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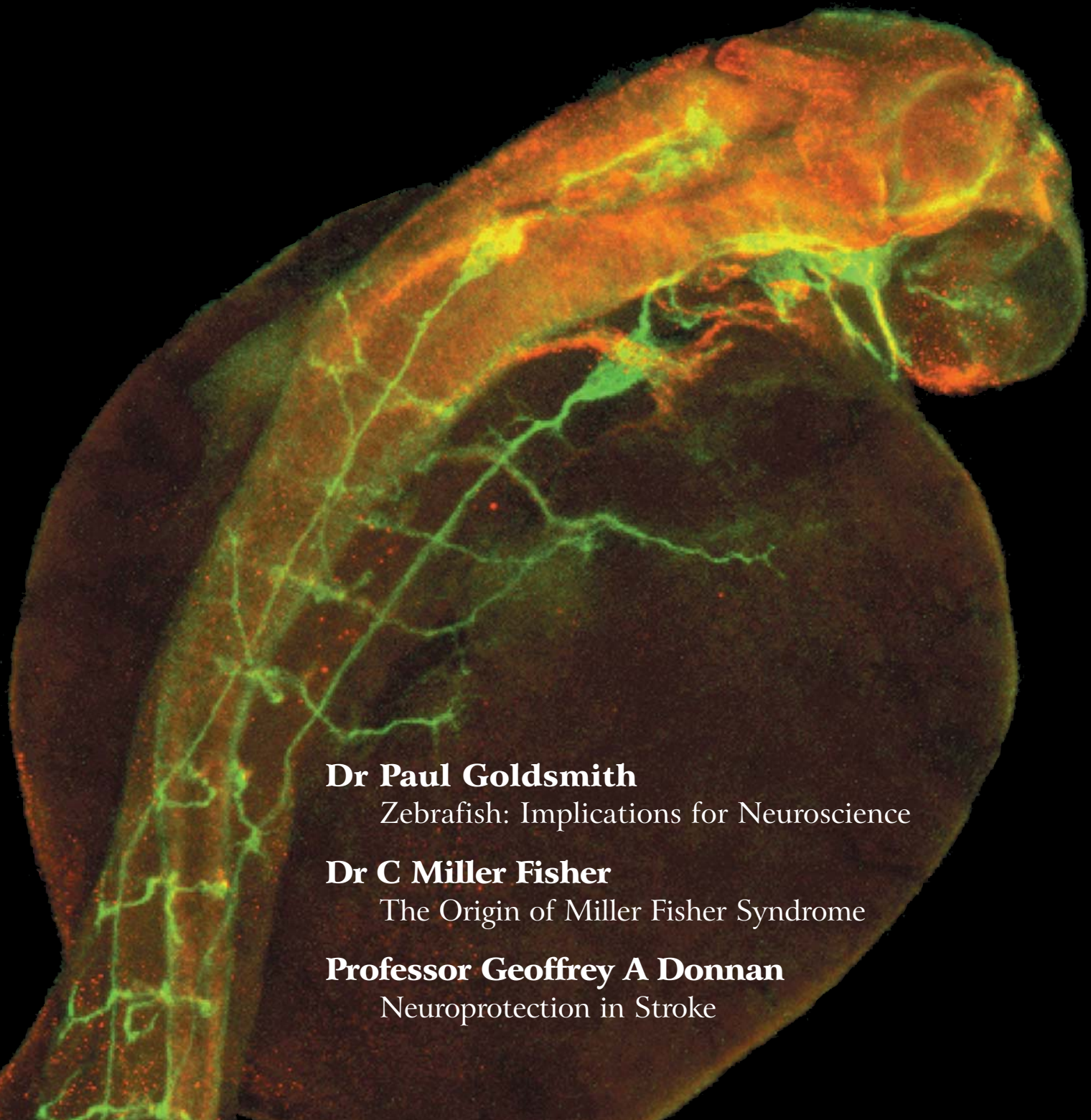

Dr Paul Goldsmith
Zebrafish: Implications for Neuroscience

Dr C Miller Fisher
The Origin of Miller Fisher Syndrome

Professor Geoffrey A Donnan
Neuroprotection in Stroke


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Presentation 'ReQuip' Tablets, PL 10592/0085-0089, each containing ropinirole hydrochloride equivalent to either 0.25, 0.5, 1, 2 or 5 mg ropinirole. Starter Pack (105 tablets), £40.10. Follow On Pack (147 tablets), £74.40; 1 mg tablets – 84 tablets, £47.26; 2 mg tablets – 84 tablets, £94.53; 5 mg tablets – 84 tablets, £163.27. **Indications** Treatment of idiopathic Parkinson's disease. May be used alone (without L-dopa) or in addition to L-dopa to control "on-off" fluctuations and permit a reduction in the L-dopa dose. **Dosage** *Adults:* Three times a day, with meals. Titrate dose against efficacy and tolerability. Initial dose for 1st week should be 0.25 mg t.i.d., 2nd week 0.5 mg t.i.d., 3rd week 0.75 mg t.i.d., 4th week 1 mg t.i.d. After initial titration, dose may be increased in weekly increments of up to 3 mg/day until acceptable therapeutic response established. If using Follow On Pack, the dose for 5th week is 1.5 mg t.i.d., 6th week 2.0 mg t.i.d., 7th week 2.5 mg t.i.d., 8th week 3.0 mg t.i.d. Do not exceed 24 mg/day. Concurrent L-dopa dose may be reduced gradually by around 20%. When switching from another dopamine agonist follow manufacturer's guidance on discontinuation. Discontinue ropinirole by reducing doses over one week. *Renal or hepatic impairment:* No change needed in mild to moderate renal impairment. Not studied in severe renal or hepatic impairment – administration not recommended. *Elderly:* Titrate dose in normal manner. *Children:* Parkinson's disease does not occur in children – do not give to children. **Contra-indications** Hypersensitivity to ropinirole, pregnancy, lactation and women of child-bearing potential unless using adequate contraception. **Precautions** Caution advised in patients with severe cardiovascular disease and when co-administering with anti-hypertensive and anti-arrhythmic agents. Patients with major psychotic disorders should be treated with dopamine agonists only if potential benefits outweigh the risks. Ropinirole has been associated with somnolence and episodes of sudden sleep onset. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Caution advised when taking other sedating medication or alcohol in combination with ropinirole. If sudden onset of sleep occurs in patients, consider dose reduction or drug withdrawal. **Drug interactions** Neuroleptics and other centrally active dopamine antagonists may diminish effectiveness of ropinirole – avoid concomitant use. No dosage adjustment needed when co-administering with L-dopa or domperidone. No interaction seen with other Parkinson's disease drugs but take care when adding ropinirole to treatment regimen. Other dopamine agonists may be used with caution. In a study with concurrent digoxin, no interaction seen which would require dosage adjustment. Metabolised by cytochrome P450 enzyme CYP1A2 therefore potential for interaction with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn. Increased plasma levels of ropinirole have been observed with high oestrogen doses. In patients on hormone replacement therapy (HRT) ropinirole treatment may be initiated in normal manner, however, if HRT is stopped or introduced during ropinirole treatment, dosage adjustment may be required. No information on interaction with alcohol – as with other centrally active medications, caution patients against taking ropinirole with alcohol. **Pregnancy and lactation** Do not use during pregnancy – based on results of animal studies. There have been no studies of ropinirole in human pregnancy. Do not use in nursing mothers as lactation may be inhibited. **Adverse reactions** In early therapy: nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope. In adjunct therapy: dyskinesia, nausea, hallucinations and confusion. Incidence of postural hypotension (commonly associated with dopamine agonists), was not markedly different from placebo, however, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur. As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely, occasionally when driving (see 'Precautions' and 'Effects on ability to drive and use machines'). **Effects on ability to drive and use machines** Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved. **Overdosage** No incidences reported. Symptoms of overdose likely to be related to dopaminergic activity.
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Alastair Wilkins is our Case Report Co-ordinator. He is Specialist Registrar in Neurology in Cambridge. His main research interests are the study of axon loss in multiple sclerosis and the molecular biology of axon-glia interactions in the central nervous system.

Roy O Weller is ACNR's Neuropathology Editor. He is Emeritus Professor of Neuropathology, University of Southampton. His particular research interests are in the pathogenesis of Multiple Sclerosis, Alzheimer's disease and Cerebral Amyloid Angiopathy.

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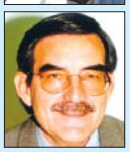
Professor Klaus Berek, Austria: Head of the Neurological Department of the KH Kufstein in Austria. He is a member of the Austrian Societies of Neurology, Clinical Neurophysiology, Neurological and Neurosurgical Intensive Care Medicine, Internal and General Intensive Care Medicine, Ulrasound in Medicine, and the ENS.



Professor Hermann Stefan, Germany: Professor of Neurology / Epileptology in the Department of Neurology, University Erlangen-Nürnberg, andspecialises in the treatment of epilepsies, especially difficult to treat types of epilepsy and presurgical evaluation, including Magnetic source imaging (MEG/EEG) and MR-Spectroscopy.

Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital. Research Dean at the medical faculty, and Chairman for the Research Committee of the Norwegian Medical Association. He chairs the scientist panel of neuroimmunology, EFNS, is a member of the EFNS scientific committee, the World Federation of Neurorehabilitation council, and the European School of Neuroimmunology board. His main research interests are neuroimmunology and neurorehabilitation.

For those of you who were too poor to go to the World Congress of Neurology in Sydney and could not therefore see the special issue of ACNR do not worry, as the two new articles in that special issue are reproduced here. This includes a wonderful account by Dr Fisher on his variant of Guillain-Barré syndrome. This article describes how the disorder was first recognised, as well as highlighting the problems of having a surname as a forename. We are very grateful to Dr C Miller Fisher for writing this article for us, which is a great inspiration for all those involved in neurological practice. It is another reminder of the value of keeping notes and details on all the cases that one encounters, especially those without a diagnosis. In addition we also include the article by Geoff Donnan and colleagues on neuroprotection in stroke. This review article highlights the problems of translating encouraging neuroprotectants from the artificial situation with strokes in animals in the laboratory to the rather more messy reality of the clinic. Nevertheless this article does highlight some encouraging trials which offer real hope in the quest to find drugs that will reduce the area of infarction, and by so doing promote recovery and reduce disability.

Our other review article is on one of the emerging new tools of modern science, the zebrafish. These animals are becoming increasing adopted in studies of neurological disorders, and Paul Goldsmith explains why this is the case and the advantages of adopting such an approach based on his own work in this area.

Roy Weller (editor of the neuropathology series of articles) and Nicki Cohen treat us to an illuminating discussion of the neuropathology of dementia, especially Alzheimer's disease. In this article, they put forward the evidence for the theory that Alzheimer's disease is as much related to problems of amyloid clearance as it is to production (see also Journal reviews ACNR 5.2.). If correct, such a theory would go some way towards explaining the link between amyloid angiopathy in the brain and this type of dementia. In addition, this article also touches upon some of the recent work on amyloid immunisation in patients with Alzheimer's disease, highlighting what this approach can achieve at the pathological and clinical level.

This issue also contains the first in a new series of articles on the neuroscience of vision, and we are extremely fortunate and grateful to Masud Husain for taking on the editorship of this new departure. The first in the series is on the retina and Sumathi Sekaran and Mark Hankins take us through this structure, which is one of the most beautiful neuronal networks of the nervous system with its interacting vertical and horizontal assemblies of cells. This account highlights the 3 pathways of light detection - rods, cones and the recently discovered melanopsin ganglion cells. This latter cell is intrinsically photosensitive and is important in circadian rhythms and pupillary responses and its behaviour is increasingly being understood, in a large part through the pioneering work of Hankins himself. This opening article in this series is a wonderfully accessible and topical discourse, and lays the foundation for what we will certainly be a highlight in the forthcoming issues.

What do you do with the "incidental" finding of an asymptomatic unruptured intracranial aneurysm? This important question, which is the case in 1 in 40 of us, is posed by Peter Whitfield in his article in the Neurosurgical Management series. The answers are to be found in his article which covers the difficulties in studies addressing such a controversial issue. The main message which comes out of this work is that the rupture rates are higher with posterior circulation and bigger aneurysms but that a large number of factors need to be considered in individual cases. As to what you do with the symptomatic aneurysm turn to the journal reviews... which reminds me to say thanks to Lucy Jones who is moving on and has decided to step down from writing journal reviews for us. If you would like to take her place, let us know.

Mike Dilley, in the rehabilitation article, discusses the neuropsychiatric problems seen in the range of patients on the neurorehabilitation wards, which includes patients with strokes, traumatic brain injury, MS as well as "functional" illnesses (see Sharpe et al ACNR 4.6). This carefully crafted article lays out the clinical features and problems with practical advice on their management, and is an extremely helpful summary of a complex area.

The first in another new series also appears in this issue. We will be discussing techniques in neuroscience - edited by our very own co-editor, Alasdair Coles. In this opening article Alastair Wilkins deals with immunohistochemistry - a technique which has its origins in the 1970s when monoclonal antibodies were first made and being used to label specific epitopes. This technique has now become routine for much experimental and clinical work and Alastair takes us through the principles with illustrations of its power. Whilst being a relatively straightforward technique, many will have experienced the fickle nature of the procedure during the course of their research.

The sponsored article takes as its theme sleepiness and fatigue in MS. This is a major problem with 70% of MS patients complaining of fatigue and 50% sleep related issues. In this article, Mike Boggild and John Thorpy discuss the distinction between fatigue and excessive sleepiness and their underlying aetiological causes and thus their optimal management.

The conference reviews include a thoroughly absorbing account by Sarah Tabrizi and Susie Henley on the recent WCN HD meeting in Manchester as well as a wonderfully entertaining, yet educational, account by Andrew Larner on the EFNS in Athens. A must read, as the nuggets of neurological knowledge are nicely interspersed with a range of amusing observations.

Finally there are the usual journal and book reviews and don't forget the web site with its clinical cases - including new ones on limbic encephalitis (see ACNR 5.4) and abnormal eyelid movements in a patient with alpha coma following a cardio-pulmonary arrest.

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

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1. Krakow K, Walker M, Otoul C, *et al.* Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology.* 2001; 56: 1772-1774. **2.** Glauser TA, Gauer LJ, Lu Z, *et al.* Poster presented at IEC, Paris, 2005.**3.** Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther.* 2000; 85: 77-85. **4.** French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. *Epilepsy Res.* 2001; 47: 77-90. **5.** Glauser TA, Gauer LJ, Chen L, *et al. Epilepsia* 2004; 45: 186.

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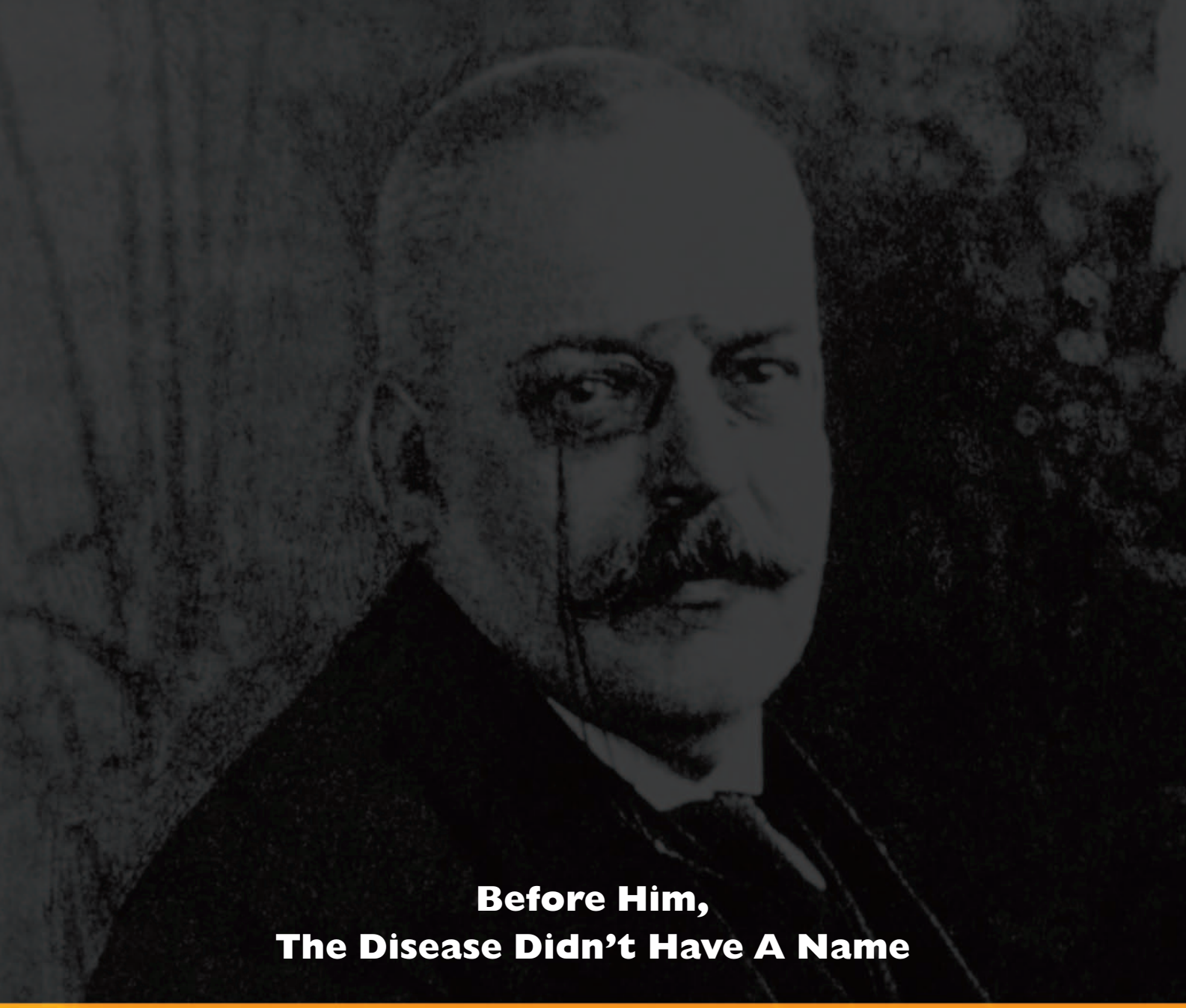

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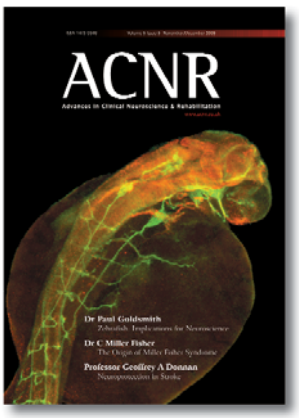

Cover picture:
Zebrafish embryo, wholemount, neurons (green), cell adhesion molecule (NCAM, red), recorded with a Laser Scanning Microscope by Carl Zeiss; author: Monika Marks, Martin Bastmeyer, University of Konstanz.

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2. Rinne UK *et al. Neurology* 1998;**51**:1309-1314.

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December 2004
STA1295

Zebrafish: Implications for Neuroscience

Zebrafish are increasingly being used by neuroscientists and pharmacologists for in vivo studies. The characteristic of zebrafish which makes them particularly attractive, is the unique combination of scalability, genetic and chemical tractability and human relevance.

Scalability: A single pair of adults will breed once a week generating 1-200 offspring per breeding. With a typical stocking density of 10 fish per gallon, a modest aquarium can generate millions of larvae per year. High throughput approaches are possible as larvae are no more than 1-2 mm in size, develop ex-utero with the basic body plan laid out in 24 hours and behavioural analysis possible from 72 hours, at a time when they are still smaller than flies.

Relevance: Zebrafish are teleosts, higher order fish and are vertebrates. Their genome has been sequenced at the Sanger Centre and is currently being annotated. Genome size is similar to humans with a high degree of conservation between protein binding domains. Though deletions, duplications and divergence of particular genes will mean that in certain areas zebrafish are less relevant than in others, something which still needs to be established, the overall assessment rates zebrafish quite close behind rodents in terms of overall relevance and considerably ahead of the invertebrate models. Anatomical and functional comparisons are gradually being published with a number of complex behaviours having been reported, including sleep, parkinsonian states and addictive responses.

Genetic and compound tractability: Zebrafish were originally proposed as an experimental species by geneticists, with the major momentum being generated in the mid 90s as a result of two large mutagenesis screens undertaken by developmental biologists. This is a reflection of their genetic tractability and has also led to the creation of a suite of tools and associated infrastructure for genetic manipulation. In terms of chemistry tractability, fish are tolerant to standard compound solvents and readily absorb compounds administered to the fish water, making assessment of action of a compound added directly to the water feasible.

Neurological models known to be in development

Parkinson's disease, Huntington's disease, Alzheimer's disease, myelination, pre-pulse inhibition, sleep, startle responses, retinal degeneration, memory, muscle disease, epilepsy.

Whilst there are all of the standard caveats of modelling complex human phenomena in a much simpler system, which brings with it both advantages and disadvantages and questions of relevance and predictability, it is also worth stressing the strong ethical argument for supplementing drosophila research with zebrafish research, using both to reduce dependence on mammalian systems.

Tools available for zebrafish analysis

- Transgenics easy to create by injection of genes.
- Gene knockdown standardly achieved through injection of morpholinos (modified oligonucleotides) directed to 5' sequence.
- Knockout possible using Tilling (Targeting Induced Local Lesions In Genomes - a method of creating stable mutant lines).

Examples of conserved pharmacology in zebrafish

- Terfenadine. QT prolongation.
- Diazepam. Sedative.
- Carbamazepine. Anticonvulsant action.
- Prednisolone. Anti-inflammatory action.
- Atorvastatin. Decreased cholesterol synthesis.
- Pilocarpine. Pro-convulsant action.

Conclusion

To date zebrafish research has largely been driven by developmental biologists. However, a second wave of zebrafish researchers is emerging; the physiologists, neuroscientists, and medically focused researchers, who are integrating zebrafish into their armamentarium, establishing what they are good for and what they are not good for in a particular area. Over the next few years, this work will begin to come through in publications.

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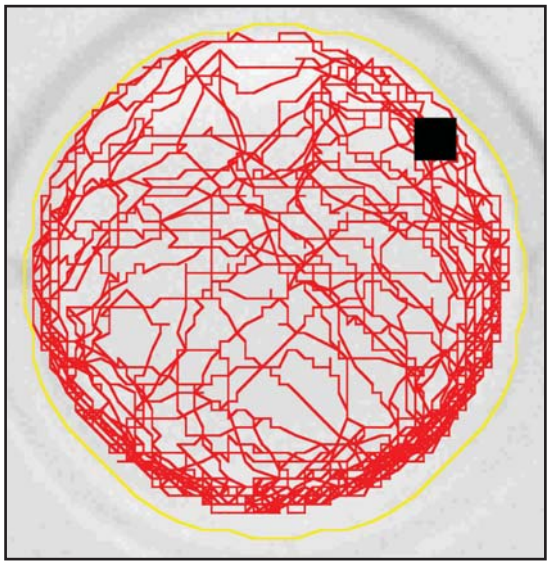
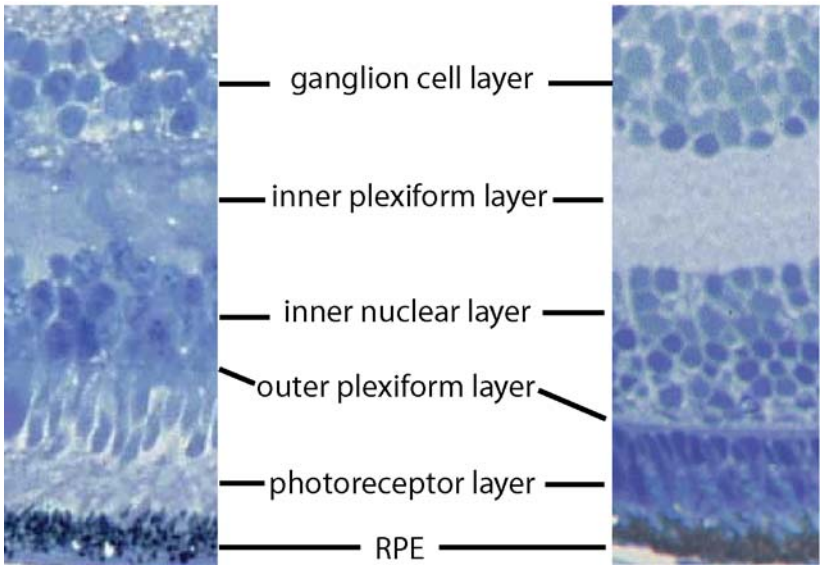


This figure illustrates a 2-mm larval zebrafish being automatically tracked. The black square marks the fish, the red lines the track it has taken. Speed and duration of movement as well as accuracy of swim can be analysed.

The retinal cell layout is highly stereotyped



These are plastic sections through an adult human (left) and embryonic zebrafish (right) retina. The type and relative positions of the various cell types are the same in both.

Neuroprotection in Stroke

Aspirin and thrombolysis are the main strategies for therapeutic intervention in acute ischaemic stroke.[1,2] Alteplase (rt-PA) has been approved as a thrombolytic agent in many countries, but its uptake has been slow because of the risk of symptomatic intracerebral haemorrhage and the short 3 hour therapeutic time window. An alternative additional intervention is neuroprotection because of its relative safety, evidence of efficacy in animal models and potential to administer in the pre-hospital setting. However none of the neuroprotective agents has proven effective in clinical trials for the last two decades. The exception is the recently presented preliminary results from the SAINT I (**S**troke - **A**cute **I**schaemic - **N**XY-059 - **T**reatment) trial in which NXY-059, a free radical scavenger, was shown to improve clinical outcomes when given within 6 hours of ischaemic stroke onset.[3] In this review we will summarise the rationale for the use of neuroprotectants and discuss their potential problems.

Basic concepts of neuroprotection

Ischaemic cascade

The ischaemic cascade is a time dependent series of neurochemical events initiated by intracerebral vessel occlusion and energy failure. Early events include the activation of glutamate receptors and influx of extracellular Ca^{2+}, while later recruitment of inflammatory cells, production of free radicals and initiation of apoptosis are seen (Figure). The basis of neuroprotection is that interruption of the propagation of these cascades allows brain tissue to be salvaged, or at least protected until reperfusion occurs. The majority of the ischaemic cascade occurs within the ischaemic penumbra.

Ischaemic penumbra

The ischaemic penumbra is functionally impaired but potentially viable tissue surrounding the infarct core[4] and may persist for up to 48 hours after ischaemic stroke onset. However this penumbral tissue is destined to be necrotic unless intervention occurs. Hence, the penumbra is the major target for intervention, either by attenuating the ischaemic cascade with neuroprotective compounds or promoting reperfusion with thrombolysis.

The main categories of neuroprotective agents and clinical trials to date

There are numerous categories of neuroprotective agents which have been shown to be effective in animal models and many have been subjected to clinical trial. While not an exhaustive list, the main categories and trials are described here and listed in the Table.

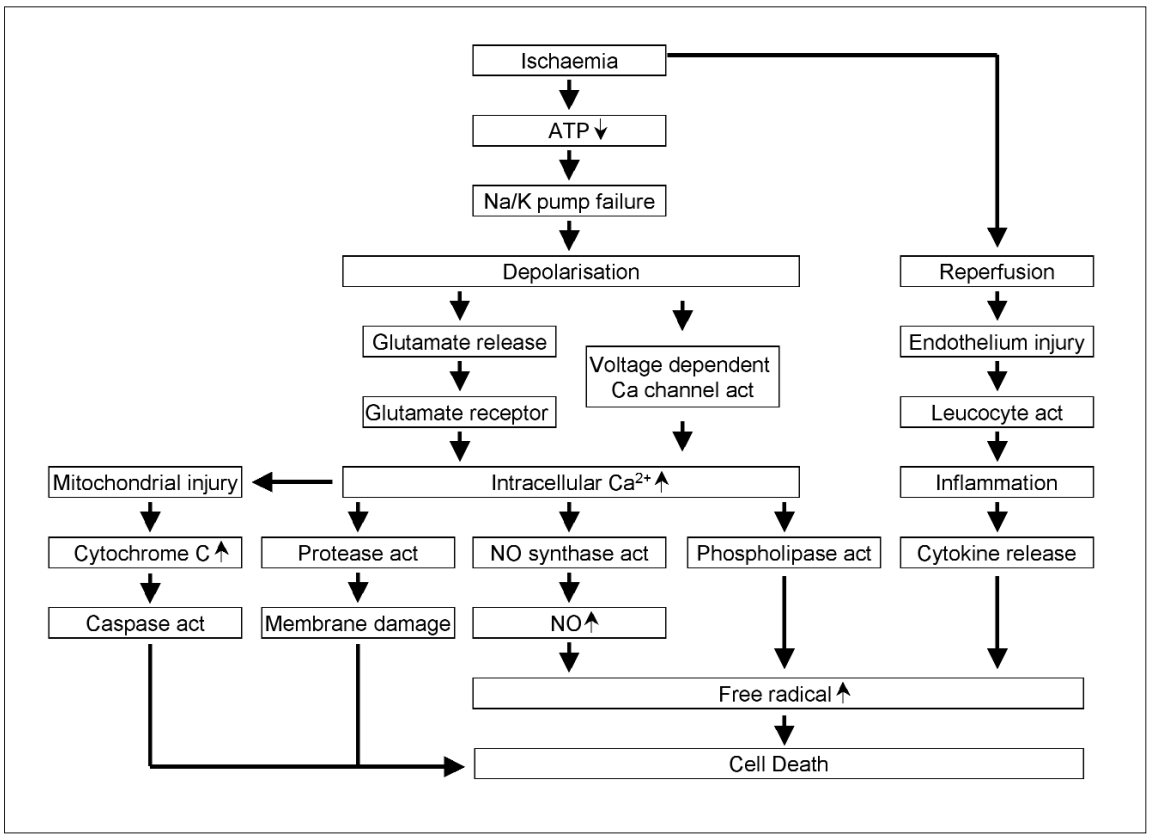
Glutamate receptor antagonists and calcium channel blockers

As mentioned earlier, focal cerebral ischaemia causes release of excitatory amino acids, principally glutamate which activates various postsynaptic receptors including NMDA (N-methyl-D-aspartate), AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) and metabotropic receptors. Activation of most of these receptors is associated with calcium influx leading to cell damage. Hence, both glutamate receptor antagonists and calcium channel blockers might have a neuroprotective role.

