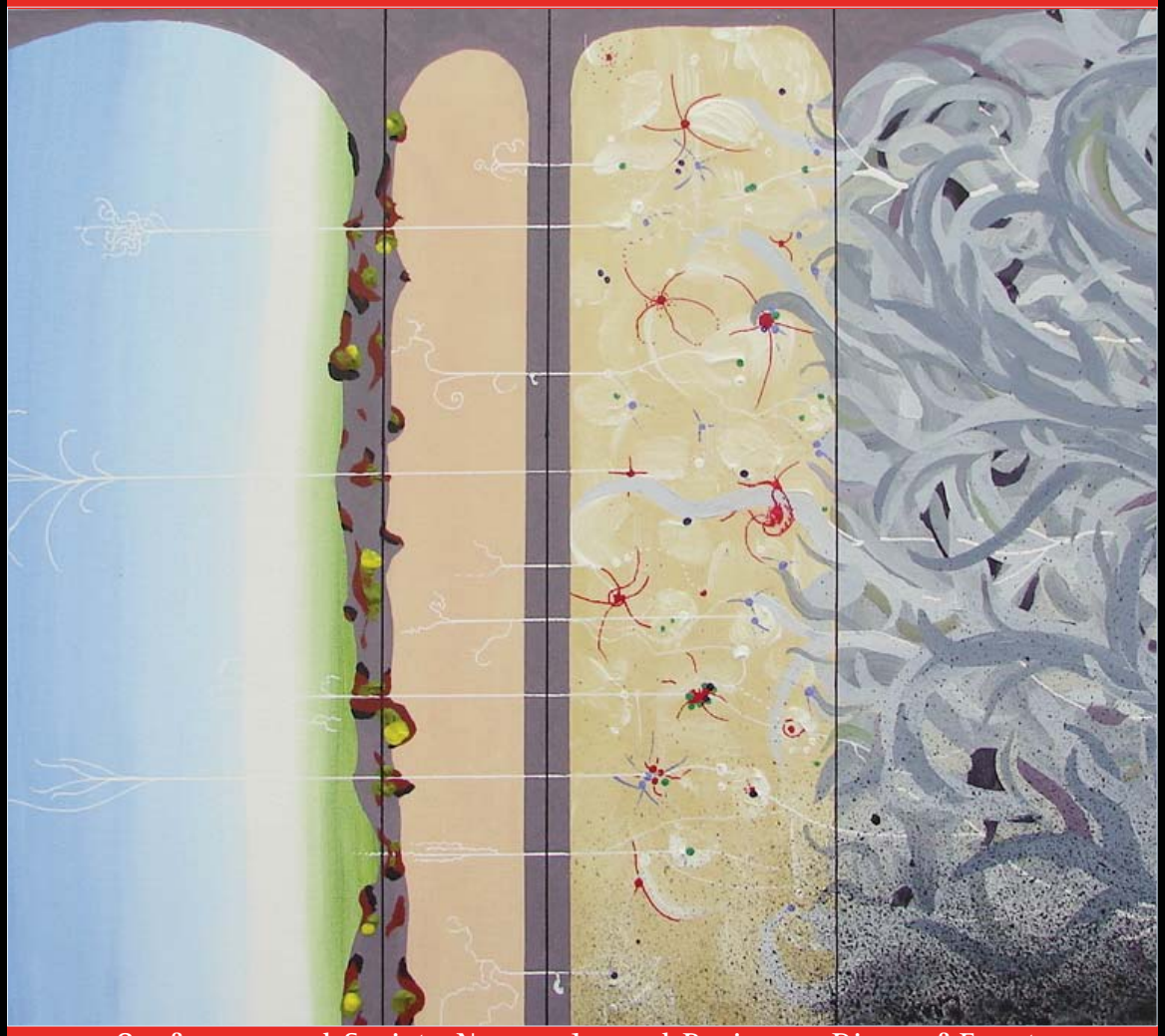
ISSN 1473-9348 Volume 7 Issue 3 July/August 2007

ACNR

www.acnr.co.uk

Advances in Clinical Neuroscience & Rehabilitation



Conference and Society News • Journal Reviews • Diary of Events

PARKINSON'S &ON&ON&ON &ON&ON&ON&

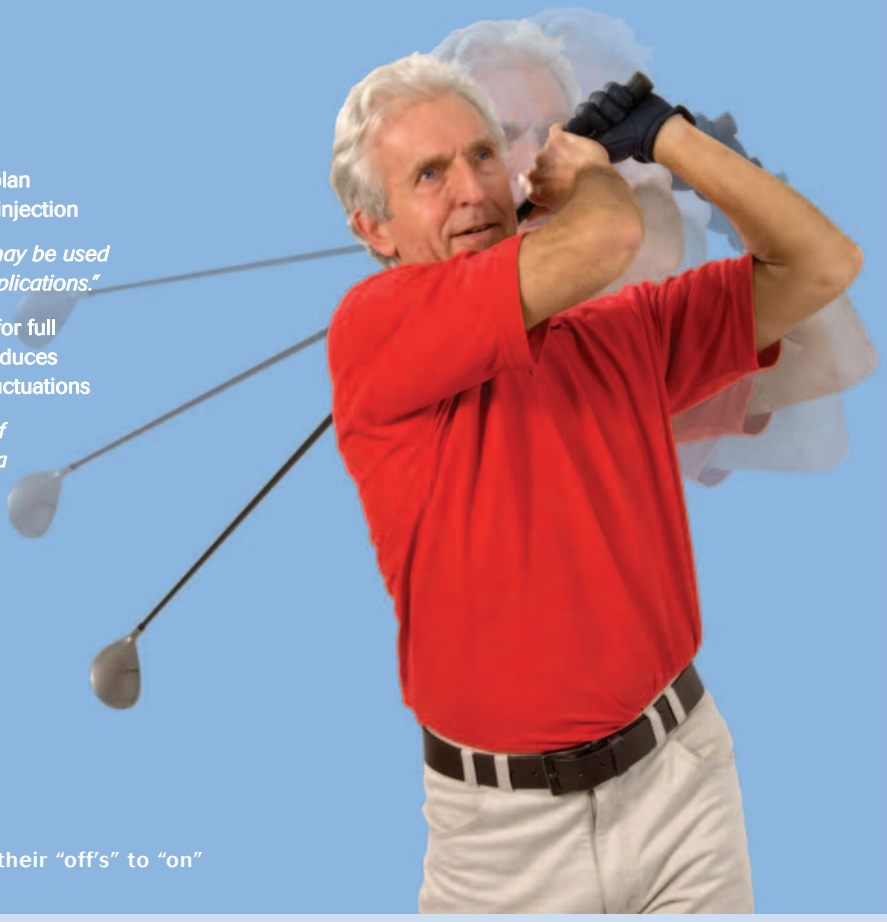
APO-go: treatment for both PREDICTABLE and UNPREDICTABLE symptoms of Parkinson's disease

Predictable symptoms: Use APO-go Pen early in treatment plan for rapid reversal of impending "off's". Simple, easy to use sc injection

Positive NICE review: *"Intermittent apomorphine injections may be used to reduce "off" time in people with PD with severe motor complications."*

Unpredictable symptoms: Use continuous APO-go infusion for full waking-day cover. Continuous dopaminergic stimulation – reduces pulsatile treatment-related complications including "on-off" fluctuations

Positive NICE review: *"Continuous subcutaneous infusions of apomorphine may be used to reduce "off" time and dyskinesia in people with PD with severe motor complications."*



Make the switch and turn their "off's" to "on"

ABRIDGED PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing. **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 decarboxylase inhibitor) 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. **Pregnancy and lactation** Not recommended for use in women of child-bearing potential or in nursing mothers. **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 concomitantly 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.* **Presentation and Basic NHS Cost:** APO-go ampoules contain apomorphine hydrochloride, 10mg/ml, as follows: 20mg in 2ml– basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled Syringes contain apomorphine hydrochloride, 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: 05928/0020 APO-go Pens: 05928/0021 APO-go Pre-filled Syringes: 05928/0025 **Legal Category:** POM. Date of **Last Revision:** February 2006. For further information please contact: Britannia Pharmaceuticals Limited 41-51 Brighton Road, Redhill, Surrey RH1 6YS APG.API.V5

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www.apomorphine.co.uk

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APG.AD.BLPump.V1 Date drawn up: April 2007

Gerald Finnerty and Claire Cheetham in their review article discuss the different levels of plasticity in the adult central nervous system, from functional changes such as those that underlie LTP to anatomical ones at the level of axonal growth and arborisation. These processes are of interest not only in terms of how they can be harnessed to effect repair but also in terms of how it becomes maladaptive in some disease states.

Neil Greenberg, Simon Wessely and colleagues have attempted to convey the facts about Gulf War Syndrome and in so doing have given us a wonderful synopsis of this mysterious disorder. Their review is a superb distillation of the literature and as they state, it would appear that "Gulf veterans seem to experience more symptoms, endorse more conditions, feel worse but are still physically functioning almost as well as those deployed to another busy and stressful operational theatre".

In the last issue of *ACNR*, Helen Thomas discussed what it was like to have a hereditary neuropathy and the problems and issues that this disorder throws up for the affected individual. It is therefore timely to have Mary Reilly and Matilde Laura educate us about this condition in their wonderfully comprehensive review - the third in our Neurogenetics Series edited by Tom Warner. This review highlights the way in which genetics has opened up this field and how one can try and organise the plethora of such conditions into some workable format for the clinic.

Dural fistulae can be difficult to diagnose and if suspected, angiography still remains the investigation of choice. In their review, William Adams and Peter Whitfield outline the various presentations of different types of dural fistulae and how they can best be classified, which in turn has prognostic and therapeutic implications. This clearly written account is lavishly illustrated with a plethora of angiograms.

In our 'Living Legends' series we are delighted to have Jean Paul Vonsattel take us through the derivation of the pathological staging system for Huntington's disease brains. In this illuminating account he leads us through the early discussions between himself, Dr Bird and Dr Richardson and unnamed others as they decided how best to tackle the neuropathology of 65 Huntington's disease brains. Their dedication to the task and their deductive powers led to the staging system that is now synonymous with Vonsattel and Huntington's disease. Again this article is an inspiration to all involved in research, especially those in the field of neuropathology.

Neuropathology in this issue takes us to the peripheral nerve and the tumours that can be found there – schwannomas and neurofibromas. The former are typically benign in nature and cause problems by local compression whilst a subtype of neurofibroma can undergo a malignant transformation. Ute Pohl explains in detail all of these differences in her excellent review and how these different tumours relate to NF1, NF2 and Schwannomatosis.

The winners of the ABN case report, Stephen Jaiser and Martin Duddy, present a patient with a myelopathy secondary to copper deficiency. The retired clergyman, who was the subject of the case, presented with a myelodysplastic syndrome and an evolving subacute combined degeneration like syndrome of the cord. Only after extensive investigation and research did the possibility of copper deficiency emerge, which on treating promptly reversed his haematological abnormality whilst stabilising his neurology. This case is therefore a reminder that copper should be looked at in cases of unexplained myelopathy especially if the patient has a haematological disorder.

Neil Scolding and colleagues have taken on the recent new guidelines for the use of β-interferon and glatiramer acetate in MS. This article (which we hope will be followed by more in a series of controversies in Neurology and Neuroscience) argues that guidelines should be balanced and evidence based and that these recent ones for MS fail on these counts. They further go on to comment that the implementation of these guidelines will have substantial economic implications for our already stretched health service. This thoughtful account is stimulating in its content and we hope readers will feel encouraged to respond and write to us about their conclusions.

How would you react to being told you have a chronic neurological problem? Ian Rogers tells us how he responded to being given a diagnosis of MS and how his computer internet search engine suffered as a result. This illuminating article highlights the advantages and disadvantages of the internet for understanding disease and its treatment. Thus whilst it led to him being enrolled in a clinical trial of disease modifying therapy it also revealed that he may develop 'brain atrophy'.

Andrew Larner once more treats us to an article on Epilepsy in the series on Neurological Literature. In this account he concentrates particularly on the work of Margiad Evans who was diagnosed with the condition in 1950, four weeks after her first seizure – well within the government guidelines!! As always, Andrew draws out many interesting points from the writings of people witnessing or experiencing epilepsy including the effects of anti-epileptic medication.

We have had some interesting names put forward as a result of our email to Consultant Neurologists, asking for suggestions for late-comers to the neurologists ball. Now we are looking for titles for films for neuroscientists and neurologists – email me at rab46@cam.ac.uk and the best will win a mystery prize.

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

Editorial board and contributors

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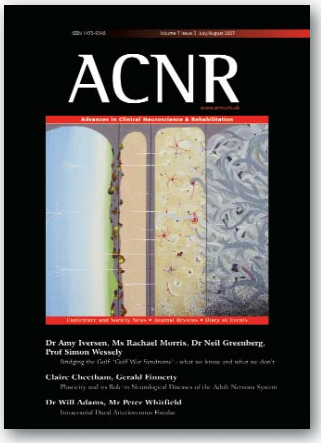
July/August 2007

ACNR is published by Rachael Hansford
Whitehouse Publishing, 1 The Lynch, Mere, Wiltshire, BA12 6DQ.
Tel/Fax. 01747 860168
Mobile. 07989 470278
Email. Rachael@acnr.co.uk
Publisher. Rachael Hansford
Design & Production Email. design.dept@sky.com
Printed by. Warners Midlands PLC, Tel. 01778 391000



The picture – 'Quatrefoil of screens partitions anamnesis morphology' - is one of 11 paintings from an exhibition entitled: "Paintaphasia: Exploring the impact of stroke and aphasia" by Peter Eccleshare. The exhibition at the Elizabeth Fry Building, University of East Anglia has been organised by Dr Simon Horton, School of AHP in collaboration with the Sainsbury Centre for Visual Arts at UEA. Peter Eccleshare is one of a group of 'aphasia experts' who help to train UEA students in supported conversation skills. His paintings represent his experiences of aphasia and provide a visual tool in the understanding of the impact of stroke and aphasia on an individual.

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The maximum dose is 1500 mg twice daily. *Adjunctive therapy: Adults and adolescents older than 12 years or weighing 50 kg or more:* 500 mg twice daily can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks. *Elderly:* Adjustment of the dose is recommended in patients with compromised renal function. *Children aged 4 to 11 years and adolescents (12 to 17 years) of less than 50 kg:* 10 mg/kg twice daily, increased up to 30 mg/kg twice daily. Do not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used. (For full dosage recommendations see SPC.) *Patients with renal impairment:* Adjust dose according to creatinine clearance as advised in SPC. *Patients with hepatic impairment:* No dose adjustment with mild to moderate hepatic impairment. With severe hepatic impairment (creatinine clearance <70ml/min) a 50% reduction of the daily maintenance dose is recommended. **Contraindications, Warnings etc.:** *Contraindications:* Hypersensitivity to levetiracetam, other pyrrolidone derivatives or excipients. *Precautions:* If discontinuing treatment reduce dose gradually as advised in SPC. Due to its excipients, the *oral solution* may cause allergic reactions (possibly delayed). *Infusion*: Keppra concentrate contains 7.196 mg of sodium per vial. To be taken into consideration by patients on a controlled sodium diet. *Interactions:* Keppra did not affect serum concentrations of phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin or primidone. Drugs excreted by active tubular secretion could reduce the renal clearance of the metabolite. Levetiracetam 1,000 mg daily did not affect the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel). Levetiracetam 2,000 mg daily did not affect the pharmacokinetics of digoxin and warfarin and prothrombin times were not modified. *Pregnancy and lactation:* Should not be used during pregnancy unless clearly necessary. Breast-feeding not recommended. *Driving, etc:* Caution recommended when performing skilled tasks, *e.g.* driving vehicles or operating machinery. **Adverse Effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (≥10%): asthenia/fatigue, somnolence. *Common* (between 1%–10%): GI disturbances, anorexia, weight increase, accidental injury, headache, dizziness, hyperkinesia, tremor, ataxia, convulsion, amnesia, balance disorder, disturbances in attention, memory impairment, emotional lability, hostility, depression, insomnia, nervousness/irritability, agitation, personality disorders, thinking abnormal, vertigo, rash, eczema, pruritus, diplopia, vision blurred, myalgia, infection, nasopharyngitis, cough increased, thrombocytopenia. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** *Tablets:* None. *Oral solution:* Store in original container. 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Bridging the Gulf: 'Gulf War Syndrome' - what we know and what we don't

Despite considerable efforts it is likely that we will never know the full story of what has become known, albeit erroneously, as the 'Gulf War Syndrome' (GWS). However, some 16 years since the 1991 Gulf War, 44% of all United States (US) Gulf War veterans receive some form of disability payments, costing $1 billion annually, and over 10% of United Kingdom (UK) Gulf veterans are in receipt of war pensions. So what is GWS and what might be its causes?

The ground phase of 1991 Gulf War lasted just four days and was a resounding military and medical military success. Traditional causes of non-battle casualties such as heat stroke and dehydration were rare. However, shortly after the war ended, reports emerged, initially from the US, of previously fit veterans developing unusual illnesses and symptoms. Media organisations quickly fuelled the emerging concerns by reporting increasing numbers of veterans having children with birth defects. Subsequently the US, and then the UK, begun to conduct formal epidemiological research.

Initial studies used data from US health registries which provided systematic clinical evaluations; the process was subsequently repeated in the UK. Analysis of pooled data from over 100,000 programme attendees did not suggest any unusual pattern of illness, instead medically unexplained symptoms and syndromes were the most common diagnoses.[1,2] However because programme attendees are self selecting the data obtained is only of limited scientific value. Nonetheless, if service during the 1991 Gulf War was associated with either a novel disease process or a dramatic elevation of a recognised but previously rare condition, then this would have been detected. Neither has happened. Furthermore, although the media reported an increase in the mortality rate in Gulf War veterans, numerous comprehensive analyses of the US and UK cohorts have not confirmed this other than an increase in accidental death, (US and UK) or suicide (US only) as observed in the aftermath of other conflicts.[3,4]

Epidemiological reports of increased rates of symptom reporting in a cohort of US Gulf veterans found that symptom-defined conditions including chronic fatigue syndrome, depression, and post traumatic stress disorder were all elevated.[5] The first UK systematic epidemiological study was undertaken by King's College London. This random sample of over 4,000 UK Gulf veterans was compared to similar numbers of active duty personnel who had deployed to Bosnia in 1992, and a further military non-deployed group.[6] We found that the Gulf group were twice as likely to report each and every one of the 50 physical symptoms enquired about. Furthermore, the Gulf cohort reported decreased health perception, but physical functioning was only very slightly different and still above expected non-military norms. Hence, Gulf veterans experienced more symptoms, endorsed more conditions, felt worse, but were still physically functioning almost as well as those deployed to another busy and stressful operational theatre.[6]

Other US, UK, Australian and Canadian epidemiological samples show essentially the same findings. Gulf War veterans report two to three times the rates of common symptoms as their non-deployed colleagues and also have more negative health perception and poorer quality of life.[7] Nearly every study also confirms that the general increase in symptoms is not a new cluster of unusual symptoms specifically linked to Gulf service, suggesting that although subjective health has been clearly impaired, there is no specific nor unique 'Gulf War Syndrome'. A distinct syndrome was reported by US epidemiologist Robert Haley, but in a small study of a single unit with a low response rate and no controls.[8] Furthermore, Haley's group has reported both central and peripheral nerve damage in the same veterans, which they attribute to exposure to a combination of chemical weapons and/or pesticides. However, expert review panels have not been convinced by either the medical evidence or the suggestion of significant exposure to chemical weapons. Our epidemiological study, and an even larger US study, failed to find evidence of significant damage to the peripheral nervous system, making exposure to organophosphate pesticides an unlikely cause of ill health.[9]

Yet, although there is no denying this change in symptoms and quality of life, it is equally clear that there has been no increase in well defined physical outcomes. For example, there has been no increase in cancer. All that has been found is a US study reporting an increase in motor neuron disease or amyotrophic lateral sclerosis (ALS) as it is known in the US.[10] Irrespective of this, whilst ALS is a devastating disease, it remains very rare in veteran populations, and cannot account for more than a tiny fraction of the observed increase in morbidity in Gulf veterans. What Gulf veterans are therefore experiencing is an increase in symptoms, but not disease.

The search for possible aetiological agents has examined a variety of sub groups of deployed personnel. However the Gulf War health effect appears to have affected deployed military groups relatively equally. For instance, there is no consistent evidence of differences in the reporting of symptoms between the Services, suggesting that any possible causative agent of GWS would have to have equally affected those who operate over

Gulf veterans experienced more symptoms, endorsed more conditions, felt worse, but were still physically functioning almost as well as those deployed to another busy and stressful operational theatre

Dr Amy Iversen is a Clinical Lecturer in Psychological Medicine at the Institute of Psychiatry with a special interest in veterans' health. She is particularly interested in the development of psychosocial interventions which address the complex needs of Gulf War veterans.

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Dr Neil Greenberg is a Military Psychiatrist who is a Senior Lecturer at King's College London. He has a keen interest in organisational mental health and, as a military officer, has a keen interest in psychological health in military personnel.

Prof Simon Wessely is a Professor of Epidemiology and Liaison Psychiatry in London. He has a keen interest in the investigation of contentious topics, including Gulf War Syndrome. He is currently the Director of the King's Centre for Military Health Research.

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sea, land or in the air. However many of the predictors of ill health in Gulf veterans are more general rather then related to Gulf service. For example, lower rank, which is highly correlated with education, is firmly associated with ill health.[11]

An interesting, but confusing, finding is the association between receiving large numbers of vaccines, given together, and subsequent self reported ill health.[5] However, detailed investigations have not confirmed that this link is immunologically mediated. It may be a result of an unknown confounder, perhaps mediated by the stress of an impending deployment. Better designed studies around either new recruits or personnel deployed to the Iraq conflict may assist.[12]

So what can we conclude?

Firstly, at the time of writing there is no evidence that history has repeated itself; thankfully there is no current evidence of a repeat of a 'Gulf War Syndrome' saga arising in personnel returning from Iraq.[13] Given also that in both conflicts the UK Armed Forces used depleted uranium munitions, gave anthrax vaccine and pyridostigmine bromide tablets, and used pesticides, yet there was only a GWS in the earlier and not the later conflict, it follows that the above factors are highly unlikely to be the cause of Gulf related ill health. Also, since the current war in Iraq is proving to be a more long lasting and difficult engagement, simplistic explanations of Gulf related illness as a manifestation of stress are also implausible. On the other hand, we cannot rule out that anxieties about so called weapons of mass destruction, which were realistic threats in 1991 but less so in 2003, may have differentially affected psychological health.

