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Gavin Giovannoni


Anti-Basal Ganglia Antibodies and their Clinical Relevance

Camilla Buckley

Diseases Associated with Antibodies to Voltage-Gated Potassium Channels

Alastair Compston

Jean-Martin Charcot on 'Sclérose en plaques'



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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with substrates or inhibitors of this enzyme – ropinirole dose may need adjustment when these drugs are introduced or withdrawn.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. 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The two review articles in this issue both take antibodies as their theme.

Camilla Buckley introduces us to the disorders associated with antibodies to the shaker family of voltage gated potassium channels. The autoimmune disorders targeting this channel include the peripheral and central nervous systems ranging from mild cramp fasciculation syndrome to limbic encephalitis and Morvan's fibrillary chorea. This article serves to educate and update us on these not uncommon disorders and is written from a perspective of great authority, coming as it does from the leading UK centre involved in the discovery and definition of these conditions.

The second review article tackles the controversial area of anti basal ganglia antibodies and their significance. Gavin Giovannoni takes us through this controversy and the work from his laboratory showing how these antibodies may underlie a number of neurological conditions, including Sydenham's chorea and encephalitis lethargica. This is a beautifully written and balanced account, which lays out the arguments for the clinical relevance of these antibodies (see also Journal reviews for more on auto-antibodies!).

The neuropathology article by Professor Jeanne Bell and Dr Iain Anthony gives us a comprehensive and beautifully illustrated review of the neuropathology of HIV and in particular a comparison of this prior to and following the adoption of HAART in 1997. In the pre-HAART era, the onset of AIDS was associated with HIV encephalopathy and/or opportunistic infections in 50% of cases with a similar proportion developing a spinal cord vacuolar myelopathy. Nowadays if the CD4 count can be restored with HAART, the chances of developing such neuropathology is significantly reduced. Interestingly, however, other aspects of the disease are becoming more common - such as the HIV associated dementia and the less severe minor cognitive motor disorder (MCMD). This "emerging" neuropathology may relate to the increased longevity of the life span of patients carrying HIV, and as such may represent the new challenge to the treatment of HIV in the developed world. This is a discussion that sadly is not to be had in the developing world, where HAART is not so readily available.

Charcot has made many contributions to our current neurological practice and this includes his work on MS. This contribution to 'sclérose en plaques' was based on only 30 patients, a topic discussed by Professor Alastair Compston - the current editor of Brain and renowned international authority on MS and historical neurology. As one would have anticipated, this article is beautifully written and lavishly illustrated with quotations from the original texts. It is once more a reminder of the power of clinical observation to expose and inform our understanding of disease pathogenesis, and how so much can be learnt by reading the works of the founders of modern day neurology.



The rehabilitation topic in this issue revolves around the very interesting concept of the neuroprotective effects of progesterone, especially in the context of traumatic brain injury (TBI). Don Stein from Atlanta, Georgia begins his discussion with the initial observations back in 1987 on the differential effects of TBI in female rats depending on whether they are in the follicular or luteal phase of their cycle. This has now been investigated and developed to the point of clinical trials, and as such may impact on the treatment of this common neurological problem (see also Journal reviews on pituitary dysfunction in TBI).

The cognitive primer by Cipelotti and van Harskamp is on dyscalculia, and we are fortunate to have such experts take us through the types of deficits that occur in this acquired disorder. This article beautifully dissects the different problems of number processing and calculation as well as outlining the logical assessment and approach to such patients, most of whom

will have damage in the region of the left parietal lobe.

Peter Whitfield and Devindra Ramnarine outline the presentation, management and natural history of acoustic/vestibular schwannomas. These tumours have an incidence of about 1:100,000 per year and have become more "common" with the advent of MRI. This article lays out the three major therapeutic approaches to these tumours - namely a conservative one (especially for small tumours in elderly patients) or treatment with stereotactic radiosurgery or neurosurgery itself.

Drugs in neurology focuses on the new potent irreversible MAO-B inhibitor, rasagiline (AZILECT®). This drug has recently been launched in the UK and has received much media attention, given its potential neuroprotective effects and value in more advanced cases of Parkinson's disease. In this article Professor David Brooks discusses the properties of rasagiline and the trial data supporting the above claims for the drug.

For those going to the World Congress of Neurology in Sydney, look out for the special issue of ACNR. This contains some of our recent articles as well as a wonderful account by Dr Fisher on his variant of Guillain-Barre syndrome. This is a truly wonderful account of how this 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. We will be reproducing this article in the UK edition at the end of the year, so don't worry - you won't miss out on his inspiring and personal account.

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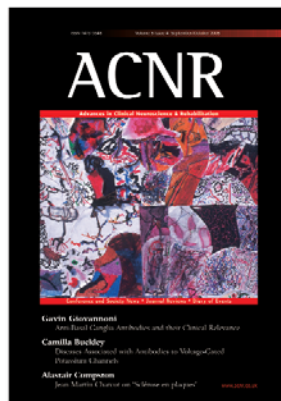
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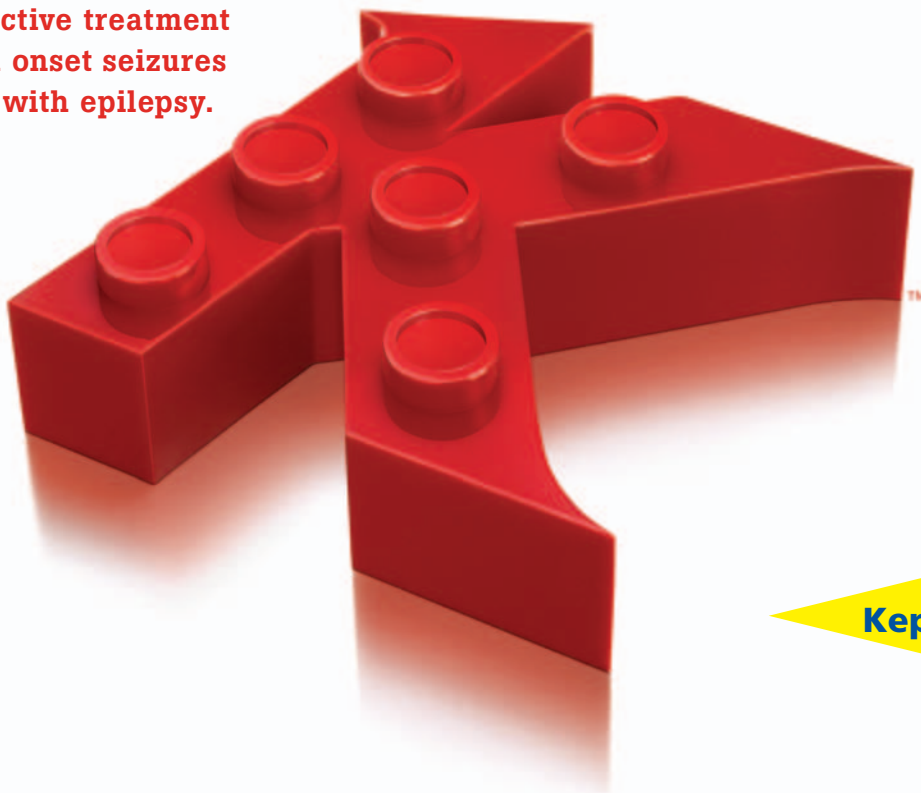
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Cover picture:

The cover image is taken from a collage called 'Pain'. The paintings were produced by schoolchildren at a series of workshops entitled 'Thinking Science Making Art', held by Dr Lizzie Burns and involving 14 junior schools in Exeter, UK. During the workshops Lizzie taught the children about the human brain, to inspire their own artistic interpretation of brain cells. These paintings were then made up into collages based on 'pain', 'cold', 'dreaming' and 'smell'.

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unless clearly necessary. Breast-feeding not recommended. **Driving, etc:** Caution recommended when performing skilled tasks, e.g. driving vehicles or operating machinery. **Undesirable effects:** Incidence of undesirable effects considered to be at least possibly related in controlled clinical studies: *Very common* (>10%): asthenia, somnolence. *Common* (between 1%–10%): GI disturbances, anorexia, accidental injury, headache, dizziness, tremor, ataxia, convulsion, amnesia, emotional lability, hostility, depression, insomnia, nervousness, vertigo, rash, diplopia. For information on post-marketing experience see SPC. **Legal category:** POM. **Marketing authorisation numbers:** 250 mg x 60 tabs: EU/1/00/146/004. 500 mg x 60 tabs: EU/1/00/146/010. 750 mg x 60 tabs: EU/1/00/146/017. 1,000 mg x 60 tabs: EU/1/00/146/024. Solution x 300ml: EU/1/146/027. **NHS price:** 250 mg x 60 tabs: £29.70. 500 mg x 60 tabs: £52.30. 750 mg x 60 tabs: £89.10. 1,000 mg x 60 tabs: £101.10. Solution x 300ml: £71.00. **Further information is available from:** UCB Pharma Ltd., 3 George Street, Watford, Herts WD18 0UH. Tel: 01923 211811. medicaluk@ucb-group.com **Date of preparation:** September 2004.

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2. Patsalos PN. Pharmacokinetic profile of Levetiracetam: toward ideal characteristics. *Pharmacol Ther*. 2000; 85: 77-85.
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particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures — in such patients the possibility of heart block or long sinus pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering from asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia,

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Anti-Basal Ganglia Antibodies and their Clinical Relevance

Basal ganglia dysfunction due to an aberrant post-streptococcal autoimmune response against neurones in the basal ganglia is the proposed pathogenesis of an emerging group of movement and neuropsychiatric disorders. Sydenham's chorea is the prototype of this group of disorders. Anti-basal ganglia antibodies (ABGA) are found in the majority of subjects with Sydenham's chorea.^{1,2} More recently other neuropsychiatric disorders or phenotypes have also been associated with ABGA. These include Tourette's syndrome,³ adult-onset tic disorders,⁴ obsessive-compulsive disorder (OCD),⁵ paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS),^{6,7} dyskinesias,⁸ dystonia,⁹ post-streptococcal acute disseminated encephalomyelitis (ADEM),¹⁰ myoclonus¹¹ and post-encephalitic Parkinsonism or encephalitis lethargica.¹² The proposal that these disorders are mediated by autoimmune mechanisms is controversial and not widely accepted.¹³ Reasons for conflicting results in this field and issues concerning the detection of ABGA have been highlighted recently.¹⁴ Differences in Western immunoblotting methods may explain the differences in the reported prevalence of ABGA in these disorders.^{15,16} Studies are currently being undertaken to reconcile these differences. The identification of the candidate autoantigens will obviously aid this process.