Although animal studies of glutamate receptor antagonists showed excellent neuroprotective effects, clinical trials in acute ischaemic stroke have been disappointing.[5] The IMAGES trial of intravenous magnesium (NMDA antagonists) within 12 hours of stroke onset was the largest yet conducted, but was negative except for the lacunar subset.[6] Trials of calcium channel blockers mainly involved nimodipine,[7] but no real benefit was found on meta-analysis.[8] Phase III trials with YM872 (AMPA antagonists) and magnesium are ongoing.

Free radical scavengers

Oxygen free radicals are produced during reperfusion as well



The ischaemic cascade leading to cell death.
Act; activation

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as ischaemia and can cause widespread damage to cellular components such as lipids, proteins and DNA, leading to necrosis or apoptosis.

In May 2005, preliminary results from SAINT I study were released.[3] In this trial NXY-059, a free radical trapping agent, was tested in patients with acute ischaemic stroke within 6 hours of onset. A significant reduction in post-stroke disability (modified Rankin Scale) was observed in NXY-059 group. Although the results need to be confirmed in other studies (SAINT II is in progress), NXY-059 might be the first neuroprotectant for the treatment of acute ischaemic stroke.

Interestingly, ebselen and edaravone, both free radical scavenging drugs, also showed favourable outcome in the clinical trials for acute ischaemic stroke,[9,10] although the time window was 16 hours and sample sizes were small.

Anti-inflammatory agents

Cerebral ischaemia triggers an inflammatory reaction, which may commence within hours and last up to several months.[11] Suppression of inflammation using a variety of drugs has been shown to reduce infarct volume in animal studies. Two leukocyte adhesion inhibitors, Enlimomab and LeukArrest, were studied in patients with acute ischaemic stroke, but did not show clinical benefit.[3,12]

Why have trials of neuroprotective agents failed?

The difficulties in translating benefits of neuroprotection in animal models to the human paradigm has probably been greater than any other area of medicine; hence, the reasons for this apparent failure are worth discussing.[13] Obviously, the two key issues are that the wrong drugs have been selected for clinical trial because of inadequate pre-clinical testing, or the right drugs have been selected but have been poorly studied in clinical trials.

Pre-morbid conditions. In pre-clinical experiments, researchers usually choose young, healthy animals. However, stroke patients are usually old and suffer from multiple chronic diseases (e.g. hypertension, diabetes). Co-morbidities in patients can affect their outcome.

White matter. In humans, the proportion of white matter is significant (about 50%), but it is smaller in rodents (about 10%).[14] Because most neuroprotectants have been developed to protect grey matter, they may be beneficial to rodents, but not humans.

Recanalisation. In many animal studies, the temporary occlusion model has been used, while in human stroke, permanent occlusion is more common (about 30% recanalisation rate at 6 hours). The temporary occlusion model may be easier for neuroprotectants to enter the ischaemic penumbra and exert beneficial effects.

Drug dose. Adequate dose escalation studies are frequently not performed in animal models and rarely in phase II clinical trials in humans.

Therapeutic windows. In many animal studies, neuroprotectants were given before or for short time windows after the onset of ischaemia. Therapeutic windows used in most clinical trials have been up to 24 hours, but more recently restricted to a more realistic figure of around 6 hours after the onset and seems late for effective neuroprotection.

Randomisation. While the majority of clinical trials have been performed in randomised, double-blinded manner this has not been the case in most animal studies.

Outcome measures. In most animal studies, efficacy of neuroprotectants has been measured by infarct volume and less frequently by functional outcomes. Although, in clinical trials the gold standard is functional outcome (e.g. Rankin Scale), magnetic resonance imaging outcomes are sometimes used in phase II trials.

Clearly there needs to be a greater rigour applied to both pre-clinical and clinical testing of neuroprotective agents. Of interest, it has been shown that when this is applied in animal models, the observed protection rates are lower. Fortunately, criteria have now been established such as described in the STAIR documents[15] and it is of interest that the NKY-059 compound investigators were one of the few groups to adhere to them.

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Table: Neuroprotective trials in acute ischaemic stroke

Proposed mechanism	*Drugs*	*Results*
Glutamate receptor antagonist		
NMDA antagonist	*Selfotel (CGS19755)*	*Complete / No benefit*
	Eliprodil	*Halted / No benefit*
	"Aptiganel (Cerestat, CNS1102)"	*Complete / No benefit*
	MgSO4 (IMAGES)	*Complete / No benefit*
	MgSO4 (FAST-MAG)	*Ongoing*
AMPA antagonist	*YM872*	*Ongoing*
Ion channel modulator		
Calcium channel blocker	*Nimodipine*	*Complete / No benefit*
	Flunarizine	*Complete / No benefit*
Sodium channel blocker	*Fosphenytoin*	*Complete / No benefit*
Potassium channel activator	*Maxipost (BMS-204352)*	*Complete / No benefit*
Free radical scavenger	*NXY-059*	*Complete / Benefit on preliminary analysis*
	Tirilazad (U70046F)	*Complete / No benefit*
	Ebselen	*Complete / Benefit on ITT analysis*
	Edaravone	*Complete / Benefit*
Anti inflammatory agents		
Anti-leukocyte antibody	*Enlimomab*	*Complete / Worsening*
	LeukArrest (9Hu23F2G)	*Halted / No benefit*
	Neutrophil Inhibiting Factor (ASTIN)	*Complete / Worsening*

The Origin of Miller Fisher Syndrome

In the original description,[1] this clinical syndrome consisted of the development of external and internal ophthalmoplegia, cerebellar ataxia in the arms and legs and absence of the tendon reflexes, over a period of four or five days. The rather acute onset of such ocular signs associated with cerebellar ataxia was apt to be alarming to a neurologist in 1955, the year the principal case was studied. The patient developed severe ataxia of gait and diplopia in 24 hours. After four days there was complete external and internal ophthalmoplegia, ataxia that precluded feeding himself and made it impossible to stand or walk unaided. On examination, along with other findings, the tendon reflexes were absent. The patient's mind was clear. The several diagnoses that came to mind included vertebral-basilar thrombosis with a stroke, Wernicke's disease, botulism, multiple sclerosis and the Guillain-Barré syndrome. The cerebrospinal fluid (CSF) contained a few lymphocytes and a normal protein.

Dr David Cogan, a world figure in neuro-ophthalmology, was asked to see the patient in consultation and strongly recommended vertebral-basilar angiography. This became the focus of debate among several consultants. At that time, the procedure was carried out by means of a direct 'stick' with a needle that passed through the common carotid artery in the neck to reach the vertebral artery. I knew of several instances in which serious complications had occurred, including death. Our patient was not generally ill and subjecting him to angiography seemed too risky. Also I vaguely recalled seeing or hearing of a somewhat similar case in Montreal in the past few years, that had recovered. The discussion was continuing when on hospital day 5, spontaneous recovery began without special therapy. In ten days improvement was remarkable. The CSF was re-examined on the 30th day and contained 348mg protein per 100ml. This swung the final diagnosis toward acute polyneuritis of the Guillain-Barré type.

It has been my custom since the days of neurological residency to keep a list of every patient examined. The cases are then sorted out according to broad categories of diagnosis – stroke, multiple sclerosis, tumour, parkinsonism etc and the largest group by far, undiagnosed.

As soon as convenient I travelled to Montreal with the undiagnosed list. In short order two cases were found, both examined in 1953. The first was examined in consultation during the acute stage of the neurological illness that had followed acute pneumonia. In a period of three days the patient developed an internal and external ophthalmoplegia absent tendon reflexes and a wide-based ataxic gait. He had pins and needles in the tips of the fingers but sensation was normal in the fingers and toes. The CSF protein was 35mg per 100ml in the acute stage of the illness and was unchanged after six weeks. The second test had been performed when investigating the possibility of Guillain-Barré polyneuropathy. Neurological recovery was slow. One month later ocular paralysis was severe. The knee and ankle jerks had returned. One year later eye movements were full. This was the case I vaguely recalled at the time of the Boston case. It clearly fit the syndrome.

The second Montreal case was seen neurologically four years after the acute illness. He recounted the story and the original record was examined at the Royal Victoria Hospital. The patient had been seen in consultation by Dr Arthur Young, a former colleague, who recorded in his examination that the eyes were fixed in mid-position with absolutely no movement. The tendon reflexes were absent. There was no paralysis or weakness but marked incoordination of all extremities was present. This was thought to be cerebellar in type. There was no sensory impairment. Ocular movements began to return in one week but in two weeks impairment was still severe. Walking improved and in five weeks he could walk in a straight line with eyes closed. In seven weeks recovery was full. The CSF was not examined.

It was quite likely that a fairly definite syndrome had been identified. The main consideration in reporting it, was to reveal an alarming neurological illness as benign and in no need of vertebral angiography. The prevention of ill-advised intervention was paramount.

A review of the literature revealed reports of several cases of acute Gullain-Barré polyneuropathy in which total ophthalmoplegia had accompanied paralysis of all four limbs. Also Collier[2] in 1932 recognised two types of clinical picture in Guillain-Barré polyneuropathy: paralysis of all four limbs with facial diplegia and paralysis of all four limbs with bilateral external ophthalmoplegia. In some of the latter cases, eye movements were severely affected and the limbs only slightly, with perhaps some extensor weakness and jerklessness. It was not appreciated at the time that a cerebellar-like ataxia of the limbs as a result of polyneuropathy was well known to French neurologists.[3] It was attributed to involvement of the proprioceptive fibers. This could explain the absence of ataxia of speech.

It can be said with complete verity that the idea of having the author's name become eponymic did not enter this author's mind ever, even slightly. In July 1957, there appeared a report of two cases by J Lawton Smith and Frank B Walsh from the Wilmer Ophthalmological Institutes of the Johns Hopkins University and Hospital, Baltimore. Both cases conformed to the original syndrome and the CSF protein was abnormally elevated. The title of their paper was – Syndrome of external ophthalmoplegia, ataxia and areflexia (Fisher). Dr Smith had been a resident in Neuro-ophthalmology with Dr David Cogan at The Massachusetts Eye and Ear Infirmary at about the time our original case was hospitalized and may have seen the case. The authors pointed out that in addition to the three main signs, there may be added facial weakness and paresthesias of various parts usually without discernible sensory loss.

1957-2005

There is not much to add since the experience of 1956. The syndrome is rare. It continues to evoke disbelief when encountered for the first time. Like the other types of Guillain-Barré syndrome, it is related to a preceding Campylobacter jejuni infection. The longtime debate whether the pathological changes in the 3rd nerves are central, peripheral or both, has been decided in favour of a peripheral location. Biochemical sculpting never ceases to amaze. I still get the odd telephone call asking if there is anything new.

Having one's name attached to a syndrome is surely flattering but not always is it straightforward. From the beginning it was a question of who was the main contributor to the elucidation of the syndrome, Dr Miller or Dr Fisher. And why was Miller's name always placed first? When a hyphen was placed between the names it became a matter of whether there were two people or just one with a hyphenated name. The disadvantage of having a surname as your forename is never-ending.

On a more serious note, it can be said that the practice of keeping track of every patient examined, which was in place when the two Montreal cases were seen, has proved invaluable. It continues even to the present. Experience is not experience unless it can be retrieved. The system must be simple lest it bog down. It should be much easier with modern computers.

To view an interview with Dr Miller Fisher, see www.museevirtuel.ca/Exhibitions/Medicentre/en/fish_vit.htm

While Neuropathologist at the Montreal General Hospital (1950-54) **Dr Fisher** proved in 1100 autopsies the importance of atherosclerosis of the carotid arteries in the neck and the occurrence of stroke. The possibility of carotid surgery was raised. In these cases there was often a history of transient paralysis, numbness or speech impairment lasting a few minutes preceding the stroke. These were termed transient ischaemic attacks (TIA's) and served as a warning of an oncoming stroke, providing an opportunity to use anticoagulants or endarterectomy in order to prevent a stroke.

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Maintenance treatment should be in the range of 0.375mg salt (0.264mg base) to a maximum of 4.5mg salt (3.3mg base) per day. Adjust dose based on clinical response and tolerability; reduce doses used in titration and maintenance phases if necessary. Treatment discontinuation: Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Reduce dose by 0.75mg salt (0.54mg base) per day to 0.75mg salt (0.54mg base) per day. Thereafter reduce dose by 0.375mg salt (0.264mg base) per day. Renal impairment: See SPC for revised dosage schedules. Hepatic impairment: Dose adjustment in hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings and Precautions:** Reduce dose in renal impairment. Inform patients that hallucinations (mostly visual) can occur. Somnolence and, uncommonly, sudden sleep onset have been reported; patients who have experienced these must refrain from driving or operating machines. (A reduction of dosage or termination of therapy may be considered). If dyskinesias occur in combination with levodopa during initial titration of pramipexole in advanced Parkinson's disease, the dose of levodopa should be reduced. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. **Drug Interactions:** There is no pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules such as cimetidine and amantadine may interact with pramipexole resulting in reduced clearance of either or both drugs. Consider reducing pramipexole dose when these drugs are administered concomitantly. The dosage of levodopa should be reduced, and other Parkinsonian medication kept constant, while increasing the dosage of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. Coadministration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** Effects of pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used in pregnancy unless the benefit outweighs the potential risk to the foetus. 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Advances in the Neuropsychiatry of Neurorehabilitation

The division of neurology and psychiatry into disciplines seen as dealing with either brain or mind, respectively, is once again being re-evaluated. Increasingly, developments in service provision and core scientific knowledge about mental health mean that the boundary between the subspecialties is being bridged. Neuropsychiatry is best defined as the interest in mental disorder associated with neurological presentations. It is an important discipline, if for no other reason than the significant burden of neuropsychiatric illness on the patient, their carers and society. Furthermore, neuropsychiatric disorders are commonplace in neurology, neurosurgery and neurorehabilitation settings. A study of new neurology referrals revealed that as many as one half of patients met criteria for a neuropsychiatric disorder and up to one third had unexplained symptoms.[1,2]

In this review, the focus is on clinical advances in neuropsychiatric disorders that may be seen on the neurorehabilitation unit. Stroke, traumatic brain injury, multiple sclerosis, delirium and functional neurological presentations, are considered in turn.

Stroke and Traumatic Brain Injury (TBI)

The prevalence of neuropsychiatric sequelae after stroke and TBI are very similar. In one study, one year after injury around 40% of patients with TBI had three or more neurobehavioural symptoms.[3] Disorders of affect, anxiety and cognitive impairment are most often reported, with a mean prevalence rate of 35% for depression and 25% for anxiety or cognitive disorders. The prevalence of psychosis after injury is rare. In contrast to stroke, TBI is associated with a higher prevalence of bipolar disorder, particularly with a periodicity of affective episodes lasting days, referred to as 'rapid cycling'. These presentations are important not only because they are common, but also as they have a negative impact on rehabilitation outcomes as well as significant effects on quality of life measures.

Mood Disorders

Mood disorders after brain injury are by and large similar to those in the absence of brain injury, although apathy and emotional lability are more often features. Impairments of communication, emotional and facial expression can make diagnosing depression more difficult. Rating scales such as the Hospital Anxiety and Depression Scale (HADS) or the General Health Questionnaire (GHQ) are useful and well validated screening tools. Stroke and TBI are significant risk factors for suicide.[4] After TBI, the standardised mortality rate from suicide is increased three-fold with 1% completing suicide over a 15-year follow-up period, in one study.[5] Hopelessness and suicidal ideation are the best indicators of suicidal risk in the mental state features identified in brain-injured populations.

Psychosis

Psychosis can present both early and late in recovery after brain injury. Early on it is most likely a sequelae of delirium. The long held hypothesis that head injury may be a causal factor in schizophrenia has not been supported by a recent comprehensive, critical review.[6]

Agitation and aggression

Agitation and aggression are more frequently seen after TBI than stroke. The more common premorbid personality characteristics of those at greater risk of TBI are likely to play a role in this. Early agitation, often associated with post-traumatic acute confusional states, predicts long-term explosive aggression.

Cognitive impairment

Brain injury may also be followed by progressive cognitive decline. Dementia pugilistica may develop years after repeated blows to the head, usually in boxers. Head injuries, particularly in men, may predispose to the devel-

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Indication	*Treatments*	*References*
Depression after TBI or post stroke	*Tricyclic antidepressants: Likely to be most effective but limited by anticholinergic side effects* *SSRI's: Such as citalopram have fewer side effects and drug interactions* *CBT: Inconclusive evidence of benefit for post stroke depression, but most promising psychological treatment. Scarce research of psychological treatment after TBI*	*Turner-Stokes and Hassan, 2002*[24] *Kneebone & Dunmore, 2000*[25] *Lincoln & Flanghan, 2003*[26] *Khan-Bourne & Brown, 2003*[27]
Treatment refractory or severe depressive episodes with suicidality	*Electroconvulsive therapy*	*Currier et al, 1992*[28]
Prevention of post stroke depression	*No evidence of benefit of antidepressants versus placebo* *May be benefit of treatment in first versus third month on 2 year functional outcomes*	*Anderson et al 2004*[29] *Narushima & Robinson, 2003*[30]
Agitation and aggression after TBI	*Beta blockers: Best evidence but limited by large doses required and significant side effects* *Carbamazepine: Common first line choice but limited evidence* *Sodium valproate: Alternative choice but limited evidence*	*Fleminger et al 2003*[31]
Abulia	*Bromocriptine: Limited evidence*	
Psychosis after TBI or stroke	*Quetiapine: Limited evidence but reasonable choice as less associated with extrapyramidal side effects; be aware of possible increased risk of cerebrovascular disease with other atypical neuroleptics*	

opment of Alzheimer's disease.[7] This is presumably due to deposition of β-amyloid in the brain at the time of injury, although evidence that it is linked to APOE status is inconsistent.

Aetiology

Fierce debate continues as to whether lesion location and particularly anterior, left hemisphere lesions are associated with post-stroke depression. A recent meta-analysis has suggested that the lesion proximity to the left frontal pole, predicted depressive illness.[8] This has been further supported in another appraisal from Finland.[9] The vulnerability of medial orbital frontal and anterior temporal lobes (being involved in social behaviour, cognition and regulation of mood) to contusions, partly explains why the neuropsychiatric consequences of TBI often supersede neurological sequelae as predictors of outcome.

Treatment

Table 1 briefly outlines treatments for various indications. Depressive symptoms should be identified carefully and treated vigorously. The fact that they are 'understandable' or consist of symptoms that may be a direct consequence of brain injury, e.g. apathy, should not prevent a trial of an antidepressant. If there is a good response, antidepressants should be continued for at least 6 months. Severe, persistent or troublesome tearfulness (emotionalism) should be treated with antidepressants, monitoring the frequency of crying to check effectiveness.

In agitation and aggression after head injury response to medication is usually seen early, within the first six weeks, and it is suggested that this is an adequate treatment period during which clinical benefit should be expected before switching to an alternative treatment. There is no evidence that aggression is different from agitation in terms of its response to medication.[10]

Multiple Sclerosis

Neuropsychiatric presentations include mood, anxiety, cognitive and psychotic disorders. The prevalence of depression in multiple sclerosis (MS) has been suggested to be higher than that seen in control groups with different neurological illnesses. However, methodological problems with regard to clinician blinding and diagnostic criteria are likely to be confounding this. A recent evaluation suggests that the lifetime prevalence rate for depressive symptoms is 40-50%.[11] Psychotic illness in MS is most commonly seen in the context of treatment with steroids, where it is often an affective psychosis, although schizophreniform psychoses are also seen. Cognitive impairment in MS has been estimated to have a prevalence of up to 50% in community samples.

Mood Disorders

Fatigue and cognitive impairment are probably more common in depressive episodes in MS and have received the most attention. The most recent studies have supported positive correlations particularly suggesting that mental fatigue[12] and impaired effortful information processing[12] are features of depression in MS. Suicide rates in patients with MS have been shown to be twice the mean rate seen in the adjusted population[14] and are most frequently correlated with living alone, alcohol misuse and depressive disorder.

Cognitive Impairment

Cognitive deficits arise early in the course of MS and often before the diagnosis has been made. The course of cognitive decline would appear to be slow in the majority of cases and risks factors for a more rapid decline include disease progression, age and worsening of physical disability. Particular impairment is seen in verbal fluency, comprehension, naming and executive dysfunction as well as memory.

Aetiology

β-interferon has been implicated in causing depression, although the evidence for this is contentious. Studies of lesion location utilising neuroimaging have been conducted in patients with MS and depression as well as psychosis. The most robustly reported findings in depression implicate more hyperintense lesions in left inferior medial frontal and greater atrophy of left anterior temporal regions.[15] It has been suggested that temporal lobe lesion location may correlate to psychotic illness.[16]

Treatments

Desipramine has been shown to be more effective than placebo in depression in MS, although anticholinergic side effects may preclude its use. SSRI's are a good first line option but the risk of causing sexual dysfunction should be monitored.

Limited evidence exists regarding the best choice of antipsychotic for treatment of psychoses in MS, although an atypical antipsychotic is a sensible choice. Cognitive impairment showed improvement in an open trial of donepezil in patients with MS.[17]

Fatigue may benefit from approaches utilised in chronic fatigue syndrome. Cognitive Behavioural Therapy for depression in MS is likely to be useful and had similar outcomes to treatment with an SSRI.[18]

Delirium

Delirium, classifed as acute confusional state in the International Classification of Diseases (ICD-10), is characterised by a disturbance of conscious level. The patient is obtunded, or drowsy, or highly distractible. Attention and concentration are impaired, e.g. as demonstrated by poor performance on a digit span. They are neither alert nor orientated and the mental state may fluctuate. The patient is likely to be agitated and frightened. Psychotic symptoms with hallucinations, often visual, and fleeting delusions may be elicited. Delirium may also present as a hypoactive withdrawn state akin to stupor.

Aetiology

Numerous physical problems, including drugs and drug withdrawal, may be aetiological factors. Agitation is often present in delirium. If the patient has been treated with antipsychotics an important differential diagnosis of the agitation is akathisia. Poor sleep, pain, constipation, and systemic illness, may be playing a part.

Treatment

Management consists of making the patient safe and then finding the cause. Nursing should be in a side room with consistent staff and plenty of light. It should be a calm environment with opportunities for undisturbed sleep.[19]

Some patients will settle with reassurance and explanation. Relatives may be able to help. Haloperidol and lorazepam may be used to produce rapid sedation. The patient should be placed on regular nursing observations, monitoring respirations and neurological state. If sedation is required for more than one or two days, use atypical antipsychotic medications, e.g. olanzapine or quetiapine, which have less chance of producing extrapyramidal side effects. Valproate, carbamazepine and beta-

blockers may also be helpful in the management of agitation and aggression as alternatives to antipsychotics where these are not tolerated or cause intolerable side effects. Avoid drug combinations that may increase agitation and aggression by increasing confusion.

Functional neurological presentations

The many different names that have been given to functional neurological symptoms including hysterical, psychogenic, somatoform, dissociative and conversion disorders is representative of the complexity of these presentations and the difficulty that doctors often have in explaining them to their patients. Nonetheless, functional symptoms are common in neurological settings with estimates of their prevalence in 10-30% of outpatients. They are associated with significant burden, particularly in terms of health economy and are enduring in around 50% of patients.

There is a wide range of possible presentations and functional symptoms can mimic most neurological disorders. The most commonly reported in one sample included pain, anaesthesia, paresis and headache.[19] Non-epileptic seizures have been estimated to be seen in 9-50% of patients in a specialist centre and can co-exist with epilepsy.

Aetiology

Despite attempts to investigate the neurobiological correlates of functional symptoms, the existing studies are small and difficult to generalise. The most popular aetiological model formulates presentations from a bio-psycho-social perspective taking into account the impact of life events (such as sexual abuse), coping style and comorbid illness. A past psychiatric history may be an important risk factor.

Treatment

The importance of communicating the diagnosis to the patient in such a way that they are not offended and engage in your management plan, is paramount.[21] Multidisciplinary rehabilitation, utilising the skills of physiotherapists, occupational therapists and cognitive therapists has been shown to be effective, although the studies that have considered this have not been randomised. A systematic review has shown that cognitive therapy is beneficial.[22] Antidepressants have been shown to be effective for both those with comorbid depression and for functional symptoms alone.[23]

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Neuropathology of Dementias

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Introduction

Dementia is a problem worldwide, not only for patients but also for carers; it affects some 5% of the elderly population over the age of 65 years[1] and the incidence increases with age. *Clinically*, dementia is defined as a syndrome of progressive cognitive decline to a degree that interferes with work, personal relationships and social functioning in the absence of delirium or major psychiatric disorder. Impairment of memory, language, perception, problem solving ability and personality are all features of dementia.[1] There are different clinical syndromes of dementia that correlate with the pathological features in the brain, although there is often some overlap between syndromes and with normal ageing.[2] In this account, we outline the general pathology of dementias and then concentrate on Alzheimer's disease to review the pathology, some of its possible causes and how immunotherapy is developing as a new treatment for Alzheimer's disease.

General pathology of dementias

The pathological features of dementias are diffuse and affect multiple areas of the brain, thus cerebral atrophy may be the only change seen macroscopically in the post mortem brain and on MRI. A common feature seen microscopically is the accumulation of insoluble proteins and peptides,[3] firstly in the extracellular spaces and in blood vessel walls and secondly within cells. The presence of vascular lesions,[4] infarcts due to cerebrovascular disease, is a further remarkably common finding. These features are summarised in the table.

Extracellular proteins accumulate in the cerebral cortex and other areas of grey matter, as plaques and in artery and capillary walls as Cerebral Amyloid Angiopathy (CAA). Chief among these proteins is Amyloid-β (Aβ) in Alzheimer's disease. Aβ is formed in the brain throughout life by cleavage of a 700 amino acid transmembrane amyloid precursor protein (APP) encoded by a gene on chromosome 21.[5] APP is cleaved by a series of secretases, resulting mainly in the production of a 42 amino acid Aβ (Aβ 1-42) and a more soluble Aβ 1-40. In Alzheimer's disease insoluble Aβ 1-42 is predominantly found in plaques in the cerebral cortex (Figure 1a) and Aβ1-40 within blood vessel walls (CAA). Aβ and other proteins, such as Cystatin and ABri (in the British type of dementia), accumulate in the brain and in blood vessel walls as CAA[6] in a range of familial dementias that are associated with genetic mutations. In Creutzfeld-Jacob disease, insoluble deposits of protease resistance prion protein (PrP) (Figure 1b) accumulate in cerebral and cerebellar grey matter and are associated with spongiform change in neuronal dendrites and with substantial loss of neurons and gliotic scarring.[2]

The *intracellular proteins* are mainly tau and synuclein; they accumulate as insoluble deposits in neurons (Figure 1c & d) and in their processes (forming dystrophic neurites), and in some cases in glial cells. Both tau and synuclein are associated with ubiquitin which suggests that there is failure of disposal of tau and synuclein through the proteosome system.[7] Tau has a role in axoplasmic transport and is normally associated with axonal microtubules. The hyperphosphorylated form accumulates with ubiquitin in neurons in dementia, forming the neurofibrillary tangles (NFTs), typical of Alzheimer's disease (Figure 1c). Synuclein is a protein associated with synapses in the brain and accumulates with ubiquitin in spherical Lewy bodies in neurons (Figure 1d), usually in the substantia nigra and in temporal cortex in Dementia with Lewy Bodies.[2] In Huntington's disease, deposits of the protein huntingtin accumulate within nuclei of neurons and there is selective loss of neurons from the basal ganglia.[2]

Dementias mostly occur in elderly patients over the age of 65 years, although early-onset familial dementias with mutations in genes encoding tau, APP, synuclein and the presenilins affect people in their 50's.[2] Age is a major risk

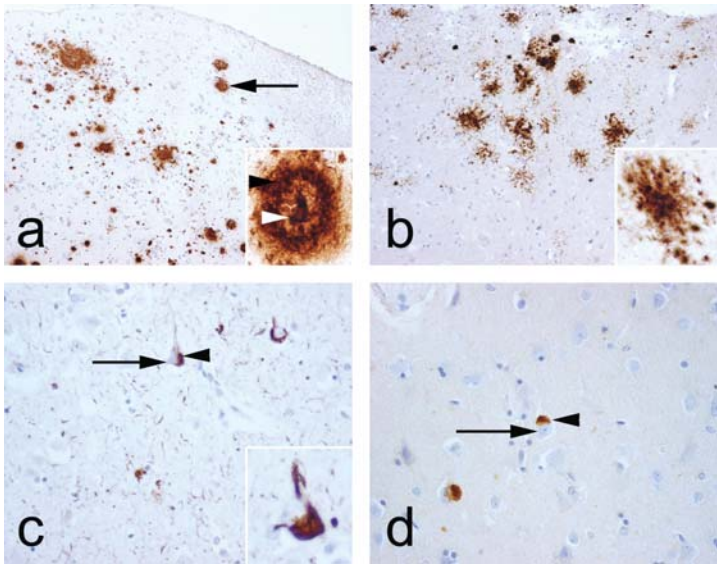

Figure 1. Accumulation of proteins in dementias

a. Aβ immunohistochemistry in the cerebral cortex in a case of AD, magnification x 10. Arrow, a non-neuritic plaque. Insert, a neuritic plaque x 40. White arrow head central core of amyloid, black arrow head surrounding dystrophic neurites.
b. PrP immunohistochemistry in the cerebral cortex in a case of new variant CJD, magnification x 10. Insert, a PrP plaque x 40.
c. Tau immunohistochemistry showing neurofibrillary tangles in the cerebral cortex in a case of AD, magnification x 40. Arrowhead, tangle. Arrow, nucleus of cortical neuron. Insert, an intracytoplasmic neurofibrillary tangle x 80.
d. Synuclein immunohistochemistry showing intracytoplasmic Lewy bodies in the cerebral cortex in a case of DLB, magnification x 40. Arrowhead, Lewy body. Arrow, nucleus of cortical neuron.