Secondly, it is unlikely that further studies will reveal much more useful information about the origins of Gulf ill health. We will have to accept that there are, and will always be, gaps in our knowledge. But we should not abandon our concerns over the health of our veterans, not least because regrettably spontaneous improvement does not seem to be the norm.[14] Instead it is time to focus our efforts on treatment, rehabilitation and improving quality of life.

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Plasticity and its Role in Neurological Diseases of the Adult Nervous System

Recovery after acute neurological damage, e.g. stroke[1] (Table 1), is believed to involve reorganisation of neural circuitry, which enables non-damaged parts of the brain to appropriate new functions. A pragmatist might reasonably argue that understanding the mechanisms underpinning plasticity is not necessary; the goal for physicians is simply to maximise plasticity and, thereby, speed recovery. However, this simple strategy may not work. Excessive or aberrant plasticity has been proposed to cause diseases (Table 1). Therefore, harnessing plasticity for therapeutic benefit requires an understanding of the process of cortical reorganisation and the underlying cellular mechanisms.

Plasticity is greatest in the CNS during developmental 'critical periods',[2,3] but the capacity for significant plasticity remains in adulthood.[4,5] This article focuses on our understanding of plasticity in adolescent and adult cortex. We discuss the role of plasticity in disease and consider approaches that may be used to enhance or reactivate plasticity.

Table 1: Neurological conditions in which plasticity may play a role

Recovery or amelioration of CNS disease	*Maladaptive plasticity*
Stroke	*Phantom limb pain*
Multiple sclerosis	*Complex regional pain syndrome type 1*
Alzheimer's disease	*Focal dystonia*
Huntington's disease	*Tinnitus*
Brain tumours	*Post-traumatic epilepsy*

Mechanisms underpinning reorganisation

Cortical reorganisation during learning or as a result of disease can be best thought of as a process that involves early functional modifications followed by structural changes that consolidate functional reorganisation (Table 2). Functional modifications typically comprise alterations in synaptic strength possibly due to long-term potentiation or long-term depression.[6,7] The ensuing structural changes have been described on multiple spatial scales. The most subtle structural changes occur at existing connections between neurons. The shape of dendritic spines, which form the postsynaptic component of excitatory synapses, may alter with modifications in synaptic strength. Strengthening or weakening of connections can be stored as changes in the number of synapses forming those connections. In contrast, formation of new connections may involve axonal growth and/or dendritic remodelling, which are commonly subsumed under the title 'rewiring'.[8] Large-scale rewiring has been described after damage to the nervous system,[9] but there is limited evidence that it occurs to a marked extent when the nervous system is intact.[10] The difference in propensity for rewiring may simply be one of degree, i.e. nervous system damage induces a more complete alteration in inputs compared with learning, or damage may enable activation of new mechanisms. Finally, neural circuits may remodel as a result of implantation of stem cells into the CNS or incorporation of new neurons following adult neurogenesis.[11]

Space restrictions mean that we cannot describe the role of plasticity in all of the conditions listed in Table 1. Instead, we briefly discuss stroke as an example of acute neurological damage and consider how plasticity may ameliorate symptomatic deterioration in Alzheimer's disease (AD).

The role of plasticity in recovery from stroke

Plasticity has been implicated in the recovery from acute brain damage.[1] Reorganisation occurs in both the perilesional cortex and in cortex distant from the stroke.[12] Structural changes provide a substrate for substantial plasticity. In vivo two-photon imaging of the dendrites of excitatory neurons reveals a dramatic increase in dendritic spine formation, which peaks 1-2 weeks after lesion, and is specific to the peri-infarct region.[13] Axonal sprouting can occur both within perilesional cortex[14] and over greater distances. Following ischaemic injury to the hand area of primary motor cortex (M1) in squirrel monkeys, axons originating in ventral premotor cortex that normally innervate M1 exhibited sharp changes in trajectory near the lesion site, and formed a novel projection to hand areas of primary somatosensory cortex.[15] However, not all reorganisation is beneficial. For example, persistent reorganisation in contralateral premotor areas following M1 lesions correlates with poor recovery.[12]

Plasticity and amelioration of Alzheimer's disease (AD)

A role for plasticity in neurodegenerative conditions may not be obvious at first glance. The pathological hallmarks of AD are amyloid plaques, neurofibrillary tangles and neuronal loss. However, loss of synapses in the hippocampus and neocortex correlates far better with cognitive decline than do the appearance of plaques or tangles.[16] Intriguingly, pathological changes begin in those brain areas with the greatest capacity for plasticity. These findings suggest that AD is primarily a disorder of synapses.[17]

There is considerable debate surrounding the molecular mechanisms underlying synaptic dysfunction in AD. It is thought that abnormal protein aggregates and/or their soluble counterparts disrupt plasticity multifariously. Whatever the mechanism(s), the outcome of synaptic dysfunction is that neurons and the circuits that they form are unable to respond to environmental changes or to store new information. Treatment strategies may, therefore, be based on enhancement of plasticity to compensate, at least in part, for the synapses that have been lost. Alternatively, approaches to reduce synaptic dysfunction by attacking the disease itself might be adopted.

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Level of structural change

Table 2. Mechanisms involved in adult plasticity

	Presynaptic	*Postsynaptic*	*Effect*
Synaptic function	*Altered probability of release*	*Changes in receptor numbers and/or properties*	*Altered synaptic strength*
Synaptic structure	*Formation/loss of axonal boutons*	*Formation/loss of dendritic spines*	*Modifies synapse number*
Neuronal Wiring	*Axonal growth or altered arbourisation*	*Dendritic growth or retraction*	*Rewiring of neuronal connections*
Neurogenesis	*Stem/progenitor cells e.g. from subventricular zone or hippocampal dentate gyrus*		*Incorporation of new neurons into circuits*

Therapeutic strategies

Experimental studies are now leading to the development of novel therapeutic strategies for disorders of the nervous system. For example, studies on the recovery of motor function following forelimb deafferentation in monkeys have led to the development of constraint-induced movement therapy. This treatment aims to reverse the phenomenon of 'learned non-use',[18] and involves restricting movement of the normal limb combined with intensive training of the paretic limb. Similar strategies have been applied to the chronic motor symptoms of stroke in humans and have led to significantly increased function of the affected arm that persists for at least two years.[18]

Enhancement of plasticity during recovery periods may be an attainable goal. Some of the factors involved in closure of developmental critical periods are known and these may contribute to the lower levels of plasticity exhibited in mature cortex. Formation of the extracellular matrix[19] and myelination[20] are required for critical period closure in visual cortex. Enzymatic degradation of chondroitin sulphate proteoglycans in the visual cortex of adult animals results in reactivation of ocular dominance plasticity.[19] Axonal regeneration following brain damage is restricted by myelin-associated proteins, which signal via the Nogo-66 receptor (NgR), thereby reducing functional recovery.[20] Therefore, temporary inactivation of NgR signalling in targeted brain areas could help to boost plasticity.

Transplantation of progenitor cells is a promising strategy for the replacement of damaged neurons and/or glia. However, progenitor cells may also enhance plasticity by mechanisms other than their incorporation into neural circuits.[21] For example, retinal progenitor cells secrete matrix metalloproteinase-2, which promotes neurite outgrowth by proteolysis of outgrowth inhibitors.[22] However, treatment strategies that provide a permissive environment for axonal growth and dendritic remodelling are not sufficient to ensure recovery. The factors that regulate formation of functional neural circuits in adult cortex need to be understood, particularly if maladaptive plasticity and its associated diseases are to be avoided.

Conclusion

Basic science has suggested new therapeutic strategies for treating brain disorders based on harnessing experience-dependent plasticity. Further advances are required before translation to the bedside becomes a reality. In particular, a more detailed understanding of the cellular mechanisms underlying cortical reorganisation is required to maximise benefit while minimising the risk of iatrogenic disease. However, the foundation is being laid for a new generation of treatments that will reduce the burden imposed by neurological diseases.

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Intracranial Dural Arteriovenous Fistulae

Intracranial dural arteriovenous fistulae (DAVF) are uncommon lesions. Their true incidence is unknown, although selected series suggest that they occur only one tenth as frequently as intraparenchymal arteriovenous malformations (AVM).[1] Since many may remain clinically silent or involute spontaneously the incidence may be an underestimate.[2] DAVF tend to present later in life than AVMs, lending support to the theory that these are acquired lesions, although presentation can be at any age.[3] A presentation with aggressive neurological symptoms is more common in males.

The fistula represents an abnormal connection between dural arteries or pachymeningeal branches of cerebral arteries and dural veins. Occasionally, as a fistula grows or becomes more diffuse, pial recruitment from parenchymal vessels can occur. In addition, dilatation of cortical veins may occur, predisposing the patient to intracranial haemorrhage. Previous surgery, ear infection and head trauma have all been cited as potential causes, although the common predisposing factor appears to be venous sinus thrombosis.[4] Venous thrombosis promotes venous hypertension, which acts as the initiating factor opening up microscopic vascular connections within the dura.[5] Maturation of these channels secondary to progressive venous stenosis or occlusion results in the development of direct shunts between the arteries and dural veins.[6] In addition, a second complementary mechanism of DAVF evolution may occur with the release of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) promoting neovascularisation and development of a DAVF.

Presentation and natural history

A wide spectrum of symptoms exists, ranging from the benign to the more aggressive. Individual lesions may regress spontaneously or follow a benign course over years. Drainage of a petrous region DAVF to the transverse or sigmoid sinus commonly produces pulsatile tinnitus, sometimes in association with an audible bruit. Depending upon the pattern of venous drainage such patients may be managed conservatively. Cavernous sinus DAVFs may develop orbital signs such as congestion, chemosis and ophthalmoplegia. Treatment is usually undertaken to protect against ocular and visual complications.

More aggressive behaviour may manifest as focal neurological deficits, a dementia-type of syndrome or cerebral haemorrhage, including subarachnoid, subdural or intraparenchymal bleeds.[7] Such features are usually considered to be due to venous hypertension, although neurological deficits may be secondary to arterial steal.[8] In a meta-analysis of 360 dural AVFs the tentorial incisura was the most ominous location, with 31 out of 32 cases associated with haemorrhagic or non-haemorrhagic stroke.[7] However the pattern of venous drainage was considered of paramount importance in predicting aggressive behaviour.[7] Angiographic features that appear to be associated with aggressive behaviour comprise leptomeningeal retrograde venous drainage, variceal or aneurysmal venous structures, and galenic venous drainage.[7,9] Treatment of DAVFs with these features warrants serious consideration.

In a longitudinal study of 117 patients with no evidence of cortical venous drainage followed over 348 patient years, observational management rather than intervention was chosen for 73 (62.4%). Five of these patients were lost to follow up. 50 patients underwent repeat angiography due to a change in symptoms. In two of these cases cortical venous reflux was seen. This appears to indicate that the risk of conversion from a benign to an aggressive DAVF is small but sufficient to warrant repeat angiography if the clinical picture appears to progress.[9]

PET based regional cerebral blood flow (rCBF) studies indicate that impaired rCBF may be important in the pathogenesis of neurological symptoms. In patients with normal cortical venous drainage, values for regional cerebral blood flow (rCBF), regional cerebral metabolic rate of oxygen (rCMRO) and regional oxygen extraction fraction (rOEF) were normal. Studies in patients with neurological symptoms and cortical venous drainage, showed reduced rCBF and mildly or markedly increased rOEF.[10]

Classification

Various classification methods have been adopted that attempt to explain the significance of the angiographic anatomy; namely, the pattern of venous drainage and the clinical presentation and outcome. The two commonly used classification systems are shown in Tables 1 and 2. With only three sub-types the Borden classification is user friendly.[3] However, the Cognard system is more detailed and elaborates on the direction of flow, whether normal (anterograde) or retrograde and the presence or absence of cortical venous recruitment. Such definition enables more accurate comparison of clinical and radiological parameters. In addition, spinal perimedullary venous drainage is specifically recognised.[11]

In a retrospective review of 102 DAVFs in 98 patients Davies et al. reported a significant correlation between

Table 1: The Borden Classification system.

Type I	*DAVF drainage into a dural venous sinus or meningeal vein with normal anterograde flow. Usually benign clinical behaviour.*
Type II	*Anterograde drainage into dural venous sinus and onwards but retrograde flow occurs into cortical veins. May present with haemorrhage.*
Type III	*Direct retrograde flow of blood from the fistula into cortical veins causing venous hypertension with a risk of haemorrhage.*

Table 2: The Cognard classification system.

Type I (Figure 1)	*Normal anterograde flow into a dural venous sinus.*
Type IIa	*Drainage into a sinus with retrograde flow within the sinus*
Type IIb (Figure 2)	*Drainage into a sinus with retrograde flow into cortical vein(s)*
Type II a + b	*Drainage into a sinus with retrograde flow within the sinus and cortical vein(s)*
Type III (Figure 3)	*Direct drainage into a cortical vein without venous ectasia*
Type IV (Figure 4)	*Direct drainage into a cortical vein with ectasia >5mm and 3x larger than the diameter of the draining vein*
Type V (Figure 5)	*Direct drainage into spinal perimedullary veins*

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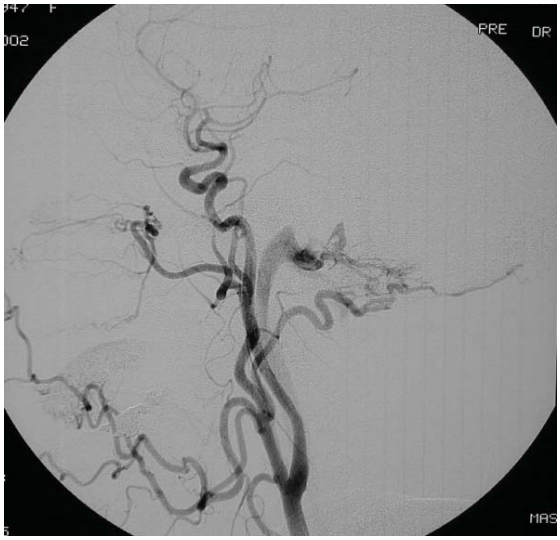


Figure 1: Type I DAVF - Left common carotid artery DSA lateral projection in a 47-year-old lady with disabling tinnitus in the left ear. This shows a Type 1 DAVF filling via transmastoid perforators of the occipital artery and draining to the sigmoid sinus. Despite some improvement of symptoms with particulate injection she requested further treatment. Injection of a 25/75 mixture of NBCA and Lipiodol into the occipital artery, with further particulate injection of the middle meningeal artery, led to a resolution of symptoms and sustained obliteration of the DAVF on 12 month follow-up angiography.

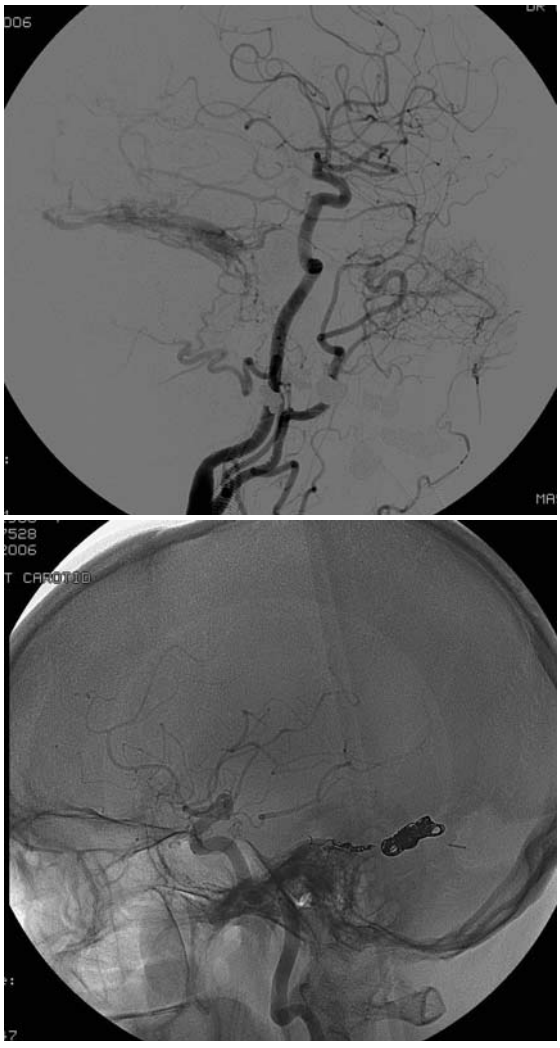


Figure 2a top: Type IIb DAVF - A lateral projection left common carotid artery injection. This 68-year-old lady presented with progressive tinnitus and ataxia a few weeks after an ear infection. She had sustained a minor head injury 2 years previously. The angiogram shows a DAVF supplied by transmastoid branches of the occipital artery, the middle meningeal artery, the ascending pharyngeal artery and tentorial dural branches of the internal carotid artery. Venous drainage to the transverse sinus was 'trapped' due to distal sinus occlusion. Retrograde cortical venous drainage occurred. Transvenous occlusion of the sinus and associated fistula was planned. This required a small craniectomy and direct placement of the microcatheter in the transverse sinus.

Figure 2b bottom: Coil occlusion of the transverse and petrosal sinuses obliterated the DAVF as shown on this 6 month follow-up angiogram.

Borden type and clinical presentation.[12] The progression of disease severity with lesion type was tracked in Cognard`s cohort of 205 patients. 27 patients had a type IIa fistula. Of these 10 (37%) had aggressive clinical symptoms manifested as headache, papilloedema or visual disturbance. In the 10 patients with type IIb DAVFs, 3 (30%) followed an aggressive course. 12 of 18 (67%) patients with type II a+b disease showed aggressive symptoms, including an intracranial haemorrhage in 1 case. 19 (76%) of 25 patients with type III disease had aggressive symptoms, including 10 (40%) presenting with haemorrhage. Twenty nine patients had type IV DAVFs with direct venous drainage into a cortical vein with ectasia. Of these, 28 (97%) had aggressive symptoms, of which 19 (66%) had haemorrhage. 6 of these patients had symptoms attributable to mass effect from the ectatic vein. The presence of direct cortical venous drainage was therefore a strong predictor of haemorrhage. Of those 12 patients with spinal perimedullary venous drainage, 6 presented with myelopathy.

Imaging

CT, MRI and angiography all have roles to play in the investigation of patients with a possible DAVF. Because the clinical and imaging features can be non-specific, the diagnosis of a DAVF is often delayed or missed. Occasionally plain films can demonstrate grooving within the skull vault due to chronic compression from enlarged middle meningeal vessels. If haemorrhage is suspected, non-enhanced CT is a pre-requisite. Venous congestion may appear as an area of low density on CT. In most institutions CT is more readily available and cheaper than MRI and so becomes the first-line investigation of patients presenting with tinnitus, headache or other vague neurological symptoms. Multi-detector CT angiography (MDCTA) can now provide high resolution detail of vascular anatomy. In the investigation of tinnitus it has the additional advantage that it can detect inner and middle ear abnormalities such as aberrant vascular anatomy or glomus tumours. Linear bony defects formed by enlarged emissary veins, similar to the grooving abnormality seen on plain film, can indicate the presence of a fistula.[13] MDCTA, because of its rapid acquisition, has a temporal advantage over static CT. This is important because of the likelihood of altered flow dynamics within a fistula. Subtle changes in contrast intensity of the cerebral vessels may be evident.[14] Arterialised venous blood within the veins draining a DAVF has increased density when compared to non-arterialised blood. Careful scrutiny of the source images with narrow window settings are required to make this distinction.

T2 weighted MRI is more sensitive to the white matter changes of venous congestion or infarction when compared to CT. It has the drawback of being less sensitive to the changes of acute haemorrhage. If dilated cortical veins are present they may be seen on conventional spin echo sequences and visualised using MR angiographic techniques such as phase contrast venography or contrast enhanced MR angiography. Benign disease, without cortical venous reflux can be missed using both CT and MRI. Conventional catheter angiography therefore remains the investigation of choice if there is a strong clinical suspicion of a fistula.

Treatment

Treatment is dependent on the clinical picture and the grade of fistula. A multidisciplinary approach involving a neurosurgeon and neuroradiologist is required. A DAVF without angiographic evidence of retrograde sinus or cortical venous drainage and presenting with a well-tolerated or non-disabling tinnitus can be managed conservatively. Techniques such as occipital artery or carotid manual compression have been reported to occasionally lead to obliteration of the DAVF although this may correspond to the natural history of the disease. If possible, patients should avoid anti-platelet agents which might prevent thrombosis. A change in symptoms warrants repeat assessment with formal angiography.

Both surgical and endovascular techniques have proven efficacy for more troublesome DAVFs. At the benign end of the spectrum, particulate trans-arterial embolisation may afford palliation (Figure 1). This can be regarded as fairly low risk but the risks should not exceed the natural history of the disease. In addition, further recruitment of fistulous channels may cause re-emergence of symptoms at a later date. For more severe disease and particularly for those patients presenting with intracranial haemorrhage or progressive neurological symptoms, treatment is indicated (Figures 2, 3 and 4). If the DAVF drains directly to cortical veins without involvement of the sinus, surgical disconnection of the arterialised draining vein(s) can be employed. This minimises the risk of future intracranial haemorrhage and is facilitated by the use of neuronavigation to localise the craniotomy. Surgery can be combined with pre-operative particle embolisation one to two days before surgery to reduce the risk of intra-operative bleeding and in some cases permit complete resection of the involved dura.

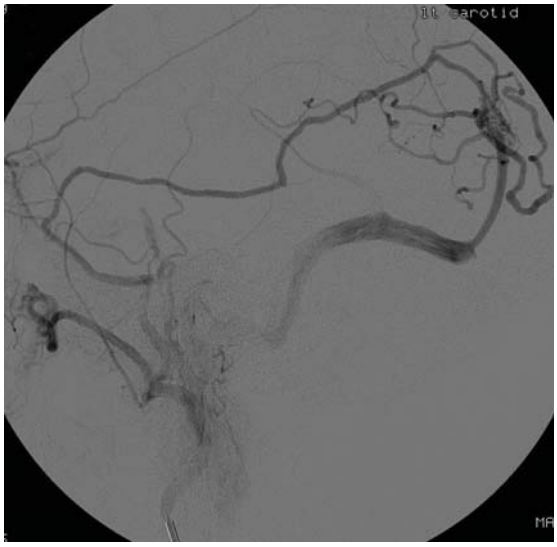


Figure 3: Type III dural fistula - This 70-year-old man presented with a left occipital lobe infarct and subsequent visual hallucinations. Selective injection into the left external carotid artery shows several small radicles from a posterior branch of the middle meningeal artery feeding into the type 3 dural fistula. Retrograde cortical venous drainage directly into cortical branches feeding into the transverse sinus was observed. The veins were not ectatic. 6% Onyx injection via a DMSO compatible microcatheter positioned at the level of the fistula completely obliterated the DAVF.