The association between a specific neuropsychiatric disorder and ABGA does not necessarily imply that these disorders are autoimmune. To establish a disorder as being autoimmune one needs to apply Witebsky's criteria of autoimmunity (Table 1).¹⁷ To do this it will be necessary to confirm the results of recent studies that have identified candidate autoantigens in these disorders^{18,19} and to establish the specificity and sensitivity of antigen-specific autoantibody assays. Kirvan et al. identified a monoclonal antibody from a subject with Sydenham's chorea with specificity for both mammalian lysoganglioside and N-acetyl-beta-D-glucosamine (GlcNAc), a dominant carbohydrate epitope of group A streptococci.¹⁸ Their human anti-lysoganglioside monoclonal antibody from a subject with Sydenham's chorea and sera from subjects with active Sydenham's chorea bind to the surface of human neuronal cells and induce calcium/calmodulin-dependent protein (CaM) kinase II activity. Convalescent sera and sera from other streptococcal diseases in the absence of chorea did not activate the kinase.¹⁸ This implicates antibody-mediated neuronal cell signalling in the pathogenesis of Sydenham's chorea. Dale and colleagues have identified aldolase C (40 kDa), non-neuronal and neuronal specific enolase (45 kDa doublet) and pyruvate kinase M1 (60 kDa) as possible autoantigens.¹⁹ These glycoytic enzymes are expressed on the surface of neurones and streptococci and are homologous with each other, which raises the possibility that ABGA are induced by molecular mimicry. Human non-neuronal enolase has previously been proposed as a candidate auto-antigen in autoimmune diseases related to streptococcal infection including rheumatic fever.²⁰ Appropriate animal models using candidate autoantigens will have to be established to build the case for autoimmune mediated mechanisms. Of note, Poynton, Paine and Holmes, between 1901 and 1903, were able to induce a disease in rabbits with features similar to rheumatic fever and Sydenham's chorea by inoculating the animals with "rheumatogenic" strains of streptococci.²¹ Three studies have used a passive transfer model by studying the effects of infusing serum con-

taining anti-neuronal antibodies from subjects with Tourette's syndrome into the striatum of rats. Two studies showed a significant increase in either oral stereotypies or episodic utterances in rats receiving higher-titre sera from subjects with Tourette's syndrome as compared to rats infused with lower-titre sera from subjects with Tourette's syndrome or controls.^{22,23} The third study using a similar methodology did not confirm these results.²⁴

In support of contemporary findings in relation to encephalitis lethargica a number of early investigators, including von Economo, detected streptococci or diplococci in the throats of patients with encephalitis lethargica during the 1917-1928 epidemic;²⁵ the gram positive organism was dismissed as being the primary aetiological agent of encephalitis lethargica as it was never isolated from the brain of terminal cases. Remarkably, an encephalitis lethargica-like illness was induced in dogs after vaccination with streptococcal isolates from patients with encephalitis lethargica.²⁵

Basal ganglia dysfunction has various manifestations, all of which fall into a relatively well-defined symptom complex or syndrome.²⁶ It is difficult to rely on the clinical manifestations to make an aetiological diagnosis in disorders due to basal ganglia dysfunction. Although a particular phenotype is typically associated with a "specific" disease entity, for example chorea or tics in Sydenham's chorea and Tourette's syndrome respectively, one would expect from applying basic principles that immune mediated basal ganglia dysfunction should result in the full spectrum of movement and emotional disorders that have been attributed to basal ganglia pathology. Huntington's disease and Wilson's disease, well-defined genetic disorders with a predilection for the basal ganglia, are associated with the full spectrum of both hyper- and hypo-kinetic movement disorders. Therefore using a biomarker, in addition to specific clinical features, would seem appropriate in defining this group of disorders.

The apparent overlap between the clinical phenotype of Sydenham's chorea, PANDAS, Tourette's syndrome and OCD, and the finding of serological evidence of recent streptococcal infection and ABGA in these disorders, suggests that they may represent one disease entity. For example, patients with PANDAS usually have psychiatric features and frequently have choreiform movements. Patients with Sydenham's chorea often have tics and OCD and patients with OCD often have tics and other subtle movement disorders. If PANDAS, Tourette's syndrome and OCD are the same disease as Sydenham's chorea why don't patients with these disorders have associated rheumatic fever? A detailed cardiac evaluation of 60 subjects with PANDAS did not reveal evidence of rheumatic carditis.²⁷ Whether or not subjects with ABGA have subtle cardiac involvement has yet to be investigated systematically. One could speculate that the current strains of streptococci that induce neuropsychiatric disease are different to those that are capable of inducing rheumatic carditis. These issues and others will hopefully be resolved once the putative autoantigens have been confirmed and further categorised.

In conclusion, immune-mediated basal ganglia dysfunction is plausible, particularly if you accept the clinical similarities between ABGA positive patients with PANDAS, Tourette's syndrome, OCD and Sydenham's chorea. At present the experimental evidence to categorise these disorders as autoimmune is incomplete, i.e. we have yet to confirm identified putative autoantigens



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and create appropriate animal models. Despite this deficiency in the experimental evidence there is a case to acknowledge immune mediated basal ganglia dysfunction as an emerging clinical entity. This is important as it has potentially major implications for the diagnosis and treatment of patients with basal ganglia dysfunction.

Table 1. Modified Witesbsky's Criteria¹⁷

1. The presence of auto-reactivity, i.e. an antibody or T cell which is self-reactive.
2. Recognition of the specific autoantigen.
3. Induction of the disease in animal model.
4. Passive transfer of the disease to the animal.*

* Criterion 4 applies to auto-antibody mediated human disease only. It is not possible to transfer a human autoimmune disease to animal via the passive transfer of autoreactive T cells as they have to by definition see their 'autoantigen' in the context of the correct MHC molecule.

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Diseases Associated with Antibodies to Voltage-Gated Potassium Channels

Potassium channelopathies are caused either by autoantibodies directed against the potassium channels or by mutations in their encoding genes. Benign neonatal febrile convulsions¹ and hereditary deafness syndromes² are associated with mutations in the KCNQ family of voltage-gated potassium channels (VGKCs) whereas neuromyotonia,³ episodic ataxia⁴ and intractable epilepsy⁵ are associated with mutations in the Shaker family of VGKCs. The phenotype of neurological disorders occurring in patients with autoantibodies against subunits of Shaker VGKCs is rapidly expanding and will be the focus of this review.

Shaker VGKCs are composed of four transmembrane α subunits associated with four intracellular β subunits (Figure 1). The α subunits (Kv 1.1 – Kv 1.7) can combine homotypically or heterotypically to generate an enormous diversity of functional VGKCs which are widely distributed throughout the peripheral and central nervous system, and are important in controlling membrane excitability. VGKC antibodies impair channel function resulting in clinical syndromes of hyperexcitability in the peripheral and central nervous systems.

Syndromes of peripheral nervous system (PNS) hyperexcitability

The spectrum of disorders of peripheral nerve hyperexcitability ranges from the mild cramp fasciculation syndrome (CFS) to the more disabling neuromyotonia (NMT). Patients with neuromyotonia usually present with muscle twitching and cramps often associated with increased sweating.⁶ They may have sensory symptoms, especially dysaesthesia without numbness, which is probably a consequence of hyperexcitability of the sensory nerves.⁷ Rarely, hand posturing resembling dystonia can be present.⁸ On examination there is visible myokymia and muscle cramps often accompanied by muscle hypertrophy. Pseudomyotonia (but rarely percussion myotonia), pseudotetany, and mild distal sensory loss may occur.

Electromyography reveals fibrillations and fasciculation potentials at rest and the characteristic multiple responses to a single stimulus. The serum creatine kinase level may be mildly elevated, and VGKC antibodies can be detected by radioimmunoprecipitation in approximately 40% of patients.⁶ The clinical syndrome is indistinguishable between patients with and without antibodies, and there appears to be no correlation between antibody titre and clinical or EMG severity.

Some patients can tolerate their symptoms without treatment once reassured as to the underlying cause, whilst others attain symptomatic relief from phenytoin, carbamazepine or lamotrigine. In the minority with persistent disabling symptoms, immunomodulatory therapies can produce clinical and electrophysiological improvement.⁹

Pathophysiology of PNS hyperexcitability

An immune-mediated pathology underlying NMT is suggested by the clinical response to immunomodulatory therapies, the association with other autoimmune diseases, and the observation that 15% of patients have a thymoma.⁶ Moreover there is experimental evidence indicating that the antibodies themselves are pathogenic. Passive transfer of IgG from NMT patients to mice results in increased quantal content at the motor endplates,¹⁰ and application of NMT sera to a neuroblastoma cell line (Nb-1) causes reduction in amplitude of VGKC currents.¹¹

Syndromes of central nervous system (CNS) hyperexcitability

Limbic Encephalitis

VGKC antibodies have recently been identified in the serum of patients presenting with non-paraneoplastic limbic encephalitis.¹² VGKC-associated LE appears to be at least as common as paraneoplastic limbic encephalitis associated with neuronal antibodies (table 1), is more common in men and has a mean age at diagnosis of 65 years. The typical presentation is with sub-acute onset of short-term memory loss, disorientation, confusion and seizures. Agitation, sleep disturbance, hallucinations and paranoid ideation can be prominent.¹³ Interestingly there is usually no clinical or electrophysiological evidence of PNS hyperexcitability. Investigations reveal hyponatraemia with urine and serum osmolarities consistent with the syndrome of inappropriate ADH secretion. VGKC antibody titres are usually greater than 400 pM and frequently above 1000 pM (normal < 100 pM). EEG reveals slowing of the background rhythms and often demonstrates an epileptogenic focus. MRI is abnormal in 75% with high signal often restricted to the hippocampi and best visualised on coronal images attained with T2 weighted FLAIR sequence (Figure 2). Neuropsychology confirms disorientation and severe impairment in verbal and visual anterograde and retrograde memory, often accompanied by confabulation.

