has been extensively rewritten and updated. This is evidenced by the 1008 pages (previous edition had 592 pages) and the numerous high quality and visually appealing figures and tables. There are 4 new very experienced authors who are thought leaders in MS (Christian Confavreux, Ken Smith, David Miller and John Noseworthy). The book itself is divided into 4 sections: (1) The story of MS (2) Cause and course of MS (3) Clinical features and diagnosis (4) Pathogenesis and treatment. Each section is further divided into chapters - 19 in total. Each section ends with a thought provoking chapter that aims to identify and debate unresolved issues.

It has always been the style of the book to have a limited number of authors covers all aspects of MS. The natural concern of 'depth', when such a huge task is handled by few, is easily allayed as one cruises through the comprehensive and thoroughly referenced chapters written by authors who have contributed immensely and guided the course of MS research into the 21st century. However it's important to know at the outset, and as stated in the preface, that the book is not intended as a compendium of research published elsewhere alone, but the authors have declared or upheld their own personal positions on many topics.

There is a paucity of subheadings. Topics often run into pages without a sub heading e.g.: Environmental factors in MS: Infections- run into 5 pages and finding the contribution of herpes virus or chlamydia, without reading a substantial portion can be daunting. Though the interested reader, searching desperately for a particular fact will plough through, the casual reader may be intimidated and may opt to skip.

The references for all the sections are placed conveniently at the end of the book which is very good. However even when arranged alphabetically and chronologically, each author has more than a handful (e.g. Kurtzke-47) and finding the right one can take more than a few minutes. A numbered approach may have been easier for the reader.

The chapter on differential diagnosis is comprehensive. But it was surprising to not to find Neuromyelitis optica there, though it has been mentioned elsewhere in the section on symptoms and signs. I would think that the distinction between MS and NMO is now sufficiently clear to consider it a different disease.

In the editors words "The aim of the book is to summarise everything of importance relating to MS from the time the disorder was first recognised to the mid 2005 and to make this synthesis useful for the interested lay person and the fully informed professional".

The book succeeds brilliantly in this. It is a 'must have' for any physician with an interest in MS and any library that boasts a section on neurology.

Anu Jacob,
Consultant Neurologist,
Walton Centre for Neurology and Neurosurgery,
Liverpool, UK.

Innovative Parkinson's therapy now available for patients with late-stage disease

There is a new alternative for sufferers of the later stages of Parkinson's disease. With the European approval of Neupro® (rotigotine transdermal patch) as an adjuvant to levodopa therapy, late-stage Parkinson's patients in the UK now have access to this novel therapy.

Developed by SCHWARZ PHARMA, Neupro® provides stable plasma concentrations

of rotigotine, a new and effective dopamine agonist. The elimination of the peaks and troughs associated with traditional oral dopaminergic therapy is thought to produce continuous stimulation of the dopamine receptors in the brain. This steady state may translate into reductions in disruptive 'on–off' fluctuations associated with long-term levodopa administration in late-stage Parkinson's patients.

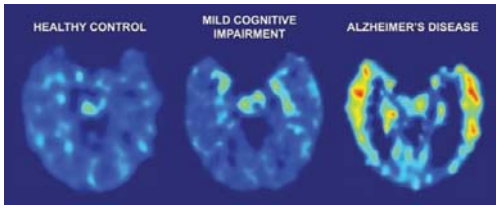
In more than 20 clinical trials, more than 2000 patients with early or advanced Parkinson's disease have been treated with Neupro®. Following the UK launch of Neupro® in April 2006, many Parkinson's patients have experienced the symptom control and ease of administration provided by the once-daily dopamine agonist patch.

For further information on Neupro®, please contact Fiona Eggleston,
Tel: +44 (0)20 8326 3135,
Email: fiona.eggleston@chameleon-uk.com

Siemens and UCLA researchers get FDA 'green light' for clinical study of Alzheimer's-specific imaging agent

Siemens Medical Solutions has announced that it will begin clinical trials for a breakthrough imaging biomarker that could potentially identify Alzheimer's disease prior to the onset of noticeable symptoms.

Siemens will collaborate with the University of California, Los Angeles (UCLA) to launch the study, which will employ a new diagnostic technique that combines a new imaging biomarker and positron emission tomography (PET) to identify Alzheimer's disease pathology specifically.