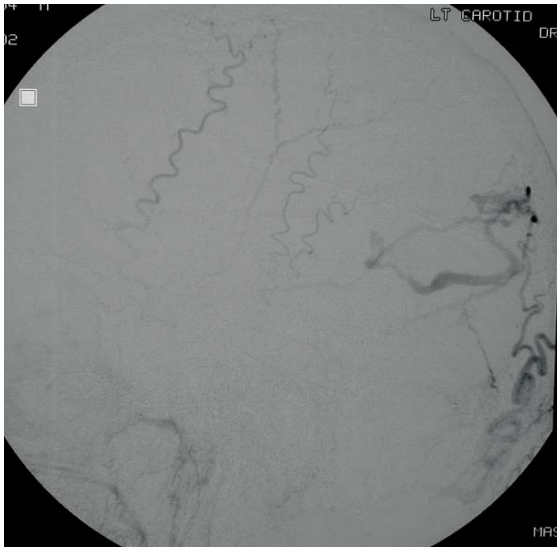
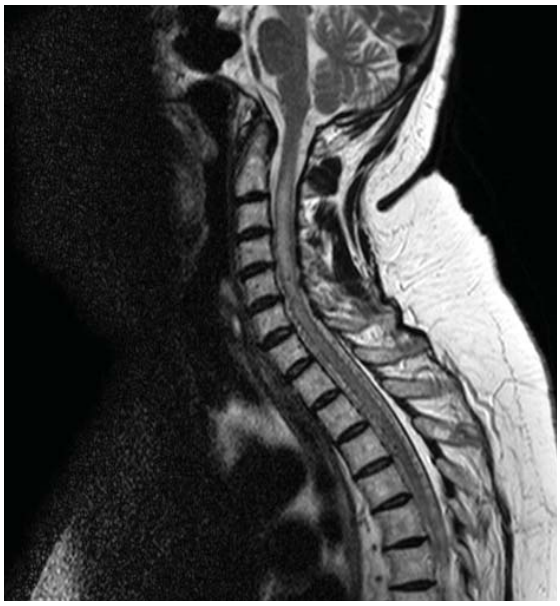


Figure 4: Type IV DAVF - A 74-year-old man presented with a coma producing intracerebral haemorrhage. An AP projection left external carotid artery injection DSA showed a DAVF draining into ectatic cortical veins.



Surgery becomes more problematic when a sinus is involved, and has largely been superseded by the use of transvenous and/or transarterial endovascular approaches.[15] The goal of treatment is to occlude the nidus of the fistula. This requires penetration of the venous side of the fistula. In cases where multiple dural feeders are present, a trans-arterial approach can promote the formation of collateral vessels and make subsequent treatment attempts more difficult. Where a transarterial approach is adopted liquid adhesive agents may be more effective at venous penetration from the arterial side to produce a cure. A retrograde approach into the venous side of a fistula requires careful negotiation of femoral catheters through the right atrium, and then deployment of coils into the receiving sinus or cortical vein. A thorough appreciation of the cerebral venous drainage anatomy is required before considering sacrifice of a vessel. When sacrificing a dural sinus it is important to ensure that any cortical venous reflux is abolished in order to minimise the risk of intracranial haemorrhage. This technique is commonly employed to treat fistulas of the cavernous sinus via a petrosal sinus. Occasionally, a sinus may no longer communicate with an internal jugular vein because of thrombosis. In these cases a direct percutaneous approach can be successful via a burr hole (Figure 2b) or orbital cut down procedure in the case of a carotico-cavernous fistula.

Radiosurgery has been used in the treatment of DAVFs. Söderman et al. treated 53 patients over a 25 year period with gamma knife radiosurgery.[16] 36 patients had aggressive shunts exhibiting cortical venous drainage. 19 of these presented with haemorrhage. 41 patients were followed up by formal angiography and 28 DAVFs were obliterated. The risk of haemorrhage exists however until complete obliteration has occurred. Radiosurgical treatment should therefore be considered if occlusion by surgical or endovascular means is not possible or carries unacceptable risks.

Summary

DAVFs can present in a variety of ways and their diagnosis can be missed on conventional cross-sectional imaging. Conventional catheter angiography remains the investigation of choice if the diagnosis is clinically suspected. A spectrum of pathology exists ranging from the benign to life-threatening. Treatment is indicated in more aggressive disease. This is characterised by cortical venous reflux on angiographic investigations. A multi-disciplinary approach is required before considering treatment, which can be surgical, endovascular or occasionally radiosurgical.

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Figure 5 left: Type V DAVF - MRI scan - This 59-year-old lady presented with an 18 month progressive myelopathy leaving her wheelchair bound. A sagittal T2 weighted MRI demonstrated high signal within an expanded cervical cord. Numerous small flow voids lying both ventral and dorsal to the cord were noted. An angiogram revealed a DAVF with drainage to spinal peri-medullary veins. Partial occlusion with a dilute 20/80 NBCA/ Lipiodol injection led to some improvement in the myelopathic symptoms.

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Adjusting to a Diagnosis of Multiple Sclerosis

Diagnosis

If I was to offer one piece of advice for those newly diagnosed with multiple sclerosis (MS) it would be avoid the internet. 'Knowledge is Power' as one national MS Society website proclaims. However, for someone with 24/7 access to the internet, and a research-based job, researching the disease had become somewhat of an obsession since my diagnosis.

I was diagnosed with MS in May 2004 age 39. Unlike many who are diagnosed there were no earlier signs of anything wrong. Indeed, in 2001 following my office medical, the doctor congratulated me for being a "model patient". However, in March 2004, I noticed that I wasn't shaving properly with my right hand and that I had become 'de-sensitised' from the waist down. I went to my GP practice three or four times in the following weeks and was eventually referred to a neurologist. Having medical insurance proved a mixed blessing: I saw a neurologist privately within a week; had an MRI the next week; and was told that I had MS the next week. Too much to take in too quickly!

What's MS really about?

Following my diagnosis, I wanted to find out more about the disease and to find an answer to the "why me?" question. I started searching the internet for answers, starting first with the national MS Society websites. Initially, I was quite upbeat as many of the national MS society websites appeared very positive about the future. Most reported that, for relapsing remitting MS, there were now treatments that could reduce relapses and the number of lesions with better ones in the pipeline. The aims of the various national MS societies also appeared impressive – "a world without MS"; "to end the devastating effects of MS"; "to find a cure" etc.

But my searching of the national MS society websites also uncovered a much more serious side to this disease. I knew that MS could involve pins and needles, and loss of feeling, but the list of symptoms on these websites were something I had not been prepared for: visual impairment / blindness; paralysis; mobility problems; bladder and bowel problems; speech problems; sexual problems; depression; and something called cognitive problems (including memory problems). Also, for the first time, I came across the term 'near normal lifespan'. I also encountered terms such as respite care, and reference to your partner becoming your 'carer'.

As my research increased, the disease seemed to get worse and worse. Many of the websites were visited by patients with more 'advanced' MS, or carers of such patients. Adverts for mobility aids, hoists, adapted cars began to play on my mind as I started to think of a future I never believed could be mine. How long could I work for? Why am I saving for a retirement? Would I see my young children grow up? The prospect of mobility problems were a particular concern – not only because I loved playing sport, but because mobility problems would end my career (my commute involves: walking to the station; overground trains; underground trains; lots of steps etc).

I was also reminded constantly about the disease through: (i) family members / friends posting me articles about miracle treatments such as Goat's serum, and a stem cell cure available in Holland; (ii) news reports of someone being prosecuted for growing cannabis for MS pain / spasticity; (iii) news reports of the 'loving husband' who helped his wife with MS commit suicide to end her suffering. Everywhere I looked there seemed to be an article about MS, or a celebrity with or affected by MS: Alan Osmond; Richard Pryor; Jacqueline du Pre; JK Rowling.

In the three years since my diagnosis the way the disease is viewed appears (to me) to have changed - MS is now often described as a neuro-degenerative disease in addition to being an inflammatory disease (the chicken and egg issue of what comes first has still to be pinned down). Many research articles have highlighted the involvement of grey matter damage in addition to white matter (myelin). Rather than being a focal disease based on lesions, MS is now considered to be a global disease of the CNS. A recent piece of research using a very powerful scanner (8 Tesla) showed that there were lots more lesions which could not be seen by normal scanners. Urgh! My research also introduced me to the world of axonal degeneration. Gone are the days when MS was just a disease where myelin was damaged. Loss of neurons and axons are now seen as the cause of irreversible disability.

Treatments

My research on treatments also left me confused. The national MS websites refer to 100+ MS drugs in trial. These include those targeting T-cells, B-cells and drugs used for other diseases such as cancer. Minocycline seems to have been examined as a possible MS treatment for some time. Then there are a host of other agents: statins; Low Dose Naltrexone (LDN); Vitamin D supplements; heavy duty antibiotics (on the basis that MS is caused by chlamydia pneumoniae); and anti-virals. Neuro-protective agents are also being examined.

Stem cells are considered by many as a possible future "cure"/ repair strategy for degenerative disease such as MS. While I'm glad to see that the UK's leading lights in Cambridge and Bristol are pushing forward in this area, there would appear to be many more years' research before such a treatment makes it to market. Of course, unproven and potentially unsafe stem cell treatments have been offered in countries where appropriate testing does not appear to be an issue. My father offered me the £15,000 to go to Holland. Thankfully, I didn't accept this!

In terms of my own treatment, I was given steroids at the time of my diagnosis and for subsequent relapses. I started my disease-modifying drug in February 2006. Unfortunately, I had further relapses in June 2006 and a very bad one at the start of October 2006. An aim of the current disease-modifying drugs is to 'slow down' the disease. But my research could not identify what bit of the disease the treatment was 'modifying' and whether it was working for me. In October I came off my disease-modifying drug as, in late November 2006, I was given the chance to be given a more powerful treatment currently being trialed – which I had come across through my internet searching! So far I am doing very well following this treatment. Mentally I feel better as I consider that I have given the disease as big a 'whack' as I could.

> While the internet can provide hope...it can also expose a patient to the realities of a disease

So in my experience, it has taken almost three years to adjust to the diagnosis. I am still working full time and am now beginning to cut down on the time I spend looking at MS websites. I'm not sure how 'normal' my response has been. But, at the end of the day, an MS patient is being asked to take on board a huge range of major changes to their lives: having a disease for the rest of one's life; possibly watching yourself deteriorate (quickly or slowly); possibly having a shorter life than the 'norm'; dealing with potentially major changes to your employment, family life, and interests (be they diving, running, hill-walking etc).

Like many with MS, I keep my fingers crossed that the big breakthroughs in understanding the disease are not too far away and that the drugs companies can develop treatments that can shut the disease down (and perhaps promote some repair!). I will, no doubt, check the web to see what comes out of this year's ECTRIMS and ACTRIMS meetings. Clinicians may wish to suggest to those newly diagnosed with MS that they do not spend too long undertaking 'research' on the internet. While the internet can provide hope, in terms of highlighting future treatments in the pipeline, it can also expose a patient to the realities of a disease (a hard one for me has been the issue of 'brain atrophy') which can be very difficult to adjust to.

Mr Ian Rogers

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1. Galetta SL, et al. *Arch Intern Med*, 2002; 162: 2161–2169.
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'Neurological Literature': Epilepsy

A classic account of epilepsy as the 'falling sickness' is given in William Shakespeare's *Julius Caesar* (1599; Act I, scene ii, lines 253-256):

> *CASCA: He fell down in the market-place, and foamed at mouth, and was speechless.*
> *BRUTUS: 'Tis very like: he hath the falling-sickness.*

However, the only use of the word 'epilepsy' in the Shakespearean canon, to my knowledge, occurs in *Othello, The Moor of Venice* (1604), spoken by Iago shortly after Othello has collapsed, having been goaded by Iago into the belief that Desdemona has been unfaithful (Act IV, scene I, lines 51-56):

> *IAGO: My lord is fallen into an epilepsy;*
> *This is his second fit; he had one yesterday.*
> *CASSIO: Rub him about the temples.*
> *IAGO: No, forbear;*
> *The lethargy must have his quiet course,*
> *If not he foams at mouth, and by and by*
> *Breaks out to savage madness.*

Considering the circumstances of the event, and Othello's rapid recovery to continue the argument with Iago, I would suggest that this was more likely to be a syncopal, rather than epileptic, event. However, in his comprehensive recording of faints and fits in Shakespeare's works, Kenneth Heaton seems ready to accept Iago's diagnosis.[1]

An episode of impaired consciousness is central to the plot of *Silas Marner, the weaver of Raveloe* (1861) by George Eliot (1819-1880), occasioning the exile of the protagonist to Raveloe, where the locals observe further attacks:

> *"… he saw that Marner's eyes were set like a dead man's, and he spoke to him, and shook him, and his limbs were stiff … just as he had made up his mind that the weaver was dead, he came all right again … and said "Good-night", and walked off."*

The locals are uncertain as to the cause of these events:

> *"Some said Marner must have been in a "fit", a word which seemed to explain things otherwise incredible; but … Mr Macey … asked if anybody was ever known to go off in a fit and not fall down. A fit was a stroke, wasn't it?"*

What influence may epilepsy have on creative endeavour? It was once thought that Vincent van Gogh suffered from temporal lobe epilepsy but in recent times there has been a move away from this idea to suggestions of borderline personality disorder[2] and bipolar affective disorder.[3] It is well known that Fyodor Dostoyevsky (1821-1881) suffered from epilepsy, and that a number of characters in his oeuvre are epileptics, their fictional experiences likely based on the author's own.[4]

"Dostoëffsky" is mentioned, in passing, in *A ray of darkness*[5] (14,19,170), a work devoted to epilepsy by the Anglo-Welsh author Margiad Evans (1909-1958).[6] An acclaimed novelist of the 1930s, Evans was first diagnosed with epilepsy at the age of 42 whilst living in Gloucestershire. Her experiences prompted her to write "the story of my epilepsy … an adventure of body and mind" (12). Her first major seizure occurred on the evening of 11th May 1950 whilst she was alone in her cottage, and is described thus (78):

> *"[I] looked up at the clock .. saw that it was ten minutes past eleven. The next thing I was still looking up at the clock and the hands stood at five and twenty minutes past midnight. I had fallen through Time, Continuity and Being."*

In the immediate aftermath, recalled later, her brain "worked … like an engine misfiring and unsteered" (80). She found herself to have been incontinent of urine (81) and later found a cut at the base of her head at the back (86).

> *"… in one moment, I realised the incredible, impossible and ghastly truth – I had had an epileptic fit." (81).*

She rebutted the suggestions of relatives that it was simply a faint (98) and that she had just passed out, showing a clear understanding of the different symptoms of syncope:

> *"I had been close enough to it to be absolutely sure that one did not faint as I had fallen. There was a sinking away, a sick feeling, and a remembrance of it afterwards." (99)*

Retrospectively, she recalled "moments of separation from my consciousness" dating back to childhood, lasting a few seconds, which had been more frequent in the previous year (38,39), episodes which might possibly have been complex partial seizures.

Seen by her general practitioner the day following the first major seizure, he immediately prescribed luminal (85) (phenobarbital) and arranged for an appointment with Professor T, "a man of international reputation" (104), who, following an EEG, confirmed the diagnosis of epilepsy when he saw Margiad on 8th June 1950 (i.e. 4 weeks after the first major seizure): "he thought that I must have a slight scar on the brain from an old injury" (106).

Two problems which are still grappled with in epilepsy management today presently became apparent: pregnancy, and impaired cognitive function.[7,8] After commencing the luminal, "I was never so tired in my life", and by 29th September 1950 Evans reported that she was "4 months gone with child" (111).

> *"Epilepsy and pregnancy. The shock of waking every morning to such a grim problem of life" (125).*

Concerns that epilepsy might be hereditary (although there was no family history; 37,105) were finally overcome, by her general practitioner

> *" … reading … a passage from Nervous Diseases by the Professor of Neurology at London University, which he said was the last and most up-to-date work on epilepsy. … there was in reality only the very slightest danger of its being hereditary." (128)*

Her baby daughter was born uneventfully, but after a post partum fit "I was never again able to feed my child" (153).

The other major issue was the effect of anti-epileptic medications ("luminal and epinutin" [sic] 108) on a creative writer:

> *"since taking drugs I cannot keep awake for those free quiet hours which were my most creative. True my power of concentration is lost also" (19)*

> *" … the drugs I have to take … make me apathetic, have faded and dulled and dimmed the powers of imagination and concentration" (189)*

In her final years, an exploratory operation revealed a brain tumour to have been the cause of her epilepsy (ref. 6, p55).

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New Guidelines for MS Treatment - no cause for celebration

In February, the Association of British Neurologists endorsed and and released the 2007 ABN Guidelines for Treatment of Multiple Sclerosis with β-interferon and Glatiramer Acetate,[1] an update of the 2001 Guidelines. We and others however view the new document with concern and dismay.

What are the changes? The first is a recommendation for starting treatment in patients with Clinically Isolated Syndromes (CIS) if accompanied by certain MR scanning changes (according to the revised McDonald criteria[2]). The second is a recommendation for starting treatment in both relapsing-remitting (RR) and secondary progressive MS after "one disabling relapse in the last year" (previously, two clinically significant relapses in the past two years were required). Additionally, there is also a recommendation that patients with RR disease may be started on therapy even if they have suffered no recent relapses at all, but if an MRI scan appears active.

Our concerns focus on the lack of clinical evidence of patient benefit for these treatment recommendations, and the cost implications to PCTs.

CIS Guidelines

The evidence for treatment in patients with CIS is based upon the ETOMS, CHAMPS and BENEFIT studies.[3-5] Each trial randomised MRI-positive patients to either placebo or β-interferon at varying doses. BENEFIT acknowledges that blinding was unsuccessful (67% of patients correctly guessing they were taking the active drug); ETOMS acknowledged the surprisingly low annual relapse rate in this selected group (placebo arm 0.43 / year). These studies reported that over a 2 to 3 year period on treatment approximately 15% of patients avoided a relapse.

It is also the case, however, that 50% of these patients would not have had a relapse whether treated or not. Indeed it is well documented that patients with CIS MRI positive or negative have a reasonably good chance of not developing further clinical symptoms of MS over a 10 year period of follow up[6] and pre-MRI natural history suggests that 1 in 5 will have no further symptoms after 25 years.[7]

These ETOMS, CHAMPS and BENEFIT data suggest that ~85% of patients starting treatment will experience no benefit (BENEFIT indicates that the "patient number needed to be treated in order to prevent one case of CDMS (ie one relapse) within the study period of 2 years is estimated to be 5.9"[3]). This equates to ~12 years of treatment (2190 injections at a drug cost alone of ~£90 000) to stop 1 relapse in 12 patients over a 2 year period. The other 11 patients experience no benefit – but will often experience unpleasant side effects and the accompanying 'medicalisation' that starting treatment with β-interferon entails.

In any case, the point has been well made that interferons even in responding patients do not 'prevent multiple sclerosis' "except with reference to a restricted window of time, which is clinically not a very meaningful way to think of therapy for a chronic, relapsing disease. As for delay, surely the CIS must be regarded as the onset of the disease in these patients, so there can be no delay."[8]

Longitudinal MRI studies clearly show that the disease process starts some while – months or years – before clinical neurological presentation. Therefore, to propose (as in these Guidelines) that the biologically rather arbitrary moment of the first clinical event has huge therapeutic significance is not rational. More than this, to recommend that we should treat six or seven patients immediately following this event, so as (in effect) to delay one relapse in one patient by perhaps six months, during a 40-50 year illness, by the introduction of a treatment that appears to have no impact on long term disability, is unsustainable. Waiting a few months for the next attack in that individual, and treating her or him alone, is surely more sensible.

After all, "people with clinically isolated syndromes, just as those with multiple sclerosis, fear future disability, not a change in diagnostic label".[9] And while we of course acknowledge the intuitive and attractive hypothetical link between early treatment and delay in long-term disability, this pre-supposes the treatment to be effective in preventing disabilty. Sadly, there is no clinical or trial evidence yet to support early treatment on grounds of preventing disability. ETOMS reported interferon to have no significant effect on the accumulation of disability,[4] and the 5 year open-label extension study of the CHAMPS cohort likewise showed a lack of effect on disability.[10] We eagerly await the results from the DoH risk-sharing scheme for patients treated as per the last ABN criteria – the UK is perhaps the last available place to test this essential hypothesis for CIS patients – but until evidence is in place it is surely incorrect to make new recommendations.

The ABN MS panel attempts to reduce mis-treating potentially benign patients by using serial MRI imaging. The Guidelines' Appendix outlines the suggested use of MRI in CIS patients. However, there is again no good clinical evidence to suggest that treating patients who have serial MRI changes rather than relapses will have any impact on future relapses or disability. Again, hypothetically this is an attractive idea but one that needs to be tested in a phase III study before, not after, becoming incorporated into Guidelines.

Another issue is that the McDonald MRI criteria are (appropriately, of course) very clearly defined and highly stringent. Properly interpreting brain lesions in this context requires close familiarity with and adhesion to the Tintore revision of the Barkhoff criteria. The Revised Guidelines manuscript indicates that "determination that a T2 lesion is indeed new can be challenging. A new T2 lesion must be of sufficient size and location to reflect one that could not have been missed previously for technical reasons of slice orientation, thickness or spacing, tissue contrast, patient motion, or other artifacts. This requires standardised scanning procedures with emphasis on careful repositioning, as well as input from qualified evaluators". At a practical level, we do not believe this is realistic outside (literally) one or two MRI-super-specialised units.

We believe that clinical outcomes (relapses) are more reliable and more relevant than MRI. Patients with more aggressive disease declare themselves early and receive treatment; those with quiet disease do not. This is currently established practice, and any signficantly alteration of this should be predicated upon clear evidence of benefit.

Single Relapse Guidelines

Many centres run relapse clinics. It is not infrequent to see a patient sustaining a relapse (often 'disabling') many years or even decades after their last event. The new criteria now recommended treatment be initiated - this despite natural history data clearly showing that the annual relapse rate on average tends to reduce over time. This raises the distinct possibility that many patients who have a very low risk of having further relapses for many years could now be started on β-interferon.

Again the rule that a significant change in practice requires an evidence base appears to have been entirely ignored.

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Costs

Our last concern relates to the added burden of cost that these guidelines, if implemented, will impose. It is important to recall that these are agents not approved initially by NICE (for use in patients with a much higher annual relapse rate). Now, the ABN proposes, on the basis of no cost-efficiency data and no evidence of long term disability benefit, a substantial increase in the number of patients receiving β-interferon (in particular from the new single relapse guideline).