The optimum treatment regime remains unclear but acute therapy with plasma exchange or intravenous immunoglobulin, accompanied by high dose alternate day oral steroids, often results in striking clinical improvement. The disorientation, seizures and hyponatraemia respond initially, followed by improvement in memory.



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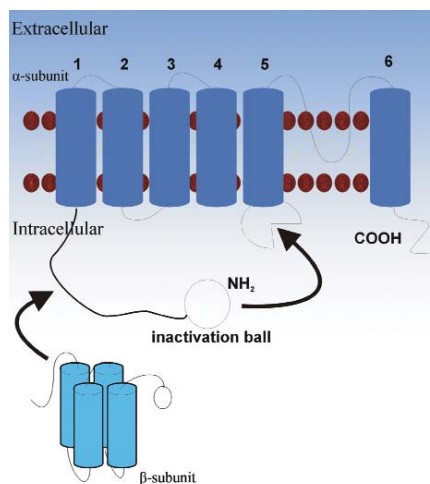


Figure 1: Cartoon showing the basic structure of the alpha and beta subunits of the voltage-gated potassium channel. Each alpha subunit is composed of six transmembrane domains with the "pore" occurring between the fifth and sixth domains, and the fourth domain serving as the voltage sensor due to its high positive charge. Each beta subunit is composed of four domains without any membrane-spanning sequences and they bind to the alpha subunits and determine the electrophysiological properties of the channel.

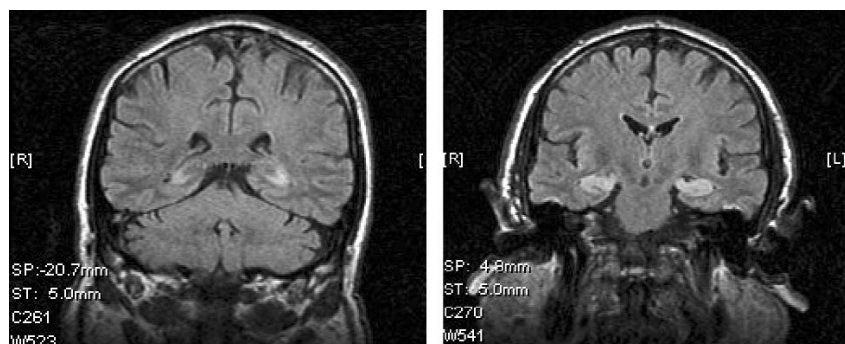


Figure 2: Coronal T2 weighted FLAIR magnetic resonance image of the brain showing the classical appearance of bilateral hippocampal high signal in a patient with VGKC-associated LE.

After several months anti-convulsant and immunomodulatory therapies can be reduced and stopped with many patients remaining free of seizures and regaining near normal memory function. This clinical improvement is accompanied in most cases by improvement on neuropsychological scores and rapid reduction in antibody titre, and in some cases by resolution of MRI changes.

Morvan’s Fibrillary Chorea (MFC)

Patients with florid neuromyotonia associated with memory disturbance, disorientation, disordered sleep and autonomic dysfunction with sweating and cardiac arrhythmias were first described by Morvan over 100 years ago. Recently serum VGKC antibodies and a clinical response to immunomodulatory therapy have been described in a few patients with this rare condition.¹⁴

Pathophysiology of CNS hyperexcitability

In contrast to paraneoplastic LE where neuronal antibodies are probably markers of cell mediated immunopathology,¹⁵ VGKC antibodies may be pathogenic: VGKC subtypes recognised by patients’ antibodies are expressed in the CNS (including the hippocampus) as transmembrane proteins that would potentially be accessible to circulating antibodies; memory dysfunction and seizures can occur in Kv1.1 knock out mice¹⁶ and in patients with inherited mutations in the Kv1.1 gene³; and there is often a striking temporal correlation between the appearance and disappearance of VGKC antibodies and the development and subsequent resolution of the clinical syndrome^{12, 13}. Direct evidence of pathogenicity from passive and

active immunisation experiments is awaited.

The factors determining the phenotype of disease in an individual patient remain unknown but are likely to include the exact composition of channels in the PNS versus the CNS, the relative affinities of antibodies from different patients for individual subunits, and variations in blood brain barrier permeability.

The clinical phenotypes associated with VGKC antibodies continue to expand, and now include patients with slower presentations of more restricted symptoms including isolated memory loss, or intractable temporal lobe seizures, who also appear to respond well to immunomodulatory therapies. Irrespective of whether the antibodies are pathogenic their identification is important as it suggests novel therapeutic options with associated improved clinical outcomes.

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Table 1: Comparison of the main clinical features in patients with limbic encephalitis (LE) and VGKC antibodies and patients with paraneoplastic LE and anti-neuronal antibodies

	VGKC antibodies	Neuronal antibodies (Hu, Ma2, CV2, CRMP5)
Location of antigen	Transmembrane	Intracellular
Regional specificity of antibody staining	Yes; mainly hippocampus and cerebellum	None; any part of neuraxis
CSF abnormalities	Rare	Pleocytosis, raised protein
Hyponatraemia	Usual	Rare
Tumour Association	Rare (occasional thymoma)	Usual (SCLC, thymoma, testicular)
Hyperintensity on T2 Weighted FLAIR MRI	Often restricted to hippocampi	Several limbic areas and may extend to brainstem
Response to treatment	Frequent. Antibody titre decreases in months	Rare (except young men with Ma2). Antibodies remain detectable
Clinical Course	Relapses may occur and are treatable	Progressive until stabilisation or death

SCLC: small cell lung cancer, CSF cerebrospinal fluid

Table 2: Characteristic clinical findings in patients with antibodies against voltage-gated potassium channels (VGKC)

	Cramp Fasciculation syndrome	Neuromyotonia	Morvan’s syndrome	Limbic Encephalitis
Muscle twitching and cramps	++	+++	++	+/-
Neuromyotonic discharges on EMG	-	++	++	+/-
Increased sweating	-	++	++	+/-
Additional autonomic features	-	-	++	-
Agitation	-	+/-	++	+++
Seizures	-	-	-	+++
Short term memory loss	-	-	+	+++

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Indication: Treatment of patients with Parkinson's disease and end-of-dose motor fluctuations not stabilised on levodopa/dopa decarboxylase (DDC) inhibitor treatment. **Dosage and administration:** Orally with or without food. One tablet contains one treatment dose and may only be administered as whole tablets. Optimum daily dosage must be determined by careful titration of levodopa in each patient preferably using one of the three tablet strengths. Patients receiving less than 70-100mg carbidopa a day are more likely to experience nausea and vomiting. The maximum Stalevo dose is 10 tablets per day. Usually Stalevo is to be used in patients who are currently treated with corresponding doses of standard release levodopa/DDC inhibitor and entacapone. See SPC for details of how to transfer these patients and those not currently treated with entacapone. **Children and adolescents:** Not recommended. **Elderly:** No dosage adjustment required. **Mild to moderate hepatic impairment, severe renal impairment (including dialysis):** Caution advised. **Contraindications:** Hypersensitivity to active substances or excipients. Severe hepatic impairment. Narrow-angle glaucoma. Pheochromocytoma. Concomitant use of non-selective monoamine oxidase inhibitors (e.g. phenelzine, tranylcypromine). Concomitant use of a selective MAO-A inhibitor and a selective MAO-B inhibitor. Previous history of Neuroleptic Malignant Syndrome (NMS) and/or non-traumatic rhabdomyolysis. **Warnings and precautions:** Not recommended for treatment of drug-induced extrapyramidal reactions. Administer with caution to: patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions, or past or current psychosis; patients receiving concomitant antipsychotics with dopamine

receptor-blocking properties, particularly D2 receptor antagonists; patients receiving other medicinal products which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias, monitor cardiac function carefully during initial dosage adjustments. Monitor all patients for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with chronic wide-angle glaucoma may be treated with Stalevo with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully. Caution when driving or operating machines. Doses of other antiparkinsonian treatments may need to be adjusted when Stalevo is substituted for a patient currently not treated with entacapone. Rhabdomyolysis secondary to severe dyskinesias or NMS has been observed rarely in patients with Parkinson's disease. Therefore, any abrupt dosage reduction or withdrawal of levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy. **Undesirable effects:** *Levodopa / carbidopa* – Most common: dyskinesias including choreiform, dystonic and other involuntary movements, nausea. Also mental changes, depression, cognitive dysfunction. Less frequently: irregular heart rhythm and/or palpitations, orthostatic hypotensive episodes, bradykinetic episodes (the 'on-off' phenomenon), anorexia, vomiting, dizziness, and somnolence. *Entacapone* – Most frequently relate to increased dopaminergic activity, or to gastrointestinal symptoms. Very common: dyskinesias, nausea and urine discolouration. Common: insomnia, hallucination, confusion and paroniria, Parkinsonism aggravated, dizziness, dystonia, hyperkinesias, diarrhoea, abdominal

pain, dry mouth constipation, vomiting, fatigue, increased sweating and falls. See SPC for details of laboratory abnormalities, uncommon and rare events. **Legal category:** POM. **Presentations, basic NHS costs and marketing authorization numbers:** Stalevo 50mg/12.5mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40, MA numbers: EU/1/03/260/002-003; Stalevo 100mg/25mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40, MA numbers: EU/1/03/260/006-007; Stalevo 150mg/37.5mg/200mg, 30 tablet bottle £21.72, 100 tablet bottle £72.40, MA numbers: EU/1/03/260/010-011. **Distributed in the UK by:** Orion Pharma (UK) Ltd, Leat House, Overbridge Square, Hambridge Lane, Newbury, Berkshire, RG14 5UX, England. **In Ireland information is available from:** Orion Pharma (Ireland) Ltd, c/o Allphar Services Ltd, Belgard Road, Tallaght, Dublin 24. Tel 01-4041600. Fax: 01-4041699. Full prescribing information is available on request. Stalevo is a registered trademark. Updated December 2004.