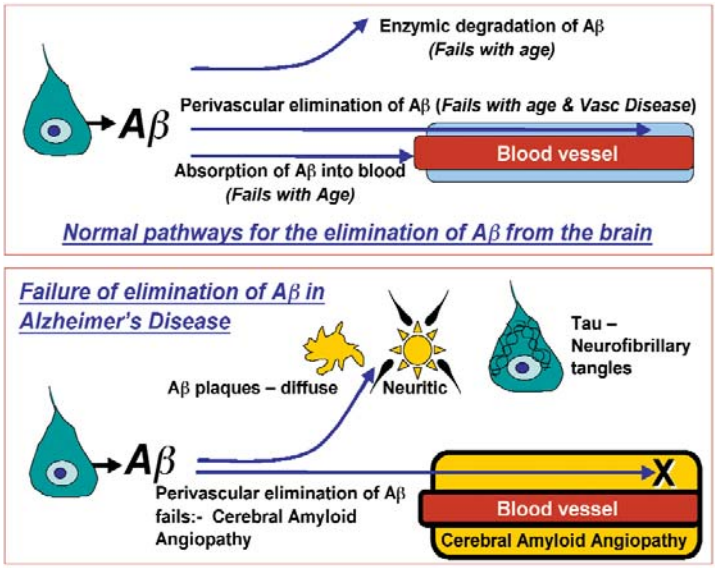

Figure 2. Elimination of Aβ in Normal brains and in Alzheimer's Disease.
In normal brain (upper panel), Aβ produced by neurons is eliminated enzymatically, perivascularly and into the blood. All three pathways fail with ageing.

In Alzheimer's Disease (lower panel), Aβ accumulates as diffuse plaques (shown by arrow in figure. 1a) and neuritic plaques, with a central core of amyloid surrounded by structurally abnormal (dystrophic) neurites (as shown in the insert of figure 1a). Tau also accumulates intracellularly in neurofibrillary tangles (see figure 1c). Cerebral Amyloid Angiopathy develops with accumulation of amyloid around blood vessels.

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Table: Pathology of Dementias as characterised by depositions of insoluble peptides and proteins within cells, in the extracellular spaces and blood vessel walls of the brain.

Dementia	*Intracellular Deposits in Neurons*	*Extracellular Deposits*	*Cerebral Amyloid Angiopathy*	*Vascular disease - Infarcts*
Normal ageing	*Tau* ↑	*Aβ* ↑	*Aβ* ↑	↑
Alzheimer's Disease	*Tau* ↑↑↑	*Aβ* ↑↑↑	*Aβ* ↑↑↑	↑↑
Vascular Dementia				↑↑↑
Dementia with Lewy Bodies	*Synuclein* ↑↑↑	*Aβ* ↑↑	*Aβ* ↑↑	↑
Frontotemporal Dementias	*Tau* ↑↑↑			↑
Corticobasal Degeneration	*Tau* ↑↑↑			↑
Multi System Atrophy	*Synuclein in glial cells* ↑↑↑			↑
Creutzfeldt -Jacob Disease		*PrP* ↑↑↑	*PrP (rare)*	↑
Huntington's Disease	*Huntingtin (Intranuclear)*			↑
Familial Dementias	*Tau* ↑↑↑ *Synuclein* ↑↑↑	*Aβ; Cystatin; ABri* ↑↑↑	*Aβ; Cystatin; ABri* ↑↑↑	↑

factor for dementias and is also a major risk factor for cerebrovascular disease. Patients with Vascular Dementia show widespread damage in the brain due to cerebrovascular disease with multiple small areas of infarction that may be recognised during life with MRI or by examination of the brain at post mortem.[2] Such patients often have cardiovascular risk factors such as diabetes and hypertension and may show stepwise progression of cognitive impairment due to the occurrence of new infarcts in the brain. Most patients with Alzheimer's disease also show evidence of cerebrovascular disease so that there is overlap between vascular dementia and Alzheimer's disease both clinically and pathologically.[8]

Pathology of Alzheimer's disease

The classical pathology of Alzheimer's disease was described 100 years ago; intraneuronal neurofibrillary tangles and the extracellular plaques of amyloid were visualised in histological sections stained with silver techniques.[2] Today, the amyloid plaques of Aβ and the NFT containing tau and ubiquitin are located by immunocytochemistry[2] (Figures 1a and 1c). The number of extracellular plaques and the distribution of neurofibrillary tangles within neurons of the cerebral cortex and hippocampus are used as criteria to diagnose Alzheimer's disease and to assess its severity.[9,10] More recently it has been shown that the level of soluble Aβ in the brain and the severity of CAA at post mortem correlate closely with the severity of dementia.[11,12]

Pathogenesis of Alzheimer's disease

Over 90% of cases of Alzheimer's disease are sporadic with no family history. Three major genes, those encoding APP, presenilin 1 and presenilin 2, are associated with inherited susceptibility[5] in the very small number of families with familial Alzheimer's disease. Apart from age, one major risk factor for sporadic Alzheimer's disease is possession of the ε4 isoform of apolipoprotein E (APOE). The 1-2% of the population who are homozygotes for APOE ε4 has an eight to ten fold increased risk of developing Alzheimer's disease and heterozygotes have a two to three fold increased risk.[13] ApoE co-localises with Aβ in amyloid plaques and in blood vessel walls; it may be involved in the aggregation of Aβ and in its clearance.[13]

The recent use of transgenic mice with mutations for human APP, presenilin and tau genes has illustrated much of the biology of Aβ and tau proteins. Cleavage of APP to form Aβ involves a number of secretases, and the presenilins are also involved in this process. Mutations in these genes result either in the overproduction of the more insoluble Aβ1-42 or in other aberrant forms of Aβ.[5] Experimental studies using double transgenic mice for mutations in the tau and APP genes[14] suggest that the accumulation of tau in neurofibrillary tangles in neurons may be induced by (and secondary to) the deposition of Aβ in the extracellular spaces of the brain.

Although there may be overproduction of Aβ or aberrant forms of Aβ in familial Alzheimer's disease, there is no clear evidence for this in the much more common sporadic form of Alzheimer's disease. This suggests that failure of elimination of Aβ from the brain may be a major factor in the pathogenesis of Alzheimer's disease rather than its overproduction. One important question, therefore, is "why does the elimination of Aβ fail in the elderly, resulting in Alzheimer's disease?"

Aβ is produced by cells in the brain throughout life and is eliminated by a number of mechanisms that fail with age. In young animals, and probably in young humans, Aβ is degraded by enzymes such as neprilysin in the brain parenchyma[15] and is absorbed into the blood by binding to a low density lipoprotein receptor related protein-1 (LRP-1);[16] in older individuals these mechanisms for the disposal of Aβ are less efficient and fail.[16] Aβ is also eliminated from the brain with interstitial fluid (ISF) by diffusion through the brain parenchyma and then by bulk flow pathways along the basement membranes of capillary and artery walls, effectively the "lymphatics of the brain"[17,18] (Figure 2). The motive force for the perivascular drainage of Aβ and ISF appears to be the pulsations in the vessel walls.[19] It is possible that cerebrovascular disease in the elderly interferes with the perivascular elimination of Aβ from the brain (by increased rigidity and hence decreased pulsation), resulting in the accumulation of Aβ in brain tissue and vessel walls that is characteristic of Alzheimer's disease[20] (Figure 2).

Therapy for Alzheimer's disease

As failure of elimination of Aβ from the ageing brain appears to be a major factor in the pathogenesis of Alzheimer's disease, therapies that remove Aβ from the brain may be beneficial. Following reports that immunisation against Aβ1-42 eliminated plaques of insoluble Aβ from the brains of transgenic APP mice,[21] clinical trials were instituted for immunotherapy in Alzheimer's disease. The study of post mortem brains from patients who died following immunisation against Aβ showed not only clearance of insoluble Aβ plaques from cerebral cortex but also showed a reduction in the number of damaged neurites containing tau protein (Figure 2) that sur-

The neuropathology of the majority of dementias is characterised by the accumulation of proteins within cells, within the extracellular spaces and in blood vessel walls indicating failure of elimination of such proteins from the ageing brain

round Aβ plaques in Alzheimer's disease.[22] However, there was no reduction in the amount of Aβ deposited in blood vessels as CAA and the drainage of interstitial fluid from white matter may also be impaired. In transgenic mice, the reduction of Aβ plaques in the brain in immunised animals is associated with a significant increase in CAA and with haemorrhages from the Aβ-laden vessels.[23]

Conclusion

The neuropathology of the majority of dementias is characterised by the accumulation of proteins within cells, within the extracellular spaces and in blood vessel walls indicating failure of elimination of such proteins from the ageing brain. Overlying the protein accumulation are the effects of cerebrovascular disease both as a cause of infarction in the brain and as a probable factor in the failure of elimination of proteins such as Aβ from the extracellular spaces and from blood vessel walls. Therapies that facilitate the clearance of Aβ from the extracellular spaces and from blood vessel walls may prevent or ameliorate Alzheimer's disease. Immunotherapy may prove to be one such therapy.

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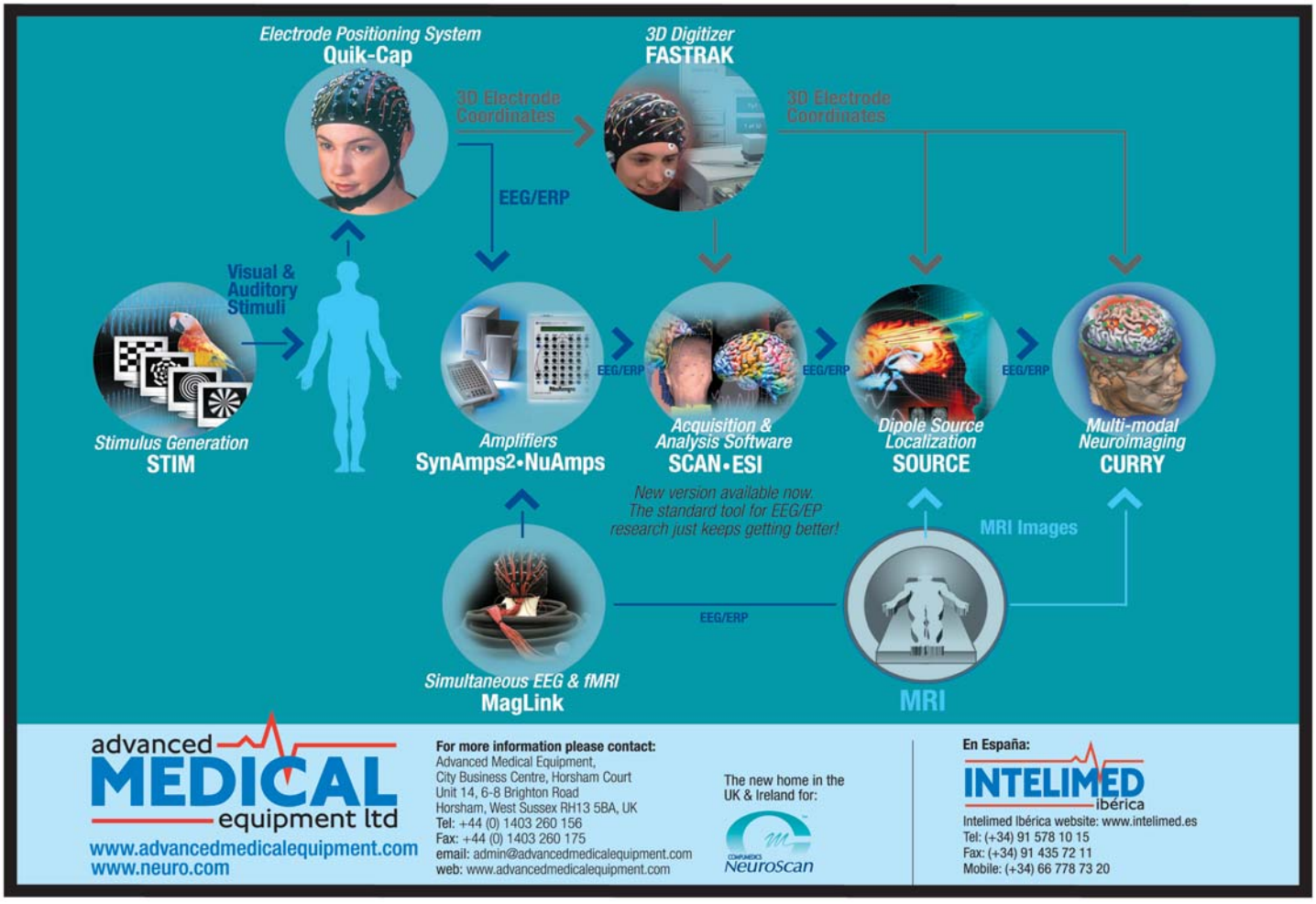

For humans, vision is the sense that dominates over all others. Our interactions with the external world, and with each other, rely heavily on what we see - or at least on what we believe we perceive. Small wonder that so much of the brain is devoted to visual processing, and that damage to the visual system often leads to profound disability.

In this edition, we start a series of primers on Visual Neuroscience, written by experts in the fields of retinal physiology, the anatomy of the visual pathways, colour vision, eye movements, visual illusions and attention. The aim of this series is to convey not only the fundamentals, but also to update readers on new and exciting developments in these fields.

Research in vision moves at an extremely fast pace, as exemplified by the new findings reviewed in our opening primer on the retina. In the last few years there has been a quantum leap in this field with the discovery of a completely new visual-sensing system that is entirely different from the classical rod and cone system. The characterisation of this novel pathway has only just begun but the findings suggest it may play a critical role in the control of circadian rhythms.

In subsequent issues, we hope to bring you up to date on a range of old and new findings in vision. We hope you will enjoy what you see.

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The Neural Retina: Three Channels of Light Detection

The retina is a neural network that has two critical functions: transduction of light into an electrical signal and the vital initial processing of visual information. Phototransduction is achieved by specialised sensory retinal neurons: The cone photoreceptor cells for bright light vision, the rod photoreceptor cells for dim light vision and the recently discovered intrinsically photosensitive melanopsin ganglion cells which have a role in irradiance detection for non-image-forming tasks. Here we will outline these three light sensing retinal channels, focusing on their principal functional features.

Basic Retinal Anatomy

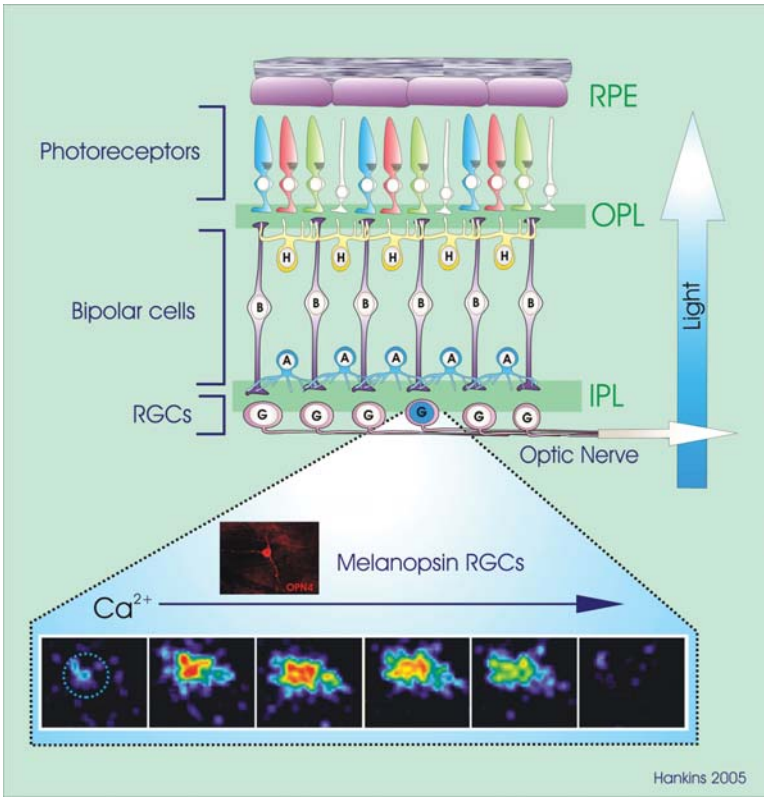
A remarkable feature of the vertebrate retina is its highly ordered neuronal organisation. The retina is composed of 3 cellular layers interspersed with two synaptic layers (Figure 1; e.g.[1,2]). The soma of the rod and cone photoreceptor cells resides in the outer nuclear layer. The inner nuclear layer contains the soma of the bipolar cells, the horizontal cells and the amacrine cells. Some amacrine cells are displaced to the ganglion cell layer, which principally contains the soma of the ganglion cells. The rod and cone photoreceptors utilise multiple parallel cellular pathways to relay the light signal to the ganglion cells, the output neurons, whose axons form the optic nerve and mainly project to the lateral geniculate nucleus and the superior colliculus. Recently, a novel class of ganglion cell has been identified that does not require rod and cone input to generate a light signal. These cells form an unexpected additional light sensitive channel in the retina and their axons project primarily to the suprachiasmatic nucleus and the pretectal nuclei.[3-5]

The Cone System

Photopic vision begins at the cone photoreceptor cells. The structure of these sensory neurons is optimised to maximise photon capture, with an elongated outer segment region packed with membranous discs embedded with either long- (LW), medium- (MW) or short- wavelength (SW) sensitive opsin photopigment (see chromaticity section). The process of phototransduction is initiated in the outer segment. Absorption of light by 11-cis retinal in the photopigment binding pocket activates a G-protein cascade that is negatively coupled to a cGMP-gated cation channel. Therefore during light stimulation the channels close and there is a decrease in the influx of cations into the cell. This results in a graded membrane hyperpolarisation and reduced glutamate release from the cone synaptic terminal.

The light signal is transmitted through the retinal network to the output ganglion cells. The cones make synaptic contacts at the outer plexiform layer with bipolar cells. Two main sub-types of cone bipolar cell are present: OFF-centre and ON-centre cells. The OFF cone-bipolar cells hyperpolarise in response to light and the ON cone-bipolar cells depolarise upon retinal illumination. These cells segregate the light signal into ON- and OFF- channels. Therefore, ON-ganglion cells fire action potentials in response to increases in retinal illumination whereas the OFF-ganglion cells respond to decreases in the illumination level. The cone to bipolar to ganglion cell pathways represent the direct route of signal transmission through the retina and form the 'vertical' retinal pathways.

Contrast. In addition to the vertical pathways, lateral pathways in the retina further process the light signal. One such system involves the horizontal cells. The horizontal cells receive inputs from several photoreceptor cells that



The neural retina is a network of neurones in contact with the retinal pigment epithelium (RPE). Classical photoreceptors (rods and cones) synapse at the outerplexiform layer (OPL). Here, bipolar cells (B) take the rod and cone signals and feed them forward to the innerplexiform layer (IPL), forming contacts with retinal ganglion cells (G), whose axons form the optic nerve. At the OPL and IPL, horizontal cells (H) and amacrine cells (A) are respectively interneurones that sub-serve lateral signal processing. Inset: a subpopulation of retinal ganglion cells (blue) expressing melanopsin, are intrinsically photosensitive and signal irradiance information to a range of retino-recipient brain areas. Calcium imaging experiments[5] reveal a network of light responsive cells in the inner parts of the mammalian retina.

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surround a central group of cones and this information is fed through to the bipolar cells. Importantly, the lateral input signal is opposite to that of the vertical pathway signal thereby producing a 'lateral inhibition' effect. Therefore the receptive fields of ON- and OFF- bipolar cells have two components: a centre and a surround. Illumination of the central area of a bipolar cells receptive field results in an ON- or OFF- centre response, whereas illumination of the peripheral receptive field results in the opposite ('opponent') response. This feature enhances contrast discrimination and thus visual signal processing is initiated within the first synapses of the retina.

Acuity. Maximum acuity in the vertebrate retina would be achieved if each ganglion cell received information from a single cone at the receptive field centre. Indeed, this is the case in the central fovea (~ 0.6° visual field). Here, LW and MW cones are packed at densities approaching 200,000 cells/mm^2 and each cone synapses with a 'midget' (small dendritic field) ON- and OFF-bipolar cell. In turn these cells feed-forward to their corresponding 'midget' ganglion cell counterpart. This wiring pattern underpins the high spatial resolution in the central retina. Interestingly, there are very few SW-cones in the central fovea and all normal human subjects are tritanopic in this region. It appears that in the central retina chromatic sensitivity is sacrificed for acuity. In the peripheral retina, the cone density is lower and the bipolar cells in this region have larger dendritic fields and summate the input from multiple cones. This convergence results in reduced acuity in the peripheral retina.

Chromaticity. In order to initiate discrimination between different wavelengths of light, the responses of the different spectral cone classes are compared in an opponent manner. In the central retina, information originating from a single LW- or MW- cone can be relayed to a single midget ganglion cell.[6] These cells are believed to generate LW and MW opponent responses suggesting that colour discrimination begins at the level of the retina. However, there is some controversy regarding how colour opponent responses are generated. The random wiring theory suggests that in the central retina (where ganglion cells receive input that originates from single cones) there should be strong opponency whereas in the peripheral retina (where information from several cones converge on to the receptive field centre of single ganglion cells) chromatic sensitivity would be reduced. However, it has been found that in the peripheral retina of macaques, LW versus MW cone opponency is no different to the centre.[7] This would suggest the presence of selective cone wiring although there is no direct evidence to support this model. The SW cone pathway utilises a specialised bipolar cell feeding on to a ganglion cell that produces a blue ON/yellow OFF response.[8]

The Rod System

The cone system is active in photopic conditions however, at low light levels the retina relies on the rod photoreceptor cells. The outer segment region of these cells contains the photopigment rhodopsin. The phototransduction pathway in the rods is essentially the same as that in cones, whereby absorption of light results in membrane hyperpolarisation. The rods feed-forward to a single dedicated bipolar cell, the rod ON-bipolar cell. These cells depolarise in response to light via a similar mechanism to that found in the cone ON-bipolar cells. At this point similarities with the cone pathway cease. In mammals the rod pathway does not have a direct connection to the ganglion cells. The rod ON-bipolar cell contacts an AII-amacrine cell, which in turn contacts cone ON- and OFF- bipolar cells. The cone bipolar cells then follow their normal synaptic route to the ganglion cell layer. Thus the cellular pathway associated with the rod cell appears to piggy-back onto the cone pathway. Other pathways for transmission of the rod signal include rod-cone coupling and a possible direct input of rods to cone OFF-bipolar cells.

Sensitivity. Compared to the cone system, the rod system is more sensitive to light, permitting vision at dim light levels. This property originates at two levels, within the rod cell itself and also within the retinal neuronal network. In the rods, a single photon activates a rhodopsin molecule and can induce a detectable single quantal change in the membrane potential. In addition, the retinal neuronal network associated with the rod pathway is convergent, permitting summation of the light signal from many rods. The rod ON-bipolar cell receives inputs from 20-80 rods and several rod bipolar cells synapse onto an AII amacrine cell. This convergence reflects a system designed for sensitivity rather than acuity. No rods are present in the foveal region and hence peak scotopic sensitivity occurs 15-20 degrees off the visual axis.

The Melanopsin Ganglion Cell System

In contrast to the classical rod and cone visual photoreceptors the intrinsically photosensitive melanopsin ganglion cells reside in the ganglion cell layer, do not have a specialised cellular structure, and depolarise in response to light (Figure 1 inset). Melanopsin is a member of a novel opsin family and has recently been shown to form a fully functional photopigment.[9] In the human retina the melanopsin ganglion cells number in the order of 2000 cells per retina. The native phototransduction cascade associated with the melanopsin ganglion cells remains unknown but it has been ascertained that the photocurrent is carried by Na^+ and Ca^{2+} ions.[3,5]

Irradiance Detection. The melanopsin ganglion cells perform a different function to the rod and cone photoreceptor cells. They signal changes in ambient lighting levels. Unlike the rods and cones, which adapt quickly to prolonged light stimuli, the melanopsin ganglion cells exhibit little adaptation. This irradiance information is used to drive non-image forming processes. For example the axons of the melanopsin ganglion cells project directly to the suprachiasmatic nucleus (the site of the central circadian pacemaker) and to the pretectum (which drives the pupillary light reflex). Importantly light responses in these retinorecipient areas persist when all rod and cone cells are lost or ablated. It has been recently shown, both in rodents and primates that the melanopsin cells also project to brain regions associated with classical image forming vision.

Interaction with Rod and Cone Systems. Recent evidence suggests that there is significant interplay between the classical photoreceptor cell systems and the melanopsin ganglion cells in the retina. The melanopsin ganglion cells receive input from the rod and cone cell pathways. Furthermore, the light responses of these cells are routed through gap-junctions to other inner retinal neurones.[5] It has also been shown in humans that the novel irradiance system plays a role in the regulation of the cone pathway at the local retinal level.[10]

Conclusions

This review has attempted to describe the key functional features of the three channels of light detection in the retina. However, this is by no means a complete picture. For example, there are over 50 types of amacrine cells but details concerning their function are unclear. Increasing evidence suggests starburst amacrine cells may be directionally sensitive, but it is unclear if this is the case in primates. There is also a dearth of knowledge concerning the melanopsin ganglion cells with regards to their physiology and connectivity. The extent of interplay between the three light sensing channels also remains to be fully explored. It is amazing that after over a century of research into retinal neurobiology details of retinal circuitry are being amended and elucidated; remarkably new photopigments and even functional retinal pathways are still being identified.

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Asymptomatic Unruptured Intracranial Aneurysms

There is widespread consensus that symptomatic unruptured aneurysms carry a substantial risk of rupture and require treatment. In contrast the management of a patient with an asymptomatic unruptured aneurysm (AUIA) remains controversial. If all AUIAs could be successfully obliterated with minimal morbidity and mortality the catastrophic consequences of a subarachnoid haemorrhage could be safely averted. However, the attendant risks of treatment may outweigh the potential benefits of aneurysm exclusion. Therefore it is important to appraise the natural history of these lesions if left untreated and balance this against the risks of treatment when formulating an evidence-based management plan.

Epidemiology

Epidemiological data can help estimate the risk of AUIA rupture. Post mortem and angiographic studies report that AUIAs are found in approximately 1-6% of the population.[1] The variability in incidence may be attributed to geographic and age profile differences in the populations studied in addition to case selection, technical and observer factors. In a systematic review Rinkel et al. conclude that the prevalence of AUIAs in adults without specific risk factors is 2.3%.[1]

A population based study with stringent case ascertainment indicates that the incidence of aneurysmal subarachnoid haemorrhage is 7.4/100 000 men and 11.9/100 000 women in South West England, with an overall rate of 9.7/100 000.[2] The relatively high prevalence of AUIA and low incidence of subarachnoid haemorrhage indicates that most AUIA do not rupture.

If all aneurysmal subarachnoid haemorrhages (1/10000 per annum) are considered to originate from AUIAs and the prevalence of AUIA is considered to be 2.3%, the risk of rupture can be estimated as 0.4% per annum. This may be an over estimate due to the unknown number of cases of rapid de novo aneurysm formation, expansion and rupture with no significant time spent in an AUIA phase. In addition, risk factors (smoking, hypertension, polycystic kidney disease) will increase the rupture rate in some patients. Assuming that virtually all AUIAs and SAH cases occur in the 60% of the population over the age of 30 years, the incidence of SAH in adults can be approximated to 1 in 6000 while the prevalence of AUIA is 1 in 26 in this population. This again infers that less than 0.5% of AUIA will rupture per annum.

Natural History Studies

It is difficult to study the natural history of AUIAs both due to the longevity required, cases lost to follow-up and the fact that cohort studies may carry significant bias due to the exclusion of patients selectively treated and not recruited for follow-up. In such studies 2 groups of patients are characterised; those with an incidental AUIA and cases with an additional AUIA. The latter group have previously had aneurysmal SAH from a separately treated culprit aneurysm. Valuable follow-up data in 142 patients with 181 unruptured intracranial aneurysms with prolonged follow-up has been reported from Scandinavia (mean follow up 19.7 years, range 0.8 – 38.9 years, 109 cases studied for at least 10 years).[3] The majority (n = 131) of these cases were additional aneurysm patients. Of these, 30 patients experienced a further SAH during follow-up. This was calculated to represent an annual rupture incidence of 1.3%. The risk factors for haemorrhage were age (inverse relationship), increasing aneurysm size and smoking. This study did not provide any robust information about the rupture risk from incidental AUIAs.

The International Study of Unruptured Intracranial Aneurysms (ISUIA) is a 53-centre study that has provided natural history data.[4,5] The 1449 retrospectively studied patients presenting between 1970 and 1991 showed that the incidence of rupture in patients with incidental anterior circulation aneurysms <10 mm in diameter was 0.05% per annum. In patients with similar size aneurysms and a previous SAH the rupture risk was 0.5% per annum. The rupture rates for aneurysms between 10-15mm approached 1% for both groups.[4] Whilst it may seem that over 3 decades the risk would be around 30%, mathematical probability indicates that it is lower at around 22%. These retrospective findings indicate a much lower rupture rate than previously reported. Although inclusion bias has been cited as a possible reason for these results, many clinicians have adopted a more conservative approach in response to this evidence.

The prospective component of the ISUIA study with recruitment between 1991-1998 followed up 1692 patients who had conservative management of incidental (1077 cases) or additional (615 cases) AUIAs for an average of 4.1 years.[5] Interestingly the incidental aneurysms were generally larger than the additional lesions. Of the 51 patients (3%) that sustained a SAH during follow-up, 41 had incidental aneurysms with no history of previous SAH (3.8%). Only 10 (1.6%) cases in the additional aneurysm group sustained a SAH. The large number of very small aneurysms in this group (80% compared to 50% in the incidental aneurysm group) probably explains the lower bleed rate. Whilst a previous SAH has been shown to be associated with a higher risk of AUIA rupture in the retrospective cohort the small numbers of prospectively observed bleeds in this group does not add credence to this conclusion. This study also reported several other notable findings related to aneurysm size and location.