These added costs relate to pharmaceutical, neuroimaging and staffing and are difficult to estimate. But if one does attempt to estimate QALY values, in drug costs alone for CIS patients, assuming the average time of disability from relapse is two months, it would be in the region of £540,000. We fear that our PCTs may react to this by increasing, rather than decreasing, their stringency and vigilance concerning funding for treating MS patients as a whole. Where they do fund treatments, then it may surely be the case that, within a fixed budget, adverse consequences must result for other patients.

Summary

The more general problem we perceive is that this document lacks balance. It concentrates exclusively on 'earlier and more' interferon treatment, while failing to acknowledge less 'positive' new information. We now have, for example, a far clearer picture since the 2001 Guidelines concerning the absence of any useful impact of IFN or glatiramer on progressive disability. But no mention is made in the current Guidelines, let alone any attempt to address, the rigorous systematic meta-analysis of the pivotal studies of interferon beta in relapsing-remitting multiple sclerosis pointing out the absence of any detectable significant effect of the interferons on the accumulation of disability,[11] or the negative Cochrane Review of glatiramer in RR-MS concluding that there was insufficient proof of any beneficial effect on relapse rate or on disability progression[12]. These surely merit attention.

We acknowledge that there is a significant discrepancy between prescribing rates in the UK (perhaps 11%) and those in the US and continental Europe (25-30%). However, to assume that this discrepancy reflects poor practice in the UK, and to generate guidelines encouraging neurologists to conform in the treatment of MS is surely a hasty conclusion. The UK has a strong ethos of practising rigorous evidence-based medicine, and this may well provide an alternative explanation for the discrepancy. If the relatively low prescribing rate is perceived as problematic, then the first step should be to gather evidence concerning the numbers of patients who meet the 2001 ABN Guidelines but who have not been offered treatment. Attempting to increase numbers of patients treated with unproven therapies may be popular but is surely not good medicine.

In summary, we would find it difficult to improve upon a recent position statement from the Mayo Clinic Neurology team – that it is best to "avoid treating those with a greater chance of benign course …, a low chance of benefit, … and those with an indeterminate prognosis (e.g. CIS…)"; and that "pronouncements and guidelines based on unproven surrogates that are weakly correlated with disability and for which long-term predictive value is unknown and not helpful."[13]

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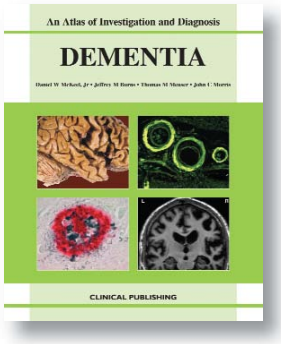
An Atlas of Investigation and Diagnosis: Dementia



DW McKeel Jr, JM Burns, TM Meuser, JC Morris
Published by: Clinical Publishing 2007
ISBN: 978-1-904392-37-8
Price: £75

This book emanates from the renowned Alzheimer's Disease Research Center at the Washington University School of Medicine in St Louis, which has been particularly influential in recent times in developing the concept of mild cognitive impairment as defined by staging with the Clinical Dementia Rating (CDR) and correlating this with neuropathological findings.

The book's title may be something of a misnomer since, although clinical features and neuroimaging are alluded to and there is an excellent chapter (2) on clinical assessment, it is neuropathology which is emphasised throughout. Chapters cover systematically the neuropathology of normal aging, of preclinical and clinical Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementias, and miscellaneous other dementing disorders including Huntington's disease, prionoses, and multiple sclerosis. As might be anticipated of an atlas, the work is beautifully illustrated with high quality images throughout.

One might quibble about the occasional absence in chapter reference lists of papers cited in the text, and sometimes a mismatch between reference and context. James Parkinson is credited with a knighthood (128) which he may, from a neurological perspective, have merited but which he surely never received (has he possibly been confused with Sir John Parkinson (1885-1976) of Wolff-Parkinson-White syndrome?).

Certainly this book will be a welcome addition to the departmental library, but as regards personal copies its appeal may be chiefly to neuropathologists.

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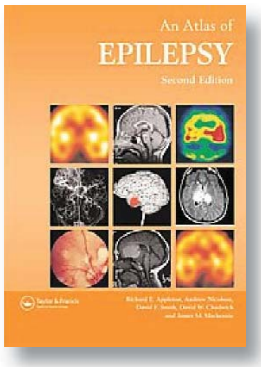
Atlas of Epilepsy, 2nd edition



Edited by: Appleton, Nicolson, Chadwick, MacKenzie, Smith
Published by: Informa healthcare
ISBN: 9781842140277
ISBN-10: 1842140272
Price: £75

Epilepsy is a rather beautiful area of neurology. The diagnosis is made mainly from the patient and eye-witness account of the event, and clinical examination usually adds little. The need to focus on the event semiology for diagnosis makes history-taking here crucial, particularly given for most cases, there is no confirmatory test to prove or disprove the clinical diagnosis (apart from the occasional patient who requires prolonged EEG monitoring). As seizures may be symptomatic of other disease, it flows into the other branches of neurology, such as oncology, vascular disease etc. It is satisfying in that diagnosing the nature of transient episodes of altered consciousness can be difficult. For those fortunate enough to work in a regional neuroscience centre, it can be immensely satisfying to be where the buck stops, and be in a position to call on the full armamentarium of neurophysiological investigations, and ultimately be able to provide a definitive diagnosis in a patient who may have carried an unsatisfactory diagnosis of probable or possible epilepsy, often for many years. Drug treatment of established epilepsy is itself an art, and epilepsy surgery is arguably the most fascinating aspect of the condition. For those cases, the aim of marrying up the clinical semiology with imaging and EEG data, proposing a hypothesis of location of seizure onset and pattern of propagation, and then testing this hypothesis with videoEEG and ictal SPECT, is especially enjoyable, and gives intriguing insight into brain-behaviour relations.

Epilepsy, however, remains challenging to epileptologists, let alone neurologists who do not subspecialise in this area. Leaving aside neurologists, with increasing subspecialisation and the disappearance of the general physicians, non-neurology hospital physicians are increasingly and understandably reluctant to diagnose and treat epilepsy, especially in view of recent medico-legal events. This is of course no bad thing, provided there are sufficient neurologists to meet the demand. There remains, however, a need for general practitioners and non-neurology hospital specialists to remain acquainted with epilepsy.

This book is well placed to educate such physicians: it aims to be an introductory text of epilepsy, and is targeted at trainee neurologists and general practitioners, but will also be of use to all hospital physicians and to neurosurgeons, and to epilepsy nurse specialists.

It is organised in the traditional manner, namely basic science, diagnosis, aetiology, prognosis, treatment. In view of its limited size and its excellent production, the book sensibly focuses on illustrations rather than text. The EEGs, imaging and pathology illustrations are uniformly excellent. It is well written, and the figure legends are comprehensive. Suitable up-to-date references and further reading are included. It is free of typos, and is well indexed. Clinically relevant studies are given due prominence, namely MRC drug withdrawal, MRC early epilepsy and single seizures, and SANAD (Standard and new antiepileptic drugs).

This book occupies a niche of being a sound atlas of epilepsy, and will be particularly useful for hospital physicians and GPs. Career neurologists will find it useful, but those subspecialising in epilepsy will want something more comprehensive like Shorvon et al's 'The treatment of epilepsy'. The book does not pretend, however, to be anything other than an atlas and introduction to epilepsy, and is recommended.

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Copper Deficiency Masquerading as Subacute Combined Degeneration of the Cord and Myelodysplastic Syndrome

Copper deficiency is an increasingly reported but under-recognised cause of blood dyscrasias and neurological dysfunction. It can present to the neurologist as a myeloneuropathy that resembles subacute combined degeneration of the cord both clinically and radiologically. We describe a patient who presented initially to the haematologists with a myelodysplastic syndrome but went on to develop a myeloneuropathy triggering the recognition of copper deficiency as the unifying diagnosis. Copper supplementation completely reversed the haematological disorder and stopped his neurological deterioration.

Case report

A 69-year-old retired clergyman, who had undergone a partial gastrectomy for a duodenal ulcer in the 1960s, presented in late 2004 to his GP with fatigue. He was found to have a normocytic anaemia (Hb 7.7g/dl, MCV 88.5fl) and leukopenia (white cell count 1.1*10^9/l) in the presence of a normal platelet count and normal B12, folate and ferritin levels. He was referred to the haematologists at his local hospital where a bone marrow biopsy showed dyserythropoiesis with vacuolated erythroid precursors, left shift of granulopoiesis, and normal megakaryocytes. Perl's stain demonstrated normal iron stores and ring sideroblasts. A diagnosis of myelodysplastic syndrome was made.

He was managed supportively over the next 18 months with recurrent red cell transfusions, as required. His white cell count remained low, with neutrophils never exceeding 0.9*10^9/l (Figure 1).

He was first seen by neurology 12 months after initial assessment having complained of ascending numbness. Examination revealed a mild spastic paraparesis with brisk lower limb reflexes, bilaterally upgoing plantars and a soft sensory level at T11. He was fully ambulant. A compressive spinal cord syndrome was initially suspected. MRI of his spine was unremarkable and, apart from his known haematological abnormalities, all investigations were normal including repeated B12 and folate levels, autoantibody screen, antineutrophil cytoplasmic antibodies, antineuronal antibodies and serology for syphilis and human T-cell lymphoma viruses. CSF was acellular with a protein of 0.4g/l and no detectable oligoclonal bands.

Further neurological deterioration occurred over the next 6 months. By this time, the patient's numbness had ascended to the level of the mid-chest and to the elbows. He complained of feeling increasingly unsteady on his feet, and was having frequent falls, particularly at night. He was only able to mobilise a few steps with assistance. His sphincter function remained normal.

On examination, tone in the upper limbs was normal. In the lower limbs, tone was markedly increased with sustained clonus at both ankles. There was mild power loss (MRC 4- to 4) in all limbs in a pyramidal distribution.

Upper limb reflexes were diminished, while lower limb reflexes were pathologically brisk with bilateral extensor plantars. Sensation to light touch and pin prick was diminished up to the waist, with a flank-sparing extension to a level of T5, and in a glove pattern up to the elbows. Vibration sense was absent to the sternum. Proprioception was markedly impaired to the proximal interphalangeal joints in the upper limbs, and to the ankles in the lower limbs. There was pseudoathetosis and sensory ataxia. He was able to stand only with support.

The patient was admitted to the regional neurosciences centre for further investigation. Haemoglobin and white cell count remained low, though the red cells were now macrocytic (MCV 103fl). B12 and folate levels were again normal. ESR was 74. CSF was acellular but contained mildly high protein levels at 0.53g/l. Nerve conduction studies showed normal amplitudes, conduction velocities and distal latencies. MRI brain was normal, however MRI of the spinal cord now showed a longitudinally extensive high T2 signal lesion in the dorsal cord (Figure 2).

The clinical and radiological findings were reminiscent of subacute combined degeneration of the cord, and although B12 levels had been repeatedly normal, functional B12 deficiency was considered possible and

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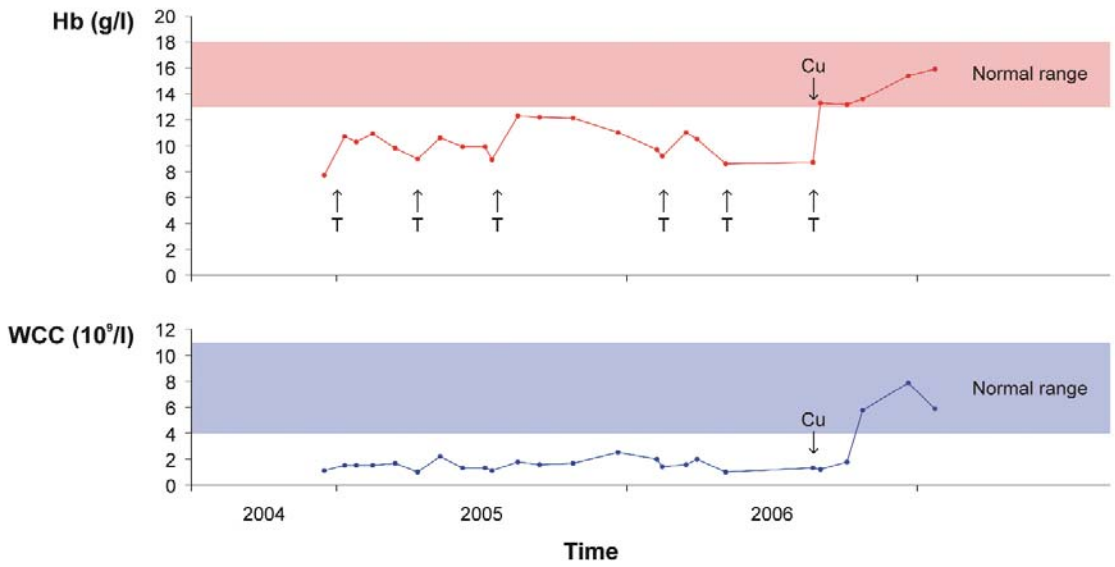
Figure 1: haemoglobin and white cell count against time. T=transfusion. Cu=initiation of copper replacement.



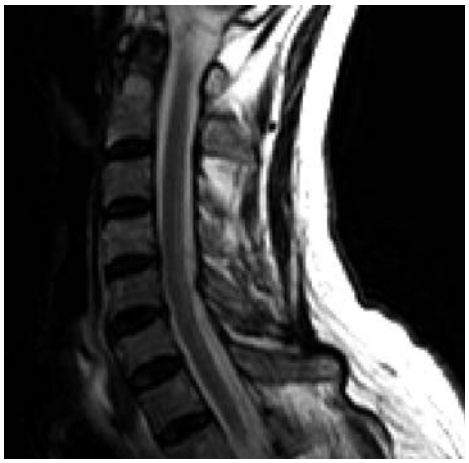


Figure 2: sagittal T2-weighted MRI demonstrating a longitudinal high signal lesion in the dorsal cervical cord.

B12 replacement was initiated. Concurrently, a literature search using the terms 'subacute combined degeneration' and 'myelodysplasia' led to case reports of copper deficiency. The patient's copper and caeruloplasmin levels were found to be undetectable, thus confirming a copper deficiency state. Zinc levels were slightly high at 24µmol/l (normal 9-19).

Oral copper supplementation equivalent to 8mg of elemental copper per day resulted in prompt haematological recovery (Figure 1) and cessation of neurological deterioration, but without functional improvement to date (now eight months into therapy).

Discussion

Copper is a micronutrient essential to the function of nervous system and bone marrow as a prosthetic group in many key enzymes, including cytochrome oxidase (respiratory chain), superoxide dismutase (antioxidant defence), dopamine β-hydroxylase (catecholamine synthesis) and methionine synthase (folate metabolism). It is contained in many common foodstuffs including meat, fish, nuts, seeds and legumes, and pure dietary deficiency is rare. Absorption occurs in the stomach and proximal duodenum. While the bulk of absorbed copper is excreted into the bile, a small proportion is incorporated into caeruloplasmin for transport to extrahepatic tissues.

Despite the recognition of copper deficiency as a cause of anaemia and neutropenia for over 30 years,[1] there is still limited awareness of copper deficiency as a cause of cytopenias. The anaemia is most commonly macrocytic, but may be normocytic or microcytic. Thrombocytopenia is rare.[2] Bone marrow assessment often shows morphological characteristics suggestive of myelodysplastic syndrome, such as ring sideroblasts and nuclear maturation changes of erythroid and myeloid precursors. As a rare and poorly recognised cause of sideroblastic myelodysplastic syndrome, copper deficiency is not listed as a differential in many current haematology textbooks[3] and the neurologist seeing such cases may be the first to make the connection.

The commonest neurological manifestation of acquired copper deficiency is a myeloneuropathy with sensory ataxia. Spinal cord MRI typically shows increased T2 signal in the dorsal cord.[4] The syndrome is thus clinically and radiologically similar to subacute combined degeneration of the cord seen with vitamin B12 deficiency, and both conditions may potentially coexist.[5]

Copper deficiency myelopathy was first described in 2001,[6] and a total of 36 cases have been reported to date.[5-16] It predominantly affects females (F:M 3.6:1), with age at presentation ranging from 36 to 78 years. The most frequent cause is previous upper gastrointestinal surgery, which has been implicated in almost half the cases.[5-11] Whilst the majority of these cases had a remote history of partial gastrectomy for peptic ulcer disease, three of them occurred following bariatric gastric surgery. The increasing use of such bariatric interventions may leave a growing number of patients at risk of copper deficiency in the future.

Further causes include malabsorption[5] and zinc overload.[5,12-16] Despite hyperzincaemia, no external source of excess zinc may be evident. Zinc induces the expression of the intracellular chelator metallothionein in enterocytes. Copper has a higher affinity for metallothionein than zinc, and thus displaces zinc from metallothionein. Copper remains bound in the enterocytes which are then sloughed into the lumen and eliminated (a mechanism exploited when using zinc as a treatment for Wilson's disease). Despite adequate investigation, approximately 25% of cases remain idiopathic.[5]

Treatment involves stopping any excessive zinc intake, and administering copper supplements. No studies have addressed the most appropriate dose, route and duration of supplementation. Several previous cases were treated with oral supplements equivalent to 2mg of elemental copper per day. A relapse was reported with this dose in a patient with a past history of gastric surgery,[9] and we therefore opted for a higher dose. Although deficiency is usually due to impaired absorption, oral supplementation is effective, and is more practical than parenteral supplements.

Haematological abnormalities resolve rapidly and completely, while the neurological decline can usually only be halted but not reversed. Where neurological recovery occurs, it tends to be limited to a subjective improvement in sensory symptoms.[6,9]

Conclusion

Copper deficiency represents a rare but treatable cause of neurological disability, which should be considered in individuals presenting with undiagnosed myelopathy. The coexistence of haematological abnormalities and a history of gastric surgery may suggest the diagnosis.

Acknowledgements

We are indebted to Gavin Winston for his help with the literature review.

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Hereditary Neuropathies

The hereditary neuropathies are a heterogeneous group of disorders that can be divided into two major subgroups: neuropathies in which the neuropathy is the sole or primary feature and neuropathies in which the neuropathy is part of a more generalised neurological or multisystem disorder. This review will focus on the common hereditary neuropathies in the first group, Charcot-Marie-Tooth disease (CMT), hereditary neuropathy with liability to pressure palsy (HNPP), hereditary sensory and autonomic neuropathy (HSAN), distal hereditary motor neuropathy (dHMN) and hereditary neuralgic amyotrophy (HNA).

Charcot-Marie-Tooth disease

CMT is the most common inherited neuromuscular disorder, affecting 1 in 2,500 individuals.[1] Although CMT is both clinically and genetically heterogeneous, the cardinal clinical features are distal muscle wasting and weakness, reduced or absent tendon reflexes, distal sensory loss and a high incidence of foot deformities. Disease onset usually occurs during the first decades of life, the course is slowly progressive, and severity is highly variable even within the same kinship, only rarely leading to severe impairment. Historically CMT has been classified into two main subgroups neurophysiologically: CMT1 (demyelinating) with upper limb motor nerve conduction velocities (MCV) less than 38m/s, and CMT2 (axonal) with upper limb MCV greater than 38m/s[2]. Dominant intermediate CMT, a subgroup of CMT with MCV ranging from 25 to 45m/s, is a recent addition to the classification.[3]

CMT can be inherited as an autosomal dominant (AD), recessive (AR) or X-linked trait. Autosomal dominant and X-linked CMT are the most prevalent forms of CMT in UK/northern European and US populations, whereas autosomal recessive CMT is more common in countries with high rates of consanguinity. Apparent sporadic cases are common and may be due to a number of causes including lack of family history, reduced penetrance, variable disease expression, de novo dominant mutations or autosomal recessive inheritance. Currently greater than 20 causative genes have been identified for CMT (Table 1).

Autosomal dominant CMT1

This is the most common form of CMT in most populations. Patients usually present with the 'classical CMT' phenotype characterised by difficulty in walking and foot deformity, usually starting in the first two decades of life. Distal wasting and weakness are generally more prominent in the lower limbs and frequently associated with distal sensory loss and reduced or absent tendon reflexes. Nerve conduction velocity is homogeneously slow with MCV in the median nerve below 38m/s. Nerve biopsy shows demyelination with typical onion bulbs reflecting repeated cycles of de- and remyelination.

The most common form is CMT1A secondary to the chromosome 17 duplication containing the peripheral myelin protein 22 gene (PMP22). This accounts for 70% of all CMT1 cases in European populations.[4] Point mutations in the PMP22 gene are rare and affected patients either have CMT1A, HNPP or a more severe form of CMT.[15]

CMT1B is a less common form of CMT1 and it is associated with myelin protein zero (MPZ) gene mutations. Patients usually present with an early onset demyelinating neuropathy (CMT1B). MPZ mutations can also cause a late onset axonal neuropathy (CMT2).[6]

Mutations in the EGR2 and LITAF genes are very rare causes of CMT1 and like PMP22, mutations in EGR2 can also present with a severe CMT1 phenotype. The final gene associated with CMT1 is NEFL,[7] although mutations in this gene more commonly cause CMT2.

Severe CMT1

A more severe form of CMT1, also called Dejerine Sottas disease (DSD) and congenital hypomyelinating neuropathy (CHN) usually presents in the first decade with very slow MCV. This is usually caused by de novo dominant mutations in the common CMT1 genes, MPZ, PMP22 and EGR2. In rare instances mutations in the same genes can be inherited as an autosomal recessive trait.[1]

Hereditary neuropathy with liability to pressure palsies

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant inherited disorder characterised by recurrent palsies at points vulnerable to pressure. It is usually due to a deletion of the same portion of chromosome 17 which is duplicated in CMT1A, but rarely it is caused by PMP22 point mutations.

X-linked CMT1

This is the second most common form of CMT and is caused by mutations in the connexin 32 gene. Clinically males are more severely affected and usually present with a demyelinating neuropathy, whereas females are less affected and often only have a mild neuropathy with nerve conduction velocities in the axonal range. Central nervous system involvement is occasionally seen but is often asymptomatic.[8]

Autosomal dominant CMT2

It is estimated that about 24% of patients with dominantly inherited CMT have CMT2. Unlike AD CMT1 where more than 95% of the causative genes have been identified, only 25% of the causative genes for AD CMT2 are known.

Mitofusin 2 (MFN2) gene mutations, which cause CMT2A, are the major cause of CMT2, causing approximately 20% of all cases.[9] Patients usually present with the 'classical CMT phenotype', which is indistinguishable

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The hereditary neuropathies are the commonest inherited neurological diseases and are a significant cause of disability in the population

Table 1: Charcot-Marie-Tooth disease: Classification and clinical features.