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Dyscalculia

Introduction

The term dyscalculia refers to an acquired disorder of number processing and calculation skills following brain damage. Henschen was the first to identify this syndrome in 1919.¹ However, for a long time dyscalculia was treated as one of the subcomponents of the Gerstmann syndrome or as an impairment due to more generalised cognitive deficits such as visuospatial and language disorders. It is now well established that impairments in number processing and calculation are independent from deficits in general intelligence, language, reading, writing, semantic memory and short-term memory.²

Acquired deficits in number processing and calculation are rather frequent after brain lesions and may result from both acute and neurodegenerative conditions. The incidence of dyscalculia in patients with either left hemisphere lesions or at the early stage of Alzheimer's disease is high.

Classification

Dyscalculia is not a unitary disorder and can take a variety of different forms. Patients may present with specific impairments in processing numbers, in calculation or in both. Table 1 provides an overview of the types of impairment.

Disorders of number processing

Patients with number processing impairments may show selective deficits in either producing (e.g. reading, writing or repeating) or in comprehending (e.g. knowing that 5 is bigger than 4) Arabic numerals (e.g. 5), verbal numerals (e.g. five) or both.

Patients with number production impairments may show selective deficits affecting syntactical or lexical processing.

- Syntactical errors involve the incorrect selection of the number class to which a number belongs (e.g. they read 600 as "sixty").
- Lexical errors involve the incorrect selection of the position of the individual elements within the correctly identified class (e.g. they read 29 as "forty-nine").

Patients with a deficit in number comprehension may no longer be able to point to the larger of two Arabic numerals (e.g. 345 and 785 or 265 and 2307) or match spoken numerals to the corresponding Arabic numeral. Deficits in number comprehension may selectively affect a subcategory of numbers or different aspects of number meaning. For example, Cipolotti et al³ described a patient who lost the meaning of numbers above 4. Patients with a selective impairment in "cardinal" (which depicts the numerosity of a set of entities and describe the manyness of the set) number meaning or "sequence" (which depicts the position of a number word in the number sequence and do not refer to numerosities) number meaning have been described.⁴

Disorders of calculation

In order to carry out a complex calculation such as 346+475, several independent calculation subprocesses are required. These include:

- The identification of arithmetic symbols (e.g. +, x, -, :)
- The retrieval of arithmetic facts. These are defined as a vocabulary of "number combinations", such as 5+3=8, 3x4=12, 10-4=6. These facts are directly retrieved from memory and the solution to these problems does not require further computational processes or strategies.
- The execution of calculation procedures. These procedures allow access to specific algorithms required to solve multi-digit calculation. Specific examples are the carrying and borrowing procedures.



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Lisa Cipolotti studied Experimental Psychology at the University of Padua and completed a PhD on Dyscalculia in 1993 at UCL. Since 1996 she has been Head of the Neuropsychology Department of the National Hospital for Neurology and Neurosurgery. Her main research is on the acquired disorders of memory, language and calculation.

Table 1 Overview of types of deficits occurring in dyscalculia

Disorders of number processing	Error example							
<i>Disorders of number production</i>	<ul style="list-style-type: none"> • Disorders of syntactical processing (<i>Syntactical errors</i>) • Disorders of lexical processing (<i>Lexical errors</i>) 	5 read as "fifty" 5 read as "seven"						
<i>Disorders of number comprehension</i>	<ul style="list-style-type: none"> • Disorders of cardinal number meaning: <i>Problems with identifying the quantity of a set</i> • Disorders of sequence number meaning: <i>Problems with identifying the position of a number in a sequence</i> 	5 is larger than 6 5 comes after 6						
Disorders of calculation		<table style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 0 10px;">47</td> <td style="padding: 0 10px;">49</td> </tr> <tr> <td style="padding: 0 10px;">$\begin{array}{r} \times 67 \\ 114 \end{array}$</td> <td style="padding: 0 10px;">$\begin{array}{r} \times 29 \\ 78 \end{array}$</td> </tr> </table>	47	49	$\begin{array}{r} \times 67 \\ 114 \end{array}$	$\begin{array}{r} \times 29 \\ 78 \end{array}$		
47	49							
$\begin{array}{r} \times 67 \\ 114 \end{array}$	$\begin{array}{r} \times 29 \\ 78 \end{array}$							
<i>Disorders of arithmetic symbol processing:</i> e.g. adding when there is a multiplication sign								
<i>Disorders of arithmetic fact retrieval:</i> e.g. patients failing to retrieve automatically arithmetical facts such as 6x5								
<ul style="list-style-type: none"> • Operand errors, if the incorrect answer is the correct answer to a problem that shares one of the operands • Operation errors, if the incorrect answer is the correct answer to another problem involving the same operands, but a different operation • Table errors, if the incorrect answer is an answer that is a product of two other single digit numbers • Non table errors, if the incorrect answer is not an operand, table or operation error 		6x5=25 6x5=11 6x5=32 6x5=41						
<i>Disorders of calculation procedures:</i> e.g. patients failing to apply specific calculation procedures such as:								
<ul style="list-style-type: none"> • Systematic smaller from larger subtraction errors • Inappropriate carry over procedures in the calculation of partial products and in the sum of partial products 		<table style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 0 10px;">$\begin{array}{r} 823 \\ - 644 \\ \hline 221 \end{array}$</td> <td style="padding: 0 10px;">$\begin{array}{r} 171 \\ - 58 \\ \hline 127 \end{array}$</td> </tr> <tr> <td style="padding: 0 10px;">$\begin{array}{r} 35 \\ \times 97 \\ \hline 245 \end{array}$</td> <td style="padding: 0 10px;">$\begin{array}{r} 723 \\ \times 57 \\ \hline 151 \end{array}$</td> </tr> <tr> <td style="padding: 0 10px;">$\begin{array}{r} 275 \\ 2995 \end{array}$</td> <td style="padding: 0 10px;">$\begin{array}{r} 385 \\ 31001 \end{array}$</td> </tr> </table>	$\begin{array}{r} 823 \\ - 644 \\ \hline 221 \end{array}$	$\begin{array}{r} 171 \\ - 58 \\ \hline 127 \end{array}$	$\begin{array}{r} 35 \\ \times 97 \\ \hline 245 \end{array}$	$\begin{array}{r} 723 \\ \times 57 \\ \hline 151 \end{array}$	$\begin{array}{r} 275 \\ 2995 \end{array}$	$\begin{array}{r} 385 \\ 31001 \end{array}$
$\begin{array}{r} 823 \\ - 644 \\ \hline 221 \end{array}$	$\begin{array}{r} 171 \\ - 58 \\ \hline 127 \end{array}$							
$\begin{array}{r} 35 \\ \times 97 \\ \hline 245 \end{array}$	$\begin{array}{r} 723 \\ \times 57 \\ \hline 151 \end{array}$							
$\begin{array}{r} 275 \\ 2995 \end{array}$	$\begin{array}{r} 385 \\ 31001 \end{array}$							
<i>Disorders of conceptual knowledge:</i> e.g. the solution of an addition problem is smaller than the addends		8+7=6						

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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. 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. Certain 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. **Side effects:** Very common (>10%) – headache. Common (>1%) – nervousness, insomnia, anxiety, dizziness, somnolence, depression, abnormal thinking, confusion, paraesthesia, blurred vision, nausea, dry mouth, diarrhoea, decreased appetite, dyspepsia, constipation, tachycardia, palpitation, vasodilatation, asthenia, chest pain, abdominal pain and abnormal liver function tests. Dose related increases in alkaline phosphatase and gamma glutamyl transferase have been observed. (See SmPC for 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:** PL16260/0001 Provigil 100 mg Tablets, PL 16260/0002 Provigil 200 mg Tablets. **Marketing authorisation holder:** Cephalon UK Limited, 11/13 Frederick Sanger Road, Surrey Research Park, Guildford, Surrey UK GU2 7YD. Medical Information Freestone 0800 783 4869 (ukmedinfo@cephalon.com). PRO809/Mar 04

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• The retrieval of conceptual knowledge. This allows the understanding of the principles underlying both arithmetic facts and procedures (e.g. the solution of an addition problem is greater than the addends).

Each of these different cognitive processes appears to be functionally independent and differentially susceptible to brain damage.

For example, patients with a selective impairment in the processing of arithmetic symbols misname and misidentify the arithmetical signs and perform the calculation according to their misidentification.⁵

Several patients have been documented with selective arithmetic fact retrieval impairment. Typically, these patients are impaired in solving very simple single digit addition, subtraction, multiplication and division problems. They produce many errors (e.g. $5+7=$ "13 roughly") and their response times are abnormally slow (e.g. >3 sec.). Deficits in arithmetic fact retrieval may be specific for type of operation. Thus, patients have been described with selective impairment or preservation in subtraction, multiplication, addition and division problems (see table 2).

Patients with selective deficits in calculation procedures may have problems in executing those procedures that specify the sequence of steps necessary to solve multi-digit problems, for example, the carrying and borrowing procedures. Patients with a multi-digit subtraction problem may systematically subtract the smaller digit from the larger one regardless of their location in the top or bottom numbers.¹¹ Interestingly, this deficit can be specific for type of procedure. Thus, patients may only have difficulties with the borrowing procedure in complex subtraction, while still being able to carry out complex addition, involving the carry procedure.