1. Incidental aneurysms less than 7 mm in diameter very rarely rupture (n = 2). Both ruptured aneurysms in this size range were posterior communicating artery aneurysms. Since no other 2 – 7 mm incidental anterior circulation aneurysms ruptured, posterior communicating artery aneurysms were speculated to carry a higher risk of bleeding and were subsequently analysed with posterior circulation aneurysms. Seven of the 10 ruptured additional aneurysms were in the 2-7 mm size bracket.
2. Larger incidental aneurysms are more likely to bleed. This conclusion was largely based upon the findings in patients with incidental aneurysms. The numbers of ruptures in the additional aneurysm group were too small to comment upon the importance of size.
3. Aneurysms in the posterior circulation had a higher rate of rupture.

The 5-year rupture rates are summarised in Table 1. In essence the annual risk of a bleed was less than 1% for aneurysms up to 12 mm diameter, only increasing to

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Table 1: 5 year cumulative rupture rates according to size and location of unruptured aneurysm (data from ISUIA study). Rupture rates between additional and incidental aneurysms only differed for aneurysms <7mm in diameter.

Aneurysm Location	<7mm Previous SAH	<7mm No SAH	7-12mm	13-24mm	>24mm
Anterior circulation (exc. P comm.)	0	1.5%	2.6%	14.5%	40%
Posterior circulation (inc. P comm..)	2.5%	3.4%	14.5%	18.4%	50%

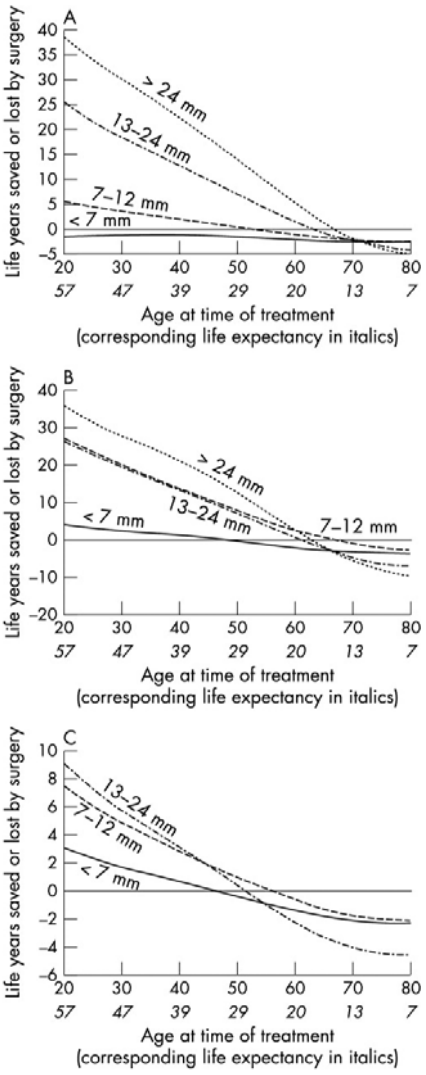

*Figure 1: Expected life years lost or gained by treatment against patient age at the time of treatment for surgical treatment of unruptured aneurysms in four size ranges: (A) Incidental aneurysms (no previous history of subarachnoid haemorrhage (SAH)) of the anterior circulation (internal carotid, anterior cerebral, middle cerebral (including posterior communicating) arteries). Note that the bleed rate used for the anterior circulation <7 mm group is not 0% per year as given by ISUIA but 0.08% calculated by including the posterior communicating aneurysms. (B) Incidental aneurysms of the posterior circulation (excluding posterior communicating artery) and (C) additional (previous SAH) aneurysms. Anatomical groups are not separated.[8]

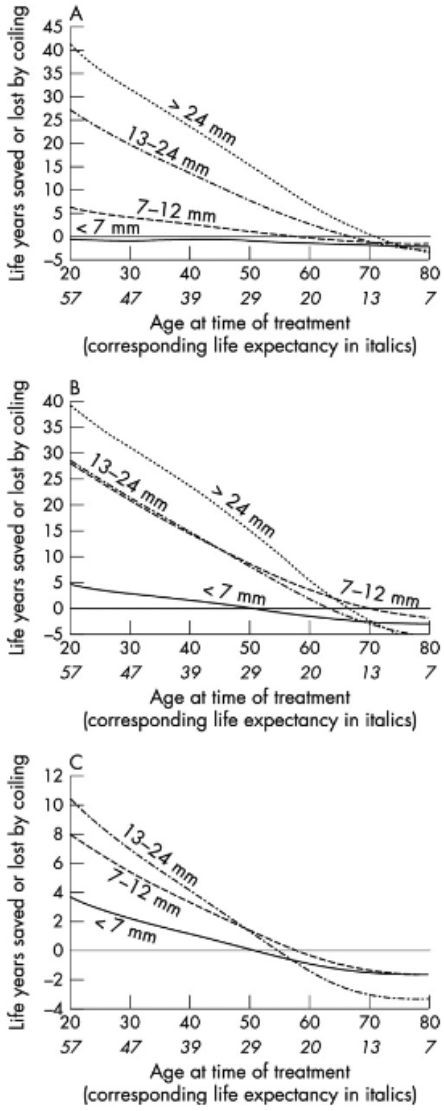

*Figure 2: Expected life years lost or gained by treatment against patient age at the time of treatment for endovascular treatment of unruptured aneurysms in four size ranges. (A) Incidental aneurysms (no previous history of subarachnoid haemorrhage (SAH)) of the anterior circulation (internal carotid, anterior cerebral, middle cerebral (including posterior communicating) arteries). (B) Incidental aneurysms of the posterior circulation and (C) additional aneurysms.[8]

*J Neurol Neurosurg Psychiatry, 2005;76:234-9. Reproduced with permission from the BMJ Publishing Group.

Table 2: Screening for incidental intracranial aneurysms

SCREENING ISSUES	*COMMENTS*
Disease should be common	*SAH is rare; incidence 1/10 000 per annum*
Disease should carry substantial morbidity	*Morbidity and mortality of SAH is substantial*
Screening test should be acceptable	*CT angiography is acceptable, sensitive and specific. Invasive angiography is not an acceptable low risk test*
An effective preventative treatment is available	*Coiling and clipping carry substantial risks*
Lead-time bias	*This is the time between diagnosis and onset of symptoms. If an aneurysm is identified but not treated the lead-time bias is increased by an infinite amount. Psychological morbidity may be considerable.*
Length bias	*Screening may detect a large number of patients with stable low risk aneurysms and miss aneurysms that develop or expand quickly.*

around 3% for lesions 13-24 mm. The rupture rate for giant aneurysms was around 10% per annum.

It is important to recognise that the ISUIA study was not a randomised-controlled trial and that many patients eligible for conservative observation were selected for surgical intervention or endovascular therapy. In addition, the use of inclusion criteria and the unknown recruitment rate question the applicability of the findings to the wider population. Despite these caveats the study does provide the best natural history data available. Future reports from ISUIA with longer follow-up will enhance the quality of the data.

Operative and endovascular treatment risks

The reporting of procedural risks is imperfect due to publication bias and criticisms of study design. Whilst the International Cooperative Study on aneurysmal SAH compared surgical treatment with overall management outcome in a cohort of 3500 cases such information is not directly applicable to the AUIA population.[6] Similarly the ISAT trial was targeted at patients treated after a subarachnoid haemorrhage.[7] The most robust information again arises from the prospective cohort of the ISUIA study where outcome was recorded in 1917 cases undergoing aneurysm clipping and 451 cases treated with endovascular coiling recruited between 1991 and 1998.[5] Risk factors for a poor outcome were posterior fossa aneurysm location, size greater than 12mm and (for surgical patients only) age. A considerable proportion of endovascular treatments only achieved partial occlusion; the long-term durability of this treatment remains under scrutiny. Overall, poor outcomes were reported in around 5-6% of clipped small and medium sized anterior circulation aneurysms in patients less than 50 years of age. Age over 50 years doubled the frequency of poor outcomes following clipping of small aneurysms. The poor outcome rate increased to around 25% for patients over 50 years with medium sized aneurysms. Morbidity from posterior fossa aneurysm surgery was even greater. Endovascular coiling of small and medium sized anterior circulation aneurysms carried a 7-8% risk of a poor outcome in patients less than 50 years old. Although these results suggest that small aneurysms are best treated with clipping it should be remembered that the patients were selected and not randomised to different treatment modalities. Giant aneurysms were rare but the risks of a poor outcome with endovascular treatment were around 15% with wide confidence limits.

Risk assessment

ISUIA and Juvela's cohort study have provided an estimate of aneurysm rupture rate over a period of time.[3,4,5] ISUIA has also provided data on treatment outcomes in patients undergoing prophylactic aneurysm treatment. For each individual the risk of treatment needs to be balanced against the risk of rupture. Using the ISUIA data and predicted life expectancy derived from the 2001 UK census, Mitchell's group plotted outcome predictive curves where

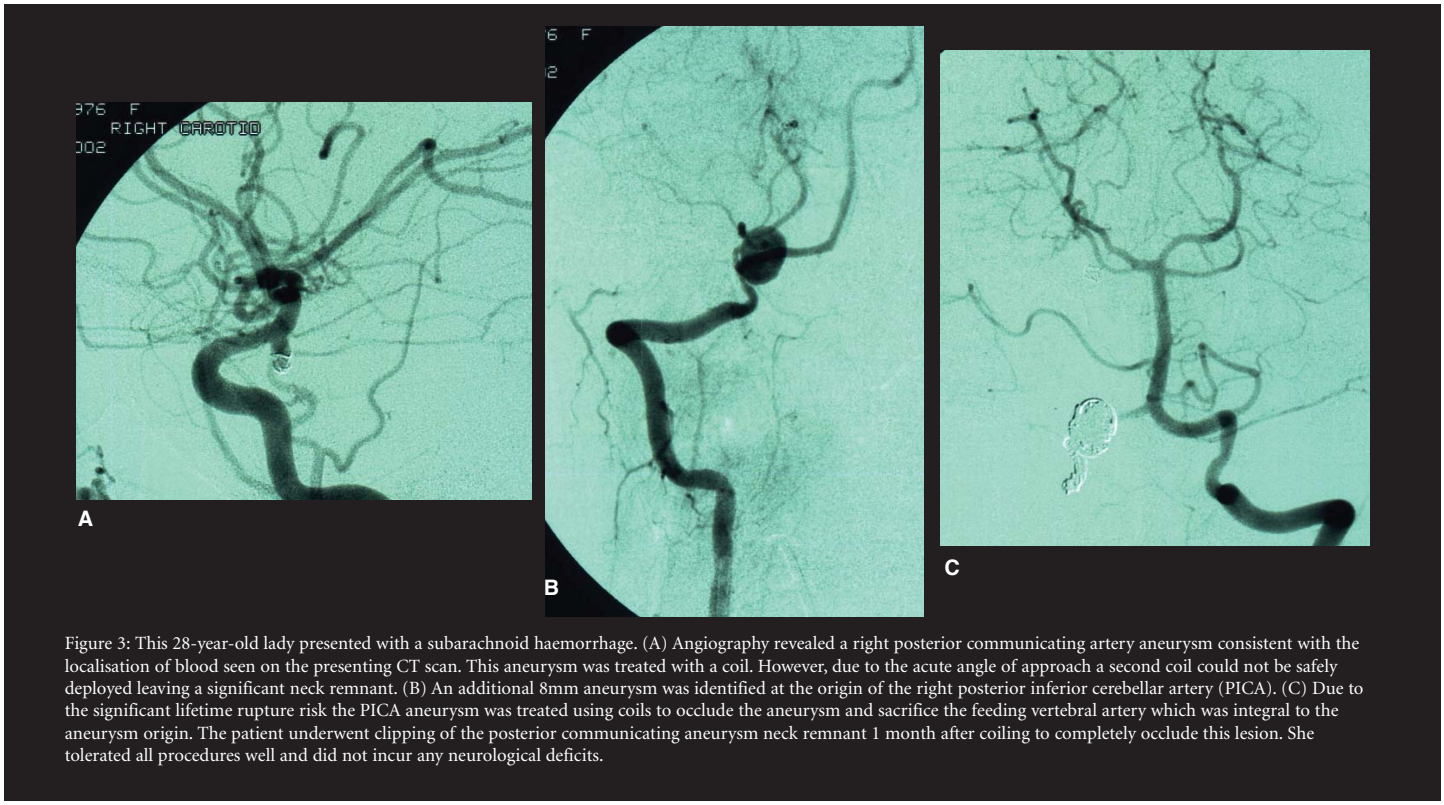

Figure 3: This 28-year-old lady presented with a subarachnoid haemorrhage. (A) Angiography revealed a right posterior communicating artery aneurysm consistent with the localisation of blood seen on the presenting CT scan. This aneurysm was treated with a coil. However, due to the acute angle of approach a second coil could not be safely deployed leaving a significant neck remnant. (B) An additional 8mm aneurysm was identified at the origin of the right posterior inferior cerebellar artery (PICA). (C) Due to the significant lifetime rupture risk the PICA aneurysm was treated using coils to occlude the aneurysm and sacrifice the feeding vertebral artery which was integral to the aneurysm origin. The patient underwent clipping of the posterior communicating aneurysm neck remnant 1 month after coiling to completely occlude this lesion. She tolerated all procedures well and did not incur any neurological deficits.

"life years saved or lost by aneurysm repair" was plotted against age at time of treatment (see Figures 1 and 2).[8] Inspection of the curves enables the clinician to ascertain the relative risks of treatment versus the saving of life years. For example, life years are saved by endovascular treatment of incidental anterior circulation aneurysms in the 13-24 mm range for patients under the age of 65 years. This model is based on the assumption that aneurysm occlusion provides robust protection from rebleeds. It does not address the cost-benefit ratio of treatment.

Aneurysm screening

Genetic factors appear to be important in the causation of intracranial aneurysms. Therefore, screening relatives of SAH victims might seem an approach worthy of consideration. However, many factors need to be considered (Table 2).

In a useful review paper, White and Wardlaw conclude that only 156/21054 (0.74%) of first degree relatives sustain a SAH in population-based longitudinal studies.[9] A recent Scottish study reported the 10-year prospective risk of sustaining a SAH for a first-degree relative of an index case as 1.2% (95% CI: 0.4 - 2%). The risk for second-degree relatives was 0.5% (CI: 0.1 – 0.8%).[10] There was a trend for the risk to be highest in families with two first-degree relatives affected and lowest if only one second-degree relative was affected. On this basis screening for aneurysms should only be offered to patients over 30 years old in families with 2 or more first-degree relatives with a history of SAH. If only 1 first-degree relative has sustained a SAH, screening is not recommended. Other at risk patients (e.g. adult polycystic kidney disease) should be advised on an individual basis. Due to the high sensitivity and specificity, rapid acquisition time and low procedural risks (x-ray exposure) CT angiography is now our screening investigation of choice, replacing invasive digital subtraction angiography and MR angiography.

Summary and case study

High quality studies have helped to improve our knowledge of the natural history and treatment risks in patients with AUIAs. Knowledge of this literature is essential to formulate an evidence-based management plan applicable to the individual patient. Factors such as life expectancy, aneurysm location and size, coupled with the individual's attitude to risk will govern the approach selected (Figure 3). Interdisciplinary teamwork between neurosurgeons and neuroradiologists is crucial to optimise evidence-based management. Widespread screening is not recommended and should be reserved for high-risk cases after discussion with the patient.

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Interdisciplinary teamwork between neurosurgeons and neuroradiologists is crucial to optimise evidence-based management

Immunohistochemistry

Immunohistochemistry (IHC) is a widely used technique employed for the determination of cell types and the demonstration of pathological changes in tissues. The technique depends on specific interactions between antibody and antigen, coupled with methods of visualisation of this interaction. IHC has important applications both in clinical diagnosis and in experimental research. Highly specific antibodies are used which recognise cellular antigens and, in general, specific epitopes of the antigen (i.e. short amino acid sequences of the antigen). The high specificity of antibodies and the use of antibodies that recognise different epitopes of the same protein allow for detection of post-translational changes of the protein which allows for detection of a variety of pathologies.

Technique

The technique of IHC is outlined in Figure 1. Tissue is fixed and prepared for analysis, and sections of tissue are cut for analysis. Blocking solutions are used to prevent non-specific antibody binding to the tissue. Sections are then incubated with the primary antibody, which is specifically directed against the antigen in question. An optimal antibody concentration must be determined in order to obtain high specificity and avoid background or non-specific staining. Sections are then incubated with secondary antibodies which react with the primary antibody and are linked either to a direct marker or to an enzyme which will be used in a chemical reaction. Direct markers of the reaction include fluorochromes which emit fluorescence on exposure to particular wavelengths of light. Three fluorochromes are routinely used: fluoroscein, rhodamine and aminomethylcoumarin (AMCA), which emit green, red and blue light respectively. Thus double or triple labelling of tissue can be performed, allowing for identification of multiple antigens on the same section (Figure 2).

Enzyme-linked secondary antibodies rely on further incubation with the substrate of the enzyme. The enzyme which is attached to the secondary antibody will catalyse a reaction converting a colourless substrate into a coloured substance directly where the antibodies have bound, thus indicating the site of binding of the antibody. For instance the enzyme horseradish peroxidase (HRP) catalyses the oxidation of diaminobenzidine (DAB) to form a highly insoluble brown end product which can be easily visualised by light microscroscopy. Furthermore the brown end-product is highly stable and specimens can thus be stored for long periods of time (Figure 3). For detection of antigens expressed at very low levels a number of amplification methods are available, allowing for the detection of very small amounts of protein in tissue specimens.

Clinical use of IHC

IHC has many clinical applications for the diagnostic analysis of pathological specimens. In neurological practice, brain tissue from biopsy or post mortem, nerve biopsies and muscle biopsies are commonly analysed by IHC techniques. In broad terms IHC is used:

1. To identify specific cell types: Cell specific antibodies are used commonly to identify tumours of the central nervous system and determine grade. Glial fibrillary acidic protein (GFAP) is an astrocytic antigen which can be studied in brain sections and may be found in an abnormal distribution in astrocytomas. GFAP staining may also be upregulated in inflammatory conditions and represents astrogliosis. Thus patterns of staining and ancillary tests are required to determine exact pathological diagnosis. Furthermore, the use of antibodies recognising immune and inflammatory cells allow for the identification of a variety of inflammatory reactions in tissue. In other circumstances, the absence of particular

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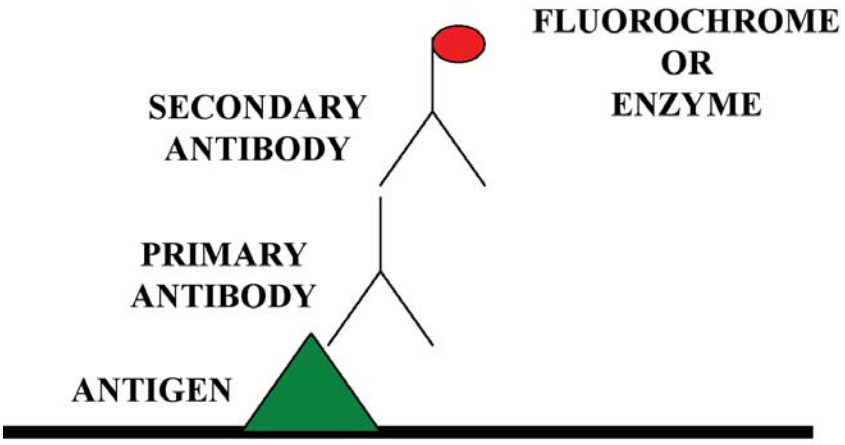

Figure 1: General principle of immunohistochemistry.

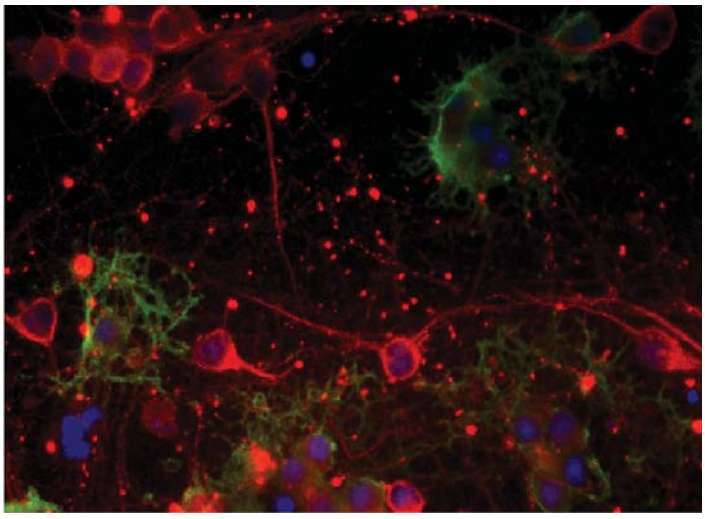

Figure 2: Triple labelling of mixed cell culture showing neurons (red) labelled for neurofilament, oligodendrocytes (green) labelled for galactocerebroside and cell nuclei (blue).

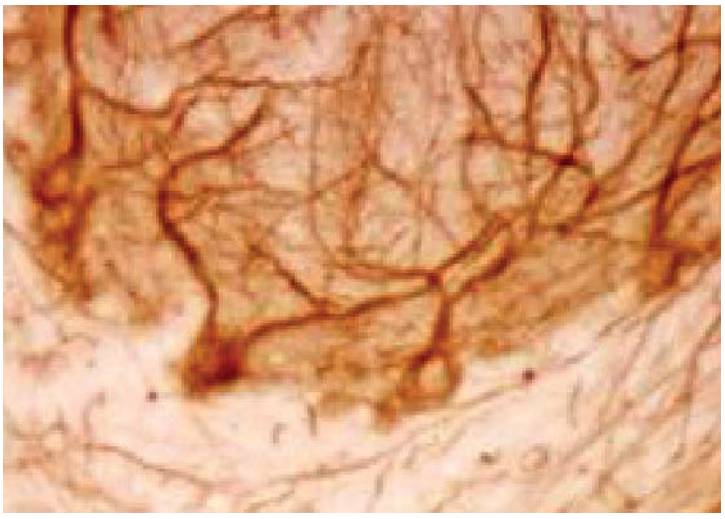

Figure 3: Identification of Purkinje cells of the rat cerebellum by detection of neurofilament staining using HRP-DAB visualisation.

cell types may give important pathological clues. For instance in acute and chronic multiple sclerosis lesions, a loss of oligodendrocyte and myelin markers are typically seen.

2. To identify abnormal protein deposits within cells: Protein aggregates are common in a variety of neurodegenerative diseases. Antibodies directed against specific proteins can recognise pathological inclusions in brain tissue. Specific patterns of antibody staining are key to pathological diagnosis of a variety of dementias. Antibodies commonly used include tau, a-synuclein, ubiquitin, prion protein and amyloid peptides.
3. To identify post-translational protein modifications: Many neurological diseases are characterised by abnormal isoforms of cellular proteins. These post-translational modifications of normal cellular proteins may be detected by the use of highly specific antibodies which can identify specific isoforms of the same protein. For instance axonal pathology, both in the central and peripheral nervous system, may be characterised by the presence of abnormal levels of phosphorylation of neurofilaments. Neurofilaments form part of the axonal cytoskeleton and, in health, are highly phosphorylated. In disease states neurofilaments may be hypophosphorylated or hyperphosphorylated. A variety of antibodies are available which recognise these abnormal neurofilament states and thus help in determination of pathological states.

Experimental use of IHC

IHC may be applied to a wide variety of experimental protocols. The technique is used in vivo and in vitro and may be used to evaluate the influence of various experimental manipulations on fundamental cellular processes such as apoptosis or cell division. Cell culture techniques are ideal for such experiments. For instance cells can be treated with bromodeoxy-uridine (BrDU) which is taken up by diving cells. IHC using antibodies directed against BrDU can then label dividing cells. Similarly antibodies against components of the apoptotic cascade are important experimental tools. More recently the development of antibodies which identify activated and non-activated components of intracellular signalling pathways allow for the analysis of cell signalling by IHC.

In vivo experiments often rely upon the need to track cells which may have been transplanted in attempts to repair lesions of the nervous system. A variety of IHC based techniques, often coupled to the use of reporter genes, facilitate this process. IHC is also commonly used for the evaluation of animal models of disease.

Summary

IHC is regularly used in clinical and experimental practice. The specificity of antibodies and the ability to detect low levels of protein renders the technique a powerful tool in pathological diagnosis. With further advances in antibody and imaging technology, further insights into the molecular pathogenisis of neurological disease will be gained over the coming years.

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Bench to Bedside: Extrapyramidal Disorders

Date – Thursday 24 November 2005
Venue - The Royal Society of Medicine, London

- Pathology of extrapyramidal disorders
- Genetic disorders
- Diagnostic imaging
- Differential diagnosis
- Three video case presentations from Hungary
- Creatin and Neuroprotection
- Future therapies
- Pharmacological Management of Parkinson's Disease
- Management of Huntington's Disease
- Surgical Treatment of Parkinson's Disease
- Management of Tremor
- Management of Dystonia

Clinical Update: Epilepsy in Adults and Adolescents

Date - Wednesday 8 March 2006
Venue - Cardiff University

- Non-Epileptic Attack Disorders: neurological and psychological aspects
- When to start treatment and with what?
- Choice, change, monitoring and withdrawal of drugs
- Adverse effects (pregnancy, toxicity, interactions with other drugs)
- Practical and psychosocial impact of epilepsy
- Long term effects – social and employment consequences
- Information needs of patients with epilepsy: a nurse's perspective (including SUDEP)

Acute Neurology for General Physicians

Date – Monday 5 December 2005
Venue - The Royal Society of Medicine, London

- Assessment of the comatose patient
- Acute headache: things you must not miss
- Fits, Faints & Funny Turns
- Acute neuromuscular weakness
- Acute Neurology of Systemic Disease
- Management of acute infection in the nervous system
- Management of acute stroke
- Dizziness
- When do I call the neurosurgeon?
- Acute neurology quiz: Test your skills

Post Traumatic Stress Disorder in the Current Climate

Date - Thursday 23 March 2006
Venue - The Royal Society of Medicine, London

- NYPD cadet data
- MRI/MRS imaging data
- Drug therapy treatment
- PTSD and primary care
- Rapid Eye Movement Desensitisation
- Psychological reactions to the London bombs in July 2005
- Co-morbidity
- Resilience and trauma: the psychological welfare of troops in Iraq
- Cognitive Behavioural Therapy

For more information or a booking form, please contact **Simon Timmis** on **0207 290 3844** or e-mail **simon.timmis@rsm.ac.uk.** You can also book online at **www.rsm.ac.uk/diary**

The Royal Society of Medicine

To list your event in this diary, email brief details to Patricia McDonnell at events@acnr.co.uk by November 30th, 2005

2005

November

British Neuropsychological Society Autumn Meeting
1-2 November, 2005; Queen Square, London, UK
E. georgina.jackson@nottingham.ac.uk
W. www.icgp.org

The International College of Geriatric Psychoneuropharmacology 2005 Annual Meeting
2-5 November, 2005; Pittsburgh, USA
W. www.icgp.org

Music Therapy in Neuro-Rehabilitation
2-3 November, 2005; London, UK
W. www.rhn.org.uk/institute/doc.asp?catid=1477&docid=1938

NANOT Annual Conference 2005: Hot Topics in Neurological Rehabilitation
3-4 November, 2005; Leeds, UK
Info. Sue Krage, Acting Conference Co-ordinator, NANOT, PO Box 315, Leatherhead KT22 2BA.
E. admin@nanot.org

8th International Conference on the Mechanisms and Treatment of Neuropathic Pain
3–5 November, 2005, San Francisco, USA
E. office@cpe.rochester.edu
W. www.neuropathicpain.org

World Congress of Neurology
5-11 November, 2005; Sydney, Australia
T. +61 292 411 478,
F. +61 292 513 552,
E. info@wcn2005.com
W. www.wcn2005.com

12th Workshop on Endoscopic Neurosurgery
6-9 November, 2005; Ghent, Belgium
W. www.neuroendoscopy.org

NEW
20th Course in Clinical EEG - Advanced Course
6-14 November, 2005; Gargnano, Italy
Info. Prof. Dr. Raffaele Canger
E. raffaele.canger@ao-sanpaolo.it

Imperial College Immunology Short Course for Clinicians & Scientists
7-9 November, 2005; London, UK
E. wcc@imperial.ac.uk

Evidence-based neurology workshop Presented by the Cochrane Neurological Network
8 November, 2005; Sydney, Australia
E. cochrane.neuronet@unimi.it

21st International Conference of Alzheimer's Disease
9-12 November, 2005; Istanbul, Turkey
W. www.adi2005.org

Adults with LCH - Orphans with an Orphan Disease
10-11 November, 2005; London, UK
E. conferences@rcplondon.ac.uk

North American Neuromodulation Society, 9th Annual Meeting
10-12 November, 2005; Washington DC, USA
T. 001 847-375-4714,
W. www.neuromodulation.org

International Postgraduate Programme 2005 Life and Health Sciences Hands on Workshop "cerebral sulci and Gyri: neuroanatomy"
12-14 November, 2005,
E. Sonia Cruz sec-pg@ecsaude.uminho.pt

35th Annual Meeting of the Society for Neuroscience
12-16 November, 2005; Washington, DC, USA
E. info@sfn.org
W. http://apu.sfn.org/am2005/

The 3rd Emirates Neuroscience Conference
12-15 November, 2005; UAE
Info. Dr Javaid Iqbal,
T. 0097142710000 ext 449 / 0097142711221,
W. www.emiratesneuroscience.com
E. jiqbal49@emirates.net.ae

MS Trust Ninth Annual Conference
13-15 November, 2005; Blackpool, UK
T. 01462 811239,
E. lucie@medivents.co.uk

Basic Spasticity Seminar
14 November, 2005; Stoke on Trent, UK
T. 01782 556226,
E. deborah.collins@uhns.nhs.uk

The European Federation of Neuropsychiatry Annual Congress
16-18 November, 2005; Munich, Germany
T. 01159-692-016, F. 01159 692 017,
E. rp@rpa.bz

University Classes in Multiple Sclerosis II
16-17 November, 2005; Lisbon, Portugal
T. +31 24 356 19 54, E. info@charcot-ms.org

3rd International Meeting on Visual and Neuromuscular Disorders
17-20 November, 2005; Havana, Cuba
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E. milalatin@aol.com

2nd International Congress on Brain and Behaviour
17-20 November, 2005; Thessaloniki, Greece
T. 302 310 994 622, F. 302 310 266 570,
E. kfount@med.auth.gr

RCN Learning Disabilities Nursing Forum Conference and Exhibition
17 November, 2005; London, UK
E. binta.patel@rcn.org.uk

British Cervical Spine Society Meeting 2005
18-19 November, 2005; Cleveland, UK
T. 01642 854413,
E. rogerstrachan@hotmail.com

NEW
Scottsdale 2005 Headache Symposium
18-20 November, 2005; Scottsdale, AZ, USA
W. www.ahsnet.org/calendar/scottsdale2005/

Information Processing - Advanced Cognitive Rehabilitation Workshop
19 November, 2005; Gatwick, UK
T. 01276 472369,
E. enquiries@braintreetraining.co.uk

NEW
XXXII Congresso Nazionale LIMPE
22-23 November, 2005; Palermo, Italy
W. www.parkinson-limpe.it/04/01.htm

NEW
LVII Annual Meeting of the Spanish Society of Neurorehabilitation (SEN)
22-26 November, 2005, Barcelona, Spain
W. www.sen.es

NEW
RSM Bench to Bedside: Extrapyramidal Disorders
24 November, 2005; London, UK
Info. Simon Timmis,
T. 0207 290 3844, E. simon.timmis@rsm.ac.uk

Risky Business - the challenges of frontal brain injury & community living
24 November, 2005; Manchester, UK
Info. JSP Manchester Ltd - Jane Warren,
T. 0161 247 7756,
E. janewarren@jsparker-associates.co.uk

Neuroprotection in Neurological Diseases: A promising therapeutic strategy or a chimera?
24-26 November, 2005; Sicily, Italy
T. 0115 969 2016, E. info@sinspn.org
W. www.sinspn.org

Introduction to Neuropsychological Rehabilitation
25 November, 2005; Ely, UK
E. alison.gamble@ozc.nhs.uk

Interprofessional Teamwork and Rehabilitation: Much Ado About Nothing?
25-27 November, 2005; Warwickshire, UK
T. 020 7647 3859,
E. internationalrehabilitation@rcn.org.uk

The 3rd International RCN Rehabilitation and Intermediate Care Nursing Forum Conference
25-27 November, 2005; Warwickshire, UK
E. internationalrehabilitation@rcn.org.uk

UKABIF Conference
25 November, 2005; Leeds, UK
T. 020 8780 4500 x 5140
E. ukabif@rhn.org.uk

Controversies in the Management of Traumatic Spinal Paralysis
29 November, 2005; London, UK
T. 0207 9351 174,
E. conferences@rcplondon.ac.uk

December

NEW
Euroconference gene and cell therapy
1-2 December, 2005; Paris, France
W. www.pasteur.fr/applications/euroconf/...