Type	Inheritance	Gene/Locus	Phenotype
CMT 1A	AD	Dup 17p (PMP22) PMP22 (point mutation)	Classic CMT1 Classic CMT1/DSD/CHN
CMT 1B	AD	MPZ	CMT1/ DSD/CHN/ CMT2
CMT 1C	AD	LITAF	Classic CMT1
CMT 1D	AD	EGR2	Classic CMT1/DSD/CHN
CMT 1	AD	NEFL	CMT1/CMT2
HNPP	AD	Del 17p (PMP-22) PMP-22 (point mutation)	Typical HNPP Typical HNPP
HNA	AD	SEPT 9	Recurrent neuralgic amyotrophy
CMT 1X	X-linked	GJB1	Males CMT1/ Females CMT2
CMT4A	AR	GDAP1	CMT1/CMT2
CMT4B1	AR	MTMR2	Severe CMT1/facial/ bulbar/focally folded myelin
CMT4B2	AR	MTMR13	Severe CMT1/glaucoma /focally folded myelin
CMT4C	AR	KIAA1985	Severe CMT1/scoliosis /cytoplasmic expansions
CMT4D (HMSNL)	AR	NDRG1	Severe CMT1/gypsy /deafness/tongue atrophy
CMT4E	AR	EGR2	CMT1/DSD/CHN
CMT4F	AR	PRX	CMT1/sensory/ focally folded myelin
CCFDN	AR	CTDP1	CMT1/gypsy/cataracts dysmorphic features
HMSN Russe	AR	10q22-q23	CMT1
CMT1	AR	PMP22 (point mutation)	CMT1/DSD/CHN
CMT1	AR	MPZ	CMT1/DSD/CHN/CMT2
CMT2A	AD	KIF1Bβ	Classic CMT2
CMT2A	AD	MFN2	Classic CMT2 / more progressive / optic atrophy
CMT2B	AD	RAB7	CMT2 with predominant sensory involvement and sensory complications
CMT2C	AD	12q23-q24	CMT2 with vocal cord and respiratory involvement
CMT2D	AD	GARS	CMT2 with predominant hand wasting/weakness or dHMN-V
CMT2E	AD	NEFL	CMT2 but can have slow MCVs in CMT1 range +/- early onset severe disease
CMT2F	AD	HSP27	Classic CMT2 or dHMN-II
CMT2G	AD	12q12-q13.3	Classic CMT2
CMT2L	AD	HSP22	Classic CMT2 or dHMN-II
CMT2	AD	MPZ	CMT1 or CMT2
CMT2 (HMSNP)	AD	3q13.1	CMT2 with proximal involvement
ARCMT2A	AR	LMNA	CMT2 proximal involvement and rapid progression described/ also causes muscular dystrophy/ cardiomyopathy/lipodystrophy
ARCMT2B	AR	19q13.3	Typical CMT2
ARCMT2	AR	GDAP1	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
CMT2X	X-linked	Xq24-q26	CMT2 with deafness /mental retardation
DI-CMTA	AD	10q24.1-25.1	Typical CMT
DI-CMTB	AD	DNM2	Typical CMT
DICMTC	AD	YARS	Typical CMT

AD = autosomal dominant; AR = autosomal recessive; Dup = duplication; Del = deletion; PMP-22= peripheral myelin protein 22; MPZ = myelin protein zero; LITAF = Lipopolysaccharide-induced tumor necrosis factor; EGR2 = early growth response 2; GJB1 = gap junction protein, beta 1; GDAP1 = ganglioside-induced differentiation-associated protein 1; MTMR2 = myotubularin-related protein 2; MTMR13 = myotubularin-related protein 13; KIAA1985 = K1AA1985 protein; NDRG1 = N-myc downstream-regulated gene 1; PRX = periaxin; CTDP1 = CTD phosphatase, subunit 1; KIF1β = Kinesin family member 1B-β; MFN2 = Mitofusin 2; RAB7 = RAS-associated protein RAB7; GARS = glycyl-tRNA synthetase; NEFL = neurofilament, light polypeptide 68kDa ; HSP 27 = heat shock 27kDa protein 1; HSP 22 = heat shock 22kDa protein 8; LMNA = Lamin A/C; DMN2 = dynamin 2; YARS = tyrosyl-tRNA synthetase; SEPT9 = septin 9.

from autosomal dominant CMT1. Neurophysiology shows MCV above 38m/s with reduced motor action potentials (MAPS) and reduced or absent sensory action potentials (SAPS). Nerve biopsy is consistent with an axonal neuropathy. Patients may have a more progressive, early onset severe phenotype. Approximately 20% of MFN2 mutations are de novo dominant, accounting for many of the 'sporadic' CMT2 cases. Extensor plantar responses and increased reflexes have been occasionally reported.

Recently, axonal CMT with optic atrophy (previously known as HSMNVI) has been shown to be caused by mutations in the MFN2 gene.[10] MFN2 gene is located near the KIF1Bβ gene which has been associated with CMT2A in a single Japanese family. As stated above, MPZ and NEFL mutations can also cause AD CMT2 and should be screened after MFN2.

Other causes of AD CMT2 are rare. RAB7 mutations cause a neuropathy with prominent sensory involvement, ulcerations, osteomyelitis and amputations whereas GARS mutations are associated with a neuropathy which is predominantly upper limb and motor (Table 1).

Table 2: Hereditary sensory and autonomic neuropathy: Classification and clinical features.

Type	Inheritance	Gene/Locus	Phenotype
HSANI	*AD*	*SPTCL1*	*Mainly sensory with complications and pain, with occasional motor problems early on*
CMT2B	*AD*	*RAB7*	*Sensorimotor but more sensory than normally seen with CMT*
HSAN 1	*AD*	*3p24-p22*	*Sensory, cough, gastroesophageal reflux*
HSAN II	*AR*	*HSN2*	*Severe sensory complications with mutilations, onset in the first 2 decades of life*
HSAN III	*AR*	*IKBKAP*	*Familial dysautonomia, Riley-Day syndrome, Prominent autonomic features, absence fungiform papillae of the tongue*
HSAN IV	*AR*	*NTRK1*	*Congenital insensitivity to pain with anhidrosis (CIPA), mental retardation, with the unmyelinated fibers being mainly affected*
HSAN V	*AR*	*NTRK1*	*Congenital insensitivity to pain with mild anhidrosis, no mental retardation, with the small myelinated fibers being mainly affected*
HSAN V	*AR*	*NGFβ*	*Congenital insensitivity to pain, minimal autonomic involvement, no mental retardation, mainly unmyelinated fibers affected*
Channelopathy associated insensitivity to pain	*AR*	*SCN9A*	*Congenital insensitivity to pain*

AD = autosomal dominant; AR = autosomal recessive; SPLTC1 = Serine palmitoyltransferase, long chain base subunit-1; RAB 7 = RAS-associated protein RAB7; HSN2 = HSN2 gene; IKBKAP = IκB kinase complex-associated protein; NTRK1 = neurotrophic tyrosine kinase, receptor type 1; NGFβ = nerve growth factor beta polypeptide, SCN9A = sodium channel voltage gated type IX alpha-subunit.

Table 3: Distal hereditary motor neuropathy: Classification and clinical features.

Type	Inheritance	Gene/Locus	Specific phenotype
dHMNI	*AD*	*Unknown*	*Juvenile onset dHMN*
dHMNII	*AD*	*HSP27*	*Adult onset dHMN/CMT2F*
dHMNII	*AD*	*HSP22*	*Adult onset dHMN/CMT2L*
dHMNIII	*AR*	*11q13*	*Early onset, slowly progressive*
dHMNIV	*AR*	*11q13*	*Juvenile onset, diaphragmatic involvement*
dHMNV	*AD*	*GARS*	*Upper limb onset, slowly progressive/CMT2D*
dHMNV	*AD*	*BSLC2*	*Upper limb onset/ sometimes lower limb spasticity (Silver syndrome)*
dHMNVI	*AR*	*IGHMBP2*	*Spinal muscular atrophy with respiratory distress (SMARD1), infantile onset*
dHMNVII	*AD*	*2q14*	*Adult onset, vocal cord paralysis*
dHMNVII	*AD*	*DCTN1*	*Adult onset, vocal cord paralysis, facial weakness*
dHMN/ALS4	*AD*	*SETX*	*Early onset, pyramidal signs*
dHMN-J	*AR*	*9p21.1-p12*	*Juvenile onset, pyramidal features, Jerash*

AD = autosomal dominant; AR = autosomal recessive; HSP 27 = heat shock 27kDa protein 1; HSP 22 = heat shock 22kDa protein 8; GARS = glycyl-tRNA synthetase; BSCL2 = Berardinelli-Seip congenital lipodystrophy gene; IGHMBP2 = immunoglobulin mu binding protein 2; DCTN1 = dynactin; SETX = senataxin

Autosomal Recessive CMT

AR CMT is less common than AD CMT, accounting for less than 10% of CMT cases in a typical northern European population. In certain ethnic groups, particularly with high rates of consanguinity, the prevalence of AR CMT is 40% of all cases of CMT.[11] Ten causative genes so far have been described for the demyelinating forms of autosomal recessive CMT, AR CMT1 (called CMT4 in many classifications), including mutations in PMP22, MPZ and EGR2 genes (Table 1). These are usually severe, early-onset disorders with moderate to severely slow motor conduction velocities. They usually have a progressive clinical course often with proximal muscle involvement. Particular genes are associated with certain clinical features or specific ethnic groups (Table 1). CMT4A, secondary to GDAP1 mutations, accounts for 25% of cases of AR CMT. GDAP1 mutations can either cause AR CMT1 or AR CMT2 and can be associated with diaphragmatic and vocal cord involvement.

Mutations in the genes encoding MTMR2 and MTMR13 cause CMT4B1 and CMT4B2 respectively, demyelinating neuropathies characterised pathologically by focally folded myelin. Other genes associated with CMT4 are periaxin and KIAA1985 (Table 1), the latter is associated with early onset of scoliosis.

Two forms of CMT4 have been reported only in gypsy communities in Europe: CMT4D due to mutations in the NDRG1 gene and a demyelinating neuropathy with cataracts and facial dysmorphism (CCFDN) due to CTDP1 mutations.

AR CMT2 is rare and only two causative genes have been identified, GDAP1 and Lamin A/C (LMNA). LMNA mutations cause a severe axonal neuropathy with proximal muscle involvement.

Dominant intermediate CMT

A 'classical CMT phenotype' characterised by intermediate nerve conduction velocities and histological evidence of both axonal and demyelinating features[12] has been described for which two causative genes have been identified to date, DNM2 and YARS (Table 1).

Hereditary sensory and autonomic neuropathies (HSAN)

HSAN is less common than CMT, comprising a group of five heterogeneous disorders characterised by variable sensory and autonomic dysfunction. Many of the causative genes have now been identified.[13,14] They can be inherited as an autosomal dominant or recessive trait. Clinical features are detailed in Table 2.

Distal hereditary motor neuropathies (DHMN)

Patients with distal HMN present with a classical 'CMT phenotype' without sensory involvement. Clinically it is difficult to distinguish distal HMN from CMT, but neurophysiology is crucial, confirming the normal sensory function. Distal HMNs were previously subdivided into seven types based on clinical features, age of onset and inheritance, but the identification of causative genes has revealed

greater heterogeneity within these groups. Genotype / phenotype details are given in Table 3 and it can be seen that three of the causative genes also cause AD CMT2 (GARS, HSP 22 and HSP 27).

Hereditary Neuralgic Amyotrophy (HNA)

HNA is an autosomal dominant disorder causing recurrent episodes of painful brachial plexopathy due to mutations in Septin 9 gene.[15] Each individual episode is clinically indistinguishable from sporadic neuralgic amyotrophy.

Conclusions

The hereditary neuropathies are the commonest inherited neurological diseases and are a significant cause of disability in the population. In the last 15 years there have been major advances in the understanding of the genetic causes of this heterogeneous group of conditions. Many of the genes are now known and the commoner genes are widely available as diagnostic tests (chromosome 17 duplication, PMP-22, CX32, MPZ, Mitofusin 2 and GDAP1 mutations). Genetic testing can be used for diagnostic, predictive or ante-natal screening. Although currently knowledge of the genetic cause of a hereditary neuropathy does not lead to a specific treatment, it can help give the patient an accurate prognosis. Many patients find it very useful to have a genetic diagnosis despite the lack of treatment options. A genetic diagnosis can prevent unnecessary tests such as nerve biopsies, especially in children, and can also prevent trials of potentially dangerous immunosuppressive treatments when a diagnosis of an inflammatory neuropathy is being considered (e.g. patients with connexin 32 mutations have occasionally being diagnosed as having chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)).

The era of potential therapies for CMT has arrived with the first large scale trials now happening for the commonest subtype, CMT1A secondary to the chromosome 17 duplication (trials of high dose ascorbic acid, which has been shown to be useful in an animal model). However, genetic counselling, appropriate physiotherapy, expert orthotic advice, orthopaedic intervention when necessary and other symptomatic interventions including pain relief still remain the cornerstones of current management. Many patients benefit from being under the care of a dedicated multidisciplinary team.

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Peripheral Nerve Sheath Tumours: what can we learn from genetic syndromes?

This article provides an overview of peripheral nerve sheath tumours (PNSTs), focusing particularly on the settings in which they occur, their pathology, and underlying genetic basis.

Developmental background

During very early development, a process known as neurulation forms the neural tube. From the posterior aspect of this tube, the neural crest is formed, which maintains its neuroectodermal origin but migrates along segmental paths to form the peripheral nervous system and related structures (including, for example, melanocytes). Within the neural crest population are sensory ganglion neurons that will reach their peripheral targets then send out axons back to synapse with the CNS, and Schwann cells (peripheral glia). Schwann cells differ from CNS glia in three main ways. One Schwann cell myelinates only one axon, while oligodendrocytes myelinate many axons. They contain a different type of myelin, including for example 'protein 0' as opposed to the 'myelin basic protein' of CNS glia; and Schwann cells support axon regrowth, whereas myelin from oligodendrocytes has been shown to inhibit axon regeneration.

What is a peripheral nerve sheath tumour?

A PNST is a tumour composed of cells resembling peripheral nerve sheath elements, primarily Schwann cells, but also perineurial cells and fibroblasts. Most of these tumours are benign and are either schwannomas or neurofibromas.[1,2] These two tumours are distinct entities with varying clinical pictures, different genetic backgrounds, and contrasting prognoses. While schwannomas are almost always benign in nature, a subtype of neurofibroma is prone to malignant transformation. The vast majority of benign PNST represent sporadic tumours, occurring as single lesions. Neurofibromas and schwannomas also commonly occur within the clinical spectrum of neurofibromatosis type 1 and 2 (NF1 and NF2), respectively. Among the malignant PNSTs (MPNSTs), half occur sporadically and half are linked to NF1. They account for 5% of malignant soft tissue tumours and 10% of tumours have been reported to occur at sites of previous irradiation. This has implications for treatment of incompletely resected neurofibromas in patients with NF1.

Clinical Features of PNSTs

Sporadic neurofibromas usually present as painless, either intraneural or extraneural masses. They occur in 5 different locations (see Table 1). In contrast to schwannomas, they are almost never associated with cranial nerves. Sporadic schwannomas arise from spinal and cranial nerves, also peripheral nerves in the head and neck, and extensor aspects of the extremities. Commonly the VIIIth (vestibular/acoustic) cranial nerve, or occasionally the Vth cranial nerve is affected. Vestibular (acoustic) schwannomas are commonly known as neuromas, but this is a misnomer as they are tumours of Schwann cells, not neurons. Depending on the location, the symptoms may vary and include hearing difficulties and facial paraesthesias from vestibular schwannomas, or pain and other symptoms from spinal nerve/cord compression. MPNSTs usually present as progressively enlarging masses, often in the extremities, or in a spinal location where they commonly present with pain.

Table 1: Neurofibromas occur in five different locations.

• *cutaneous nodule (most common)*
• *circumscribed mass in a peripheral nerve*
• *plexiform enlargement of a major nerve trunk (plexiform neurofibroma)*
• *diffuse but localised involvement of skin and subcutaneous tissue*
• *extensive involvement of soft tissue of a body area (localised gigantism)*

Pathology of PNSTs

Both schwannomas and neurofibromas are benign tumours that by definition are WHO grade I, and thought to arise from mutated Schwann cells. Macroscopically, schwannomas are said to exist as a single mass with peripheral nerve stretched along one aspect, whereas a neurofibroma expands the nerve fascicle and therefore has numerous axons running through it (see Figure 1). Many of the tumour cells stain with antibodies to S-100, which simply reflects their neuroectodermal origin. On closer inspection, these two tumours have many other differences.

Neurofibromas demonstrate uniform histological appearances, featuring a mixture of scattered cell types including neoplastic Schwann cells, perineurial-like cells and fibroblasts, in a matrix of mucoid substances and scattered collagen fibres, typically giving a 'shredded carrots' appearance (Figure 1). Mitotic activity is low.

Schwannomas are usually biphasic in appearance with cellular 'Antoni A' and hypocellular 'Antoni B' areas, palisaded nuclear arrangements into 'Verocay bodies' and a low mitotic rate. Rarer variants include the cellular schwannoma with a higher reported proliferation rate, and others.

Malignant PNSTs

MPNSTs are relatively rare, clinically aggressive and morphologically variable, with a tendency towards divergent mesenchymal differentiation. As these tumours often arise from a precursor lesion (plexiform neurofibroma) they are also thought to be Schwann cell-derived. They classically have densely cellular fascicles, a high mitotic rate and

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Table 2: A Comparison of NF1 and NF2.

	NF1	*NF2*
Frequency of disease	*Approx. 1 in 3000*	*Approx. 1 in 40 000*
Genetics	*AD*	*AD*
Mutated protein	*Neurofibromin chr17q11*	*Merlin/Schwannomin chr22q12*
Classical PNST features	*Neurofibromas, either multiple, or a single plexiform lesion*	*Schwannomas, typically of vestibular nerve, and classically bilateral*
Propensity for malignant transformation	*5% of plexiform neurofibromas; 50% of MPNSTs are linked to NF1*	*Schwannomas may very rarely undergo malignant transformation.*
Other possible Neurological features	*Sphenoid wing dysplasia, Macrocephaly, Epilepsy, Glial tumours (optic nerve)*	*Meningiomas Glial tumours*
Other clinical features	*Café au lait spots, Axillary freckling, Sarcomas, Lisch nodules in iris*	*Posterior subcapsular lens opacity, Cerebral calcification*

AD = autosomal dominant

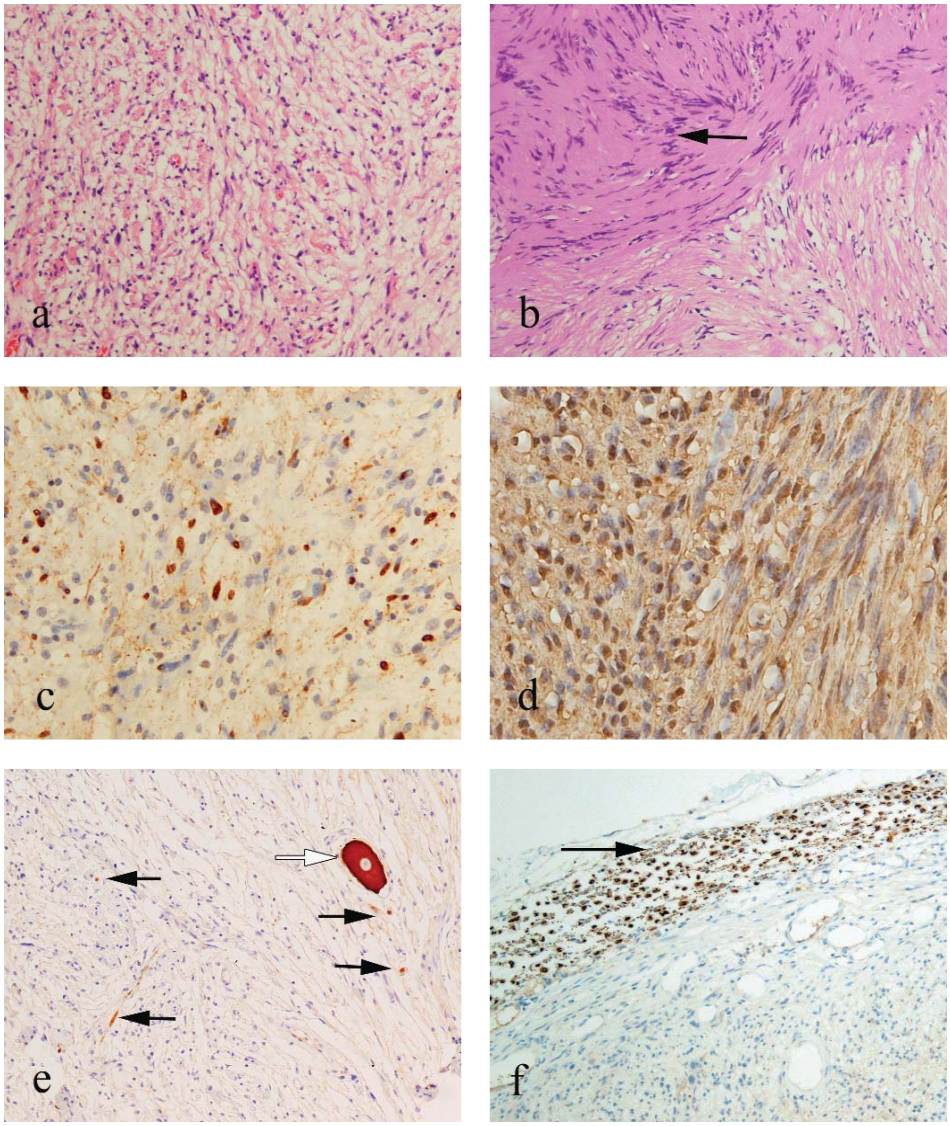

Figure 1: Comparison of typical histological features of neurofibroma (pictures on the left), versus schwannoma (on the right).

a- Haphazardly arranged cells with wavy nuclei, including neoplastic Schwann cells, perineurial-like cells and fibroblasts on a background of mucoid material and strands of collagen, H&E

b- Biphasic architecture of a schwannoma with compact Antoni A pattern featuring Verocay bodies (arrow), and loosely textured Antoni B tissue (bottom right), H&E

c- Neurofibroma showing S-100 reactivity in neoplastic Schwann cells only

d- Schwannoma showing more widespread S-100 immunopositivity.

e- Neurofibromas grow within nerves, trapping both axons (black arrows) and an occasional ganglion cell (white arrow), (neurofilament protein, NFP, immunohistochemistry).

f- Schwannomas displace the nerve containing NFP-positive axons (arrow) towards the periphery.

necrotic areas. Immunohistochemically, the majority (50-70%) of tumours express S-100, but this is only seen in scattered neoplastic cells. A minority of cases demonstrate unusual histological features such as epithelioid morphology (epithelioid MPNST) and divergent differentiation (glandular MPNST, malignant Triton tumour). The WHO classification of tumours assigns a grade III or IV to this neoplasm and its variants. The differential diagnosis for a malignant PNST is wide, including cellular schwannoma/neurofibroma, sarcoma, and, in a gastrointestinal location, gastrointestinal stromal tumour (GIST) or gastrointestinal autonomic nerve tumour (GANT).