Few patients with deficits in conceptual knowledge have been reported. These patients may show a poor understanding of the conceptual aspects of calculation. For example, they produce highly implausible errors (e.g. the solution of subtraction is greater than the minuend) or may not apply very basic arithmetic principles such as order irrelevant-principle in multiplication ($4 \times 12 = 12 \times 4$) or repeated addition of the second operand ($4 \times 12 = 12 + 12 + 12 + 12$).⁸ Selective preservation of conceptual knowledge in the context of severe dyscalculia is also on record.¹² Intact conceptual knowledge may be critical in develop-

ing rehabilitation procedures for arithmetic deficits (see below).

Assessment

A variety of tasks may be used to assess number processing and calculation (see table 3). Recently, a battery of Number Processing and Calculation (NPC) has been standardised by Delazer et al.¹³ Error analyses are also very useful additions to the assessment. They provide invaluable information regarding the type of functional impairment the patient presents.

Localisation

Numerical skills have a discrete and independent brain substrate. The majority of evidence based on lesion studies has indicated the involvement of the left posterior areas. The reports available do not allow for a conclusive localisation of lesions within the left posterior quadrant. However, it appears that the left parietal lobe plays a crucial role. Recent neuroimaging studies have investigated the neuronal correlates underpinning number processing and calculation. They often report large neuronal networks of parietal, pre-

frontal and cingulate areas. In particular, the horizontal segment of intraparietal sulcus bilaterally (HIPS) and the inferior frontal gyrus and the precentral sulcus are mostly implicated.¹⁴

Treatment and recovery

Data on recovery from dyscalculia is rare, however partial recovery occurs in most patients with dyscalculia following vascular lesions.¹⁵ According to the specific type of dyscalculia, different kinds of rehabilitative intervention may be required. Principles of treatment in rehabilitation of dyscalculia mainly consist of:

- reteaching lost arithmetic fact knowledge via extensive training
- errorless learning
- the use of back-up strategies based on the principles underlying arithmetic facts such as the order-irrelevant principle like $8 \times 6 = 6 \times 8 = 48$, decomposition strategies like $4 \times 8 = 2 \times 8 + 2 \times 8 = 32$ or repeated addition of the second operand ($3 \times 5 = 5 + 5 + 5 = 15$).

Case reports show improvement following intense rehabilitation of arithmetic facts and number transcoding deficits.¹⁶

Table 2: Examples of patients with selective impairments/preservations of arithmetic facts

		Multiplication	Subtraction	Addition	Division
Subtraction preservation	BB (Pesenti et al., 1994) ⁶	x	✓	x	-
Subtraction impairment	SS (van Harskamp et al, 2002) ⁷	✓	x	✓	-
Multiplication preservation	JG (Delazer and Benke, 1997) ⁸	✓	x	x	x
Multiplication impairment	VP (van Harskamp and Cipolotti, 2001) ⁹	x	✓	✓	-
Addition impairment	FS (van Harskamp and Cipolotti, 2001) ⁹	✓	✓	x	-
Division impairment	CB (Cipolotti and de Lacy Costello, 1995) ¹⁰	✓	✓	✓	x

✓ = spared; x = impaired; - = not tested

Table 3: Assessment of numerical processing and calculation

Number processing tasks	
Number production	<ul style="list-style-type: none"> • Reading • Writing to dictation • Repetition • Transcoding between Arabic numerals and verbal numerals (5→five)
Number comprehension	<ul style="list-style-type: none"> • Magnitude comparison of Arabic numerals or written/spoken number names (e.g. 12-21) • Analogue number scale task (scale from 0-100, marked at 25; 50; 75, show me 25) • Parity judgment (odd or even number?)
Calculation tasks	
Arithmetic symbol processing	<ul style="list-style-type: none"> • read • point • write the arithmetical signs
Arithmetic fact retrieval	Simple arithmetic problems across the four basic operations such as $4+2$, 3×4 or $5-2$, $6:3$.
Procedural knowledge	Multi-digit calculation, such as $294+12=306$
Conceptual knowledge	Arithmetical principles such as commutativity ($a+b=b+a$); repeated addition; $10a \times 10b$; multiplication/division inversion; $a-1b$; $a+1$; $a-1$; addition/subtraction inversion

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(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. Pramipexole should not be used during breastfeeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, confusion, dizziness and peripheral oedema (occurred more often than with placebo). More frequent adverse reactions in combination with levodopa were dyskinesias. Constipation, nausea and dyskinesia tended to disappear with continued therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin

is titrated too fast. Mirapexin has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. Libido disorders (increase or decrease), pathological gambling, especially at high doses generally reversible upon treatment discontinuation. **Overdose:** There is no clinical experience with massive overdosage. Expected adverse events include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive measures may be required, along with gastric lavage, intravenous fluids and electrocardiogram monitoring. **Basic NHS Cost:** 0.125mg (0.088mg) x 30 £9.25, 0.25mg (0.18mg) x 30 £18.50, 0.25mg (0.18mg) x 100 £61.67, 1.0mg (0.7mg) x 30 £58.89, 1.0mg (0.7mg) x 100 £196.32. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D55216 Ingelheim am Rhein, Germany. **Marketing Authorisation Number:** Mirapexin 0.088mg (0.125mg) x 30 tablets EU/1/97/051/001; Mirapexin 0.18mg (0.25mg) x 30 tablets EU/1/97/051/003; Mirapexin 0.18mg (0.25mg) x 100 tablets EU/1/97/051/004; Mirapexin 0.7mg (1.0mg) x 30 tablets EU/1/97/051/005; Mirapexin 0.7mg (1.0mg) x 100 tablets EU/1/97/051/006. Further information is available from Boehringer Ingelheim Ltd., Eylesfield Avenue, Bracknell, Berkshire RG12 8YS. **Date of preparation:** June 2005.

Code: PPX0113
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Progesterone in the Treatment of Traumatic Brain Injury

Background

At present there is no safe and effective treatment for the acute stages of traumatic brain injury (TBI). While a number of approaches have been tried (barbiturate coma, hypothermia, mannitol, glucocorticosteroids and hyperbaric oxygen, among others), none have proven effective in clinical trials.¹ In fact, recently a major trial (CRASH) of intravenous corticosteroids in adults (n=10,008) with TBI reported a highly significant increase in death rates six months after injury (3.4% over controls) following methylprednisolone treatment.²

Neurosteroids and Traumatic Brain Injury

Investigating the question of whether female laboratory rats recover better than males after extensive bilateral damage to the medial frontal cortex (MFC), our laboratory hypothesised that the hormonal status of the female at the time of injury would significantly affect the extent of recovery. We found that females in the luteal stage at the time of injury showed significantly more functional recovery in spatial learning tasks and less brain swelling compared to females in the follicular phase at the time of injury.³ When males were given post-TBI injections of progesterone (4mg/kg for 5 days), they showed decreases in cerebral oedema and improved recovery on spatial learning and sensory motor tasks and these beneficial effects could be seen even if treatment was delayed by up to 24 hours.^{4,5}

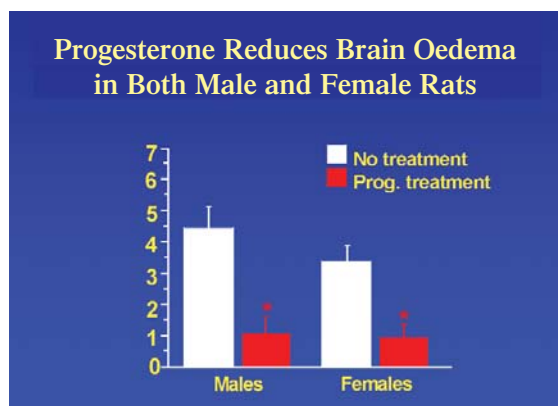


Figure 1. By 24 hours after bilateral contusions of the medial frontal cortex, post-injury progesterone significantly reduces cerebral oedema in both adult male and female rats. In a middle cerebral artery occlusion (MCAO) model of ischaemic stroke in rats, progesterone reduced tissue water content significantly.⁶

Mechanisms of Action

We now know that after brain injury, natural progesterone given to both males and females can: (1) easily cross the BBB and reduce oedema to barely measurable levels; (2) reduce lipid peroxidation and the generation of isoprostanes, which contribute to post-injury ischaemic conditions; produce metabolites which (3) decrease pro-apoptotic and increase anti-apoptotic enzymes; (4) reduce the expression of pro-inflammatory genes and their protein products; (5) reduce the area of necrotic cell death and improve behavioural outcomes; (6) protect neurons distal to the site of injury which would normally die after TBI; (7) enhance remyelination in young and aged rats with degenerative disorders; (8) produce significant sparing of cognitive, sensory and spatial learning performance in laboratory rats after bilateral injury of the MFC.⁷

Progesterone's Neuroprotective Effects

Inflammatory immune reactions. A growing literature shows that progesterone and its metabolites modulate glial cell activity to control the flow of water in and out of brain cells, and can reduce programmed cell death and the synthesis of inflammatory factors that can kill neurons hours to days after the initial injury.⁹ As an anti-inflammatory agent, progesterone has been shown to reduce the response of natural killer cells as well as other known initiators of inflammation.¹⁰

Ischaemia. Progesterone reduces the size of infarcts caused by MCAO in rats and mice.¹¹ Accompanying this decrease are improvements in body weight and neurological outcomes. Progesterone appears to be effective in treating acute global ischaemia in cats,¹² where ischaemia causes a loss of 54-85% of neurons in the CA1 and CA2 subfields. After pre- and post-treatment with progesterone in female cats, neuronal loss was reduced to between 21-49%.