2nd West of England Seminar in Advanced Neurology (Bath Course)
1-2 December, 2005; Bovey Tracy, UK
E. cgardnerthorpe@doctors.org.uk

The American Epilepsy Association 29th Annual Meeting
2-6 December, 2005; Washington, USA
T. 001 860 586 7505, F. 001 860 586 7550.

Cognitive Rehabilitation & Physiotherapy
3 December, 2005; Gatwick, UK
T. 01276 472369,
E. enquiries@braintreetraining.co.uk

NEW
RSM Acute Neurology for General Physicians
5 December, 2005; London, UK
Info. Simon Timmis,
T. 0207 290 3844,
E. simon.timmis@rsm.ac.uk

Info 2005 - International Neurology Forum
5-8 December, 2005; Nha Trang City, Vietnam
T. +972 4 9541870,
E. hannal@netvision.net.il

41st National Congress of the Turkish Neurological Society
5-10 December, 2005; Istanbul, Turkey
T. +90 05337432958,
E. info@noroloji.org.tr

Fatigue After Brain Injury
9 December, 2005; Ely, UK
T. 01353 652165,
E. alison.gamble@ozc.nhs.uk
W. www.ozc.nhs.uk

Advanced Spasticity Seminar
12 December, 2005; Staffordshire, UK
E. deborah.collins@uhns.nhs.uk,
T. 01782 556226.

Neurology Medical Evening Update
13 December, 2005; Edinburgh, UK
E. a.fairbairn@rcpe.ac.uk
T. 0131 225 7324.

Cochrane Systematic Reviews in Practice: Multiple Sclerosis
16-17 December, 2005; Madrid, Spain
E. cochrane.neuronet@unimi.it

2006

January

NEW
Regional Asian Stroke Conference
5-8 January, 2006; Chennai, India
W. www.stroke-india.org/main.asp

NEW
Attention and Executive Skills
12-13 January, 2006; Ely, UK
Info. Alison Gamble,
T. 01353 652165,
E. alison.gamble@ozc.nhs.uk
W. www.ozc.nhs.uk

NEW
The Society for Research in Rehabilitation Winter Conference
17 January, 2006; Manchester, UK
T. 0161 295 7014,
E. j.fletcher@salford.ac.uk
W. www.srr.org.uk

Latsis Colloquium: Early Language Development and Disorders
26-28 January, 2006; Geneva, Switzerland
W. www.unige.ch/fapse/PSY/LATSIS/

February

International Neuropsychological Society (INS) 34th Annual Meeting
1-4 February, 2006; Boston, USA
Info. International Neuropsychological Society
T. +(614) 263-4200, F. +(614) 263-4366
E. ins@osu.edu, W. www.the-ins.org/meetings

3rd International Meeting on Neuromuscular and Visual Disorders
1-5 February, 2006; Havana, Cuba
E. jgut@infomed.sld.cu or milalatin@aol.com

International Congress on Gait & Mental Function
3-5 February, 2006; Madrid, Spain
T. +972 3 9727555, E.gait@kenes.com

NEW
International Comprehensive Update on Diagnostics and Therapeutics in Epilepsy (CUTE)
4-5 February, 2006; New Delhi, India
W. www.iamst.com/

3rd Mediterranean Congress of Neurology in conjuction with 7th Cairo International Neurology Conference
8-11 February, 2006; Sharm el Sheikh, Egypt
T. +357 25 720554,
E. congress@congresswise.com

NEW
British Neuropsychiatry Association Annual Meeting
9-10 February, 2006; London, UK
Info. Jackie Ashmenall,
T/F. 020 8840 9266,
E. admin@bnpa.org.uk or jashmenall@yahoo.com

4th World Congress of Neurorehabilitation
12-16 February, 2005; Hong Kong
F. +852 2547 9528, E. info@wcnr2006.com

NEW
International Stroke Conference 2006
16-18 February, 2006; Kissimmee, FL, USA
W. http://strokeconference.americanheart.org/portal/strokeconf...

NEW
7th International Conference on New Trends in Immunosupression and Immunotherapy
16-19 February, 2006; Berlin, Germany
W. www.kenes.com/immuno/prog.asp

Short Courses: Neurological Anatomy
20-22 February, 2006; London, UK
T. 020 7405 3474,
E. neurosurgery@rcseng.ac.uk

World Parkinson Congress
22-26 February, 2006; Washington, USA
E. info@worldPDcongress.org
W. www.worldpdcongress.org

NEW
NANOS 2006 Meeting
25 February - 2 March, 2006; Tucson, AZ, USA
W. www.nanosweb.org/meetings/nanos2006/

March

The Social Brain II - See The Bigger Picture
March 2006; Glasgow, UK
T +44 (0)141 331 0123,
E. registration@mindroom.org

NEW
The Annual Global Conference on Neuroprotection and Neuroregeneration
1-3 March, 2006; Uppsala, Sweden
W. www.gcnpnr.org/2006/gcnn2006.html

NEW
Annual Meeting of the American Society of Neuroimaging
2-5 March, 2006; San Diego, CA, USA
W. www.asnweb.org/

International Symposium on Clinical Neurology and Neurophysiology
6-8 March, 2006; Tel Aviv, Israel
W. www.neurophysiology-symposium.com

NEW
RSM Clinical Update: Epilepsy in Adults and Adolescents
8 March, 2006; Cardiff, UK
Info. Simon Timmis,
T. 0207 290 3844, E. simon.timmis@rsm.ac.uk

NEW
6th Advanced Amputee & Prosthetic Rehabilitation Course
13-15 March, 2006; London, UK
Info. BSRM, T. 01992 638865, E. admin@bsrm.co.uk W. www.bsrm.co.uk

International Society for Stem Cell Research

San Francisco, USA, 23-25 June, 2005.

The International Society for Stem Cell Research (ISSCR) held its 3rd annual meeting in San Francisco on June 23 - 25th, 2005. The meeting was opened with an exciting speech by Mr Gavin Newsom, the mayor of San Francisco who has recently signed a lease for the San Francisco headquarters of The California Institute for Regenerative Medicine (CIRM). Mr Robert N Klein, an energetic 60-year-old entrepreneur, who rose to public prominence last year, spearheading the campaign that convinced California's voters to back a plan to create a $3-billion public fund to advance research on human stem cells, delivered the keynote speech. He spoke of global partnerships and long-term investments in the field of stem cell research, which will save many billions of dollars in the future, and he encouraged complementary and collaborative research.

Robert N Klein's commitment to advancing stem cell research originated in his youngest son diagnosis with juvenile diabetes and his mother suffering from Alzheimer's disease.

Many excellent scientific talks and poster sessions showed exciting data and covered the breadth of stem cell biology: from rodent and human stem cells to adult and embryonic stem cells. This conference provided a good opportunity for scientists from all over the globe to interact with industry, lawyers, clinicians, patient groups and the media.

One of the fundamental questions that the researchers are trying to understand is how stem cells self renew and become specialised cells in different tissues. Professor Elaine Fuchs from the Rockefeller University presented work questioning how multipotent stem cells of mammalian skin respond to various external cues to coordinate changes in transcription, cell polarity, adhesion and cytoskeletal dynamics. The work in her group shows that the basement membrane beta1-Integrins provides a natural mechanism for asymmetric cell division and stem cell fate determination. Dr. Sean Morrison's group from the University of Michigan has identified cell surface receptors of the SLAM (Signalling Lymphocyte Molecule) family, including CD150, CD244 and CD48 that are differentially expressed among functionally distinct human stem cells. These markers can be used to follow these cells as they differentiate.

The prospective clinical utility of human embryonic stem cells depends on being able to culture the cells in conditions that maintain their pluripotency as well as their genetic and epigenetic stability. Professor Roger Pedersen and colleagues from the University of Cambridge have shown that certain key epigenetic regulators are faithfully maintained in human embryonic stem cells grown in culture, suggesting that their epigenetic status would not be a barrier to their clinical use. Not only does this suggest that human embryonic stem cells are epigenetically quite robust, but it allows us to analyse the epigenetic regulation in early cell types, which is an aspect of human development that was previously difficult to study.

Transplantation of stem cells or their derivatives, and mobilisation of endogenous stem cells in adult brain, have been proposed as future therapies for neurodegenerative disorders such as stroke and Parkinson's disease. Professor Olle Lindvall and colleagues from Lund University in Sweden have shown that lesions in the striatum and cortex caused by stroke lead to neurogenesis in the damaged areas. Stroke increases the number of neural stem cells in the subventricular zone, which then migrate to the damaged striatum, where a few of them differentiate into striatal neurons. This brain repair capacity after stroke was also shown in aged rats. In other experiments neural stem cells were transplanted to the damaged striatum after stroke and resulted in the neural repopulation of the damaged area and in recovery of behaviour, proving that the brain may be repaired by endogenous as well as exogenous neuronal stem cells.

Some scientists, many from outside of the United States, are studying human embryonic stem cells. They are developing better ways to grow these cells in culture and ways to manipulate them to form more specialised cell types. This is important because it is not the undifferentiated embryonic stem cells that might be used for treating patients, but the more specialised cells obtained from them. Today we have a total of 155 stem cell lines, largely created in the U.S. despite President Bush's restrictions on federal funding (although states such as California are acting independently to create better lines). Next in line is Sweden, which has a total of 33 lines. Rising Asian economies such as South Korea, India and Singapore are pouring funds into creating new lines; they have 24, 10 and 7 stem cell lines, respectively. The UK has 3 lines, Spain 2 , and finally Iran has 1 line of embryonic stem cells.

A team of scientists at Wake Forest University's Institute for Regenerative medicine are trying to engineer human organs by taking a thumbnail-size biopsy of the patient's own organ, harvesting and nurturing the cells then putting them in a collagen scaffold system - a biodegradable foundation used to encourage stem cell growth. Since the body can integrate only a small amount of tissue without blood vessels, the bioscaffold that has been created is able to preserve the organ's native vascular network and tissue micro-architecture. In this way Dr. Anthony Atala's group has seeded stem cells on the liver matrix that remain viable and progressively organises into a vascularised three-dimensional tissue structure.

Progress in the field of stem cells has been very significant over the past few years, and most attending scientists left with a new level of enthusiasm and new ideas. There are many more fundamental questions to be answered about stem cells and how they can be used for regenerative medicine. Hopefully, these questions will be answered in the future ISSCR meetings: June 29th – July 1st 2006; Toronto, and June 17th-22nd, 2007; Cairns.

Zhale Bandpey,
Cambridge Centre for Brain Repair, Cambridge.

The British Neuropsychiatry Association Annual Meeting

9/10 February 2006

The Institute of Child Health, Guilford Street, London

- Sleep
- Neuropsychiatry/Schizophrenia
- Functional Movement Disorders

The BNPA is pleased to announce their next 2 day Annual Meeting in February 2006, which promises to be even more stimulating, diverse and informative than usual.

A more detailed programme and booking form can be found on our website www.bnpa.org.uk

For details of exhibition/sponsorship opportunities, contact Jackie Ashmenall on
Phone/Fax 020 8840 9266
Email: admin@bnpa.org.uk or
jashmenall@yahoo.com

World Congress on Huntington's Disease

Manchester, UK, 10-13 September, 2005.

The World Congress on Huntington's Disease took place over 3 days in Manchester, UK. It was preceded by the 2nd Plenary meeting of the European Huntington's Disease Network (Euro-HD) which is a European-wide organisation aiming to coordinate research efforts across the continent. This meeting opened with a discussion of current issues in HD, in particular targets for intervention, how to predict clinical benefit from preclinical models and possible biomarkers to track disease progression. The thirteen working groups spent a productive day and the final reports were very promising, with a number of groups (cognitive phenotype, behavioural phenotype, motor phenotype, imaging) coming up with quick and useful assessment batteries to be made available to all centres; others emphasised the need to improve guidelines (e.g., quality of life, standard of care) and are currently working on this; others summarised very promising recent research (e.g. biomarkers, genetic modifiers).

The main Congress took place in Manchester's beautiful Midland Hotel. It began with a very interesting summary of the history and genetics of HD by Peter Harper, in which he spoke about both the early pioneers in HD research and the discrimination that those with genetic disorders have faced, and still face. He pointed out that HD has become a model for genetic disorders, from gene mapping and genetic prediction, to collaboration with patient and family associations, notably the International Huntington's Disease Association and the Hereditary Disease Foundation.

The body of the conference then focused on pathogenic mechanisms, genetics, biomarkers, and clinical care, and the main points are summarised below.

The variability in phenotype is reflected in different patterns of cell loss, e.g. those with predominantly motor symptoms show significant cell loss in the motor cortex but not in the cingulate cortex, whilst the reverse is true for patients with predominantly mood symptoms (with the same CAG repeat length). Work is ongoing to look at other brain regions and carry out more prospective studies. The mutation in HD probably leads to multiple parallel pathways with knock-on effects and therefore it could be vital to tackle the mutant protein rather than processes further downstream. Cdk5 can reduce the ability of caspases to cleave Htt which reduces the rate of formation of toxic fragments, but once these fragments start to form they stop Cdk5 from working, so its protection is then reduced. An alternative strategy is to increase clearance of the mHtt, and rapamycin, which increases autophagy, appears to speed up removal of the mHtt exon 1 fragment; mice treated with a rapamycin ester have improved behaviour and reduced aggregation. Further work on reducing cleavage and increasing clearance is needed.

Different phenotypes have different paths of progression, and genetic analysis is important

when searching for treatments as it can provide rules for identifying modifiers of the disease. It has been shown that a TAA repeat on the 3'UTR of the GRIK2 gene accounts for up to 4% of the variance in age of onset; i.e. it has an effect, but only in a small number of people. Correlating shared alleles with age of onset in about 800 DNAs from affected sibling groups has led to the discovery of a pre-onset modifier on chromosome 6; this gene is now being searched for.

Patients of African ancestry HD-like2 is seen in up to 40% of patients with HD symptoms and it is now routinely tested for in diagnostic examination.

The pre-symptomatic testing program is now widely accepted and is a model for other disorders, although uptake is less than expected. There is poor follow-up in those individuals who were most anxious or distressed before testing, and the guilt often felt by at-risk individuals who have a negative test result, as well as the stress or inability to cope felt by partners of those who have a positive test result. These three groups would benefit from further counselling and better follow-up. It was also recommended that sometimes it might be appropriate to delay testing and treat psychiatric disorders in order to prevent an adverse emotional response.

Biomarkers need to be objective and reliable, change predictably over time (preferably linearly and with more than 2% change per year in order to be detected), should predict end points, and should be associated with known pathology mechanisms. Potential biomarkers are MRI, fMRI, PET, MRS, neuropsychology, genome, metabolomic, proteomic. One possible marker is caudate or putamen volume which appears to change linearly over time, to predict onset of motor symptoms, and is related to pathological changes in the striatum. PET imaging has shown reduced adenosine in the caudate, which might be useful in tracking disease progression. 11C-PK11195 PET has shown that there is abnormal microglial activation, associated with neuronal dysfunction (measured by 11C-raclopride PET) in pre-symptomatic patients, and since minocycline inhibits microglial activation it might be useful to trial minocycline in this patient group. Considerations, which need to be taken into account with any biomarker, are its cost, time, invasiveness, site reliability, rate of change, linearity of change, and the disease stage(s) during which change is observed.

The EHDI study on the effect of riluzole in HD showed no effect on any of the outcome measures. A trial of Ethyl-EPA showed some improvement only in those patients with fewer than 45 CAG repeats, suggesting that EPA is most effective in the high chorea, later age of onset (lower CAG repeat) group.

The conference highlighted the need for multidisciplinary teams to work well together and for hospital and community workers to communicate. Although it seems likely that non-pharmacological treatments such as physiotherapy, occupational therapy, and speech therapy would have much to offer the HD patient, there are very few objective studies of this and more work needs to be done to assess systematically what is needed in HD and how it works. The needs of the patient change as the disease progresses. Several speakers stressed the importance of making the patient and family aware of what was going to happen so that they could plan ahead, for example making advanced directives whilst still capable, discussing what care they would like, talking about the use of PEG. There are also clearly different standards of care depending on whether a patient goes to a specialist HD home, or a general long-term care facility and more resources and/or education of carers could improve this.

The conference drew to a close with talks about possible new treatments. A number of drugs have been tested for their ability to manage the motor symptoms of the disease but few have had useful effects. There are far fewer good quality studies focusing on behavioural and cognitive symptoms. Future studies are looking at effects of CoQ10, creatine, phenylbutyrate, minocycline, and it may be that combination therapies are more effective.

A mechanism to target the HD gene is RNA interference (RNAi). RNAi is a natural phenomenon that stops messenger RNA from making proteins. It is mediated by small (~20 nucleotide) non-coding RNAs which are complementary to the target gene. It's been shown that RNAi delivered by virus to cells with mutant Huntingtin can reduce aggregates, and in the HD-N171-82Q mouse RNAi reduces protein expression in vivo and improves cognitive and behavioural measures. This technique needs to be investigated in primate models, and also delivery methods, targets within the brain, and measures of efficacy in humans need to be discussed, but it appears to be well tolerated in the rodent models and to silence the gene for a significant period of time.

Striatal grafts of foetal tissue have been successful in animals and a number of human trials are underway. In France a safety and efficacy trial in 5 patients found that hypermetabolism correlated with regions of striatal grafts in 3 patients who stabilised on a variety of measures; a 60-patient multi-centre trial is now planned. Using a different technique grafts were less successful on 7 late stage patients in the States; although 1 post-mortem showed good survival of the graft, there were no changes in neuropsychology or PET 12 months post-operatively. The Nest-UK HD study had a successful safety trial with 4 patients undergoing unilater-

al grafts without surgical complication. An efficacy trial, with 10 patients having bilateral grafts over 2 years, is currently on hold pending the EU Tissue Directive, but should be running again soon. A number of issues are still being debated, such as methods, where grafts are best placed, patient selection and assessment, as well as what tissue to use, for example xenografts or stem cells rather than foetal tissue.

The conference ended with a succinct summary of the 3 days' talks by Anne Young, and the feeling, as she put it, that "the future is now"; we can look forward to news of much more progress, particularly in the advance of possible therapies, when we meet in Dresden in 2007.

Susie Henley and Sarah Tabrizi, Institute of Neurology, London.

Primary Care Neurology Congress

Manchester, UK, 29 September, 2005.

The unifying theme of the recent PCNS Congress in Manchester was that many neurological conditions presently dealt with in secondary care can potentially be treated in primary care. Appropriately trained GPs, especially the new GPs with Special Interests (GPSI), working together with multidisciplinary teams tailored to the individual conditions, can manage most patients, leaving secondary care to deal with the more severe or atypical cases. In this way, waiting lists can be cut and more patient-centred services delivered. This type of medical service fits closely with the new GMS Contract and with the recently published National Service Frameworks (NSF) from the Department of Health (DoH).

Dr Chris Clough from King's College Hospital, London reviewed the recent NSF for Long Term Conditions. This was published in April 2005 in response to patient concerns about delays in access to care and poor and/or inconsistent services. The NSF has 11 quality requirements applying to services, patients, carers and the community sector, with an overall theme of the patient being able to see "the right person at the right time at the right place". Key requirements include prompt recognition, diagnosis and treatment, appropriate emergency and acute management and early and specialist rehabilitation. To deliver all this, the right expertise, access and skills have to be in place, and multidisciplinary teams used for the delivery of the services. Lessons that need to be applied include examining patient pathways, the use of appropriate professionals, who may need to acquire new skills, and working in teams across primary and secondary care. The way forward is to bring together all stake holders in PCT and regional networks and develop training schemes with common stems to develop competencies for all appropriate professionals.

Dr Andrew Hansen from Bradford reviewed the case mix of neurological symptoms seen in primary care. Many patients with neurological symptoms do not have any serious or neurological disease, especially those with headache, dizziness, tremor, blackouts and sensory disturbances. Most of these patients can in fact be managed in primary care. He described the experience in Bradford, where new epilepsy and community neurology services run by GPSIs have resulted in reduced waiting times for patients and freed up appointments with consultants.

Dr Chris Manning from Primary Care Mental Health and Education (primhe) discussed methods to manage multiple morbidities. Forty percent of patients attending their GP have mental health problems, which often manifest as physical symptoms, especially pain. Chronic pain is linked to depression and the risk of suicide. Dr Manning suggests that we "dump Descartes and mind-body splitting" and treat patients holistically. The first step is a 'therapeutic interview', which can elicit reliable data and help to define the management plan.

Dr Susan Mitchell from Mid-Surrey and Ms Lynda Finn from the MS Society described the Neuro-Pact service that has been developed in Surrey to improve services to patients with multiple sclerosis (MS). These patients have huge needs for care from neurologists, GPs, nurses, allied health professionals (e.g. physiotherapists, occupational therapists and psychologists) and social services. Neuro-Pact brings together all these professionals bringing their knowledge and special skills to bear in integrated community-based services. Clinics run by the Neuro-PACT network, GPs and specialist nurses all aim to support the patient and their family at home. The support of the MS Society and other support groups, together with a recently-developed Expert Patient Programme (EPP) are invaluable in this.

Ms Mary Baker of the European Parkinson's Disease Association chaired a question and answer session with a Parkinson's disease patient and carer. Both emphasised the key roles of specialist nurses, speech therapists and community support workers and that it was essential to listen to the needs of patients and their carers. In addition Ms Baker emphasised that "GPs need to be supported in their roles by secondary and tertiary care specialists".

Dr Andrew Dowson from the Migraine in Primary Care Advisors (MIPCA) reviewed current evidence-based guidelines for headache in the UK. Guidance is published covering screening, diagnosis, management and follow up, and a primary care headache team is advocated. In general, tension-type headache and uncomplicated migraine can be managed in everyday primary care, more complicated migraine and chronic headaches by GPSIs, with referral restricted to the rarer headache subtypes. All these initiatives, which were published several years ago, dovetail with current GMS and NSF recommendations.

Mr Stephen Duckworth from Kent and Dr Helen Hosker from Manchester reviewed management of stroke patients in primary care following the introduction of the new GMS Contract and the NSF for older people. These initiatives have had a large influence on primary care stroke management and have resulted in protocols and audits being developed. Looking to the future, it is desirable to develop an integrated stroke service, clinical trials in primary care and trained professionals to meet needs. Much networking between all the stakeholders is required to make this happen.

Dr Yvonne Hart from Oxford and Dr Greg Rogers from Kent outlined a multidisciplinary approach to epilepsy management. Epilepsy is a highly impactful condition and the aim of therapy should be to make the patient seizure free. A shared-care strategy is implemented, with the GP conducting diagnosis and long term monitoring while the specialist conducts diagnosis, investigations, the management plan and re-evaluation when problems present. Other services are introduced as required. A network of GPSIs has been set up to manage epilepsy in their locality and form a resource to epilepsy colleagues. Commissioning is based in the PCT and forms a locally enhanced service. In the future it is envisaged that primary care will play this integral part in epilepsy services across the country.

Dr Steve Iliffe from the Royal Free Hospital, London presented a joint initiative with the Alzheimer's Society to improve the ability of GPs to manage dementia in conjunction with voluntary services. Currently there is little experience in primary care for managing this complex condition. A CD-ROM based educational project has been set up to rectify this situation, involving small group learning and computer decision support. The curriculum covers diagnosis, investigations, medications, communicating with the patient and carer, and sources of help. A randomised study showed that this education increased GPs' detection rate and knowledge of dementia. The programme is now being rolled out throughout England and Wales, and research networks are being set up.

In conclusion, many of the most common and severe neurological conditions can be managed in primary care by multidisciplinary teams coordinated by GPSIs and utilising the experience of voluntary agencies. Locality-based schemes have proved successful and are likely to be rolled out nationwide. Dr Dowson stated that "The way forward is different professions with special interests". The end result is that most patients are managed rapidly and appropriately in their own localities while secondary care services are reserved for more severe and/or atypical cases. In turn, access to secondary care is faster than has been the case previously due to a reduction in the size of waiting lists.

Pete Blakeborough, Freelance Medical Writer.

European Federation of Neurological Societies

Athens, Greece, 17-20 September, 2005.

Athens: the "cradle of civilisation"; the "birthplace of democracy", one early success of which was the judicial murder of one of its citizens, Socrates, memorialised (by Plato) for the penetration of his intellect despite his protestations of ignorance. Would his modern day successors find enlightenment or confusion at the 9th Congress of the EFNS? Amongst 9 plenaries, 13 short communications sessions, 18 focused workshops, > 1000 posters (some strangely familiar from ENS 2005!), 4 special sessions, and drug company sponsored satellite symposia, spread over 3 days and 5 floors of the splendid Megaron Athens International Conference Centre, the authors present selected highlights, reflecting, at least in part, their inability to be in more than one place at one time.

Parkinson's disease (PD) and other movement disorders

In a session entitled "Mysteries of PD" we learned that involvement of the dorsal nucleus of the vagus may be implicated in swallowing problems and constipation and age-related cell loss from the ventral tier of the substantia nigra may make normal elderly people appear stooped and have difficulty getting out of a chair. John Hardy (NIH, USA), the only speaker dressed in red shorts, gave an excellent talk drawing together some aspects of the molecular bases of different dementing illnesses and describing how in α-synuclein inherited diseases, the age of onset inversely correlates with the dose of genetic abnormality such that 4 copies leads to a disease onset at age 30 and 3 copies at onset age about 45-50. With relatively small changes having such a profound affect, it is quite possible that smaller changes due to subtle changes in regulators could be implicated in disease in sporadic cases. In the follow-on session, the greatest mystery of all seemed to be that whatever new drug is trialled in PD seems to give 1 hour extra on-time per day, rasagiline or rotigotine. We keenly await a combination miracle pill of 24 new medications to give continuous on.

Amyotrophic lateral sclerosis/Motor neurone disease (ALS/MND)

A plenary devoted to ALS/MND, the first of its kind at a European neurological meeting according to one speaker, included an update on genetics, wherein Andersen (Umea, Sweden) contradicted textbook teaching that 5-10% of MND cases are familial. He stated that the correct figure was at least 20% when a careful family history was taken (cases may be autosomal recessive as well as dominant, or there may be incomplete penetrance), including the delicate topic of non-paternity (estimated to be 5%, although the Liverpool press recently reported a 50% rate in a local commercial clinic!). The heterogeneity of SOD1 mutations, 119 described to date, mostly missense, was presented. Ludolph (Ulm, Germany) was sober about therapeutic prospects, enumerating the difficulties in extrapolating from mouse models to man. Part of the problem is that the pathogenesis of ALS remains unclear; double transgenic mice carrying SOD1 and dynein mutations, both of which may individually produce an ALS/MND phenotype, seem functionally better than animals carrying a single mutation.

Myasthenia gravis

In a sponsored session devoted to myasthenia gravis, the pathology and treatment were reviewed. The evidence base for thymectomy remains tenuous, although current common practice of offering the treatment to those under 40 was endorsed. Immunosuppressive agents were reviewed and mycophenolate will probably emerge as a useful treatment with more trial evidence to support its use than some of the things we currently use – methotrexate, for example.