Investigations

Depending on the site of the lesion and the overall clinical picture; dermatological, neurological, radiological, pathological and genetic investigations may be necessary.[3] Bilateral vestibular schwannomas are pathognomonic for NF2 (Figure 2), and a number of dermatological lesions are characteristic of NF1 (see Table 2). In both NF1 and NF2, approximately half of all cases are due to newly acquired germline mutations, and there is no family history; however the genetics are largely understood and testing can be performed.

Neurofibromas and NF1

Although any subtype of neurofibroma may be seen, the cutaneous and plexiform types are characteristic of NF1. Within the diagnostic criteria for NF1[4], a patient has two or more neurofibromas of any type or one plexiform neurofibroma. Although mostly histologically benign, many neurofibromas will grow throughout life and may cause severe disfigurement, sometimes impairing vital functions. Plexiform neurofibromas have an approximate 5% risk of malignant transformation.

Schwannomas and NF2

NF2 associated vestibular schwannomas tend to differ from sporadic schwannomas by way of their early age of presentation, lobulation and classical eventual bilaterality. They show similar clinical presentations to sporadic schwannomas, namely hearing difficulties, or spinal symptoms. Apart from the common type, the variant of plexiform schwannoma is typically seen in NF2. Recently, the diagnostic criteria for NF2 have been revised: while the original criteria for NF2 required a family history of the disease or bilateral vestibular schwannomas,[5] the current diagnostic criteria are based on the facts that other lesions often precede vestibular schwannomas, and that a family history is lacking in 50% of cases.[6]

Schwannomatosis

Schwannomatosis is a recently recognised third major form of neurofibromatosis that causes multiple schwannomas without vestibular schwannomas.[7] Patients with schwannomatosis represent 2.4 to 5% of all patients requiring schwannoma resection and approximately one third of patients with schwannomatosis have tumours limited to a single limb or segment of spine. Epidemiologic studies suggest that schwannomatosis is as common as NF2, but that familial occurrence is rare. Patients with schwannomatosis present with pain which remains the primary clinical problem and indication for surgery. Revised diagnostic criteria have recently been published.[8]

Genetic background

Neurofibromas

The NF1 gene encodes the protein neurofibromin, which is highly expressed in the nervous system. It reduces cell proliferation via both the inactivation of the proto-oncogene p21/Ras, and the control of a kinase (serine/threonine kinase mTOR).[9]

Both sporadic and NF1-associated neurofibromas have been shown to harbour mutations in the NF1 gene or carry deletions affecting the gene.[10] There is no hot-spot mutation in the gene, and numerous mutations have been identified. Interestingly, significant differences in gene expression were found between dermal and plexiform neurofibromas.[11]

Schwannomas

Mutations in the NF2 gene are implicated in the formation of sporadic and NF2-linked schwannomas. In most cases, loss of the remaining wild-type allele of the gene on chromosome 22 is associated with the NF2 mutation (akin to Knudson's two-hit hypothesis[12]). Loss of the NF2 protein merlin/schwannomin appears to be the majority feature of schwannomas, strongly suggesting this as a critical event in schwannoma formation. Merlin is linked to the actin cytoskeleton and has several functions, including inhibition of proliferation.[13] Similar to NF1, the NF2 gene has not demonstrated hot-spot mutations, and sporadic lesions cannot be genetically differentiated from NF2-linked cases.

Familial Schwannomatosis

This is not linked to NF2 mutations but has recently been reported to be associated with germline mutations of INI1/SMARCB1.[14,15]

MPNST

The mutations seen in NF1-associated benign neurofibromas are also seen in MPNSTs in patients with NF1. Sporadic MPNSTs also have NF1 gene mutations, probably due to their origin. Genetic events implicated in malignant transformation from neurofibroma to MPNST include mutations of p53 and CDKN2A, genes which are involved in cell cycle control. Unlike other sarcomas, no specific chromosomal changes have been demonstrated. Recently, expression array studies have revealed differentially regulated genes ('signatures') for MPNST versus neurofibromas, but again no differences between those that were sporadic and those that were linked to NF1.[11,16]

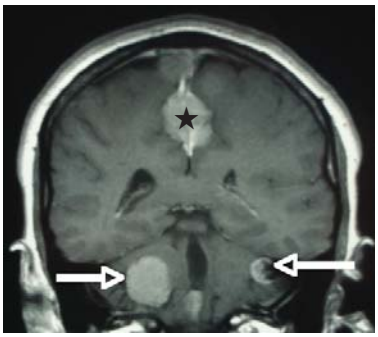

Figure 2: T1- weighted, contrast-enhanced MRI showing coronal section of brain (hemispheres, cerebellum/brain stem). The two arrowed lesions are bilateral vestibular schwannomas. A parasaggital meningioma (star) is also seen. This combination is characteristic of NF2 (picture kindly provided by Mr JR Pollock, Consultant Neurosurgeon, Queen's Hospital).

Summary

Peripheral nerve sheath tumours are common, mostly benign and usually sporadic tumours with considerable clinical significance due to their association with the neurofibromatoses (NF1, NF2 and the more recently recognised familial schwannomatosis). The most frequent PNSTs are schwannomas and neurofibromas, the latter of which can show malignant transformation (plexiform subtype). Malignant PNSTs are strongly linked to NF1 (50%). The genetic background of PNSTs is largely known, and while genetic testing is possible for all neurofibromatoses, the specific clinical presentation of neurofibromatosis 1 or 2, or even schwannomatosis, is often pathognomonic. Diagnostic criteria for NF2 and schwannomatosis have recently been revised.

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Pathologic Staging of Huntington Disease

The late Dr Edward Pierson Richardson Jr, and Jean Paul Vonsattel, MD.

The grading system or pathologic staging applies to the postmortem categorisation of brains from individuals who carried the clinical diagnosis of Huntington disease (HD). The development of this grading system is the result of a widespread collaboration. It included the participations of families, clinicians, pathologists, and neuroscientists. This grading system stages the extent of striatal changes and is widely used as a research tool. The hallmark of HD is the gradual atrophy of the striatum, which is the only site where neuronal loss is associated with 'active' reactive, fibrillary astrocytosis. The degeneration has an ordered, topographic distribution. The tail of the caudate nucleus shows more degeneration than the body, which in turn is more involved than the head. Similarly, the caudal portion of the putamen is more degenerated than the rostral portion, and the dorsal regions are more involved than the ventral ones. Most investigations using HD postmortem brain samples since 1985, when the findings were published, include a correlation between results and grade or neuropathologic severity.[1] I discuss here how this grading system was developed, and how it happened that I had the opportunity to participate in its crystallisation.

My training in neuropathology started in 1978, in the 'Division Autonome de Neuropathologie' in Lausanne, Switzerland. The late Dr Theodore Rabinowicz, then director of the Division, encouraged me to join the Massachusetts General Hospital (MGH) in Boston to expand my professional experience. The late Dr Edward Pierson Richardson Jr was then the director of the laboratory of neuropathology at the MGH. In February 1981, I joined Dr Richardson's team. From the outset, Dr Richardson's scientific rigour and dedication profoundly impressed me.

In 1978, Harvard University had recruited Dr Edward Denis Bird to establish what is now known as the Harvard Brain Tissue Resource Center (or BTRC, as it was then called). The BTRC was not fully functional during its construction. Nonetheless, brains were collected for research. Each brain obtained was sectioned fresh sagittally through the corpus callosum. One-half was frozen en bloc as soon as possible after death, and stored at -80°C. The contralateral half was immersed in formalin and kept in storage until the logistics were in place for performing the neuropathological evaluation. Thus, fixed, half-brains accumulated. Each one was to be thoroughly evaluated to reach the best diagnostic categorisation through a rigorous clinicopathological correlation. Unless indicated otherwise by the clinical history, it was assumed that the changes observed in the fixed half-brain would be representative of the changes involving the frozen contralateral half. The frozen brains in storage were not eligible for disbursements to investigators, as definite diagnoses were not assigned to them. In June 1981, while Dr Richardson and I were evaluating surgical specimens microscopically at the MGH, Dr Bird brought a set of histology slides. He was anxious to find out whether the histology sections exhibited the changes confirming the clinical diagnosis, which would determine whether a request of tissue samples for research could be fulfilled. Kindly, Dr Richardson provided Dr Bird the response he sought. This event triggered the fruitful collaboration between Dr Bird, Dr Richardson, and me that led to the neuropathological staging of HD.

My doubt about the value of the effort increased when a senior scientist from whom I sought advice stated: "Once you've seen one HD brain, you've seen them all"

In the meantime, up to 80 formalin-fixed half-brains, including more or less 65 that were from individuals who carried the clinical diagnosis of HD, had to be evaluated neuropathologically. Dr Richardson suggested that I perform the examination of these brains under his supervision. At first, I hesitated, especially given the number of brains involved and my conviction to return to Switzerland within the next six months. My doubt about the value of the effort increased when a senior scientist from whom I sought advice stated: "Once you've seen one HD brain, you've seen them all." That the brunt of the degenerative process was allegedly confined to the striatum further contributed to my indecision. However, I realised that evaluating these brains would afford the opportunity to work closely with Dr Richardson, whose extraordinary personality I gradually became aware of. Together, we designed a plan for performing the macroscopic and microscopic examinations of these brains. We employed a standardised protocol whereby each fixed half-brain would be sectioned, using external landmarks, to optimise the comparison between brains. Up to ten half-brains were sectioned during one session, each yielding 30 or more coronal slices from the cerebral hemisphere alone. Among them, four were selected for the ultimate comparisons. They were aligned on a table: a row per brain, and a column per the landmark specific to each one of the four slices. The landmarks included the nucleus accumbens, the anterior commissure, the subthalamic nucleus, and the lateral geniculate body. That most of the brains were from HD patients influenced our perception of their abnormalities. It was puzzling that among them, and despite the clinical data, were brains with apparently normal striatum on gross examination, which includes the caudate nucleus, putamen (together forming the neostriatum), and the globus pallidus. However, under the microscope, changes were detected. Initially fourteen, later eighteen, defined sites were selected for harvesting blocks to be processed for microscopic evaluation. These blocks were obtained from each of the fixed half-brains available to facilitate comparisons among brains from the same or different disease processes, and from controls. To secure diagnostic accuracy, additional blocks were harvested as per the findings during the macroscopic evaluation.

Prof Jean Paul Vonsattel is Professor of Pathology at the Presbyterian Hospital and is the Director of the New York Brain Bank of Columbia University, New York, NY. He received his MD from the Medical School of Lausanne, Switzerland, and trained in Pathology and Neuropathology in Lausanne, and Harvard. His field of interest focuses on the neuropathology of neurodegenerative diseases.

Correspondence to:
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Columbia University,
Children's Hospital,
Tunnel T8 3959 Broadway
New York, NY, 10032.

The second series of 10 brains of the backlog, which were processed macroscopically, included one from an HD patient who had committed suicide, and whose father had died of the disease. On gross examination of the coronal slices, the rostral part of the neostriatum appeared normal. However, the body of the caudate nucleus was half the expected thickness, and the tail was barely distinguishable. The globus pallidus was unremarkable. Microscopic examination revealed neuronal loss and gliosis involving the dorso-paraventricular region of the head of the caudate nucleus, the nearby caudo-putaminal gray bridges, and the dorsal third of the putamen, although no volume loss was noticeable on gross examination. Furthermore, subtotal neuronal loss involved the tail of the caudate nucleus and, to a lesser extent, the body. Evidently, this brain displayed changes involving the neostriatum that were detectable in the early stage of the illness. Thus, the question was raised whether this gradient of neuronal loss and gliosis reflected the temporo-spatial, selective vulnerability of the HD striatum. Our interpretation of the findings was that the dorsal third of the rostral neostriatum is especially prone to degenerate in contrast to the relatively preserved ventral third including the nucleus accumbens. That the transition third exhibited the microscopic features of its two flanked zones supported the claim. Thus, within the degenerated part, reactive astrocytes were the predominant cells, while neurons were virtually absent. In contrast, the relatively preserved area displayed the normally expected cellular population, and was distinguishable from the intercalated zone, in which a mixture of apparently normal or degenerating neurons and reactive astrocytes were identifiable. The initial awareness of the regional heterogeneity of the cellular population of the neostriatum at different periods of the toxic process needed to be confirmed. The serial processing of a pool of brains from carefully categorised HD patients according to a strictly applied protocol did indeed allow reliable comparison of changes at different stages of the same disease.[2] Concomitant to these evolving observations, a group of basic scientists including Dr Nancy Wexler, James Gusella, and Marcy MacDonald were deeply involved in the search for the gene causing HD. Close interaction with members of the group contributed to the consolidation and improvement of the grading system, which has 5 grades (0-4) of severity of striatal involvement. The awareness of the dynamic research on HD steadily increased the donation of brains, which was coordinated by Tom Stevens, among others. Thus, the spectrum of the disease became gradually evident and was critically and constructively verified and improved by collaborators such as Drs. Robert Ferrante, Marian DiFiglia, and Tessa Hedley-Whyte. Dr Eric Myers assessed the hereditary and clinical features pertaining to the brains evaluated, and analysed the correlations between them and the grade assigned to the brains.[3] When the candidate genes became available long before the actual gene was identified, the samples that were most suitable for the tests were those from patients whose anterior neostriatum (e.g., at the level of the nucleus accumbens) was moderately involved. Indeed, these samples displayed within the same section the three previously mentioned zones of the neostriatum: one that was gliotic and devoid of neurons dorsally; an intermediary one less involved than the dorsal one; and the relatively preserved nucleus accumbens, which provided a kind of internal control.

The widely used grading system has helped to identify the earliest histopathological and biochemical changes in HD. For example, the analysis of low-grade HD striatum showed that immunoreactive encephalin-containing neurons projecting to the external segment of the globus pallidus were more affected than the substance P-containing neurons projecting to the internal segment. It established that the striatal degeneration in HD appears to move simultaneously in a caudo-rostral direction and in a dorso-ventral/medio-lateral direction.

References

1. Vonsattel J-P, Myers RH, Stevens TJ et al. *Neuropathological classification of Huntington's disease.* Journal of Neuropathology and Experimental Neurology. 1985;44:559-77.
2. Vonsattel J-PG, DiFiglia M. *Huntington disease.* Journal of Neuropathology and Experimental Neurology. 1998;57:369-84.
3. Myers RH, Vonsattel JP, Stevens TJ et al. *Clinical and neuropathologic assessment of severity in Huntington's disease.* Neurology. 1988;38:341-7.

Conference Report

Primary Care Neurology Society Meeting

Birmingham, UK, 17 May, 2007.

The Primary Care Neurology Society (P-CNS; www.p-cns.org.uk) seeks to develop links between primary and secondary care in order to optimise the care and management of patients with neurological disorders. A select audience (GPs and specialist nurses vastly outnumbering neurologists) converged on the Birmingham Hippodrome to hear presentations on a variety of topics of mutual interest and concern, including dementia, stroke and TIA, Parkinson's disease, epilepsy and headache.

A number of talks focused on how much GPs can and/or should do before involving secondary care, particularly in light of NICE or expert guidelines; for example whether or not to give a trial of medication in suspected Parkinson's disease prior to the recommended referral to an 'expert' for diagnosis (Paul Morrish), or diagnosing dementia and using the dreaded 'D' word (Louise Robinson). A study suggesting an average four year delay from first GP-recorded symptoms of dementia to actual diagnosis (Fam Pract 2007;24:108-16) may reflect, at least in part, diagnostic and therapeutic nihilism in this area, although with the latest (2006) NICE guidance on cholinesterase inhibitor use (and non-use) such reticence may not necessarily seem inappropriate. Interestingly, an absolute criterion for referral to the speaker's clinic was GP performance of the MMSE, whereas we have found that less than 20% of referrals to a dedicated Cognitive Function Clinic report this as having been done. There was no firm guidance to GPs on the best screening or assessment tool for dementia, the MMSE being described as "the best of a bad lot". P-CNS would seem ideally placed to investigate this further, and provide advice. On the other hand, it might perhaps be seen as odd that the subject of dementia should be on the conference agenda when NICE/SCIE guidance essentially envisages no role for neurology in the diagnosis and management of this condition, despite its being the archetypal disease of higher brain function.

In a discussion on TIA/stroke (Ganesh Subramanian) it was suggested that any cerebrovascular neurological event lasting longer than one hour, rather than the current twenty-four hours, should be regarded as a stroke rather than TIA, and the ABCD2 risk stratification for TIA was promoted for wider use. Practical advice was on hand for the management of difficult problems, including neuropathic pain (Chris Wells), for which codeine is apparently worse than placebo. Delegates were urged to consider the possibility of a neuropathic component to many chronic pain syndromes, including low back pain, with the therapeutic options that this may open up. The recognition of epilepsy syndromes was covered (Richard Hills) with the aid of illustrative video-EEGs, but some eyebrows were raised when the findings of the recently published SANAD trial (see ACNR 7(2): 39-40) were called into question on methodological grounds. A talk on the diagnosis and management of headache (Andrew Dowson) prompted lively debate. The need to recognise concurrent anxiety, depression, and social phobias which may drive the illness behaviour in chronic headache was emphasised, a point also relevant to neuropathic pain.

The need for a collaborative approach between neurologists and GPs is self-evident and will hopefully engage more practitioners, especially neurologists, in future P-CNS meetings.

CAH Fisher, Marches Surgery, Leominster
AJ Larner, WCNN, Liverpool, UK.

1st London Colloquium on Status Epilepticus

London, UK, 12-14 April, 2007.

I was looking forward to three packed days of presentations on status epilepticus – a condition that causes much clinical angst – and it was a rewarding meeting. It seems to me that beyond travelling to an interesting destination for a few days, a conference presents itself as a platform for information that might directly impact on the attendees' knowledge and hence practice. But there is a more covert value – putting a person's work into context. How does a given researcher think things through, respond to questions, or to another's work? Subsequently one can read articles differently, the 'between the lines' fills out.

Professor Sloviter started the day on the molecular nature of status epilepticus. He had been asked to be controversial and he rose to the occasion, questioning the applicability of animal models to human temporal lobe epilepsy and arguing for a different kindling paradigm. During the day talks highlighted different aspects of basic science, including neuroreceptors, modifiers of injury such as inflammation, a subject's age and germline or mitochondrial genes. Appropriately the day ended with Professor Meldrum's synopsis of past studies and future horizons.

The next day concerned more clinical aspects. The central theme seemed to be how to define the various manifestations of status –convulsive versus non-convulsive, partial versus generalised, prospectively or following a response to treatment – in order to study its natural history and management. This is a treacherous area as clinical signs do not always give an accurate view, but the patients who are better described clinically and in terms of investigations are not necessarily representative. The paucity of good data on treatments and outcomes needs to be addressed and the studies by Profs Neville and Bleck (amongst others) showed that well designed studies can take us forward.

In the absence of evidence, treatment and management seem to produce the most divergence of opinion. This may be because we all have to act under these circumstances and treat dangerously sick patients; we are influenced by the medical culture we work in – interventionalist or conservative, our personal approach to medicine – heroic or cautious, in the context of our society's view of good medicine – "the more tests and drugs the better!" to 'do you really have to give anything else – can't we wait and see?' Hence in discussions clinicians were often very sure of what they might do under certain circumstances but this may be quite different to what is done by others.

Matthew Walker introduced the topic of neuroprotection and emphasised the 'obvious dichotomy between neuronal damage and epileptogenesis', and subsequent presentations also discussed the circuitry problem and the effects of preconditioning and drug resistance.

Outcomes for cognition and development of epilepsy in adults and children who have been in generalised or non-convulsive status were presented and there was a general feeling that the natural history of status does need further clarification.

A wide range of issues were put before the delegates in poster presentation ranging from basic science to the relational psychiatric treatment of 'status pseudoepilepticus' by way of several interesting clinical series and vignettes. The most frequent theme, no doubt due to its novelty, was of cases where intravenous levetiracetam was given to patients in status.

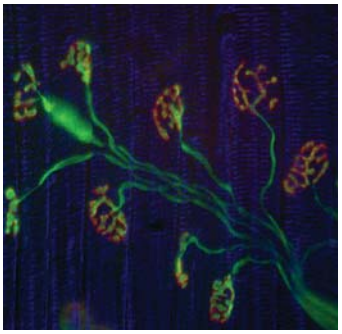
The last talk of the meeting looked at what guidelines exist. It was helpful to consider studies of the utility and uptake of other guidelines prior to the next day's workshop to develop recommendations and options for the treatment of status epilepticus in Europe - a report of which will follow.

The first London Colloquium on Status Epilepticus was everything one could want in a conference – Professor Shorvon's team brought international experts to discuss their understanding and research in a difficult and clinically relevant area. The organisers had asked the first speaker of each section to be controversial and this generated lively discussion. It brought clinicians and bench scientists together. There was time to discuss issues in the breaks and meet new colleagues in the field.

Bridget MacDonald, Consultant Neurologist
Mayday Hospital, Croydon, UK.

PREVIEW: Moving Forward with Motor Neurone Disease: a translational research symposium

The Royal Society of Edinburgh, UK, 29-30 August, 2007.



Motor Neurone Diseases (MND), including amyotrophic lateral sclerosis (ALS) and spinal muscular atrophies (SMA), have variable onset and rate of progression, but are united by motor neurone death, limited efficacy of treatment and an absence of any cure. A coalition of basic scientists and clinicians, based mainly in Edinburgh, involved in studying the biology of motor neurones and/or motor neurone disease formed The Edinburgh Motor Neurone Disease Research Group (EdMoND) in 2006. We held a successful local colloquium in our first year, but for 2007 we have invited key speakers from the clinical and research communities in the UK and USA, as well as from the EdMoND group, to take part in a 2-day Symposium on translational research into MND. The meeting will focus on developing national and international collaborations in order to bring about improved understanding and more effective treatment of MND. The Symposium will bring together those involved in wide-ranging aspects of MND research, with sessions on: cognitive function; roles of neuronal activity and glia in cellular mechanisms of degeneration; motor neurone development and SMA; molecular and cellular biology of ALS; and neuroprotective and regenerative strategies for developing more effective treatments.