Functional outcomes. Damage to the frontal cortex will produce enduring bilateral sensory neglect of the forelimbs and tongue. In our studies, five days of post-injury treatment with progesterone significantly improved spatial learning and sensory performance compared to injured, untreated counterparts. Chen et al. also showed that progesterone can decrease sensory neglect and enhance sensorimotor performance after MCAO in the rat.¹³

Progesterone, Oestrogen, and MPA

Synthetic and proprietary hormones such as medroxyprogesterone acetate (MPA) may have different effects from natural progesterone in post-injury treatment. Long used in hormone therapy (HT), MPA is still widely available, but it does not mimic all the protective effects of natural progesterone, and could be a confounding variable if it were haphazardly selected for clinical testing for TBI. These differences may affect functional outcome measures, some of which can be substantially negative, such as enhancing of bone loss,¹⁴ and preventing the reduction of atherosclerotic plaques in monkeys.¹ Recently Simoncini and colleagues¹⁵ reported that MPA and natural progesterone have different effects on levels of LDL and HDL cholesterol. Our own preliminary data show that MPA can reduce cerebral oedema after TBI, but unlike progesterone, MPA did not result in any behavioural recovery on the tasks we used. MPA is used instead of progesterone in mouse models of sexually transmitted diseases to increase infectibility because progesterone does not have this effect. According to one recent paper, MPA increases susceptibility to genital herpes (HSV-2) ten times more than does natural progesterone.¹⁶ Because of its ready availability, it is likely that MPA will be used again in "off-label" applications unless its differential impact on outcomes compared to natural progesterone can be clarified.

Another important concern is how progesterone and its metabolites compare to oestrogen in reducing the effects of TBI in both males and females. Unlike oestrogen, which can exacerbate brain injury, especially in animal models of ischaemic stroke,¹⁷⁻²⁰ progesterone can be given to both males and females without affecting gender and sexual functions. A recent federally supported clinical trial at Emory University using progesterone to treat TBI yielded extremely promising results (soon to be published) and found no adverse events attributable to progesterone administration.



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Conclusion

The recent work on progesterone as a potential therapeutic agent in TBI has produced reliable and consistent results across species (mice, rats, cats) and in a number of injury models (TBI, stroke, spinal cord injury, soft tissue injury). Although progesterone's main effects in TBI may be to reduce cerebral oedema and stem the secondary loss of vulnerable nerve cells, it has a number of other beneficial properties. The literature indicates that progesterone is a potent anti-inflammatory, anti-apoptotic agent with some anti-oxidant properties that help to protect against the eventual breakdown of cell membranes that cause the death of neurons and glia.

In light of the recent failures of clinical trials with pharmacological agents that appear to target very selective mechanisms of injury/repair, progesterone, with its multitude of beneficial actions, may have more promise for further study and development as a safe and effective therapeutic agent in the treatment of CNS disorders.

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Effects of Advances in Therapy on the Neuropathology of HIV Infection

Introduction

Since the emergence of the Human Immunodeficiency Virus (HIV) pandemic in the early 1980's considerable progress has been made in our understanding of this retrovirus and of its effects on the human body, yet despite years of dedicated research there remain many unanswered questions. The introduction first of Zidovudine (AZT) in 1987 and then highly active anti-retroviral therapy (HAART) [Box 1] in 1997 has undoubtedly had a beneficial effect on disease progression but has not eliminated infection. By means of preventing different aspects of viral replication, HAART generally succeeds in reducing plasma HIV load to undetectable levels and partially restores CD4 lymphocyte counts. Thus HIV has increasingly become a chronic infection with relatively long life expectancy. From the point of view of understanding the disease process it is essential to evaluate the effects of therapy on the pathogenesis. This review will present a comparison of the neuropathology of HIV before and after the advent of HAART.

Box 1: HAART components and drugs in use

Class of drug	Name of drugs
Nucleoside Reverse Transcriptase Inhibitors	AZT Zidovudine
	DDI Didanosine
	d4T Stavudine
	3TC Lamivudine
	DDC Zalcitabine
	ABC Abacavir
Non-Nucleoside Reverse Transcriptase Inhibitors	NVP Nevirapine
	EFV Efavirenz
Protease Inhibitors	IDV Indinavir
	SQV Saquinavir
	RTV Ritonavir
	NFV Nelfinavir

Soon after the discovery of HIV the central nervous system (CNS) was identified as a major target for virus induced changes and for opportunistic conditions [Box 2]. Cognitive impairment was present in 20-30% of pre-HAART cases, with many going on to develop HIV associated dementia (HAD). HAD presented as a subcortical dementia with cognitive symptoms including impaired memory and concentration, mental slowing and difficulty in multi-tasking. Behavioural difficulties included apathy, withdrawal, irritability and personality changes, while motor changes included clumsiness or slowing of fine movement and gait unsteadiness. To date the exact pathogenesis of HAD remains elusive. Although there have been reports of HIV DNA recovered from neurones¹ the consensus opinion is that direct infection of neurones by HIV does not occur and is therefore not a contributing factor in HAD. Microglia appear to be the only cell type capable of supporting productive HIV infection in the brain. HIV encephalitis (HIVE) is common in infected individuals who develop dementia; however neither HIVE nor brain viral load correlate well with dementia. The pathological features which are most closely linked with dementia are the activation of microglial cells and the influx of macrophages particularly in the basal ganglia.² Neurotoxicity and the underlying causes of neurological symptoms are most likely multifactorial in origin.

Pre-HAART neuropathology in HIV infected subjects

When examined before the onset of AIDS, the brains of HIV infected individuals show relatively minor changes. There is no evidence of HIVE, opportunistic infections or lymphomas, though there is often a low grade lymphocytic leptomeningitis and perivascular lymphocytic cuffs found within the brain.³ Myelin pallor, gliosis and macrophage activation have also been reported.

With the onset of AIDS, the most significant pathological features in the brain are the presence of HIVE and/or opportunistic conditions in up to 50% of individuals. The immune privileged status of the brain and consequent restricted/limited potential for immune reactions to occur within the brain, coupled with the failure of the peripheral/systemic immune system in AIDS, make the brain a prime site for the development of opportunistic conditions. The major AIDS-related CNS opportunistic pathologies, together with their aetiological agents, are given in Box 2. It is often difficult to assess the changes induced directly by HIV in AIDS patients if confounding opportunistic conditions are also present.

White matter damage is apparent in some subjects, with and without HIVE, varying from minor pallor to widespread breakdown, the latter frequently showing axonal damage in the form of β amyloid precursor protein accumulation in white matter varicosities and axonal bulbs (Figure 1). Examination of brains with no evidence of opportunistic conditions reveals changes in the blood vessels including calcification, vasculitis and infarcts. In AIDS brains with no opportunistic conditions and no HIVE, the perivascular lymphocytic infiltration observed in pre-symptomatic subjects is not usually noted, although in HIVE some lymphocytes are commonly found in the brain parenchyma.

Pre-HAART, approximately 50% of AIDS cases showed vacuolar myelopathy with myelin pallor and macrophage accumulation in the dorsolateral tracts in the spinal cord.

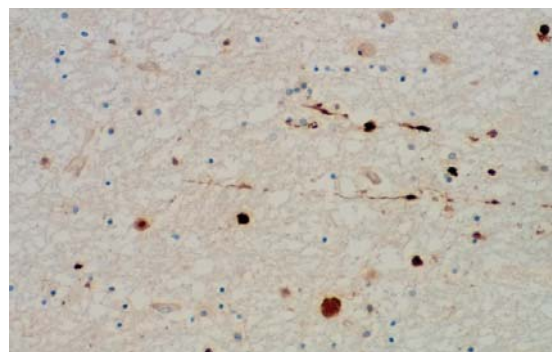


Figure 1: Accumulation of β -amyloid precursor protein (β APP) in white matter varicosities and axonal bulbs. (x100).

Changes in the incidence of HIVE and opportunistic conditions in the brain since the introduction of HAART

Reports of recent autopsy series show a decrease in HIVE and most opportunistic CNS conditions in subjects treated with HAART [Box 2]. In Edinburgh the incidence of HIVE has fallen by approximately 50%, as has evidence of Cytomegalovirus (CMV) infection in the brain; rates of toxoplasma infection have fallen to almost zero; in contrast progressive multifocal leukoencephalopathy (PML)



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Box 2: Major CNS pathologies in HIV infected individuals

Major CNS pathologies	Aetiological agent	Pathological basis	Change in incidence since the introduction of HAART (based on worldwide reports)	References
HIV encephalitis (HIVE) Figure 2	HIV [retrovirus]	Infection of microglia/macrophages leading to formation of multinucleated giant cells and microglial nodules. Immuno reactivity for HIV antigens (p24, gp41).	↓	[13, 14]
Cryptococcal meningo-encephalitis	Cryptococcus neoformans [encapsulated fungus]	Cryptococcus proliferates in the sub-arachnoid space and in the deep grey matter. Immune response in HIV is often sparse with focal collections of macrophages and formation of giant cells.	↓	[7]
CMV encephalitis Figure 3	Cytomegalovirus [herpes virus]	Variable pathology, from isolated cytomegalic cells to severe necrotising hemorrhagic encephalitis. The most common pattern is a diffuse microglial nodular encephalitis in deep grey matter.	↓	[13, 14]
Toxoplasmosis	Toxoplasma gondii [Protozoa]	Focal lesions of varying size often with necrotic centre. Granulomas may be present and microglial nodules may contain encysted organisms or free tachyzoites.	↓	[13, 14]
Primary central nervous system lymphoma (PCNSL) Figure 4	Epstein-Barr virus (EBV) [herpes virus]	Often diffuse multi-focal tumours. Lymphoma cells tend to be distributed around blood vessels forming concentric layers of perivascular cuffs. Malignant cells are of B lymphocyte origin and are invariably infected with EBV and express the viral antigens EBNA-2 and LMP-1	↓	[15]
Progressive multi-focal leukoencephalopathy (PML)	JC virus [polyomavirus]	Foci of myelin pallor in the subcortical white matter or at grey/white matter junction. Viral inclusions in oligodendrocytes and bizarre enlarged astrocytes are usually present. Viral DNA is detectable by in-situ hybridisation.	– (no change)	[13]
VZV encephalitis	Varicella Zoster Virus [Herpes virus]	A variety of neuropathologies may occur including: multifocal encephalitis, ventriculitis, necrotising myelitis and vasculopathy resulting in cerebral infarction.	Pre-HAART VZV was a rare CNS complication. Post-HAART reports suggest the incidence of VZV may be increasing	[14]

and Primary CNS lymphoma (PCNSL) show much smaller changes [Box 3]. Reports from other studies around the world also suggest significant decreases in most of the common CNS opportunistic conditions, particularly those associated with low CD4 counts [Box 2]. It is interesting to note that the overall incidence of conditions such as PCNSL decreased dramatically with the introduction of HAART. However, after stratification on CD4 cell count, the incidence changes little for those who still have low CD4 counts despite therapy. The proportion of patients with low CD4 count, who are at greatest risk of developing lymphoma, has greatly decreased since the introduction of HAART.