"With this imaging biomarker, we may not only have better early diagnosis of the disease but also the possibility of treating people to delay the onset of symptoms," said Dr. Gary Small, Researcher, Professor of Psychiatry and Bio-behavioural Sciences, UCLA and co-inventor of the biomarker.

After the Phase I study, depending on its outcome, the company will initiate a larger multi-centre clinical trial.

Further information can be found at:
Siemens Medical Solutions,
Tel: +44 (0)1344 396000,
Email: medmarketing.med.gb@siemens.com
Web: www.siemens.co.uk/medical

Innovative Siemens system provides new views of blood vessels, tissue and organs

Siemens has introduced the AXIOM Artis dBA Twin biplane radiography system, its latest imaging system for universal angiography and neuroradiology. Together with the new flat detector technology and syngo DynaCT software, the system delivers unique acquisitions thanks to its extremely high contrast and soft tissue differentiation. The flexible system enables fast display of anatomy in two planes, and also supports the physician's workflow through programmable detector positioning and intelligent collision protection.

With the optional syngo DynaCT, Axiom Artis dBA Twin achieves soft tissue differentiation comparable to computed tomography

(CT) acquisitions. As a result, intracranial bleeding can be detected faster and brain tissue can be displayed in greater detail than ever before.

Physicians using the latest version of syngo DynaCT receive clinically relevant results within one minute, supporting therapy decision-making without subjecting the patient to an additional CT or magnetic resonance imaging (MRI) examination.

For further information about Siemens,
Tel: +44 (0)1344 396000,
Email: medmarketing.med.gb@siemens.com
Web: www.siemens.co.uk/medical and www.siemens.com/DynaCT

Epilepsy Action campaigns to save epilepsy specialist nurses

Epilepsy Action is campaigning to save the jobs of the many epilepsy specialist nurses who have been threatened with redundancy, reduced working hours, or spending less time on specialist duties due to cuts in NHS funding.

Epilepsy Action has written to its members and local MPs in areas where there is a threat to epilepsy specialist nurses, asking them to write to local health trusts requesting that they review these changes. They have also generated publicity through the media and a number of MPs have asked questions in Parliament.

The All-Party Parliamentary Group on Epilepsy met on 4 December 2006 to discuss the threats to specialist nurses. An Early Day Motion (number 541) has been tabled in Parliament to gather signatures from MPs who support the issue. Healthcare professionals can support the campaign by contacting their local MP to request that they sign the Early Day Motion.

For further information please contact Michaela Miller on
Tel: +44 (0)113 2108877 or
Email: mmiller@epilepsy.org.uk

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Please refer to the SmPC before prescribing ARICEPT EVESS 5 mg or ARICEPT EVESS 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. Orodispersible tablet which should be placed on the tongue and allowed to disintegrate before swallowing with or without water. Treatment should be initiated and supervised by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Monitor regularly to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. **Pregnancy:** Aricept should not be used unless clearly necessary. **Lactation:** Excretion into human breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. As with all Alzheimer's patients, ability to drive/operate machinery should be routinely evaluated. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. May interfere with anticholinergic agents. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT EVESS 5 mg; white, embossed, orodispersible tablets, packs of 28 £63.54. ARICEPT EVESS 10 mg; yellow, embossed, orodispersible tablets, packs of 28 £89.06. **Marketing authorisation numbers:** ARICEPT EVESS 5 mg; PL 10555/0019 ARICEPT EVESS 10 mg; PL 10555/0020. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM **Date of preparation:** December 2006

Information about adverse event reporting can be found at www.yellowcard.gov.uk
Adverse events should also be reported to Eisai Ltd on 0208 600 1400 or Lmedinfo@eisai.net

References: 1. Aricept SmPC **2.** Aricept Evess SmPC **3.** Rivastigmine SmPC **4.** Galantamine SmPC **5.** Galantamine XL SmPC **6.** Memantine SmPC **7.** Data on File Studies 015, 016 and 017 (Eisai Ltd, Pfizer Ltd)
Date of preparation: January 2007
AR1016-ARI984 12-06

Eisai Pfizer