The meeting will be held at the Royal Society of Edinburgh and will be fully catered during both days. The venue is in the centre of the historic city of Edinburgh and the meeting occurs towards the end of the Edinburgh International Festival, so why not combine science with culture and join us this August in Edinburgh?

Places are limited to 150 delegates but Registration is only £50, thanks to the generosity of our sponsors. Limited accommodation is available at additional cost. On-line Registration and Abstract submission for the Poster sessions are open now and until 16th July at:
http://www.edinburghneuroscience.ed.ac.uk/MNDmeeting2007

We are extremely grateful to the following for their generous sponsorship of the Symposium: The Scottish Motor Neurone Disease Association, Wyeth Research, Edinburgh Neuroscience, The Anatomical Society, Olympus microscopes, The Scottish Centre for Regenerative Medicine, The Centre for Neuroscience Research, The Motor Neurone Disease Association, The School of Biomedical Sciences, The Physiological Society, Leica Microsystems, and Media Cybernetics.

MS Frontiers

London, UK, 14-15 June, 2007.

MS Frontiers 2007 was the largest MS Society conference for professionals yet, providing collaboration between the MS Societies of the UK, US, Australia and Canada and bringing together experts from across the world to speak on MS research. This year there were over 350 delegates and 35 renowned speakers, providing the opportunity for researchers and healthcare professionals within the multiple sclerosis field to present their latest work, share ideas and identify key challenges for the future. International speakers included Claudia Lucchinetti, Professor of Neurology at the Mayo Clinic in Minnesota, Professor Trevor Kilpatrick, Head of the Centre of Neuroscience at the University of Melbourne, Australia, and Professor Brenda Banwell, Director of the Paediatric Multiple Sclerosis Clinic at the University of Toronto, Canada.

The Inaugural Ian McDonald Memorial Lecture paid tribute to Ian McDonald, who died in December last year but who made a unique and unparalleled contribution to our understanding of MS. Ian McDonald was a true leader in the research field and made important contributions in the areas of genetics, physiology and most recently imaging. With the support of the MS Society, he pioneered the use of magnetic resonance imaging in improving the diagnosis and understanding of MS and importantly, the way in which we can use imaging to improve and speed up clinical trials. It is highly appropriate that his name has been applied to the Keynote Speaker session of the MS Frontiers Conference as a tribute to his lifetime of achievements. This year the Keynote Speaker was Lawrence Steinman, Professor of Neurology at Stanford University who presented work on future therapies for MS. He spoke about two negative regulators, aB Crystallin and PPAR-α, and a positive regulator of autoimmunity, osteopontin, which play key roles in MS. He introduced research about how sex hormones and the fact that women develop more robust immune responses than men, make them much more likely to develop autoimmune conditions such as MS.

An outstanding presentation was given by Brian Weinshenker, Professor of Neurology at the Mayo Clinic on his recent work on Neuromyelitis optica (NMO). In recent years, analysis of the clinical course, pathological features and radiological features of the condition have distinguished it as separate from MS. Brian Weinshenker's discovery of a specific antibody (NMO-IgG) in patients with NMO, but not in patients with MS has opened new avenues for understanding the pathogenesis of NMO, as this is the first instance in which a specific target for an immune reaction resulting in an inflammatory demyelinating disease in humans has been identified. NMO-IgG is now used as a clinical test for NMO and will hopefully provide considerable insight into the pathogenesis of the condition.

Several sessions of the conference focused on the global patterns in the epidemiology of MS and the roles of genes and the environment in the development of the condition. Dr Eli Silber, Consultant Neurologist at Kings College Hospital, London spoke about racial differences and their role in NMO and MS development, as well as presenting evidence of a large latitudinal role in MS development, while Professor Alastair Compston, Head of the Department of Clinical Neurosciences at the University of Cambridge, spoke about discovering candidate genes and new technologies which are allowing discovery of further associations. The conference then turned to The Canadian Collaborative Study on Genetic Susceptibility to MS, which involves 30,000 MS individuals. George Ebers, Professor of Neurology at Oxford University, presented his studies showing how familial recurrence, adoptees, half-sibs, step-sibs, conjugal pairs, parental transmission, intrafamilial migration and familial autoimmunity have allowed more insight into MS susceptibility. He also identified a category of alleles which are protective against MS and may offer the potential for novel treatment targets.

Brian Weinshenker's discovery of a specific antibody (NMO-IgG) in patients with NMO, but not in patients with MS has opened new avenues for understanding the pathogenesis of NMO

Subsequent to the educational trip to India organised by the UK's Multiple Sclerosis Society in conjunction with the MS Society India, Lekha Pandit, Professor of Neurology at the KS Hegde Medical Academy, Derlakatte, India also introduced a session about MS in India and the issues facing the country.

Breakout sessions allowed the delegates to branch off into their preferred specialities, with one session covering rehabilitation, exercise and quality of life for people with MS, while the other detailed current research into models of MS including humanised mice and Professor Robin Franklin's work on stem cells, precursors and myelin repair at the Centre for Myelin Repair in Cambridge.

The conference next turned its attention to the pharmaceutical research and development priorities, with a panel of representatives from companies such a Biogen, GSK, Schering and Genzyme answering questions about their short and long term goals and how they felt partnerships between industry and academia could be improved to provide better products and services for people with MS. They commented on their current clinical trials and were asked about their plans for novel therapeutics for progressive MS.

The final session of the conference found Dr Alasdair Coles, Consultant Neurologist at the University of Cambridge, and ACNR's Co-Editor, giving his thoughts on some of the current and potential treatments for MS and how the risks of taking these treatments were perceived and understood by patients. He summarised his trial data on alemtuzumab (Campath-1H), as well as some other disease modifying agents and focused on the sort of information patients received about treatments, side effects and MS disease course and whether it was possible to individualise MS risk. He ended by urging people to consider the mismatch between the type of data we obtain from trials, which last two to three years, and the knowledge we need about the effect these drugs will have over a lifetime in order to be able to convey accurate risk information to patients. He also questioned who should be responsible for the final decision on which risks are justifiable.

The conference was a huge achievement, encouraging communication, cooperation and collaboration throughout the many disciplines involved in MS research. The conference provided a forum for the best minds in the field to come together to relay information and promote understanding in order to move us closer to discovery of potential treatments for people with MS. Interviews with the scientists and a full conference breakdown are available at http://www.mssociety.org.uk/

Dr Laura Bell, Research Communications Officer, Multiple Sclerosis Society.

PREVIEW: Syringomyelia 2007: 2nd International Symposium on Syringomyelia and Chiari

Rugby, UK, 23-26 October, 2007.

In association with the University Of Birmingham, the Society Of British Neurological Surgeons and the Spine Society of Europe

The last international syringomyelia symposium was held in Kobe Japan 2000. It is with great pleasure that we invite you to the historic town of Rugby, UK, to join a meeting of specialists in the management of syringomyelia, at an international symposium arranged by the Ann Conroy Trust. The event is to be held at the ancient seat of learning and the birthplace of Rugby Football, Rugby School.

The aim of the symposium is to define the present state of understanding of syringomyelia and related disorders, discuss controversies in practice and provide direction for future research.

Keynote speakers include Edward Oldfield (USA), Thomas H Milhorat (USA), Tatsuya Nagashima (Japan), Marek Czosnyka (UK), Graham Flint (UK), Dieter Grob (UK), Ulrich Batzdorf (USA) Jorg Klekamp (Germany), and Clare Rusbridge (UK).

Invited professionals include Neurosurgeons, Paediatric Neurosurgeons, Spinal Injuries Specialists, Neurologists, Spinal Orthopaedic Surgeons, Specialists in Pain Management, Physiologists, Radiologists & Veterinary Specialists.

Human & Veterinary Medicine

Syringomyelia is a condition that affects several mammalian species. This is a unique opportunity for clinicians and scientists from the worlds of human and veterinary medicine to collaborate and exchange knowledge and understanding.

Delegates Social Programme

A full programme offers delegates and accompanying persons the very best of English heritage from the historic heart of England.

Register Now!

For more detailed information please go to www.syringomelia2007.org
Continuing Professional Development approval applied for

Symposium topics will include:

- Historical perspectives
- Hindbrain related syringomyelia
- Post-traumatic syringomyelia
- Mathematical modelling
- Idiopathic syringomyelia
- Tumours
- Scoliosis
- Arachnoiditis
- Tethered cord
- Paediatric aspects
- Genetics
- Epidemiology
- Aetiology
- Pathology
- Psychological aspects
- Nursing aspects
- CSF physiology
- Clinical presentation
- Radiology
- Electrophysiology
- Surgical approaches
- Pain management
- Experimental work
- Rehabilitation
- Medico-legal aspects
- Veterinary aspects
- Patient Perception

Events Diary

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 10 August, 2007

2007

July

Meeting the Challenges of Severe Aphasia
5 July, 2007; Connect, London
E. carolecross@ukconnect.org,
www.ukconnect.org/connectcourses_19_92.aspx

Aime 2007 Workshop: Artificial Intelligence In Functional Neuro-Imaging
8 July, 2007; Amsterdam, The Netherlands
Sennay Ghebreab, E. ghebreab@science.uva.nl

27th International Epilepsy Congress
8-12 July, 2007; Singapore
T. +353 1 205 6720, F. +353 1 205 6156,
E. Singapore@epilepsycongress.org,
www.epilepsysingapore2007.com

The Autistic Spectrum - Insights into Causes, Management and Treatment
10 July, 2007; London, UK
T. 01722 716007, www.mahealthcareevents.co.uk

Neurology Review 2007
10-20 July, 2007; Rome, Italy
T. +1 800 422 0711, F. +1 727 527 3228,
E. sandra@continuingeducation.net

Pain and the Brain
11 July, 2007; Livingston, UK
T/F. 020 8394 0400, www.physiouk.co.uk

3rd Congress of the International Society for Vascular and Cognitive Disorders (VAS-COG)
11-14 July, 2007; San Antonio, USA
http://vas-cog.org/vas-cog2007/index.html

Pain and the Brain
12 July, 2007; Manchester, UK
T/F. 020 8394 0400, www.physiouk.co.uk

7th IBRO World Congress of Neuroscience
12-17 July, 2007; Melbourne, Australia
E. ans@sallyjayconferences.com.au,
www.ans.org.au/anshome.htm

Techniques and Applications of Molecular Biology: A Course for Medical Practitioners
16-19 July, 2007; Coventry, UK
T. 024 7652 3540,
E. Charlotte.Moonan@warwick.ac.uk,
www.warwick.ac.uk/go/bioscienceshortcourses

Olfaction & Neuroscience Symposium
24-25 July, 2007; Wye, Kent
E. jvoliver@semiochemica.org.uk

Translational Research Symposium: Moving Forward with Motor Neurone Disease
29-30 July, 2007; Edinburgh, UK
E. Edinburgh.neuroscience@ed.ac.uk,
www.edinburghneuroscience.ed.ac.uk/MNDmeeting2007.html

25th Annual National Neurotrauma Society Symposium
30 July-1 August, 2007; Kansas City, USA
www.neurotrauma.org/2007/index.htm

August

International Dysarthria Conference: Whats New?
2-3 August, 2007; Sheffield, UK
www.trainingmadeeasy.co.uk/

Social Communication Following Brain Injury
10 August, 2007; Ely, UK
Tel. 01353 652176.

Eurepa Distance learning course on Genetics of epilepsy (III.) (Autumn 2006 to Spring 2007)
15 August, 2007; Application Deadline
Verena Hézser-v.Wehrs
T. +49 521 144 4310,
F. +49 521 144 4311,
E. office@epilepsy-academy.org,
www.epilepsy-academy.org

9th Nordic Meeting In Neuropsychology
19-22 August, 2007; Göteborg, Sweden
E. nordic2007@neuropsykologi.org

Baltic Sea Summer School on Epilepsy
19-23 August, 2007; Lithunia
E. ruta.mameniskiene@yahoo.com,
www.epilepsy-academy.org

13th International Congress of Immunology
21-25 August, 2007; Rio de Janeiro, Brazil
www.immunorio2007.org.br/

11th Congress of the European Federation of Neurological Societies
25-28 August, 2007; Brussels, Belgium
T. +43 1 889 05 03,
F. +43 1 889 05 03 13,
E. headoffice@efns.org

Annual British Association of Cognitive Neuroscience (BACN)
29-31 August, 2007; Dundee, UK
www.dundee.ac.uk/psychology/bacn/welcome.htm

September

MSc Advanced Neuroimaging
1 September, 2007; London, UK
Tel. 020 7837 3611.

The Pharmacological Treatment of Epilepsy, 2nd Eilat International Educational Course
2-9 September, 2007; Eilat, Israel
E. eilatedu@targetconf.comwww.eilat-aeds.com

Epilepsy, Behaviour and Neurology: An integrated approach to childhood epilepsy
4 September, 2007; London, UK
For further information contact Felicity Pool,
T. 01342 831202, E. fpool@ncype.org.uk

World Federation of Sleep Research Societies World Congress
1-8 September, 2007; Cairns, Australia
www.icmsaust.com.au/wfsrs2007

The Pharmacological Treatment of Epilepsy, 2nd Eilat International Educational Course
2-9 September, 2007; Eilat, Israel
F. +972 3 5175155,
E. eilatedu@targetconf.com,
www.eilat-aeds.com

Glial Cells in Health & Disease: VIII European Meeting
4-8 September 2007; London, UK
Laura Milne, T. 0870 143 6981,
F. 020 7808 5620,
E. info@euroglialcell.org,
www.euroglialcell.org

An extended version of this diary is available on our website at http://www.acnr.co.uk/regular.htm

A Royal Society of Medicine Symposium with the Neurocritical Care Special Interest Group of the Association of British Neurologists

Neurocritical care

Date - Monday 15 October 2007
Venue - The Royal Society of Medicine

This meeting aims to present the state of the art in key areas of Neurocritical Care medicine. The topics of this symposium have been carefully selected for their relevance to acute medicine's demands on the neurologist, and are presented by international leaders in the field.

Topics include: • Neuromonitoring in critical care • Management of acute cerebral haemorrhage • Management of refractory status epilecticus • Thrombolysis and reperfusion

Speakers will include:
Professor Stefan Mayer, Columbia University, USA
Professor EelcoWijdicks Mayo, Rochester, USA
Dr Maxwell Damian, UHL, Leicester
Professor Tom Bleck, Chicago, USA

For more information or a booking form, please contact **Bina Arpino** on **0207 290 3946**. You can also book online at www.rsm.ac.uk/diary

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The Medical Genetics Section of the Royal Society of Medicine presents

The Muscular Dystrophies - An International Meeting

Monday 19th November 2007

Venue: Royal Society Of Medicine, London

This meeting on the muscular dystrophies explores the clinical features and genetics of these various disorders including congenital, Duchenne and Becker, limb girdle, distal, facioscapulo-humeral and Emery-Dreifuss forms as well as myotonic dystrophy. There will also be contributions on recent developments in gene therapy and stem-cell therapy.

Trainees in clinical genetics and neurology are especially welcome.

For the full programme and to book online go to www.rsm.ac.uk/genetics
For further information contact
Ruth Cloves
Email: genetics@rsm.ac.uk
Tel: +44 20 7290 2985

The Royal Society of Medicine

MOTOR NEURONE DISEASE ASSOCIATION

Toronto 2007

18th INTERNATIONAL SYMPOSIUM ON ALS/MND

1-3 December 2007
Toronto, Canada

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

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

Moving Forward with Motor Neurone Disease: *a translational research symposium*

EdMoND
Edinburgh Motor Neurone Disease Research Group

29-30th August 2007
at
The Royal Society of Edinburgh, George Street, Edinburgh, UK

The Edinburgh Motor Neurone Disease Research Group is hosting a two-day Symposium on ALS and SMA, aimed at building collaborations between biomedical scientists and clinicians in order to bring about improved understanding and more effective treatment.

Maximum of 150 delegates.
Registration: **£50** including full catering during both days.
Limited accommodation available at additional cost.

Deadline for online registration and poster abstract submission: **16th July**.

For further information and registration, visit:
www.edinburghneuroscience.ed.ac.uk/MNDmeeting2007

Sponsored by : The Scottish Motor Neurone Disease Association, Wyeth Research, Edinburgh Neuroscience, The Anatomical Society, Olympus microscopes, The Scottish Centre for Regenerative Medicine, The Centre for Neuroscience Research, The Motor Neurone Disease Association, The School of Biomedical Sciences, The Physiological Society, Leica Microsystems and Media Cybernetics.

EDITOR'S CHOICE

Myelin and madness

Neuregulin 1 (NRG1) is a growth factor which binds to its receptor, erbB4, and by so doing mediates of its effects on normal development, especially of oligodendrocytes. Interestingly this system has been linked genetically to schizophrenia and bipolar disorders – disorders which some have considered to be neurodevelopmental in origin. In this study Roy et al have used mice in which erbB signalling in oligodendrocytes is blocked by expression of a dominant negative erbB receptor. These mice were then shown to:

a) have alterations in oligodendrocyte morphology, number and function including thickness of myelin sheath, which was less in transgenic mice but with increasing numbers of smaller less branched cells, all of which reduced the conduction velocity of action potentials (at least in the optic nerve anyway);
b) have increased levels of functional dopamine transporters and D1 receptors as evidenced by direct measurement and response to injections of amphetamines;
c) exhibit behavioural alterations suggestive of neuropsychiatric disorders, such as hypoactivity in open field testing, with more time spent in the periphery suggestive of increased anxiety. Furthermore, using a social interaction test they found abnormalities in transgenic mice compared to wildtype.

This all suggests that abnormalities in normal oligodendrocyte development leads to subtle changes in defined neurochemical pathways with behavioural consequences and as such the problem in psychiatric disorders is as much to do with the white matter as anything else. Obviously this paper has focused on NRG1 erbB4 effects on oligodendrocytes and inferred its link to the other abnormalities when of course they may all be primarily affected by an abnormality in this pathway. It does though raise many interesting questions about how different neural elements speak to and affect each other and in particular how oligodendrocytes may instruct the dopaminergic system to behave normally. - ***RAB***

Roy K, Murtie JC, El-Khodor BF, Edgar N, Sardi SP, Hooks BM, Benoit-Marand M, Chen C, Moore H, O'Donnell P, Brunner D, Corfas G.
Loss of erbB signalling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders.
PNAS
2007;104:8131-6.

COGNITION: The Green-eyed monster

★★★ RECOMMENDED

When a colleague does well (gets a grant, merit award, paper published) do you feel pleased or jealous? And if he or she does badly, do you gloat or commiserate? These 'social competitive emotions' have been studied by a group from Haifa, Israel. 48 subjects with focal brain damage and 35 age-matched controls were asked to judge whether a picture showed a face that was envious, gloating or sympathising with a person. The character in question was a little cartoon head called 'Yoni' for no clear reason. He was surrounded by photos of four different young women with various facial expressions. If Yoni smiled, whilst the woman he was looking at was sad, he was said to be gloating; if Yoni was sad when the woman he started at was happy, he was envious; and if Yoni shared the facial expression of the woman, he was identifying with her. The main result was that patients with ventromedial frontal brain damage lost the ability to work out when Yoni was being jealous or gloating, but could spot when he was identifying with the woman. And those with right-sided lesions had more trouble recognising envy, whereas those with bilateral or left-sided damage could not identify gloating. At p values of 0.074 (which ordinary people call non-significant, but this group describe as 'marginally significant') patient with left inferior parietal damage had impaired gloating recognition, but could identify envy easily. The authors says this fits with Davidson's 'valence theory' which seems altogether improbable to me, that the left hemisphere is dominant for 'positive' emotions (in the sense that gloating is pleasurable) whereas the right is dominant for 'negative' emotions. The anatomical details are beside the point. What is remarkable is that the cognitive kits for recognising identification, envy and gloating are different. Should we read any moral 'design' into the fact that empathising seems to be a distributed function, difficult to disrupt, whereas envy, and even more so gloating, require complex intact pathways? ***-AJC***

Shamay-Tsoory SG, Tibi-Elhanany Y, Aharon-Peretz J.
The green-eyed monster and malicious joy: the neuroanatomical bases of envy and gloating (schadenfreude).
BRAIN
2007 Jun;130(Pt 6):1663-78.

REHABILIATION: research of research on efficacy

Those working in the field of brain injury rehabilitation can sometimes feel as if the dominant force in research focuses on the efficacy of the intervention as a whole rather than an analysis of what particular aspects of rehabilitation work and why. Unfortunately as rehabilitation is often perceived as an optional attachment to good medical care rather than a core service, there is an ongoing anxiety on the part of those working in the field of brain injury rehabilitation to prove that what they do 'works' in the same way as a drug for hypertension or a new surgical technique. The variability in type of brain injury, the state of the pre-injured brain and the individual circumstances of the brain-injured individual mean that trying to pin down evidence-based conclusions in this population has proven very difficult. The large meta-analysis illustrates this point very well. As well as looking at the efficacy of inpatient rehabilitation per se, the authors have examined the available research surrounding some of the thorny questions that provoke such debate amongst rehabilitation professionals. When should rehabilitation start? how long should it go on for?, what should its intensity be? and does community or vocational rehabilitation work? Not surprisingly, the authors found that one of the main difficulties in answering these questions comes from the variability in outcome measures adopted by different research groups. In terms of measuring the effectiveness of inpatient rehabilitation, different groups had used the Barthel index, the FIM, the Ranchos Los Amigos level of Cognitive Functioning Scale, Glasgow Outcome Scale, length of hospital stay and return to work. The trials were almost all retrospective or single group intervention and indicated limited evidence for the effectiveness of inpatient rehabilitation, while the one randomised controlled trial demonstrated moderate evidence. The authors rightly state that there is a great variability of the programs and patient populations. This makes meaningful comparisons difficult. As one could probably predict, the other conclusions from the analysis revealed that there was evidence, albeit limited, to support earlier, more intense rehabilitation that continued in the community and was supported by a vocational element. The authors conclude that standardisation of outcome measures would allow more meaningful comparisons between studies. Perhaps more pertinently, however, they speculate that "…further research may well find that optimal timing and duration of rehabilitation is unique to each patient…" - ***LB***

Cullen N, Chundamala J, Bayley M, Jutai J.
The efficacy of acquired brain injury rehabilitation.
BRAIN INJURY
2007 Feb;21(2):113-32.