Gray et al⁴ have also described 'burnt out' forms of HIVE, Varicella Zoster Virus (VZV)

encephalitis and toxoplasmosis in which neither inflammatory infiltrates nor the causal agent could be detected. It is plausible that these 'burnt out' lesions may have resulted from clearance of virus or protozoa by an immune system re-constituted by therapy, with the patients then dying later of an unrelated cause. There have also been reports of subjects who had poorly controlled HIV replication in the brain despite HAART and who displayed intense perivascular infiltration of macrophages and lymphocytes, together with widespread myelin loss and axonal injury, thought to be due to rapid influx of inflammatory cells into the CNS.⁵ Vacuolar myelopathy has not been reported in HAART treated individuals.

Cognitive deficits in HIV (pre and post HAART)

The introduction of AZT led to a decrease in the incidence of HAD and the subsequent introduction of HAART has caused a significant further reduction. However the overall prevalence of HAD appears to be rising, probably as a result of infected individuals living longer with effective therapy.⁶ In the pre-HAART era HAD was invariably associated with patients with low blood CD4 counts (<200). Since the introduction of HAART the number of cases who have low CD4 counts and dementia has decreased significantly while the number who develop dementia and have higher CD4 counts (>200) has remained relatively stable.⁷ Thus the proportion of dement-

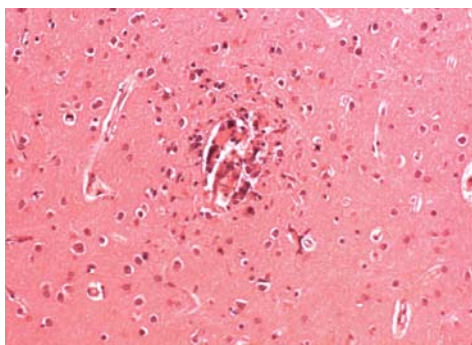


Figure 2: HIVE with giant cells (H&E) (x100)

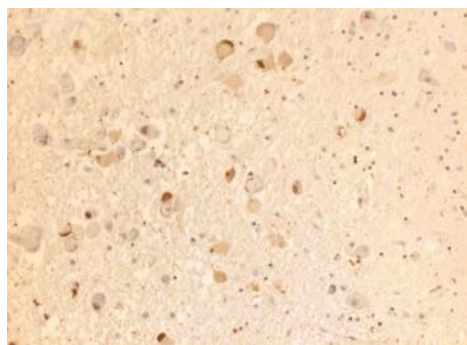


Figure 3: Cytomegalovirus (CMV) encephalitis (x100)

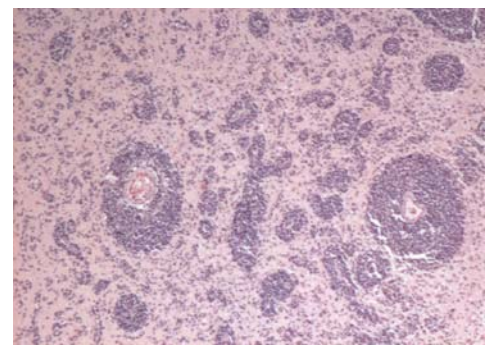


Figure 4: PCNSL - lymphoma cells forming concentric rings surrounding blood vessels. (x40)

Box 3: Incidence of HIV and CNS opportunistic conditions at autopsy in Edinburgh

	Pre-HAART (n=228)	Post-HAART (n=44)	% change
<i>HIVE</i>	21.5	6.8	- 68
<i>Lymphoma</i>	5.3	6.8	+ 28
<i>Toxoplasma</i>	4.4	0	- 100
<i>CMV</i>	9.2	4.6	- 50
<i>PML</i>	2.2	2.3	+ 5

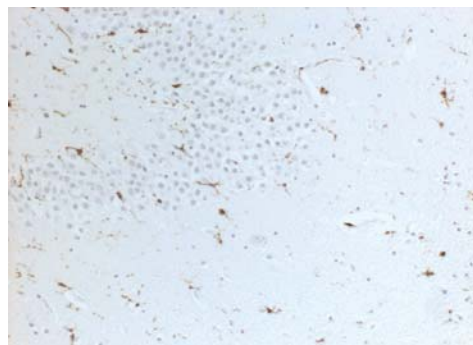


Figure 5: CD68 positive microglia in the hippocampus of a HAART treated subject. (x100)

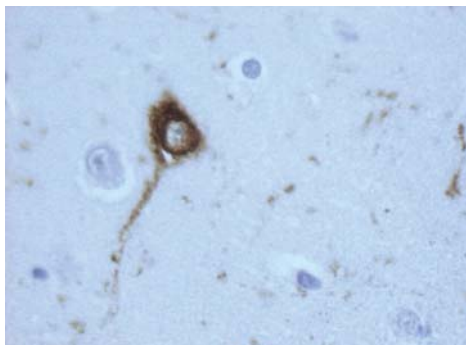


Figure 6: Tau (AT8) in the hippocampus of a HAART treated subject - Neurofibrillary pre-tangle. (x400)

ed subjects with CD4 counts greater than 200 has increased since the introduction of HAART. At the same time, a less severe neuropsychological dysfunction, known as minor cognitive motor disorder (MCMD), has become more common than HAD. Symptoms of MCMD include impaired attention, impaired memory, slowed movement and personality changes. Symptoms in MCMD are milder than HAD and have less impact on daily life.

The reports of Brew and Cysique et al., utilizing PET scans and neurocognitive assessment, suggest an increasing involvement of the hippocampus in cognitive dysfunction in HAART treated subjects.^{8,9} Early reports in the pre-HAART era linked HAD to basal ganglia dysfunction (i.e. a subcortical dementia).² Given the increase in life expectancy of HAART treated subjects, the report by Valcour et al¹⁰ suggesting that older age is associated with increased prevalence of HAD in HIV infected subjects, gives cause for concern for the future of this population.

Clinical markers of cognitive defects (HIV dementia)

In contrast to observations in pre-HAART individuals in whom there was a relationship between cerebrospinal fluid (CSF) or plasma markers and the neurological status, a recent study by McArthur et al¹¹ has shown no such relationship in HAART treated individuals. These markers included CSF HIV RNA levels and plasma levels of monocyte chemoattractant protein 1 and tumor necrosis factor alpha. HAART may substantially attenuate the degree of central nervous system HIV infection and immune activation, and in HAART users, the CSF HIV RNA load may fail to discriminate between milder degrees of HAD and MCMD.

Recent findings in the CNS in HAART treated subjects

Although patients benefit from HAART in terms of control of viral replication and immune reconstitution, the long term effects of both HIV infection and of therapy on the brain remain uncertain.

Analysis of microglia/macrophage levels has shown that levels in the basal ganglia in HAART treated cases are greater than those observed in pre-symptomatic cases before the advent of HAART, though lower than those observed in AIDS cases. However in the hippocampus a large increase in microglial activation is observed in HAART treated subjects, above the levels previously seen in both pre-symptomatic and AIDS cases, despite there being no obvious stimuli such as HIV or opportunistic conditions present within these brains (Figure 5). This degree of neuroinflammation gives cause for concern as to the long term consequences for patients maintained in this state. In the non-HIV infected population neuroinflammation has been linked with Alzheimer's disease. A recent report by Green et al¹² has demonstrated that the deposition of beta-amyloid, one of the key pathological characteristics of Alzheimer's disease, is common in HIV positive patients treated with HAART. In similar studies our group have demonstrated the increased presence of hyperphosphorylated Tau protein, another key pathological characteristic of Alzheimer's disease and other dementias, in the hippocampus of HAART treated subjects (Figure 6).¹³

Future challenges

While the incidence of dementia may be decreasing there has been limited study of the minor and more subtle neuropathological changes in HAART treated individuals, which may become significant for patients who live longer. In particular the reports of increased deposition of both amyloid and hyperphosphorylated tau in HAART treated individuals require further investigation. To date most pathological studies have focused on the overt major pathologies and associated dementia. As the incidence of these decreases with improved therapy, future studies should aim to determine the pathological basis of the more minor cognitive defects and of psychological symptoms such as depression which contribute significantly to neuromorbidity in HIV infected subjects.