Alzheimer's disease (AD) and other dementias

The EFNS guidelines on the diagnosis and management of AD and other dementias (Eur J Neurol 2000;7:133-44) are currently being updated. A focused workshop presented the provisional revision. Significant changes included the relegation of mandatory testing for vitamin B12 and syphilis, and greater emphasis on MRI (although no specific protocol was given) and use of CSF biomarkers (Aβ, tau). The audience raised few objections to the projected changes, although one wonders whether such a forum is the best way to seek constructive criticism. It would be interesting to know how widely the original guidelines were adopted or used, since in this age of "guideline fatigue" there is a risk that this may be another worthy yet largely ignored document. Moreover, because the guidelines are (deliberately?) not explicit or operationalised, terms such as "atypical presentation", "rapid progression", and "appropriate counselling" remain open to individual interpretation.

Sleep-related disorders

In a plenary devoted to sleep apnoea syndromes, Santamaria (Barcelona, Spain) pointed out that these may parallel neurological disorders (stroke, dementia, PD), be secondary to neurological disease (multiple system atrophy, neuromuscular disease, syringobulbia; ?PD), or induce neurological disease (stroke). Sleep apnoea is thus both a risk factor for and a consequence of stroke; whether these are independent is not clear. Bassetti (Zurich, Switzerland) reviewed studies of sleep apnoea prevalence in acute and subacute stroke and TIA, with variable results but around 50% in each case. In neurodegenerative disease, there is similar uncertainty, with figures around 10-20% in AD and PD. In MSA, snoring needs to differentiated from stridor. Both may be treated with CPAP, although this does not influence REM sleep behaviour disorder which also occurs in MSA (and PD dementia).

Stroke

A plenary devoted to the vexed issue of vascular dementia/vascular cognitive impairment (VaD/VCI) was prefaced by the familiar call to action from Hachinski (London, Canada). From the therapeutic standpoint, Erkinjuntti (Helsinki, Finland) showed that there is clearly a cholinergic deficit in VaD/VCI and reviewed the various studies of cholinesterase inhibitors in this situation, finishing with a plea to "start early" (just as UK regulators may be ensuring that we don't start at all). Early therapy is key to the efficacy of thrombolysis in acute stroke, but how may this be organised in rural areas, where distance precludes rapid transfer to teaching/university hospitals? Vatankhah (Regensburg, Germany) reported a "telethrombolysis" service in Bavaria, showing its feasibility, safety and good outcomes. Neuroprotection is undergoing a renaissance (see Geoffrey Donnan article in this issue of ACNR), with trialists having learned from thrombolysis trials how critical the timing of drug administration may be. The free-radical scavenger NXY-059 has shown early promise in a European trial (SAINT 1) and is now being tried across the world (SAINT 2).

Epilepsy

On a subjective judgement, levetiracetam took the honours for most posters. A drug company symposium addressed the real, not simply potential, problems of generic prescribing.

Multiple sclerosis

Unlike the ENS meeting, MS has a rather recessed position at EFNS, perhaps related to the temporal proximity of the ECTRIMS meeting.

Headache

This topic, the Skoda of neurology, continues to emerge from the gloom to the limelight. In an excellent session we learned that transcranial magnetic stimulation (TMS) has suggested altered thalamic sensitivity in patients suffering migraine with aura. Transformed migraine is a common problem, often analgesia related, but carries a disappointing prognosis with 60% relapse at one year; the speaker argued for early and aggressive treatment with prophylactic agents. Patients with this problem may have reduced metabolic activity in the orbitofrontal cortex, which in other patient groups is associated with compulsive and addictive behaviours. There are now three genes known to be associated with familial hemiplegic migraine and all

affect ion channels. So, is sporadic migraine an ion channel disorder? Evidence is being sought but at the moment remains speculative. For those treating the genetic condition, this speaker recommended flunarizine. Peter Goadsby remains one of the UK's most successful imports. His cocktail of science, clinical observation and pragmatism, topped with delicious irony in describing the trigeminal autonomic cephalalgias, was a highlight of the meeting. I don't see much SUNCT but when I do I shall now know to give lamotrigine – not much use for most other headaches. Why do all these related conditions respond to such different treatments?

Eye movements

Unusually, a session was devoted to eye movements, which are such an accessible model of the nervous system that their science is fascinating. Saccades were described by John Leigh, a true master of the topic (an article by him will be appearing in a future issue of ACNR as part of the Neuroscience of Vision series). He linked the science of the excitatory burst neurones and inhibitory omnipause neurones to the patterns of eye movements seen in clinical conditions. Other excellent presentations in this meeting concerned eye movement abnormalities in basal ganglia disorders, the vestibulo-ocular reflex (VOR), including useful demonstration of how best to test it clinically. The question is, though it all made perfect sense at the time – how long will we remember it?

"Neurology and Art" and "History of Neurology"

The history special session focused, appropriately, on Ancient Greek medicine. Neurology of art examined neurological disorders in artists, many included in the book edited by Bogousslavsky and Boller, reviewed in this issue of ACNR. Ravel's Bolero cropped up twice: to accompany a pathography of Ravel who may have developed Pick's disease; and as the stimulus for an artwork completed by a patient with frontotemporal dementia reported by Bruce Miller (San Francisco, USA).

The social event of the meeting was a ballet of "Zorba the Greek" performed by the National Ballet of the Budapest Opera and the Greek Philharmonic Orchestra in the Odeion of Herodes Atticus, an amphitheatre added by the Romans to the base of the Acropolis in about 167 AD. In the story by Nikos Kazantzakis, made famous in film by Anthony Quinn, Zorba grasps life with a passion verging on Hedonism that infects those he comes into contact with. The music by Mikis Theodorakis is melodic and enjoyable and ended with 4 encores of the classic theme played on the Santuri. The dancing and singing were first class and the atmosphere of history on a warm night with the full moon shining onto the stage was unbeatable.

Andrew J Larner, Walton Centre for Neurology and Neurosurgery, Liverpool and Mark Manford, Addenbrooke's Hospital, Cambridge.

CONFERENCE PREVIEW: World Parkinson Congress

22-26 February, 2006; Washington DC, USA.

The first-ever World Parkinson Congress is scheduled to be held from February 22-26, 2006 in Washington, DC. This unique gathering brings together leading researchers, clinicians, allied health professionals (nurses, physical and occupational therapists, speech pathologists, art or dance therapists, nutritionists, dieticians, counsellors, social workers), caregivers and people with Parkinson's disease.

The Congress will feature an extensive programme of plenary sessions, symposia and workshops with presentations and discussions devoted to prevention, diagnosis, treatment and the future of Parkinson's disease research. Workshops will address everything from basic scientific research and translational and clinical science to models of care delivery and national and international approaches to curing Parkinson's. The Congress will also provide opportunities to complete coursework for CME credit.

The Programme Committee for the Congress has organised a varied and extensive programme; there is something of interest for each attendee. The programme has nearly 300 faculty who will address Parkinson-related issues in one of three categories: Science; Care Delivery and Quality-of-Life; and Policy.

Science sessions are designed to offer in-depth presentations focused on specific cutting-edge research in the field of Parkinson's disease. The sessions are geared at physicians, scientists, researchers and those interested in understanding the basic and clinical research conducted to better understand the many facets of PD.

Care Delivery and Quality-of-Life sessions are designed to offer concentrated sessions that focus on the best care delivery practices as well as other quality-of-life topics. Areas covered include speech pathology, physical therapy, occupational therapy, mental health, social work, nutrition, and neuroscience nursing. These sessions will also include topics that look at the therapeutic value of art and creativity and PD, the power of optimism and hope when dealing with Parkinson's disease and the improvement in quality-of-life when exercise is included in the daily routines of those living with the disease.

Policy sessions are designed to highlight domestic and international policy surrounding Parkinson's disease, chronic diseases for our ageing society and advocacy training. Issues range from funding for research in the neurosciences to current stem cell policy. These sessions will appeal to anyone involved in policy making and to those who are interested in better understanding how policy affects research and work in the area of Parkinson's.

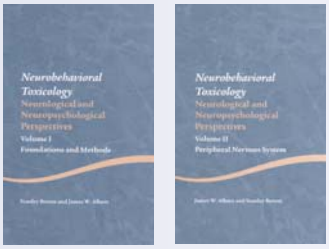
The ultimate goal of the Congress is to advance an all-encompassing approach to the treatment of Parkinson's by bringing together the full spectrum of those who serve the Parkinson's community and those who live with the disease.

A preliminary programme, list of speakers, exhibit details, hotel and registration information are available at www.worldpdcongress.org. The deadline for discounted registration is January 16, 2006.

Neurobehavioral Toxicology
Neurological and Neuropsychological Perspectives

Edited by **James W. Albers** and **Stanley Berent**, University of Michigan Medical School

Volume I: Foundations and Methods
ISBN: 1-84169-564-5
Volume II: Peripheral Nervous System
ISBN: 1-84169-565-3
Volume III: Central Nervous System
ISBN: 1-84169-636-6 (Coming in mid-2006)



This three-volume set provides a thorough background to the emerging field of neurobehavioral toxicology by looking at current clinical approaches and tests, and assessing current clinical research. The analysis of the impact of toxins on the human nervous system is particularly and increasingly pertinent given the ongoing expansion of pharmaceuticals, industrial hazards, biological warfare and global pollution. These books will become an essential reference and resource for practicing neurologists and neuropsychologists, occupational medicine physicians and medical toxicologists.

August 2005 / Hardback / £59.95 per volume

Taylor & Francis
Taylor & Francis Group

See www.psypress.co.uk for more details.

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

Recovery after Stroke

There is now quite an array of textbooks concerning stroke although the balance has very much shifted towards acute stroke, stroke neurology, and intervention in the early phase. There is, by comparison, a relative paucity of books dealing with the aftermath of stroke and this book aims to try and redress some of the balance. Largely, it is a book aimed at the physician caring for the stroke patient in the rehabilitation phase but as part of the stroke rehab library it will probably be looked at by senior nursing staff and therapists involved in stroke rehabilitation.

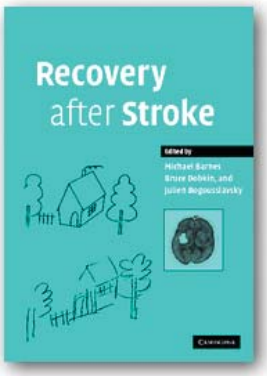
It is a comprehensive book of 25 chapters written by different authors, largely from Europe and North America, ranging from background epidemiology, aetiology and secondary prevention stroke through to the patients' perspective of their stroke. In between there are chapters ranging from the regenerative ability of the CNS after stroke and cerebral reorganisation, through to the evidence base for early rehabilitation in hospitals and the community, physical recovery, speech recovery, cognitive recovery, depression, sleep disorders and autonomic disorders amongst others. As such, the range of topics covered is extremely comprehensive.

One chapter follows the next but this is not the sort of book which one would read cover to cover, one would tend to read two or three related chapters at a time. Each chapter is extremely well referenced, indeed often rather over-referenced (for example, the first chapter on epidemiology, aetiology and avoiding recurrence is thirty pages long but is followed by fifteen pages of references, and that on abnormal movements after stroke contains fifteen pages of text followed by twelve pages of references!).

Many of the chapters concentrate on mechanisms and pathogenesis of differing impairments and handicaps with a heavy bias towards research, somewhat at the expense of a problem orientated approach which would be rather more useful to the clinician involved in routine patient care. I suspect this is going to limit the book's readership quite considerably. It therefore comes as quite a relief in the chapter on sleep disorders after stroke to come across a section subtitled 'Practical guidelines for the management of sleep-wake disorders'. Such a section in many of the chapters would have been extremely welcome.

This book will appeal to those specifically interested in stroke rehabilitation, particularly from an academic point of view, but will probably find its way on to more stroke rehabilitation unit library shelves rather than one's own personal bookshelf at home.

Peter Martin, Addenbrooke's Hospital, Cambridge.



Edited by: Michael Barnes, Bruce Dobkin, and Julien Bogousslavsky
Published by: Cambridge University Press
Price: £95
ISBN: 052182236X

Neurological Disorders in Famous Artists
Frontiers of Neurology and Neuroscience, Volume 19

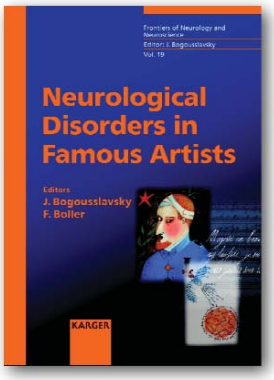
Seldom have I been as excited by the prospect of reading a neurology book, no doubt a reflection of my skewed priorities (which regular readers of ACNR may be aware of). This slim volume does not disappoint expectations. Three broad groups of artists and their possible diagnoses are considered: writers, painters, and musicians. This undertaking of course faces the 'problem of the frame' (p. 66), the limited documentary material which may be adduced from contemporary accounts ('second hand' history taking), abetted in some cases by the authors' own writings which 'speak directly to the clinician's ears' (p. 18). There is something involuntary in this latter experience, an approach which undoubtedly enrages devotees of the evidence-based movement. Pathography is the ideal word for these pieces, since as well as its usual meaning ('description of a disease') it might also be considered an example of a blend, or what Humpty Dumpty calls a portmanteau word, pathological biography, thus packing up two meanings in one word.

In the first group are (with presumed diagnoses): Guillaume Apollinaire (subdural haematoma secondary to non-penetrating missile injury); Guy de Maupassant, Friedrich Nietzsche, and Alphonse Daudet (neurosyphilis); Flaubert (epilepsy, speculated to be due to an occipital lobe arteriovenous malformation); Edgar Allan Poe (complex partial seizures, complicated or caused by substance abuse); Dostoevsky (temporal lobe seizures); and Immanuel Kant (dementia, possible Lewy body type). Adding to the fascination, the influence of these experiences on the writings of some of these authors is also traced. The chapter on Daudet, the longest in the book, complements his own account of locomotor ataxia, *La Doulou*, recently translated as *In the land of pain* by the author Julian Barnes. A possible delineation of a frontal lobe syndrome in a tale by Poe is not mentioned (see Altschuler, Lancet 2004;363:902).

A 1948 paper in *Brain* (71:229-241) by Alajouanine, in which he described the consequences of aphasia in a writer (Valery Larbaud), a musician (Maurice Ravel), and an unnamed painter, forms the basis for three chapters. Careful medical detective work by François Boller has identified the painter as Paul-Elie Gernez; it is suggested his style became less poetic following his aphasia. More devastating was the effect of Alzheimer's disease on the output of Carolus Horn (1921-1992), the sparing of artistic drive but with production of gradually more abstract works, ultimately degenerating to scribble, being in some ways reminiscent of the experience of William Utermohlen, another artist affected with Alzheimer's (see Crutch et al., *Lancet* 2001;357:2129-2233). Caspar David Friedrich (major depression) and Vincent van Gogh (bipolar disorder) complete this section. Besides Ravel, the musicians include: Musorgsky (chronic alcoholism); Handel, Haydn, and Vissarion Shebalin (cerebrovascular disease); George Gershwin (tumour); and Robert Schumann (focal or musician's dystonia).

Professors Bogousslavsky and Boller are to be congratulated on this superb collection, which is beautifully illustrated. Though it does not retail cheaply, many neurologists will nonetheless want this book in their personal libraries. A second volume might also be considered, for example to consider the effects on creativity of dementia (Dean Swift, Iris Murdoch) or synaesthesia (Messiaen, Nabokov).

AJ Larner; Cognitive Function Clinic, WCNN, Liverpool.



Edited by: J Bogousslavsky, F Boller
Published by: Karger
Price: CHF 109.50
ISBN: 3-8055-7914-4

An expert view on sleep and multiple sclerosis

It is estimated that 70% of patients with multiple sclerosis complain about fatigue. In addition, more than 50% of MS patients, when asked about the quality of their sleep and sleep-related issues, complain that their sleep is inadequate, that they either have insomnia or that they feel un-rested after night time sleep. Wanting to understand more about fatigue and sleep disorders and their relationship to multiple sclerosis, Consultant Neurologist Mike Boggild, from the Walton Centre in Liverpool put a series of questions to Sleep Expert and Associate Professor of Neurology Michael Thorpy, from the Sleep Wake Disorders Center; Albert Einstein College of Medicine, New York. This article summarises their discussion.

Dr Mike Boggild

Dr Boggild is Consultant Neurologist at The Walton Centre for Neurology and Neurosurgery in Liverpool. His area of expertise is Multiple Sclerosis. His research interests include disease modifying treatments in MS, genetic markers and outcome and qualitative research in MS.

Professor Michael Thorpy

Dr Michael Thorpy is Director of the Sleep-Wake Disorders Center at the Montefiore Medical Center, Bronx, New York. Both a clinician and a well-published researcher, Dr Thorpy serves as Associate Professor of Neurology at Albert Einstein College of Medicine.

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Introduction by Dr Mike Boggild

A significant number of patients with multiple sclerosis report that they are fatigued.[1] Fatigue is an important symptom to consider because it affects patients' social lives, occupations and other activities of daily living. A key question for neurologists is whether or not a fatigued patient may be suffering from an underlying sleep disorder, resulting in excessive sleepiness, and what action should be taken. In the UK we have relatively few neurologists and even fewer who specialise in sleep disorders. In addition, existing sleep services are overrun, so it would be unrealistic to refer every multiple sclerosis patient who complains of fatigue or excessive sleepiness. Wanting to know more about this and how MS specialists can best manage the problem of sleep disorders in multiple sclerosis, I approached US sleep expert, Dr Michael Thorpy. His views were most illuminating on the management options available to help alleviate these complex and troubling symptoms that, in my experience, affect at least two-thirds of patients.

How can fatigue and excessive sleepiness be differentiated?

About 70% of patients with multiple sclerosis complain about general fatigue. In addition, more than 50% of MS patients, when asked about the quality of their sleep and sleep-related issues, complain that their sleep is inadequate, that they either have insomnia or that they feel un-rested after night time sleep. So there seem to be two areas of fatigue; one of which is related, specifically, to sleep disturbance, while the other is related to general tiredness. These two areas are not the same and it is important to recognise this because their management strategies differ. Fatigue is a mental and physical tiredness that is independent of being sleepy. A patient who is sleepy has an increased propensity to fall asleep, and, will, for example, fall asleep quickly if they were put in a darkened room; a patient who is just fatigued will not. If a patient is suffering from excessive sleepiness, the focus is on establishing the issues that are affecting the quality or quantity of night time sleep or on specific neurological abnormalities that are causing an increased sleep predisposition during the day time that disturbs night time sleep. In a fatigued patient, the focus is on the primary disease process. In multiple sclerosis it is the direct consequences of the neurological disturbance associated with the disease, for example, depression, physical weakness and poor physical fitness that causes fatigue.

What factors underlie fatigue and excessive sleepiness?

Studies have shown that multiple sclerosis patients with severe fatigue have decreased cerebral metabolism, cortical metabolism and basal ganglia metabolism compared to multiple sclerosis patients without fatigue. The current thinking is that primary MS fatigue is probably due to some central nervous system disconnection between cortical and deeper structures. Depression also plays a role in MS-related fatigue. The first thing to do is to establish the factors that underlie the fatigue, then treat (pharmacologically or by other means) accordingly. It is also important to recognise that a patient may be using the word, 'fatigue', to describe sleepiness; patients do not tend to say 'I am excessively sleepy', or 'I have severe sleepiness', though this may be what they are suffering from. Instead, patients tend to use vague expressions such as 'I have a loss of energy', 'I can't concentrate' or 'I feel weak'. If a patient uses these sorts of expressions, they should trigger the question in the physician's mind: Is this fatigue or is the excessive sleepiness symptomatic of a sleep disorder? In order to understand this better, a physician can ask direct questions about nocturnal sleep (amount of nocturnal sleep, quality of nocturnal sleep) and about any tendency for daytime sleepiness. Excessive daytime sleepiness is symptomatic

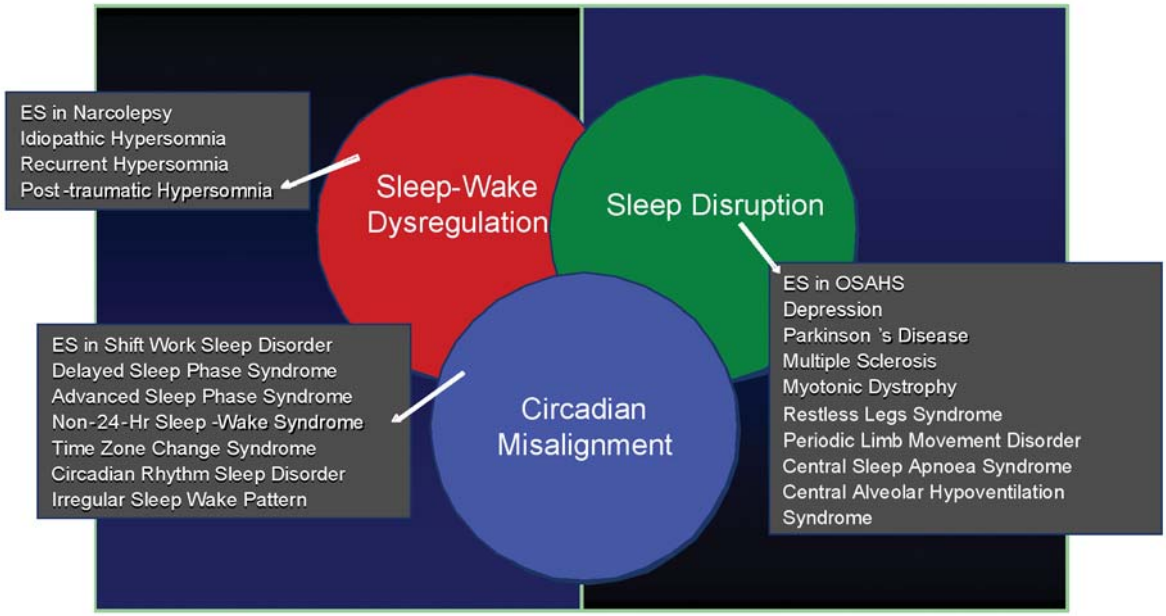
Figure 1

Trigger words patients use to describe they are sleepy

- 'I have a loss of energy'
- 'I can't concentrate'
- 'I feel weak'

1. MacAllister WS, Krupp LB. *Multiple sclerosis-related fatigue.* Phys Med Rehabil Clin N Am 2005;16483-502.

Figure 2: Causes of Excessive Sleepiness



of a sleep problem which could be due to sleep-wake dysregulation, sleep disruption or a circadian misalignment.

What sort of sleep problems might MS patients suffer from?

In multiple sclerosis patients with sleep disturbance, some patients may have primary insomnia, that is, insomnia unrelated to any psychiatric, medical or other identifiable reason.

In the general population, over 30% of people complain of primary insomnia, so this is likely to be an issue in multiple sclerosis patients, too. But, in addition, there are sleep problems that can occur more commonly in multiple sclerosis and cause disrupted sleep. For example, patients may experience leg-jerking movements, periodically, during night time sleep that affects sleep quality due to frequent arousals. Patients are unaware of these movements, and these are distinct from restless leg syndrome, which affects around 10% of the general adult population. Periodic leg-movements affect around 36% of multiple sclerosis patients and this is a symptom they are unaware of, unlike the feeling of restless legs. Periodic leg movements occur every 30-40 seconds, particularly in the non-REM stage of sleep. And though patients are unaware of them, bed partners may be, so information from them can be very helpful in deciding if this is a factor contributing to sleepiness. Studies have not shown a greater prevalence of sleep apnoea in the MS population when compared with controls, but sleep apnoea occurs commonly in the general population, so some multiple sclerosis patients may also be affected by this sleep problem. Other unusual sleep disorders have been associated with MS, including REM-like features on multiple sleep latency tests that are similar to narcolepsy. There are some histocompatibility similarities between narcolepsy and multiple sclerosis that raise the issue that some of these patients may, in fact, have some specific, sleep-wake alteration that may predispose them to excessive sleepiness. If somebody with multiple sclerosis is spending a lot of time in bed during the day, there may be a tendency to develop prolonged napping and sleep during the day that takes away from night time sleep. This means it is important to ask about the whole sleep-wake pattern.

Can you explain the sleep/wake process?

Wakefulness and sleep (and the transition from one state to the other) are regulated by neuroanatomical, neurochemical and circadian systems, but no single brain centre is responsible for the whole sleep-wake cycle. 'Being awake' involves two, parallel pathways that activate the cortex: one arises from neurones in the brainstem - the classical reticular activating system (RAS); the other a newly-characterised, neuronal projection from the hypothalamus that incorporates the sleep-wake 'switch'. The latter involves three distinct hypothalamic structures that play a key role in promoting either sleep or wakefulness: the ventrolateral preoptic area (VLPO - sleep-promoting), the tuberomamillary nucleus (TMN - wake-promoting) and the suprachiasmatic nuclei (SCN - site of the 'internal clock' that regulates circadian rhythm).

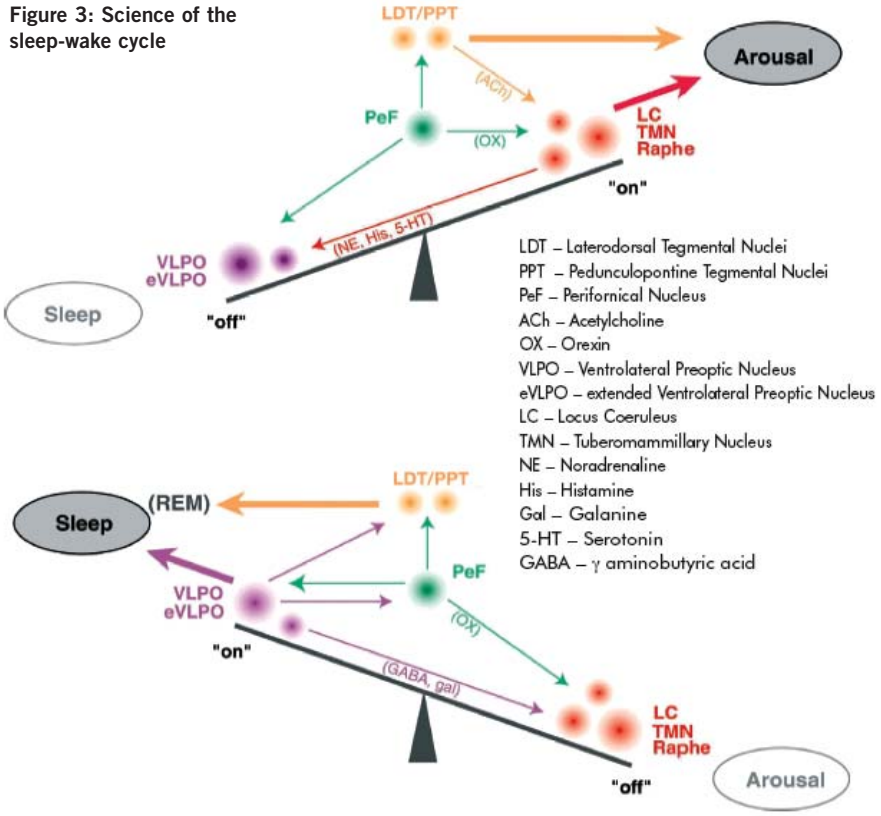
The sleep-wake 'flip-flop' switch

One model of the normal sleep-wake cycle proposes that VLPO and TMN neurones inhibit each other, thus causing oscillations between wakefulness and sleep in a rhythm determined by the internal clock in the SCN. This is elegantly described by Saper et al who discuss the concept of a reciprocal switching circuit - or 'flip-flop' switch - which means the brain can be either 'on' (calm wakefulness) or 'off' (asleep). The two halves of the flip-flop circuit, by each strongly inhibiting the other, create a feedback loop that is bi-stable, meaning there are two possible stable patterns of firing, with a tendency to avoid intermediate states.

The self-reinforcing firing patterns of the flip-flop switch produce a degree of resistance to switching when one side is firing briskly, which confers stability to the system. So, what flips the switch? When major influences come into play, such as circadian sleep drive or an accumulated homeostatic need for sleep, the relative balance of mutual inhibition might gradually shift. When this pressure to change becomes great enough, the same feedback properties that allow the flip-flop circuit to resist change will suddenly yield and rapidly produce a reversal of the firing patterns. The flip-flop switch therefore changes behavioural state infrequently but rapidly, in contrast to the homeostatic and circadian inputs, which change continuously and slowly.

The relatively recent discovery of the neuropeptide, hypocretin (orexin), has thrown further light on how stability of this switch is maintained. It is now thought that hypocretin neurones might act as a 'finger', pressing the flip-flop switch into the 'wakeful' position, and preventing inappropriate switching into the 'sleep' position. It would follow that an unstable switch could lead to insomnia or to unwanted, rapid transitions into sleep during wakefulness, e.g. as seen in narcolepsy.

Figure 3: Science of the sleep-wake cycle



Adapted from Saper C. The Sleep Switch: Hypothalamic Control of Sleep and Wakefulness. Trends in Neurosci 2001: 24: (12) 726-731

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How should these problems be investigated?

The first thing is to understand the sleep-wake cycle by gleaning information with regard to sleep from a patient diary/sleep log. The next step is to determine, via symptom history, if there is anything to suggest a primary sleep disorder. If the patient has significant daytime sleepiness, and simple adjustments to sleep timing and pattern have been made but the problem still exists, electrophysiological tests are useful to see what is happening to the quality of night time sleep. In addition, a multiple sleep latency test gives objective information on sleep drive throughout the daytime. The Epworth Sleepiness Scale (ESS) is a particularly helpful scale to use with a patient that has an increased physiological drive for sleep. This scale provides useful information about sleepiness and its relation to everyday activities of daily living.

What questions can neurologists ask to elicit a potential sleep disorder?

If a patient answers yes to the questions listed below, this should alert a physician to a potential sleep disorder diagnosis:

- Do you snore?
- Do you gasp during sleep?
- Do you choke during sleep?
- Do you have breathing difficulties during sleep?
- Do your legs jerk while you're asleep at night? (partner reporting)
- Do you have difficulty falling asleep?
- Do you have difficulty remaining asleep or early morning awakening?
- Do you take frequent daytime naps?