PARKINSON'S DISEASE: Falling asleep with PD

There has been a great deal of interest in the prevalence, type and cause of sleep disturbance in Parkinson's disease, perhaps triggered by the issues of somnolence with dopamine agonists some 5-10 years ago. Whilst abnormalities of sleep are now recognised and may even precede the onset of Parkinson's disease, the aetiology underlying it is not fully understood, although the role of hypocretin/orexin in this has been an active area of research. It is therefore timely that two papers in Brain have recently reported on the loss of orexin in Parkinson's disease. In both papers the authors demonstrate that there is a loss of orexin neurons in the hypothalamus. In addition Fronczek et al showed that there are Lewy bodies in the hypothalamus and reductions in CSF as well as prefrontal orexin levels, whilst Thannickal et al have shown that the loss of orexin neurons increases with disease progression and is associated with the loss of melanocyte stimulating hormone producing neurons in the hypothalamus as well. This latter population of neurons has also been associated with actions in controlling

the sleep wake cycle. Therefore these two papers both point to pathology in the hypothalamic orexin system in Parkinson's disease and as such a possible explanation for the number of sleep problems in PD. Of course these studies have only shown an association and to prove causality will be a bit more tricky. - ***RAB***

Thannickal TC, Lai Y-Y and Siegel JM.
Hypocretin (orexin) cell loss in Parkinson's disease.
BRAIN.
2007 Jun;130(Pt 6):1586-95.
Fronczek R, Overeem S, Lee SYY, Hegeman IM, van Pelt J, van Duinen SG, Lammers GJ and Swaab DF.
Hypocretin (orexin) loss in Parkinson's disease.
BRAIN
2007 Jun;130(Pt 6):1577-85.

BRAIN INJURY: poor effort on test results and its relation to distress, personality and litigation

The assessment of the cognitive performance of an individual following traumatic brain injury is of fundamental importance in delineating the deficits that may be present and hence planning further rehabilitation and re-integration into society. While certain parameters such as the extent of damage identified on brain imaging, duration of coma and post-traumatic amnesia are all considerations in the prognostication of brain injury survivors, they do not tell the whole story. An assessment of possible deficits through a battery of validated neuropsychological tests is felt to represent a reasonably 'objective' picture of the state of an individual's cognitive performance. This paper examines the effects of poor effort on performance in neuropsychological testing, and how this may be assessed. Of 618 patients attending an emergency department following mild traumatic brain injury, 110 agreed to undergo formal neuropsychological testing 6 months later. The Amsterdam Short Term Memory Test (ASTMT) was used to assess bias or poor effort. This involves reading five noun words aloud and then repeating them to the assessor after a short distraction task. Validation studies have previously demonstrated high average scores for healthy subjects and patients with closed severe head injuries. The other assessments performed included memory, general intelligence, processing speed and attention. Poor performance in these areas was associated with poor effort as determined by the ASTMT. Poor effort was also associated with depressive symptoms, post-traumatic stress, fatigue and reduced motivation. While the authors are clear that these results need to be interpreted with caution, given the relatively low number of participants and the potential bias in symptomatic patients putting themselves forward for evaluation, their findings do provoke an interesting discussion about the robustness of cognitive evaluation methods in brain injured patients. Effort testing may be important in delineating cognitive deficits occurring as a consequence of brain injury and pre-existing issues unrelated to the injury which can affect performance in formal assessments. - ***LB***

Stulemeijer M, Andriessen TM, Brauer JM, Vos PE, Van Der Werf S.
Cognitive performance after mild traumatic brain injury: the impact of poor effort on test results and its relation to distress, personality and litigation.
BRAIN INJURY
2007 Mar;21(3):309-18.

STROKE: Mirror therapy for the – is it the illusion that counts?

★★★ RECOMMENDED

Recently there has been considerable interest in applying mirror therapy to stroke rehabilitation. The interest was sparked by Ramachandran's work with amputees who suffer phantom limb pain. His patients reported that they could move and relax the painful phantom limb by viewing their contralateral limb through a mirror. The mirror was positioned so that the unimpaired limb 'appeared' to occupy the place of their phantom. Since this discovery researchers have tried using the mirror trick to enhance the sensory input relating to stroke patient's efforts to move in the hopes that this would improve motor recovery. Reports of small studies have held promise for mirror therapy in improving movement in paretic arms and hands. Now a randomised controlled trial of 40 patients has reported benefits for leg recovery from using mirror therapy. Sütbeyaz and colleagues treated comparable groups of stroke patients with impoverished lower limb movements with mirror therapy or with a sham treatment. Patients in the intervention group were positioned in a semi reclined sitting position on a bed. A mirror was placed between their legs and perpendicular to the midline and the patient was asked to move both feet in and out of dorsiflexion while watching the image of the unimpaired limb in the mirror. The mirror was reversed in the control sham treated group so that the non-reflecting side was used. Patients practised moving like this for 30 minutes a day, five days a week for four weeks. This intervention was in addition to their normal rehabilitation programme. Significant differences between groups in leg movement recovery and function measured by the FIM were found six months after treatment. This is a remarkable result; differences between groups in rehabilitation trials are not often so long lasting. However it is not clear from the study whether viewing the unimpaired foot through a mirror would be better than viewing actual movements of the affected foot. Both groups were effectively denied sight of the impaired foot because it would have been behind the mirror. A second control group is needed to determine whether the sight of an unimpaired limb superimposed on the place of the affected one is better than the actual sight of the impaired limb itself. What the study does suggest is that visual information about lower limb movements helps their recovery. This is important because very often patients are not positioned so that they can see either of their feet moving. – ***AJT***

Sütbeyaz S, Yavuzer G, Sezer N, Koseoglu BF.
Mirror Therapy Enhances Lower-Extremity Motor Recovery and Motor Functioning After Stroke: A Randomised Controlled Trial.
ARCHIVES PHYSICAL MEDICINE AND REHABILITATION
2007;88:555-9.

COGNITION: Ventrolateral frontal cortex and eye movement control

★★★ RECOMMENDED

The frontal lobes of the cerebral cortex have long been associated with the ability to inhibit stimulus driven actions and this includes eye movements. Indeed in 1985 Guitton et al were the first to examine the performance of frontal lobe damaged patients in antisaccade tasks. In such a task individuals are prompted to execute a saccadic eye movement in the opposite direction to the direction of the stimulus presented to them. However, which point of the prefrontal cortex mediates this effect is not known. In this recent study Hodgson et al addressed this issue using a group of 23 frontal lobe damaged patients who were tested in a rule switching task. All patients had isolated focal lesions rather than multiple infarcts and an age-matched control group of 21 individuals were also studied. 16 out of the 23 patients also completed the pro and antisaccades tasks and eye movements were recorded using a video based pupil tracker and were visualised off line. With the use of a custom software program saccades were identified and artefacts removed.

The rule switching task consisted of three boxes outlined in black on a dark grey background which were presented either in the center or 9 degrees to the right or left of the central fixation spot. A coloured circle was presented in the central box which instructed the individual according to the colour (red/blue) where to look, right or left. For the pro/antisaccades the trials were formed by the initial presentation in the center of the screen of a white spot of 0.5 degrees diameter. After 500msecs the spot was extinguished and then reappeared in either the left or the right response box. For the antisaccades trials individuals were instructed to look to the opposite direction to the target stimulus while for the prosaccadic trials individuals were required to fixate on the target stimulus. Results from this study clearly indicated that damage to the ventrolateral frontal cortex significantly impaired performance in both the oculomotor rule switching task and the standard antisaccades task. In particular, in the case of the rule switching task, patients with left ventrolateral damage had increased contralateral saccade errors in the task but were able to correct these errors in 68% of the trials. On the other hand, patients with right ventrolateral damage were able to correct only 30% of these errors. For the antisaccades task patients with either left or right ventrolateral damage appeared to be equivalently impaired and patients presenting with any other type of frontal damage had increased contralesional errors.

The results from this study support the initial hypothesis that the ventrolateral frontal cortex plays a crucial role in the inhibitory control of action during cognitive tasks as well as having a role in the inhibitory control of the saccadic eye movements. Any damage to this region either in the left or right hemisphere seems to contribute in failures to suppress stimulus-cued saccades in an antisaccades task as well as in the rule switching tasks. Why do patients with a right ventrolateral region seem to significantly fail to correct for response errors? As the authors suggest this could be due to an additional functional specialisation for the monitoring and controlling of behaviour on arbitrary task rules. Could deficits in inhibitory control over saccades have potential consequences for patients in the real world? – ***CA***

Hodgson T, Chamberlain M, Parris B, James M, Gutowski N, Husain M, Kennard C.
The role of the ventrolateral frontal cortex in inhibitory oculomotor control.
BRAIN
2007 Jun;130(Pt 6):1525-37.

Ian McDonald Memorial Lecture

The MS Society has named the Keynote Speaker session of the MS Frontiers Conference 'The Ian McDonald Memorial Lecture.' The Ian McDonald Memorial Lecture pays tribute to the lifetime achievements of Ian McDonald who died in December last year. Ian made a unique and unparalleled contribution to the understanding of MS and was a leader in the research field, making important contributions in the areas of genetics, physiology and most recently imaging.

With the support of the MS Society, he pioneered the use of magnetic resonance imaging in improving the diagnosis and understanding of MS and importantly, the way in which imaging can be used to improve and speed up clinical trials.

This year the Keynote speaker was Lawrence Steinman, Professor of Neurology at Stanford University who presented work on future therapies for MS. He spoke about two negative regulators, aB Crystallin and PPAR-á, and a positive regulator of autoimmunity, osteopontin which play key roles in MS.

Lawrence Steinman receiving a presentation for his talk.

Biogen Idec young investigators travel grants

Biogen Idec, through The European Charcot Foundation, has provided an unrestricted educational grant to sponsor 20 young investigators with a travel grant of €1000 to attend the University Classes in Multiple Sclerosis IV.

Applicants must be active in MS research, and be under 35 years of age. Applications have to be backed up by the Head of Department with a letter of recommendation. Grants will be allocated in order of application. A cheque of €1000 will be handed to the Young Investigators at the end of the University Classes in Multiple Sclerosis IV.

Deadline for applications is October 15th, 2007. Email applications to M Friedrichs, m.friedrichs@charcot-ms.eu

European Federation of Neurological Societies fellowship awards to young neurologists 2007

In 2007, the EFNS offered up to eight fellowships to support young European neurologists to carry out research projects in clinical neurology. The objective is to support young and active neurologists wishing to expand their knowledge in neurology by working on scientific projects, and most of all, to study the practice of neurology in different countries, and thereby also creating new and international connections. Accordingly, the research work must be carried out at a European academic neurological department outside the country of residence.

The duration of the project should ideally be 12 months. The award consists of the net salary in accordance with the salary scale of the host institution up to a max. of €1,600 per month plus travel expenses. Eligible are candidates from European countries up to 35 years of age who are affiliated to a European academic neurological department.

Information on the EFNS Fellowship 2008 will be available on the website soon at www.efns.org

The following persons were awarded the EFNS Fellowship 2007:

- Dr Irene Martinez Torres Valencia, Spain
- Dr Anna-Elisabetta Vaudano, Rome, Italy
- Lavinia Dinia, Genova, Italy
- Juan Nuno Parracho Guerra da Costa, Lisbon, Portugal
- Dr Zoltan Horvath, Szeged, Hungary
- Luigi Romito, Milano, Italy
- Oliver Summ, Münster, Germany

Clearly better light on fluorescence microscopy

A high performance LED light source providing up to ten precise excitation wavelengths ideal for fluorescence microscopy has been launched by Carl Zeiss. Called Colibri, the computer-controllable unit will switch wavelengths in microseconds yet produces no heat or vibration, resulting in high contrast images rich in fine detail. The Colibri is ideally suited to replace metal halide light sources in all fluorescence microscopy applications, particularly in live cell imaging and other work with sensitive living specimens.

The intensity of the narrow-band LEDs (light emitting diodes) can be rapidly and accurately set for any wavelength, either from Zeiss' AxioVision software or directly from the manual controller. This allows users to balance the intensity of multiple excitation wavelengths and capture the result in a single image rather than taking multiple colour images and then attempting to balance the comparative intensities in software. The fine control of intensity also offers maximum protection for specimens and the narrow emission band produces a high signal-to-noise ratio, which is particularly significant for the detection of weak signals and fine details. The reproducibility of the illumination conditions is particularly important in medical diagnostics where documentation is made in accordance with GxP guidelines.

Rather than switching between wavelengths using filters, the different LEDs in Colibri are opto-electronically switched at extremely high speed – an important asset in multi-wavelength and kinetic studies. Also, because no movement is involved, vibration is eliminated leading to accurate and highly resolved image capture.

LEDs convert electricity very efficiently into light and, unlike traditional light sources, the Colibri does not generate radiant heat. Therefore, microscope incubators can be used immediately without waiting for thermal conditions to stabilise and the minimisation of heat build-up results in more stable conditions during prolonged experiments. The full potential of Colibri is displayed in the Cell Observer HS high speed live cell imaging system.

For more information E. micro@zeiss.co.uk

Baroness Susan Greenfield CBE to speak at Headway Conference

Baroness Susan Greenfield, CBE, will be joined by other leading professionals in the field of brain injury on Monday 22 October 2007 to speak at Headway's high profile conference in Stratford-upon-Avon. The conference is sponsored by Charles Stanley Stockbrokers. Early bird delegate places are available now and booking could not be easier.

For further information please see www.headway.org.uk or E. eventsandconferences@headway.org.uk

Multiphoton laser scanning microscope

An image showing YFP-expressing cortical neurons of the mouse from layers IV and V, courtesy of M. Fuhrmann and J. Herms, Department of Neuropathology and Prion Research, Ludwig Maximilians University, Munich, Germany.

Zeiss has overcome the challenge of imaging deep inside living tissues with the launch of the LSM 5 MP multiphoton laser scanning microscope. The instrument uses longer-wavelength, femtosecond lasers to create and detect fluorescence signals at a depth of up to 500μm, illuminating cellular structures in great detail whilst eliminating phototoxic cellular damage caused by high intensity light.

The LSM 5 MP is based on the recently launched Axio Observer inverted research microscope platform and takes advantage of its sophisticated optical features. Highly efficient coatings on the optics ensure minimal power losses of the directly coupled femtosecond lasers while advanced filter technology guarantees efficient suppression of stray and excitation light and extremely sensitive detection of fluorescent signals.

The W Plan-Apochromat objective lens boasts 20x magnification at a numerical aperture of 1.0 and a working distance of 2mm. It is ideally suited to multiphoton electrophysiology experimentation, allowing larger areas to be imaged with unsurpassed resolution and brilliance. The specially designed objective lenses feature optical correction in the near infra red (NIR) 700-1100nm spectral range to reduce absorption and scatter. This allows the NIR laser to penetrate tissue to greater depths working in ultrashort pulses of up to 170kW at a frequency of 76 to 90 MHz.

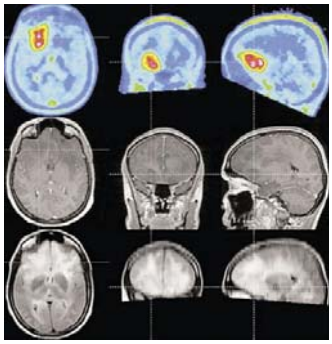
For more information E. micro@zeiss.co.uk

New ultrasound device for neurovascular, vasospasm and PFO monitoring from Spencer Technologies

Spencer Technologies is dedicated to developing innovative ultrasound systems to aid the diagnosis in neurovascular disease and monitoring for PFO using patented Power M-Mode technology and clinically proven embolus detection algorithms. The new ST3 – PMD150 is the only system designed for routine PFO detection with dedicated protocols and report formats. Ease-of-use is key to the ST3 operation allowing the clinician to focus on the patient and work flow in a busy clinic. No other company is focused more on neurovascular diagnosis and PFO detection than Spencer Technologies. The ST3 – PMD150 is a compact portable system with a host of features not available on competitors units.

For more information contact Pulse Medical, Tel/Fax. 01482 473803 or E. sales@pulsemedical.co.uk or Spencer Technologies Europe, Tel: 01420 88688 or E. sales@spencertechnologies.eu or visit www.spencertechnologies.com

Newworld's first system capable of simultaneous imaging of the brain by MRI and PET demonstrated by Siemens



Siemens Medical Solutions showed a prototype for the world's first fully-functioning imaging system capable of performing simultaneously Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET).

Siemens Medical Solutions has shown a prototype for the world's first fully-functioning imaging system capable of performing simultaneously Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). The first in-vivo human brain simultaneous MR-PET images were acquired in the Siemens facilities in USA. Testing of this new prototype MR-PET will start before the end of 2007.

MR-PET presents a leap forward in imaging capabilities. Siemens is the first company to have realised an MR-PET prototype, which brings the exceptional soft tissue contrast and high specificity of MR together with PET's excellent sensitivity in assessing physiological and metabolic state. The first MR-PET images were acquired with support of Dr David Townsend and Dr Claude Nahmias, both from the University of Tennessee, USA, and Dr Heinz-Peter Schlemmer, Dr Claus Claussen and Dr Bernd Pichler, all from the University Tübingen in Germany. MR-PET has the potential to become the imaging modality of choice for neurological studies, certain forms of cancer, stroke and the emerging study of stem cell therapy.

For further information Tel. 01344 396317 or see www.siemens.com

BUPA Hospital Manchester increases clinical capabilities with SOMATOM Emotion 16

Pictured by the SOMATOM Emotion are (L to R): Sue Branfield, Imaging Manager, Dr Simon Taggart, Consultant Physician, Dr Peter Norburn, Consultant Radiologist, Dr Sylvia Rimmer, Consultant Radiologist, Ole Gunnar Solskjaer, Manchester United FC, Janine Brown, Radiology Administrator, Cathryn Skinner, Specialist Radiographer and Saima Naheed, Radiographer.

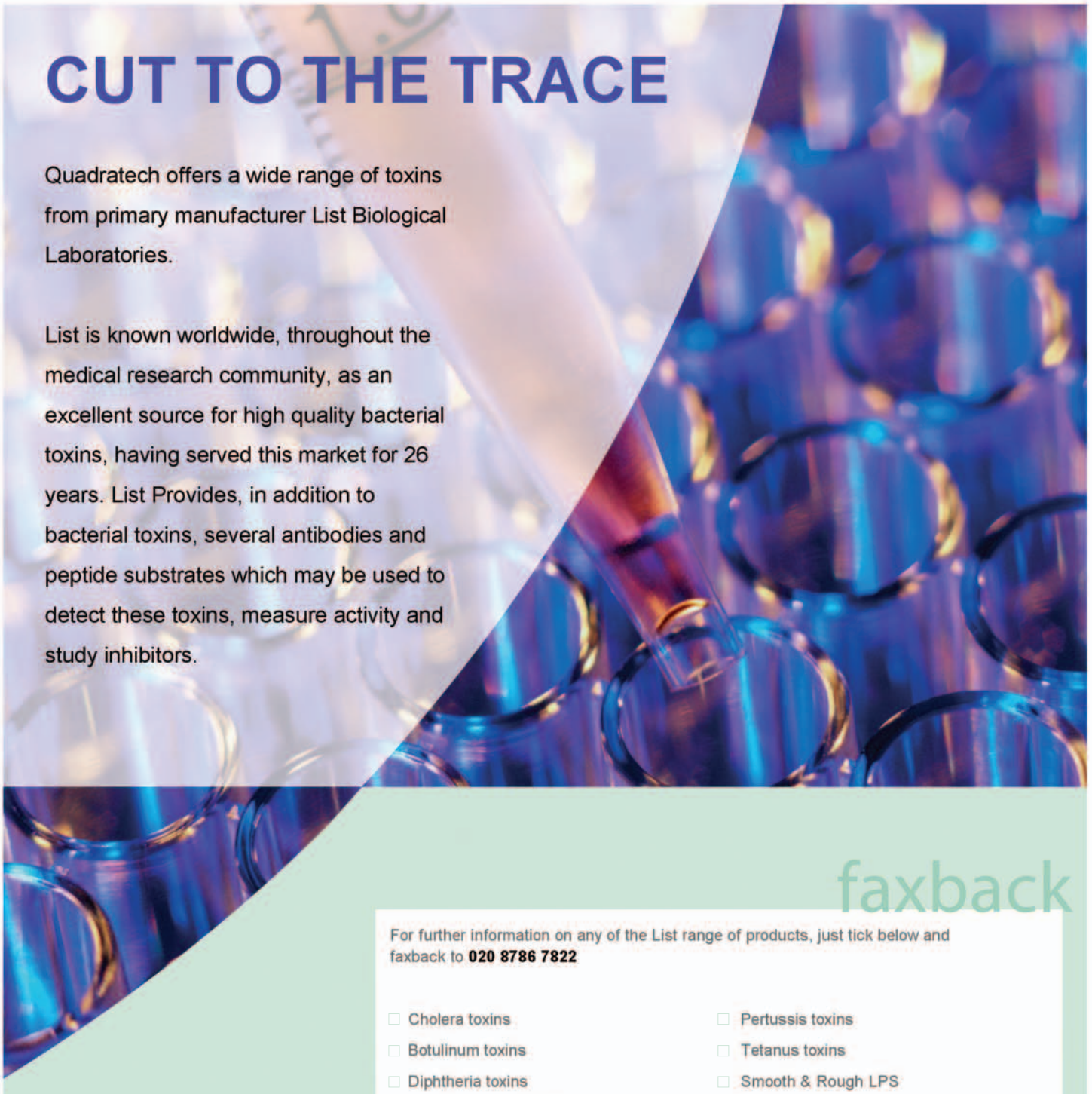
BUPA Hospital Manchester has installed the SOMATOM Emotion 16 from Siemens Medical Solutions to help expand its services, produce faster imaging and enhance its clinical capability. The new equipment was officially opened by Ole Gunnar Solskjaer of Manchester United FC.

The SOMATOM Emotion performs routine clinical CT with great speed and efficiently integrating high quality imaging applications into daily clinical practice. With the Emotion's flexibility, clinicians are able to perform routine examinations, such as chest, abdomen and head, with the option for more advanced applications - like syngo Neuro DSA - which greatly improve the diagnostic workflow.

Sue Branfield, Imaging Manager at BUPA Manchester said, "The SOMATOM Emotion 16 significantly improves the patient experience and allows us to address the more demanding needs of the physicians. The technology, which generates detailed images in a significantly short period of time, ultimately provides our patients with more accurate diagnoses and our staff with improved throughput."

For more information Tel. 01344 396317 or see www.siemens.com

CUT TO THE TRACE



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ARICEPT® EVESS® (donepezil hydrochloride orodispersible tablet)
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

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