What can be done to help a patient with fatigue and/or excessive sleepiness?

There are a number of circumstances that can worsen fatigue, such as excess heat, and these should be avoided. Other aspects of behaviour, such as timing of daily activities and spacing out work activities, can be modified in favour of reducing fatigue. If depression is an underlying factor, this should be dealt with. Moreover, it is important to assess the impact of MS medication on sleepiness as some drugs can impair alertness during the day. Amantadine may be useful in mild cases of fatigue as a small clinical benefit may be gained.

In more severe cases, modafinil, which promotes wakefulness, is recommended as it is beneficial in cases of excessive daytime sleepiness. Modafinil reduces the effect of the symptom of excessive sleepiness, but how it works is not really known. We know modafinil may influence the sleep-wake cycle and affect the brain stem system involved in alertness and wakefulness. If the patient is excessively sleepy, modafinil could be added to the management strategy once the factors causing the excessive sleepiness are dealt with. Other medications, ranging from stimulants to selegiline, may be worth considering, but these are associated with either a higher adverse event potential or there is limited data on their usefulness and efficacy in the multiple sclerosis population. With respect to a primary sleep diagnosis, treatment should be directed specifically towards that. For example, if the patient has a sleep-related breathing disorder a CPAP (a continuous positive airway pressure) device or other treatments directed at relieving the respiratory disturbance may be recommended.

Are there any lessons to be learnt from using modafinil in MS patients?

> It is important to choose the correct patients. Some of the earlier clinical studies seemed to indicate that modafinil was not effective in treating fatigue, and to a greater extent this is true. Modafinil treats excessive sleepiness, it is important to differentiate between a patient with fatigue and one who may be fatigued and have excessive sleepiness. Whilst a high proportion of patients report fatigue, few differentiate this from excessive sleepiness, so it is important to ask the right questions before you prescribe modafinil.

It may also take a bit of time for a patient to get a good response. Sometimes, the medication needs to be titrated, and so a patient may need to be maintained at a lower dose for a period of time before the dose is increased appropriately.

Initial studies showed that 200mg was effective, but we now know that in most cases patients do better on 300-400mg doses. The recommended approach is start low and go slow. My practice is to divide a 200mg dose into a 100mg morning dose, followed by another 100mg dose around noon for a week. I would then give 200mg twice daily for two weeks in a month. If there is no benefit, treatment is discontinued.

What are the side effects of modafinil?

The main side effects are headache, nausea and nervousness. Usually, these are self-limiting and can be helped, in some cases, by reducing the dose. In multiple sclerosis patients experiencing such side effects, it may be prudent to use half a tablet of the lowest dose (100mg) for a while until symptoms disappear, then increase to a more appropriate dosage.

Do patients develop tolerance to modafinil?

To date there have been over 200,000,000 patient days experience with modafinil and long-term, open-label studies in the US have shown that tolerance hasn't developed over prolonged periods of time when using modafinil in narcolepsy patients. Such data does not yet exist for the MS population.

Key points:

- Fatigue and excessive sleepiness are two symptoms that differ in their clinical manifestation and management
- Patients who are fatigued may not report that they are also experiencing excessive sleepiness
- Many patients with MS may be excessively sleepy due to sleep disruption or an underlying sleep disorder
- Amantadine may be beneficial in treating mild cases of fatigue.
- Modafinil 200mg – 400mg is effective in treating excessive sleepiness associated with chronic pathological conditions, including narcolepsy, obstructive sleep apnoea-hypopnoea syndrome and moderate to severe chronic shift work sleep disorder.

Brian Simpson – A Case History

Brian Simpson was first diagnosed with multiple sclerosis in 2001 after presenting to his GP with an episode of blurred vision. He had also been experiencing spells of unexplained tiredness which, following the diagnosis of MS, were recognised as being disease-related symptoms. For Brian, such regular periods of fatigue and tiredness were a particular concern since his physically demanding job as a fireman required him to be alert and awake. He was well aware that suffering an episode of excessive sleepiness at work could endanger his and others' safety and so he approached his GP to ask about possible treatment options.

Brian was initially offered treatment with amantadine, an established drug mainly used for the treatment of Parkinson's disease, but which has some effect on MS fatigue. He tried the drug for several days, but experienced a variety of side effects and his neurologist offered him Modafinil as an alternative.

Brian was treated with Modafinil, 200 mg, to be taken first thing in the morning, and immediately began to feel the benefits. His energy levels whilst at work remained steady and continued to do so during the evenings at home with his family. Moreover, he suffered no major side effects.

As a result, he has continued with the treatment now for 12 months and remains enthusiastic about its effects. "Being on Modafinil allows me to play football on a Sunday in the park with my kids and it allows me, at work, to push myself further than maybe I would have done." Treating his daytime excessive sleepiness with Modafinil has allowed Brian to be active, live a normal life and gain back some control over the disease.

(Patient's name has been changed)

Reading List

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5. Saper C. (2001) The Sleep Switch: Hyprothalamic Control of Sleep and Wakefulness. Trends in Neurosci 24: (12) 726-731.
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11. Rammohan KW. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry. 2002 Feb; 72(2): 179-83.

UK ABBREVIATED PRESCRIBING INFORMATION:

▼PROVIGIL® 100 mg and 200 mg tablets (modafinil)

Please refer to UK Summary of Product Characteristics (SmPC) before prescribing.

Presentation: White to off-white tablets containing modafinil 100 mg or modafinil 200 mg (debossed with "PROVIGIL" on one side and "100 MG" or "200 MG" on the other). **Indication:** Excessive sleepiness associated with chronic pathological conditions, including narcolepsy, obstructive sleep apnoea/hypopnoea syndrome and moderate to severe chronic shift work sleep disorder. **Dosage and Administration:** *Adults: Narcolepsy and Obstructive Sleep Apnoea/Hypopnoea Syndrome:* 200 - 400 mg daily either as two divided doses in the morning and at noon or as a single morning dose according to response; **Shift Work Sleep Disorder:** 200 mg daily taken as a single dose approximately 1 hour prior to the start of the work shift. *Elderly:* Treatment should start at 100 mg daily, which may be increased subsequently to the maximum adult daily dose in the absence of renal or hepatic impairment. *Severe renal or hepatic impairment:* Reduce dose by half (100 - 200 mg daily). *Children:* Not recommended. **Contra-indications:** Use in pregnancy and lactation, uncontrolled moderate to severe hypertension, arrhythmia, hypersensitivity to modafinil or any excipients used in PROVIGIL. **Warnings and Precautions:** Patients with major anxiety should only receive PROVIGIL treatment in a specialist unit. Sexually active women of child-bearing potential should be established on a contraceptive programme before taking PROVIGIL. Blood pressure and heart rate should be monitored in hypertensive patients. In patients with obstructive sleep apnoea, the underlying condition (and any associated cardiovascular pathology) should be monitored. Patients should be advised that PROVIGIL is not a replacement for sleep and good sleep hygiene should be maintained. PROVIGIL is not recommended in patients with a history of left ventricular hypertrophy, cor pulmonale, or in patients who have experienced mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia. Studies of modafinil have demonstrated a low potential for dependence, although the possibility of this occurring with long-term use cannot be entirely excluded. PROVIGIL tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption. **Drug Interactions:** Modafinil is known to induce CYP3A4/5 (and to a lesser extent, other) enzymes and so may cause clinically significant effects on other drugs metabolised via the same pathways. Examples include ciclosporin, HIV-protease inhibitors and most of the calcium channel blockers and statins. The effectiveness of oral contraceptives may be impaired through this mechanism. When these are used for contraception, a product containing at least 50 mcg ethinylestradiol should be taken. A number of tricyclic antidepressants and selective serotonin reuptake inhibitors are largely metabolised by CYP2D6. In patients deficient in CYP2D6 (approximately 10% of the Caucasian population) a normally ancillary metabolic pathway involving CYP2C19 becomes more important. As modafinil may inhibit CYP2C19 lower doses of antidepressants may be required in such patients. Care should also be observed with co-administration of other drugs with a narrow therapeutic window, such as anticonvulsant or anticoagulant drugs. As clearance of warfarin may be decreased when PROVIGIL is administered concomitantly, prothrombin times should be monitored regularly during the first 2 months of PROVIGIL use and after changes in PROVIGIL dosage. **Undesirable effects:** *Very common (>10%)* - headache. *Common (>1%-10%)* - nervousness, insomnia, anxiety, dizziness, somnolence, depression, abnormal thinking, confusion, paraesthesia, blurred vision, nausea, dry mouth, diarrhoea, decreased appetite, dyspepsia, constipation, tachycardia, palpitation, vasodilatation, abdominal pain, asthenia, chest pain and abnormal liver function tests. Dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed. *Uncommon (>0.1%-1%)* side effects include arrhythmia, bradycardia, extrasystoles, hypertension, hypotension, dyspnoea, asthma, leucopenia, diabetes mellitus, hyperglycaemia, hypercholesterolaemia and movement disorders (See SmPC for other uncommon side effects). **Basic NHS cost:** Pack of 30 blister packed 100 mg tablets: £60.00. Pack of 30 blister packed 200 mg tablets: £120.00 **Marketing Authorisation Numbers:** PL 16260/0001 PROVIGIL 100 mg Tablets, PL 16260/0002 PROVIGIL 200 mg Tablets. **Marketing Authorisation Holder:** Cephalon UK Limited. **Legal Category:** POM. **Date of Preparation:** June 2005. PROVIGIL and Cephalon are registered trademarks. Full prescribing information, including SmPC, is available from **Cephalon UK Limited**, 11/13 Frederick Sanger Road, Surrey Research Park, Guildford, Surrey UK GU2 7YD, Medical Information Freefone 0800 783 4869 (ukmedinfo@cephalon.com).

EDITOR'S CHOICE

MULTIPLE SCLEROSIS is more than one disease

For decades, people interested in multiple sclerosis have kicked this issue around: are we studying one disease or several? It is not a trivial question. Because the search for a unitary cause, genetic or environmental, is doomed if multiple sclerosis is a ragbag of different diseases. And, even more importantly, different forms of multiple sclerosis may require different treatments. In recent times, the collaboration between Claudia Lucchinetti and Brian Weinshenker of the Mayo Clinic and Hans Lassmann of the Centre for Brain Research in Vienna, has contributed several key papers that suggest multiple sclerosis is more than one disease. They showed that multiple sclerosis pathology can be divided into four types (I through to IV) [*Lucchinetti C, Ann Neurol. 2000;47(6):707-17.*] and that about half of patients with aggressive acute demyelinating syndromes respond to plasma exchange [*Weinshenker BG, Ann Neurol. 1999;46(6):878-86.*]. They now do the obvious thing: see whether those patients who respond to plasma exchange have distinctive pathology of their multiple sclerosis lesions. Obvious certainly, but not straight forward, as it is hardly usual practice for people with multiple sclerosis to undergo a brain biopsy! So this research letter in the Lancet focused on that rare group of patients who present with brain lesions which have to be biopsied because of diagnostic uncertainty… and who then do not respond to corticosteroids, making plasma exchange the next stage of treatment. They describe 19 such patients. Of these 10 patients responded to plasma exchange, of whom all had "Type II" pathology, which is characterised by immunoglobulin deposition and complement activation. In contrast, none of the 9 patients who failed to respond to plasma exchange had Type II pathology. Rather they had a mixture of Types I and III, neither of which include those hallmarks of antibody-mediated pathogenicity. This is neither a robust nor comprehensive study. Important details, such as CSF or radiology, are absent. Nonetheless, it is a spur to investigators to develop non-invasive techniques to distinguish the different forms of multiple sclerosis, to assist the scientist and clinician alike. ***-AJC***

Keegan M, Konig F, McClelland R, Bruck W, Morales Y, Bitsch A, Panitch H, Lassmann H, Weinshenker B, Rodriguez M, Parisi J, Lucchinetti CF.

Relation between humoral pathological changes in multiple sclerosis and response to therapeutic plasma exchange.

LANCET

2005 Aug 13-19;366(9485):579-82.

DEMENTIA: and brain biopsy

★★★ **RECOMMENDED**

The antemortem diagnosis of dementia is almost invariably clinical, and at least as far as Alzheimer's disease (AD) is concerned this is usually corroborated post-mortem, in 80-90% of cases in the best hands. Occasionally, however, the need for tissue diagnosis in a patient experiencing cognitive decline is felt to outweigh the potential surgical risks of brain biopsy. How useful is this investigation? This retrospective study looked at 90 consecutive brain biopsies performed for dementia at the National Hospital, Queen Square, a tertiary referral centre, over a 14 year period (1989-2003), hence around 7 biopsies per year. All were undertaken to exclude a reversible (inflammatory or infectious) process. 90% were non-dominant frontal lobe biopsies, 6% produced inadequate samples, and 11% were associated with biopsy-related complications (seizures, infection, haemorrhage) but without lasting sequelae. Biopsy led to a specific diagnosis being made in 57% of cases, the most common diagnoses being AD, Creutzfeldt-Jakob disease (CJD), and inflammatory disorders. 10% of biopsies revealed a potentially reversible cause, mostly inflammatory but with one case of Whipple's disease. An elevated CSF cell count was a predictor, albeit not a very powerful one, of inflammatory pathology. In 11% of cases, treatment was directly determined by biopsy (increase or reduction in immunosuppression; antibiotics for Whipple's; cholinesterase inhibitors for AD). Outcomes were not recorded in detail, so it is not clear if any demented patient "reversed". The largest single category of biopsy diagnosis (37%) was non-specific gliosis variably affecting the cortex and white matter. The constellation of behavioural change, increased CSF protein and matched serum and CSF oligoclonal bands predicted this pathological finding. What relationship, if any, this non-specific gliosis has to progressive subcortical gliosis of Neumann (and whether it may have a specific neuroradiological/spectroscopic correlate; JNNP 2003;74:404) will require further investigation; three such cases coming to post-mortem had final diagnoses of CJD, multiple sclerosis and CADASIL. As the authors state, the risk:benefit analysis for brain biopsy for dementia is finely balanced. It might also be questioned whether the findings of a tertiary referral centre may be generalised: at a regional neuroscience centre, I have not requested a brain biopsy for dementia after nearly 6 years in post. A prospective, preferably multi-centre, study is required.- ***AJL***

Warren JD, Schott JM, Fox NC, Thom M, Revesz T, Holton JL, Scaravilli F, Thomas DG, Plant GT, Rudge P, Rossor MN.

Brain biopsy in dementia.

BRAIN

2005;128(9):2016-2025.

PARKINSON'S DISEASE: When divided they fall? Effects of dual-tasking on attention and gait

Dual task paradigms measure how performance of one task is affected by performance of another. When a task is cognitively demanding performance of a simultaneous second task is thought to put extra strain on existing resources. This paper looks into the relationship between cognitive functioning and gait, and compares the effects of dual tasking on features of gait in people who have Parkinson's disease, and in controls. There were 30 patients and 28 demographically matched healthy controls. The patient group were known to have poorer balance than the control group and had fallen significantly more frequently during the previous six months. Inhibitory control and response switching were assessed in all individuals prior to the dual task research using standard tests of executive functioning. While executive functioning was significantly worse in the patient group, preliminary memory tests did not differ significantly between the two groups. When interpreting the results that follow, perhaps these initial investigations were relatively more fatiguing to the patients than to the controls. Measures of executive function correlated significantly with variability of gait during performance of dual tasks, but not during ordinary walking. Gait speed was decreased in both patients and controls when they performed dual tasks. Gait variability during dual tasks was increased in patients when compared to ordinary walking. The authors suggest that while attention may be necessary in all individuals to maintain some aspects of gait, like speed of walking, other aspects, like regulating gait variability, may also become cognitively demanding in Parkinson's disease patients. This could partially explain patients' tendencies to fall in the real world where multiple demands are placed on a person's attention. The authors also suggest researching whether cognitive enhancing therapies would have beneficial effects on gait control and whether there is rehabilitation value in encouraging patients to maintain their stability during walking by focusing their attention on gait. The paper provides some tentative evidence to support the value of patients sitting down when performing complex tasks, specifically those requiring listening comprehension. Does paucity of gait hinder aspects of cognitive function through diversion of resources? Because gait is so useful to neurologists in illuminating aspects of health, disease and disability, it will be vital that clinicians and other scientists combine their knowledge in order to extract the array of questions interesting research like this poses. - ***LAJ***

Yogev G, Giladi N, Peretz C, Springer S, Simon E S, Hausdorff J M.

Dual Tasking, gait, rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding?

EUROPEAN JOURNAL OF NEUROSCIENCE

2005:22:1248-56.

STROKE: Infarcts in migraineurs

★★★ **RECOMMENDED**

Migraineurs are at risk of silent posterior circulation (PC) infarcts, particularly in the cerebellum (Kruit et al, 2004). The present study aimed to characterise the neuroimaging topography of PC infarcts in migraineurs. Using a population based survey of 6491 Dutch adults aged 20-60 years from the Genetic Epidemiology of Migraine (GEM) study, 863 cases of migraine were identified. From this group, 134 cases of migraine without aura (MO), and 161 cases of migraine with aura (MA) were selected. Matched controls were selected from the GEM cohort, making a total of 435 subjects in the whole study. Each subject was subject to a telephone interview, MRI of the brain, drawing of blood (for cholesterol, but not thrombophilia screens), and a physical examination. 8.1% of MA, 2.2% of MO and 0.7% of controls had clinically silent PC territory infarcts. In total, 60 infarcts were identified: 81% were in the PC territory in the MA group, 47% were in the PC territory in the MO group and 41% were in the PC territory in the control group. Most PC territory infarcts were located in the cerebellum, and most were junctional as opposed to territorial, particularly in the MA group. Eleven subjects had multiple infarcts (59% of migraine cases, 25% of controls). Multiple PC lesions were exclusively in migraineurs. In

migraineurs, cardiovascular risk factors were not higher in the infarct group. In migraineurs with PC infarcts, the highest risk was in MA patients with a high attack frequency (at least 1 per month), odds ratio 15.8. In summary, MA patients with a high attack frequency were at risk from border zone cerebellar infarcts. Cerebellar dysfunction has been recognised previously in migraineurs but a structural basis has not been identified. Border zone infarcts were postulated to result from decreased perfusion pressure and subsequent emboli formation, furthering low blood flow. Low cerebral blood flow during and up to a day after a migraine attack has been described, possibly due to cortical spreading depression, coagulopathy or release of vasoactive peptides. SCA watershed zones were particularly vulnerable perhaps due to the longer course of the SCA branches compared with PICA and AICA branches. Because of the predominance of junctional zone infarcts, lack of small vessel disease (as identified by deep white matter lesions and periventricular white matter lesions) and the lack of association of infarcts with cardiovascular risk factors in migraineurs, the pathophysiology of such infarcts is more likely due to low cerebral blood flow than ischaemic vessel disease. - ***WAP***

Kruik MC , Launer LJ, Ferrari MD, van Buchem MA.
Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study.
BRAIN
2005;128; 2068-77.

Kruik MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD.
Migraine as a risk factor for subclinical brain lesions.
JAMA
2004;291: 427-34.

EPILEPSY: Are seizures dangerous to a baby in utero?

Teratogenicity is a thorny issue in the management of epilepsy in women of childbearing age. For most patients with mild epilepsy, I have taken a reassuring line about the epilepsy at least and not fussed too much about the occasional patient with mild partial seizures who abandon their tablets, openly or covertly. These authors describe a woman with mild partial seizures, comprising twitching of the right side, pallor and sweating, occurring only 6 times per year. In the seventh month of her pregnancy she presented with two consecutive seizures leading to a fall. She had a further seizure whilst being monitored associated with a tachycardia. Her baby experienced a bradycardia from a baseline of 150-160 down to 70 per minute in the absence of uterine contractions. Whilst the significance of the change is unclear, it contradicts conventional wisdom that seizures where oxygenation is maintained have no significant effect on the foetus and raises the possibility that mild epilepsy can affect a baby. The contrary evidence comes from epidemiological studies in which pregnancies in patients on no medication fared just as well as controls. I shan't change my advice on the basis of this one case, although autonomic effects of seizures are common……-***MRAM***

Sahoo S, Klein P.
Maternal complex partial seizure associated with fetal distress.
ARCHIVES OF NERUOLOGY
2005;62:1304-5.

REHABILITATION: Keep moving is best for hemiplegic shoulders

Recovery of upper limb function is notoriously poor after stroke. One of the reasons for this is the loss of integrity at the shoulder. During the early weeks following stroke when the arm is immobilised due to weakness, the muscles and soft tissue structures that normally keep the head of the humerus tight in the glenoid fossa lengthen under the weight of the arm. Once this has occurred it is difficult for patients, who may be recovering muscle activity, to regain shoulder stability and to move the shoulder effectively. Functional electrical stimulation is used to prevent and to remediate shoulder subluxation in some centres but in most places in the UK treatment is conservative and therapists rely on slings, shoulder supports and positioning. Now a group in New York have found some benefit in using a tool that is normally used after orthopaedic surgery: Continuous Passive Motion (CPM). Occupational therapists and physiotherapists do not usually use CPM with stroke patients. Although some do advocate regular passive movement, in practice little time is given to this in stroke rehabilitation. In their study (n= 35), Lynch et al. randomly assigned stroke patients with very weak arms to daily CPM for twenty days or to a daily range of motion group in addition to their normal therapy programme. The affected arm of the patients in the CPM group was supported in a rigid brace while the shoulder was ranged to 90° of abduction for 15 minutes and 80° of external rotation for 10 minutes each day. The control group ranged their own arm in a daily group led by an Occupational Therapist. The exercises focused on the shoulder, elbow and hand for ten minutes each. A therapist who was blinded to group allocation assessed shoulder stability, motor impairment, muscle tone and pain before and after the treatment. CPM treated patients showed more improved shoulder joint stability than the control group. This result did not quite reach significance. No differences in the other variables were found. This was a small study investigating a new treatment and extension of this work to a larger trial would be worthwhile. It would also be interesting to find out why CPM might improve shoulder stability. Is the improvement due solely to sensory stimulation or are the patients inadvertently being provided with a low level of activity-assisted practice? The positions achieved in the support of the CPM machine are impossible for patients to achieve without assistance. Is it the amount of repetition, the extent of the ranging or the position in which it is done that is important? There are many questions to answer in further investigations of this promising therapy, not least is: Why are we so slow in taking principles from orthopaedics and applying them in neurological rehabilitation. – ***AJT***

Lynch D, Ferraro M, Krol J, Trudell CM, Christos P, Volpe BT.
Continuous passive motion improves shoulder joint integrity following stroke.
CLINICAL REHABILITATION
2005;19: 594-9.

STROKE: to clip or coil?

This is a serious trial, by anyone's standards: comparing endovascular or surgical treatment of intracranial aneurysms in 2143 patients with subarachnoid haemorrhage. The results are well known because the trial was stopped early. At an interim analysis, looking at death and dependency at one year, there was a significant benefit for coiling. This was reported in the Lancet in 2002, causing much debate and ruffling of partisan feathers. Now, in the same journal three years later, we have the complete report of all the one-year data and some long-term follow-up (with c. 100 patients in each arm at 7 years). The chance of death or dependency at one year after an aneurysmal subarachnoid is 24% with coiling and 31% with clipping, an absolute risk reduction of 7%. In other words, for every 1000 patients treated with an endovascular approach, 74 patients avoid death or dependency. This early survival advantage is maintained for up to seven years. And another point in favour of coiling was that there was a significantly reduced risk of epilepsy compared to the surgical procedure. Although the numbers of patients having re-bleeds after either procedure was low (28 in total), these usually occurred after coiling. Game and match. Step aside clippers for the coilers…. - ***WAP***

Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, Sandercock P; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group.
International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion.
LANCET
2005 Sep 3-9;366(9488):809-17.

DEMENTIA: The pathological basis of semantic dementia

★★★ **RECOMMENDED**

The nosology of frontotemporal dementia (FTD), the blanket term under which SD falls, is somewhat confusing, and the clinical classification does not parallel the pathological classification. Furthermore, many patients evolve from one clinical diagnosis to another with time. Finally, it can be difficult to distinguish with certainty the different diagnoses, and the precise definitions of some clinical diagnoses have been questioned. Traditionally, tauopathies consist of largely Pick's disease (part of the FTD classification), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), or neurofibrally tangle dementia. Ubiquitin-positive inclusions exclusively, are found predominantly in motor neuron disease dementia (FTD-MND). Rhys Davies [an ACNR reviewer!] and colleagues describe, in a relatively large pathological case series of SD, the predominant pathological features, as well as the pathological distribution and a retrospective review of case notes. Thirteen of 18 cases were ubiquitin-positive only (motor neuron disease inclusion dementia, MNDID) although one case also had Alzheimer's disease (AD) pathology, 3 had Pick bodies, and 2 had AD pathology. All cases, by inclusion had semantic impairment, and all had bilateral frontotemporal atrophy on imaging. Eight had behavioural disturbance and motor symptoms were infrequent although patients were not routinely assessed once global dementia occurred. One of the MNDID cases developed MND one year before death, and one had dysphagia and dysphonia ante-mortem and one had a family history of MND. Five MNDID cases also had pathology in the motor system. One of the AD cases had ubiquitin-positive inclusions exclusively in the inferior olivary nucleus. Interestingly, of the MNDID cases, 6 had inclu-

sions in the inferior olivary nucleus and two of these had inclusions exclusively in the inferior olive (i.e. not in the usual site of the cortex and dentate gyrus). This study shows that the pathological hallmark of SD is MNDID. It was suggested that MND and SD may lie on a spectrum, with a predilection of ubiquitin-positive inclusions for the corticospinal tracts and the anteroinferomedial temporal lobe, respectively. The anteroinferomedial temporal focus for SD, predicted from imaging, pathological and animal studies, was confirmed. Due to this relatively well-circumscribed predilection, clinical features rarely overlap, or do so only in subtle ways or at the end stage of the disease. Interestingly, one of the two cases with exclusively inferior olivary inclusions was the case with MND. It may be that inferior olivary pathology is predictive of MND. The authors concluded that SD cases may be predicted to have MNDID, pathologically. - ***WAP***

Davies RR, Hodges JR, Kril JJ, Patterson K, Halliday GM, Xuereb JH.
The pathological basis of semantic dementia.
BRAIN
2005;128; 84-1995.

EPILEPSY: Shaker or faker?

Epilepsy or non-epileptic seizure (NES)? We all get caught out from time to time and the quest for the infallible test continues. This study reviews some of the things that people have done to try and diagnose patients. The authors tried to be as scientific as possible in selecting only papers where sensitivity and specificity of the technique in question could be measured. They looked at various measures including psychometric assessment, seizure semiology or post-ictal symptoms, seizure induction techniques and prolactin levels. They found 33 studies they could measure. If you can trigger a seizure by saline injection or hypnosis, then the specificity for NES approaches 100%. Is this ethical? Is it more important to be ethical and wrong or use a questionable technique and get the right answer and treatment for your patient? We all know that prolactin levels are most helpful in tonic-clonic seizures so this, and the timing of the sample, needs to be considered in interpreting the results. SPECT scanning had a sensitivity of 70% and specificity of 80% - so much for modern imaging. The presence of pre-ictal pseudosleep requires EEG diagnosis but was 100% specific for NES (only 23% sensitive). If a patient has a convulsive seizure then the absence of synchronised movements of upper and lower limbs and the absence of vocalisation at the beginning or end of a seizure had 96% sensitivity and 96% specificity for NES. Home videoing may be of value even without EEG. Most other ictal features are relatively unhelpful – particularly when compared against frontal lobe attacks. Of course the bottom line is that without the gold standard of video-EEG telemetry we will always make mistakes. But for those of us without ready access to gold, there are some things that can provide additional support to a diagnosis that often has to be made by sixth sense. - ***MRAM***

Cuthill FM, Espie CA.
Sensitivity and specificity of procedures for the differential diagnosis of epileptic and non-epileptic seizures.
SEIZURE
2005;14:293-303.

REPAIR: Functional neurons from the adult brain

★★★ **RECOMMENDED**

Neurogenesis persists into adulthood in the mammalian brain in the subventricular zone (SVZ) and dentate gyrus (DG) of the hippocampus in many species including humans. The extent to which neurogenesis occurs in humans is the subject of debate, particularly as it is difficult to fate map proliferating cells in humans. Neural precursor cells (NPC) have been isolated in vitro from human brain, from resection specimens and post-mortem, but it is unclear whether these cells are relevant to brain function or whether they are artefacts of culture. It has been shown that NPC from humans can form cells which express neuron specific markers, and also that these possess some characteristics of neurons, namely excitability, although this can also occur in developing glia. Thus, the ability of NPC to form functional neurons have not yet been demonstrated in humans in vitro. Moe et al (2005) have cultured NPC from the SVZ, from temporal lobe resection specimens on patients with epilepsy, and characterised their properties in vitro, using a combination of electrophysiology and channel blockers. NPC can be grown in culture as neurospheres. Neurospheres are aggregates of cells, and with time in culture, it is those cells that can self renew that are selected for. Neurospheres can be dissociated into single cells and the cells differentiate after removal of mitogens and addition of serum. They show that during the first week of differentiation in vitro, some cells express neuronal markers. During the second week, they express voltage gated-K+ channels and then voltage gated Ca2+ channels, which produce small action potentials (AP). It was suggested that the repolarising currents mediated by the K+ channels were required to offset excess Ca2+ entry to the developing neurons or, more likely, that these currents are required for migration. In the third week, the cells developed voltage gated Na+ channels, which mediated a broad high-threshold AP. These evolved into short-lasting low-threshold repetitive AP seen in mature cortical neurons. Furthermore, by the end of the fourth week of differentiation, GABAergic and glutamatergic post-synaptic currents were observed, indicating synaptic connectivity. The authors thus demonstrated that functional neurons can be produced from NPC isolated from the adult human brain. This observation provides an essential step in the therapeutic application of such cells, as well as the suggestion that functional neurogenesis may occur in the adult human brain. - ***WAP***

Moe MC, Varghese M, Danilov AI, Westerlund U, Ramm-Pettersen J, Brundin Svensson LM, Berg-Johnsen J, Langmoen IA.
Multipotent progenitor cells from the adult human brain: neurophysiological differentiation to mature neurons.
BRAIN
2005;128:2189-99.

GLIOMAS: How they attract haemopoetic stem cells

Many types of stem and progenitor cells are attracted to tumours, as well as other pathologies such as stroke and neurodegeneration. Because gliomas are deeply infiltrating and are relatively resistant to radio- and chemotherapy, an autologous cellular vector is an attractive option for therapy. Tabatabai and colleagues have elucidated the molecular mechanism of the tropism of haemopoetic precursor cells (HPC) to intracerebral gliomas. Granulocyte colony stimulated factor (G-CSF) was used to mobilise HPC, which were then harvested, labelled and injected intravenously into nude mice which had previously been transplanted with human glioma cells. The HPC were found in the gliomas but not elsewhere in the brain. The labelled HPC continued to express CD34 and did not express markers of neurons or glia, indicating that the label was specific and that the cells did not undergo phenotypic transformation. In vitro, HPC migrated towards supernatant from glioma cells, which was blocked by addition of a neutralising antibody to CXCL12. CXCL12 is the major cytokine for stem cell homing to bone marrow. Next, glioma cells in which expression of transforming growth factor b (TGFb) had been blocked by RNA interference, were transplanted into rat organotypic hippocampal slices. The disabling of TGFb reduced the migration of HPC towards the glioma. This TGFb-dependent attraction was found to be dependent on CXCL12, and, in parallel, matrix metalloproteinase (MMP-9) and stem cell factor (SCF). MMP-9 and SCF work in parallel to CXCL12 because they are unable to overcome CXCL12 neutralisation and MMP-9 does not increase CXCL12 levels. TGFb is upstream of these factors because addition of exogenous TGFb could not compensate for the loss of the other factors. Similarly, MMP-9 is up-stream of SCF. Additionally, CXCL12 is essential for chemotaxis because the other factors lose their chemoattractive ability when CXCL12 is neutralised, but CXCL12 can compensate for loss of SCF. The study shows that CXCL12 is the essential factor in chemoattraction of glioma cells to HPC, which is dependent on TGFb, with MMP-9 and SCF as synergistic agents. This finding has implications for the development of cellular vectors, which could target glioma cells. - ***WAP***

Tabatabai G, Bahr O, Mohle R, Eyupoglu IY, Boehmler AM, Wischhusen J, Rieger J, Blumcke I, Weller M, Wick W.
Lessons from the bone marrow: how malignant glioma cells attract adult haemopoetic progenitor cells.
BRAIN
2005;128:2200-11.

REPAIR: The old story of hippocampal neurogenesis, its regulation and significance

★★★ **RECOMMENDED**

There is no doubt that new neurons (neurogenesis) are constantly being born in the adult mammalian hippocampus, and that this gets less with ageing. Furthermore the functional significance of these new neurons is in the acquisition of certain forms of memory and exercise and environmental enrichment can both increase hippocampal neurogenesis and learning – ergo., what happens if you physically exercise the aged mammal in terms of neurogenesis and learning? Well obviously you can't study grandma on the treadmill, so Gage and colleagues have used the aged mouse, a running wheel and the Morris water maze. This study clearly shows that neurogenesis is increased in the aged mice with physical activity, and that the new born neurons have normal morphology and that this is associated with improved retention of information in the Morris water maze (but not causally proven to be). This occurs without any changes in angiogenesis – the latter often being thought of as going hand in hand with neurogenesis. This is an exciting study and suggests that keeping active in old age is

good for the hippocampus, if not the knees. This study comes on the back of another interesting paper, this time in Neuron by Tozuka et al. In this paper, the authors show that excitatory GABAergic stimulation of the transiently amplifying neuronal precursor cells in the dentate gyrus of the hippocampus is important in their neuronal differentiation. Furthermore this GABergic input is from the hippocampal circuitry itself, suggesting that the level of electrical activity within the hippocampus controls the rate of neurogenesis. This suggests that using the hippocampus, through mental activities for example, may increase neurogenesis. So goodness knows what would happen if you thought hard whilst running!? However apart from the obvious benefits that may be there for us all, these papers raise many questions not least about what happens in disease. For example, what does all this mean for the patient with temporal lobe epilepsy on treatment with drugs that interfere with GABAergic neurotransmission? Therefore we are once more challenged to think about how the brain behaves in a dynamic way in both normal ageing and in disease and how this may be harnessed to manipulate this network for clinical good. - ***RAB***

Van Praag H, Shubert T, Zhao C, Gage FH.
Exercise enhances learning and hippocampal neurogenesis in aged mice.
JOURNAL OF NEUROSCIENCE
2005;25:8680-5.

Tozuka , Fukuda S, Namba T, Seki T, Hisatsune T.
GABAergic excitation promotes neuronal differentiation in adult hippocampal progenitor cells.
NEURON
2005;47:803-15.

EPILEPSY: Announcement for medicolegal practitioners

The authors describe three cases who had peripheral injuries and later developed epilepsy arising from the cortical representation of the affected part. The first was a 23 year old man who caught his right hand between mechanical rollers, sustaining soft tissue injuries. A day later he developed jerking movements of the right hand 20 times daily and three months later started having nocturnal tonic clonic seizures. MRI and SSEP were normal. Video-EEG telemetry showed stereotyped supplementary motor type seizures and in the one localisable attack, onset was in the left parasagittal region. The second patient was a 27 year-old woman who had two maternal uncles with epilepsy. At the age of 19 she sustained a cigarette burn to medial surface of the left middle finger, causing blistering. Within 24 hours she started to have recurrent bouts of tingling affecting the tip of the burned finger which over the following months spread to affect the whole arm and upper torso and increased in duration to 30 seconds. After 5 months the pain became more intense and she would cry out and have clonic movements of the left side. She had sensory signs of bilateral carpal tunnel syndrome. She was treated with carbamazepine for a presumed pain syndrome, which was tapered during video-EEG telemetry. She had supplementary motor type seizures affecting the left side of her body, which secondarily generalised on one occasion. EEG was non-specific and MRI was normal but interictal PET showed hypometabolism in the right parietal lobe. The third patient was a thirty-seven year-old man who burned his right hand at the age of 4 and 6 months later developed sensory seizures affecting his right hand and evolving into hemiclonic and occasionally generalised seizures. Investigations were non-localising. We are used to thinking of sensory stimuli as seizure triggers; simple such as photic stimulation or complex such as startle. But this is causation at a different level – epileptogenesis rather than trigger. The onset of seizures within 24 hours in two cases is persuasive but also means that much of the wiring for focal seizures was already present and relatively minor changes induced by altered sensory input could rapidly lead to seizures. Does the heightened sensory stimulus act as a form of kindling? I look forward to animal models that explain the mechanism. - ***MRAM***

Spiller AE, Guberman, A, Bartolomei F, Zifkin B and Andermann F.
Epileptogenesis due to peripheral injury as a cause of focal epilepsy.
EPILEPSIA
2005;46:1252-5.

Would you like to join ACNR's reviewer's panel? For more information, email Rachael@acnr.co.uk or tel: 01747 860168

News

Teaching depends on Carl Zeiss

Axiostar plus from Carl Zeiss.

Axiostar plus microscopes installed in the Department of Biological Sciences at Imperial College, London.

The department of Biological Sciences at Imperial College London now has 150 Zeiss Axiostar Plus microscopes installed and working in their teaching labs. In a massive exercise to replace the entire stock of 30 year old student microscopes, chief technician Ian Morris chose Zeiss microscopes after sampling units from every major manufacturer.

"Our new microscopes had to be light and easily transportable with excellent optics and upgrade options to cope with the rapid developments in modern microscopy. But they also had to be robust enough to withstand the demands of a generation of inexperienced users while staying within our budget. The Zeiss Axiostar fitted the requirement perfectly", says Morris.

The entire order was delivered in one shipment in less than 12 weeks, with Zeiss personnel unpacking and installing every unit. "As well as keeping to the agreed delivery schedule, which is extraordinary with an order of this magnitude, each and every microscope worked right out of the box. I will not hesitate to come back to Zeiss for any future requirements", adds Morris.

For further information, contact Carl Zeiss Ltd, Tel. 01707 871233.

Extreme performance comes to Cambridge

The MRC Cognition and Brain Sciences Unit in Cambridge is set to have the first 3T MAGNETOM Trio with Tim technology in the UK. 3T with Tim is said to shorten scan times with unheard of acceleration (PAT) factors, leading to brilliant resolution of the most microscopic pathologies.

Project leader Dr Adrian M. Owen, Senior Scientist at the Cognition and Brain Sciences Unit, (in the digger) holds a short ceremony to mark the turning of the first turf at Cambridge Brain Research Unit.

Functional Neuro imaging is being applied in many different areas of Cognitive Neuroscience. In many cases, this research relies upon support from healthy volunteers although Neuro imaging studies are also being conducted in various clinical populations, including depression, anxiety, Parkinson's disease and Alzheimer's disease.

A high-field 3T system is essential for cognitive research allied to psychology which the centre will carry out. Much of the research can be generalised as brain mapping to improve the Unit's understanding of the function of particular areas of the brain, although this is pure research rather than clinical. Vast amounts of data are collected during the scanning process; in fact twenty patients' data would take six months to process even with the most sophisticated current computer hardware. The centre has installed a Terabyte tape robot.

"We are looking forward to having our own system, not only because it will give us more scanning time but because it will provide our PHD students with the flexibility to be more experimental in their research. Previously, our students and researchers had to work up their whole project in advance to effectively prove their experiment would work and provide an achievable outcome," said Dr Adrian M Owen, Senior Scientist at the Cognition and Brain Sciences Unit. "Now we will be able to allow students to work iteratively on a project, trying out novel ideas with the additional scan time available and developing their research ideas as they go along.

For more information please contact Mike Bell on Tel. 01344 396317.

Digitimer DS5 Stimulator - Isolated computer controlled stimulation

Digitimer will soon be launching the DS5 Bipolar Constant Current Stimulator. The DS5 has been developed in collaboration with Prof. Hugh Bostock (Institute of Neurology, London), who uses QTRAC software with the DS5 to facilitate threshold tracking measurements. Although the DS5 has been primarily designed for studies of peripheral nerves, it is hoped that it will be popular with any researchers who want to safely apply computer-controlled constant current stimuli to a subject or patient.

The DS5 is not a traditional "pulse stimulator", as it produces an isolated constant current stimulus proportional to an input voltage, with the shape of the input waveform describing the stimulus shape. When driven by a computer, the DS5 can generate a stimulus consisting of sine waves, ramps, square waves or arbitrary waveforms.

The DS5 stimulator has four input voltage ranges (making it widely compatible with other hardware) and three stimulus output ranges (±10mA, ±25mA and ±50mA).

For more information call Digitimer on Tel. 01707 328347 or Email. sales@digitimer.com

New scientific pack on The Lightman®

The Electrode Company specialises in non-invasive monitoring, optical sensors and high performance pulse oximetry. Recent surveys of SpO2 sensors in leading UK hospitals has shown that between 10% and 35% of those tested were outside acceptable limits, and represented a clinical risk to patients. The company's Lightman® microspectrometer can easily detect the accuracy of these sensors.

The company has just updated its scientific pack on the Lightman instrument and it contains comprehensive clinical references on the performance of the instrument in the testing of pulse oximeters' accuracy. It is not unusual to find pulse oximeters with sensors that may have light wavelength errors of sufficient magnitude to compromise patient safety.

The Lightman instrument is described as a miniature spectrometer that calibrates itself using an internal, highly stable emission source, prior to every sensor test. The portable Lightman tests circuit integrity and measures LED wavelength spectrum and light output, within the sensor wherever it is located in the hospital. The calculated sensor accuracy at critical SpO2 levels appears on The Lightman screen, enabling inaccurate and/or faulty sensors to be rapidly identified and withdrawn from clinical use.

At the James Paget Hospital, Great Yarmouth, Simon Brook in the Medical Electronics Department is delighted with his UK manufactured Lightman, as his previous tester had to go to the US for calibration every year. He has found it useful for routine checks on new pulse oximeter probes, and for finding reported probe faults on existing equipment.

At the King George Hospital in Ilford, Clinical Engineering Manager Marino D'Aliessio has conducted probe surveys on existing Trust equipment, resulting in replacement of some pieces. Surveying of new purchases has found calibration problems, resulting in free replacement by the manufacturers. The Lightman is used as a normal checking procedure during the annual maintenance and overhaul process.

For more information on The Lightman, or for a copy of the Scientific Pack and/or latest newsletter, Tel. 01633 861772.

The Genie

Everyone should be able to stand from time to time for various health reasons and carers should not have to injure their backs. The Genie has been designed with these points in mind.

The Genie is a good indoor/outdoor wheelchair which has been successfully crash tested and is appropriate for all levels of dependency. With its pressure management seating it offers comfort, in a variety of positions. Sit, stand and snooze, you can even lie flat if you want to. The Genie is electronically controlled usually by a joystick or its own unique closed loop head control system, but other methods are available if required. Each Genie is 'Tailor made' to suit the customer's needs. It is very manoeuvrable and will turn within its own wheelbase, which makes it great around the house and in tight spaces. Normal doorways are no problem – so no building work. Starting at £5,400.00 – with most packages not exceeding £5,900.00 - the Genie is affordable and definitely worth considering.

For more information Tel. Easy Care Products on 01952 610300.

PD Connect meetings – Management strategies throughout Parkinson's disease

PD Connect is a series of 13 evening meetings sponsored by GlaxoSmithKline, Alliance Pharmaceuticals and GE Healthcare. The content of the meetings has been developed in collaboration with nine leading PD specialists. The aim of a PD Connect meeting is to provide delegates with an overview of up to date management strategies in Parkinson's disease, from diagnosis through to the palliative stage of the disease.

Forthcoming meetings are as follows: Wednesday 2nd November, Lancaster House Hotel, Green Lane, Ellel, Lancaster; Tuesday 15th November, Southampton Hilton Hotel; Thursday 17th November, The Kohn Centre, The Royal Society, 6-9 Carlton Terrance, London; Tuesday 22nd November, St Edmund Hall, Oxford, OX1 4AR; Wednesday 7th December, De Vere St. David's Park Hotel, Ewloe, Nr. Chester.

If you would like more information or to attend one of the meetings please Tel. Mark Lawson on 0207 331 5320, or Email. mark_lawson@uk.cohnwolfe.com

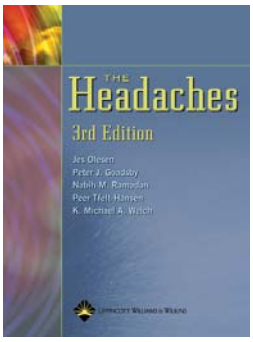
New Books in Old-Age Psychiatry and Neurology from Taylor & Francis

Taylor & Francis is the leading publisher in the field of Psychogeriatrics and here are some of their recent highlights: Psychiatric Issues in Parkinson's Disease: A Practical Guide by Matthew Menza and Laura Marsh; Psychosis in the Elderly by Anne Hassett, David Ames and Edmond Chiu; Trial Designs and Outcomes in Dementia Therapeutic Research by Kenneth Rockwood and Serge Gauthier; Dementia with Lewy Bodies and Parkinson's Disease Dementia by John O'Brien, David Ames, Ian McKeith and Edmond Chiu; And coming out soon, Geriatric Medicine for Old-Age Psychiatrists by Alistair Burns et al. and Stroke Medicine by Martin Brown.

For more information and to order online visit the website at www.tandf.co.uk/medicine or to request a catalogue, send an email to info.medicine@tandf.co.uk, or Tel. 0207 017 6192.

Please visit www.tandf.co.uk/eupdates to receive email updates about journals, books and other news within your areas of interest.

The Headaches, 3rd edition

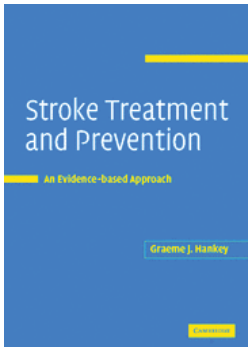


Lippincott Williams and Wilkins are pleased to announce the arrival of The Headaches, 3/e to complement their existing range of neurology titles. The Headaches, by Jes Olesen, Peer Tfelt-Hansen, K Michael A Welch, Peter J Goadsby, Nahib M Ramadan, has been established worldwide as the definitive, encyclopaedic reference on headaches. This edition has been thoroughly updated by leading international authorities who examine over 100 types of headache from first time migraines to thunderclap and hypnic headaches. Evidence based treatment recommendations and tables of controlled clinical trials help medical professionals to confidently assess and treat many types of headaches in a variety of patients.

LWW offers a comprehensive line of health-science books and new media with thousands of well-known titles, from reference tools to comprehensive research and education information for medical specialists and students.

For more information visit www.Lww.co.uk

Coming soon - Stroke treatment and prevention - An evidence-based approach



This invaluable reference by Graeme Hankey of the Royal Perth Hospital, Australia, provides clinicians caring for stroke patients with evidence for best practice in stroke treatment and secondary prevention. It describes all available treatments, and, where available, the highest level of evidence for their safety and effectiveness. The evidence for each treatment is followed by the author's interpretations, and the implications of the evidence in the care of stroke patients. This is therefore an essential resource for clinicians, translating into practice advances that have been made in the treatment and prevention of stroke, and suggesting the most appropriate interventions.

For further details of this and other Cambridge University Press stroke books, go to www.cambridge.org/neurology or Tel. 01223 326016.

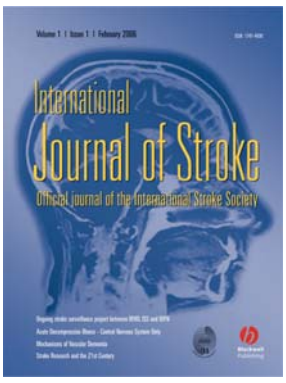
International Journal of Stroke

Blackwell Publishing is pleased to announce the launch of the International Journal of Stroke, a new journal in partnership with the International Stroke Society, edited by Geoffrey Donnan.

The first issue of the journal will cover: Prognosis and Management in the First Few Days After a TIA or Minor Ischaemic Stroke; Acupuncture for Stroke in China: Needing More High-Quality Evidence; Ultrasound Enhanced Thrombolysis for Stroke; Carotid Angioplasty and Stent Placement for Treatment of Carotid Stenosis: Past, Present, and Future; Intracerebral Hemorrhage: Effective Therapy at Last?

If you would like to receive the first issue for free in November 2005, email. kate.brothwell@oxon.blackwellpublishing.com or join the launch of the journal on Thursday 10th November at the Blackwell Publishing stand at the World Congress of Neurology.

Subscribe now - Members of the International Stroke Society will receive the journal as part of their membership. For more information, please visit www.internationalstroke.org



Carl Zeiss continues to dominate Microscopy Awards

For the fourth year in a row a Carl Zeiss Microscopy product is a winner of the coveted R&D 100 Award, which recognises the excellence and innovation of the 100 most important technical products launched worldwide. The award was presented to the Zeiss LSM 5 LIVE, the world's fastest confocal imaging system that features a new optical design specially developed for real time examination of fast processes in living specimens.

The judges were impressed by the new instrument's unique combination of scanning speed, image quality and sensitivity. Collecting up to 1,010 confocal images per second, the LSM 5 LIVE allows scientists for the first time to capture dynamic processes in living specimens with a time resolution down to one millisecond. The precise optics, creative beam splitter design and innovative beam delivery opens a new time window in confocal fluorescence microscopy.

"This latest award confirms the innovation strategy that drives new product development and provides our customers with tools that enable them to perform their tasks more quickly, efficiently and successfully," says Aubrey Lambert, Carl Zeiss UK.

For more information Tel. 01707 871233.

Early treatment demonstrates impressive protection against disease progression in newly emerging MS

Individuals who have reported a first clinical attack suggestive of multiple sclerosis (MS) double their chances of not progressing to develop MS if they start early treatment with Betaferon® 250mcg (interferon beta-1b) rather than placebo, suggest results of the multinational BENEFIT* trial unveiled recently at the joint ECTRIMS/ACTRIMS Congress.

Left untreated, about half of the people who experienced a first clinical attack suggestive of MS developed MS within the first six months, as defined by the McDonald criteria. Additionally 85% went on to be diagnosed with CDMS within two years.[1]

"The BENEFIT results with Betaferon show a very pronounced and statistically robust effect on the development of MS for people who are at risk," said Ludwig Kappos, Professor of Neurology and Clinical Neuroimmunology at the University of Basel, Switzerland and lead investigator of the BENEFIT study. "The BENEFIT study was rigorously controlled and will support doctors making early treatment decisions with a high-dose, high-frequency therapy after a single clinical event. These data further support the opinion that the earlier you treat with an effective therapy, the better the outcome."

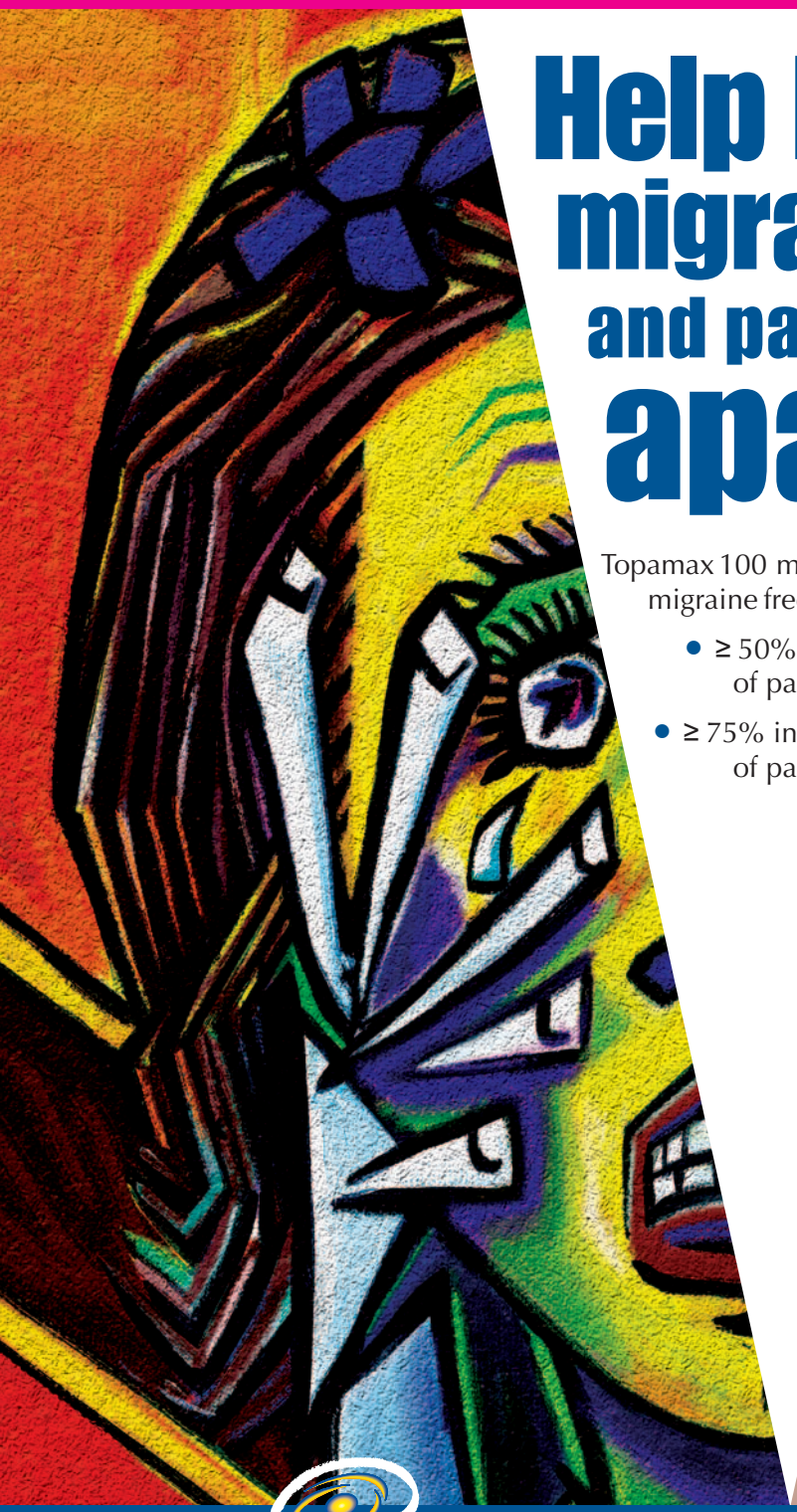
For more information Email. nlim@schering.co.uk or Tel. 01444 465717.

* Betaferon®/Betaseron® in Newly Emerging MS For Initial Treatment

Reference

1. L Kappos. *Betaferon® in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT): clinical results.* Presented at ECTRIMS/ACTRIMS 2005.

NOW LICENSED AS A NEW SPECIALIST OPTION IN MIGRAINE PROPHYLAXIS



Help keep migraines and patients apart

Topamax 100 mg/day reduced migraine frequency by:

- ≥ 50% in 46% of patients[1]
- ≥ 75% in over 25% of patients[1]

TOPAMAX® (topiramate)

Every migraine-free day is a good day

TOPAMAX® Abbreviated Prescribing Information. Please read Summary of Product Characteristics before prescribing. Presentation: Tablets: 25, 50, 100, 200 mg topiramate. Sprinkle Capsules: 15, 25, 50 mg topiramate. **Uses: Epilepsy**: Monotherapy: Newly diagnosed epilepsy (age ≥ 6 years): generalised tonic-clonic/partial seizures, with/without secondarily generalised seizures. Adjunctive therapy of seizures: partial, Lennox Gastaut Syndrome and primary generalised tonic-clonic. Conversion from adjunctive to monotherapy: efficacy/safety not demonstrated. **Migraine prophylaxis** when 3 or more attacks/month; attacks significantly interfere with daily routine. Six monthly review. Use in acute treatment not studied. Initiation: specialist care. Treatment: specialist supervision/shared care. **Dosage and Administration**: Oral. Do not break tablets. Low dose initially; titrate to effect. Renal disease may require dose modification. **Epilepsy**: Monotherapy: Over 16 years: Initial target dose: 100 mg/day (two divided doses; maximum 400 mg/day). Children 6 to 16: Initial target dose: 3-6 mg/kg/day (two divided doses). Initiate at 0.5-1 mg/kg nightly with weekly or fortnightly increments of 0.5–1 mg/kg/day. Doses less than 25 mg/day: Use Topamax Sprinkle Capsules. Adjunctive therapy: Over 16 years: Usually 200-400 mg/day (two divided doses; maximum 800 mg/day). Initiate at 25 mg daily with weekly increments of 25 mg. Children 2 to 16: Approx. 5-9 mg/kg/day (two divided doses). Initiate at 25 mg nightly with weekly increments of 1-3 mg/kg. **Migraine**: Over 16 years: Usually 100 mg/day (in two divided doses). Initiate at 25 mg nightly with weekly increments of 25 mg. Longer intervals can be used between dose adjustments. Children under 16 years: Not studied. Sprinkle Capsules: take whole or sprinkle on small amount (teaspoon) of soft food and swallow immediately. **Contra-indications**: Hypersensitivity to any component. **Precautions and Warnings**: Withdraw gradually. Renal impairment delays achievement of steady-state. Caution with hepatic impairment. May cause sedation; so caution if driving or operating machinery. Depression/mood alterations have been reported. Monitor for signs of depression; refer for treatment, if appropriate. Suicidal thoughts: Patients/caregivers to seek immediate medical advice. Acute myopia with secondary angle-closure glaucoma reported rarely; symptoms typically occur within 1 month of use and require discontinuation of Topamax and treatment. Increased risk of renal stones. Adequate hydration is very important. Bicarbonate level may be decreased so monitor patients with conditions/drugs that predispose to metabolic acidosis and reduce dose/discontinue Topamax if acidosis persists. Galactose intolerant, Lapp lactase deficiency, glucose-galactose malabsorption: do not take. **Migraine**: Reduce dose gradually over at least 2 weeks before discontinuation to minimise rebound headaches. Significant weight loss may occur during long-term treatment. Regularly weigh and monitor for continuing weight loss. Food supplement may be required. **Interactions**: Possible with phenytoin, carbamazepine, digoxin, hydrochlorothiazide, pioglitazone, oral contraceptives, haloperidol and metformin. Caution with alcohol/CNS depressants. **Pregnancy**: If benefits outweigh risks. Discuss possible effects/risks with patient. Contraception recommended for women of childbearing potential (oral contraceptives should contain at least 50 µg oestrogen). **Lactation**: Avoid. **Side Effects**: Abdominal pain, ataxia, anorexia, anxiety, CNS side effects, diarrhoea, diplopia, dry mouth, dyspepsia, headache, hypoaesthesia, fatigue, mood problems, nausea, nystagmus, paraesthesia, weight decrease, agitation, personality disorder, insomnia, increased saliva, hyperkinesia, depression, apathy, leucopenia, psychotic symptoms (such as hallucinations), venous thrombo-embolic events, nephrolithiasis, increases in liver enzymes. Isolated reports of hepatitis and hepatic failure when on multiple medications. Acute myopia with secondary acute-angle closure glaucoma, reduced sweating (mainly in children), metabolic acidosis reported rarely. Suicidal ideation or attempts reported uncommonly. Bullous skin and mucosal reactions reported very rarely. **Pharmaceutical Precautions:** Tablets and Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed. **Legal Category:** POM **Package Quantities and Prices**: Bottles of 60 tablets. 25 mg (PL0242/0301) = £20.92, 50 mg (PL0242/0302) = £34.36; 100 mg (PL0242/0303) = £61.56; 200 mg (PL0242/0304) = £119.54. Containers of 60 capsules. 15 mg (PL0242/0348) = £16.04, 25 mg (PL0242/0349) = £24.05, 50 mg (PL0242/0350) = £39.52 **Product licence holder**: JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ. UK. **Date of text revision**: August 2005. **APIVER150805**.

Reference: 1. Bussone G, Diener H-C, Pfeil J *et al.* Topiramate 100mg/day in migraine prevention: a pooled analysis of double blind randomized controlled trials. Int J Clin Pract 2005: 59(8); 961-968.

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