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Presentation: Each tablet contains 62.5mg pyridostigmine bromide (equivalent to 60.0mg of the base). **Indications:** Myasthenia Gravis, paralytic ileus and post-operative urinary retention. **Dosage and Administration:** *Myasthenia Gravis* – **Adults** – Doses of 30 to 120mg are given at intervals throughout the day. The total daily dose is usually in the range of 5-20 tablets. **Children** – Children under 6 years old should receive an initial dose of half a tablet (30mg) of Mestinon; children 6-12 years old should receive one tablet (60mg). Dosage should be increased gradually, in increments of 15-30mg daily, until maximum improvement is obtained. Total daily requirements are usually in the range of 30-360mg. The requirement for Mestinon is usually markedly decreased after thymectomy or when additional therapy is given. When relatively large doses of Mestinon are taken by myasthenic patients, it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects. It should be noted that the slower gastro-intestinal motility caused by these drugs may affect the absorption of Mestinon. In all patients the possibility of "cholinergic crisis", due to overdose of Mestinon, and its differentiation from "myasthenic crisis" due to increased severity of the disease, must be borne in mind. **Other indications:** **Adults** – The usual dose is 1 to 4 tablets (60-240mg). **Children** – 15-60mg. The frequency of these doses may be varied according to the needs of the patient. **Elderly** – No specific dosage recommendations. **Contra-indications, Warnings etc:** **Contra-indications** – Gastro-intestinal or urinary obstruction, known hypersensitivity to the drug and to bromides. Extreme caution is required when administering Mestinon to patients with bronchial asthma. **Warnings** – care should also be taken in patients with bradycardia, recent coronary occlusion, hypotension, vagotonia, peptic ulcer, epilepsy or Parkinsonism. Lower doses may be required in patients with renal disease. **Use in pregnancy:** The safety of Mestinon during pregnancy or lactation has not been established. Experience with Mestinon in pregnant patients with Myasthenia Gravis has revealed no untoward effects. Negligible amounts of Mestinon are excreted in breast milk but due regard should be paid to possible effects on the breast-feeding infant. **Side effects:** These may include nausea and vomiting, increased salivation, diarrhoea and abdominal cramps. **Drug interactions** – None known. **Pharmaceutical Precautions:** **Storage** – Recommend maximum storage temperature 25°C. Protect from light and moisture. **Legal Category:** POM. **Package Quantities:** Amber glass bottles with aluminium screw caps and desiccant, containing 200 tablets. **Basic NHS Price:** £48.12 **Product Licence Number:** PL 15142/0006. **Product Licence Holder:** Valeant Pharmaceuticals Limited, Cedarwood, Chineham Business Park, Crockford Lane, Basingstoke, Hampshire RG24 8WD Telephone: +44 (0)1256 707744 e-mail: sales@valeant.com Internet: www.valeant.com **Date of Preparation:** August 2004.

References:

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2. Buckley C. Diagnosis and treatment of myasthenia gravis. Prescriber 2000;19
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Management of Patients with Vestibular Schwannomas

Introduction

The term acoustic neuroma is a misnomer on two accounts. These benign tumours usually arise from the Schwann cells at the myelination-glia junction of the superior division of the Vestibular Nerve. As they grow from the internal auditory canal into the cerebello-pontine (CP) angle, they invaginate the arachnoid and remain covered by it regardless of size.¹ With increasing use of MRI the detection of vestibular schwannomas has increased to around 1/100000 per year.² This represents around 6-10% of all intracranial tumours.

The loss of a tumour suppressor gene on the long arm of chromosome 22 has been found in 40% of cases.³ The presence of bilateral vestibular schwannomas is diagnostic for neurofibromatosis II.

Progressive hearing loss (59%), tinnitus (13%) and imbalance (10%) are the most common presenting symptoms caused by vestibular schwannomas.⁴ These are followed by sudden hearing loss (8%), facial numbness (3%), headaches (1%) and visual disturbance (1%). Large tumours (>3 cm) can cause brainstem compression and obstructive hydrocephalus. Rarely communicating hydrocephalus secondary to elevated CSF protein can occur. Physical signs include sensorineural hearing loss, an attenuated corneal reflex, facial hypoesthesia, diplopia and cerebellar signs. Facial weakness is a rare finding on presentation.

Investigations

MRI with gadolinium contrast is the imaging investigation of choice (Figure 1). Vestibular schwannomas enhance and can be differentiated from CPA meningiomas as they expand the porus acusticus, lack a dural tail and have an acute rather than an obtuse angle at the petrous face. The CISS sequence is also useful to delineate the course of the neurovascular bundle in the CP angle. A pure tone audiogram (Figure 2) and speech discrimination testing (where appropriate) determine the level of hearing improvement and help judge the value of attempting hearing preservation treatment.

Management

Management of patients with vestibular schwannomas is determined by several factors including symptoms, patient age, co-morbidity, tumour size, rate of growth and patient preference.

Treatment options are:

1. Conservative management with planned tumour surveillance
2. Stereotactic radiosurgery
3. Microsurgery

Conservative management

The frequent use of MRI scans has increased the detection of small asymptomatic tumours and small intracanalicular tumours presenting with unilateral hearing loss. A 'watch, wait and rescans' approach to these lesions is often adopted as intervention does carry risk.

Analysis of 13 studies involving 903 patients managed conservatively (mean tumour size of 10 mm diameter) shows that 49% of tumours showed growth on subsequent radiological imaging, 47% showed no growth while 4% regressed. The average growth rate was 1.87 mm/year.⁵ Tumour growth was reported as high as 30 mm/year in one patient. 20% of 804 patients managed conservatively subsequently required intervention mostly as a result of progression of symptoms.

In elderly patients with co-morbidity, the conservative approach may be most appropriate due to the risks of inter-

vention. The optimal frequency of repeat imaging is not clearly defined. We monitor patients with interval scans at 6 and 12 months after presentation and then annually.

Stereotactic radiosurgery

Leksell described Gamma-knife Radiosurgery for Acoustic Neuromas in 1971.⁶ It has been used for the treatment of small to medium sized tumours and incompletely resected lesions. The rapid return to normal activity and avoidance of an open procedure are attractive alternatives to microsurgery. The treatment aims to prevent further growth and maintain neurologic function.

Of 162 consecutive patients followed up for a minimum of 5 years in Pittsburgh, tumour size diminished in 61.7%, remained static in 32.7% and showed slow growth in 5.6%. Normal facial and trigeminal nerve function was evident in 79% and 73% respectively at follow-up.⁷ The Sheffield group reported a tumour control rate of 92% among 234 tumours treated over a 4-year period with only 3% of patients requiring microsurgery.⁸

Ionising radiation is associated with a risk of malignant transformation in benign tumours. The frequency of this complication is difficult to ascertain. The Sheffield group has reported 1 case of malignant transformation among 800 patients with vestibular schwannomas treated by Stereotactic radiosurgery.⁸

Microsurgery

Microsurgery is the treatment of choice for large vestibular schwannomas and is worthy of consideration in patients with small and medium sized tumours. Three surgical approaches to the CP angle may be adopted. Each has merits and drawbacks.

1. Retrosigmoid approach
2. Translabyrinthine approach
3. Middle fossa approach

Retrosigmoid approach

A craniectomy just posterior to the sigmoid sinus with retraction of the cerebellum provides good visualisation of the CP angle component of a vestibular schwannoma.¹ Intra-operative facial nerve monitoring helps to identify the facial nerve as it is very often stretched out over the anterior aspect of the tumour. Limitations of this approach include the retraction of the cerebellar hemisphere, which may be excessive especially with



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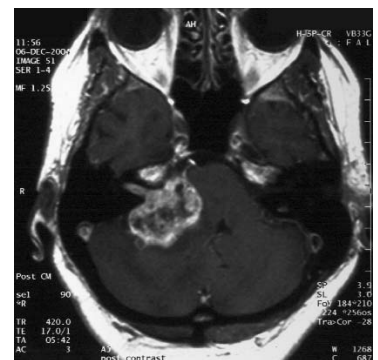


Figure 1: T1 MRI with Gadolinium showing a right vestibular schwannoma.

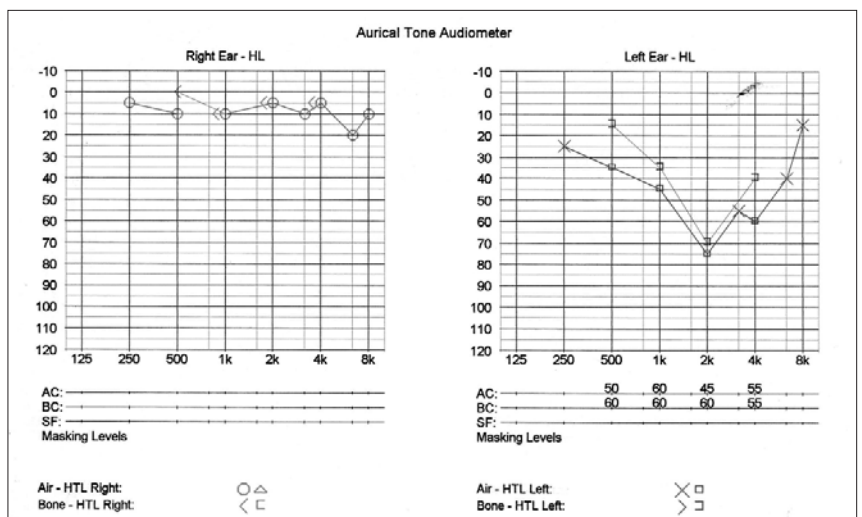


Figure 2: Pure tone audiogram demonstrating left sided mid frequency sensorineural hearing loss, characterised by impaired bone and air conduction.



Figure 3: Patient with right-sided facial weakness (House-Brackmann grade 4). Note the facial asymmetry at rest (figure 3a). Eye closure is incomplete but Bell's phenomenon is present whereby superior rotation of the globe protects the cornea from exposure keratitis (figure 3b).

Table 1: Gardner-Robertson Scale¹³

Grade	Description	Pure tone audiogram Hearing loss (dB)	Speech discrimination (%)
I	Good-excellent	0-30	70-100%
II	Serviceable (Can use telephone)	31-50	50-69%
III	Non-serviceable	51-90	5-49%
IV	Poor	91-max	1-4%
V	None	Not testable	0

Table 2: House-Brackmann grading of Facial Weakness – A PRACTICAL GUIDE¹¹

Grade	Description based on Observation of Eye Closure
1	Normal facial function in all areas
2	Can close eye
3	Can only just close eye
4	Unable to close eye, but obvious facial movements
5	Just perceptible movement of any part of face
6	No movement

larger tumours. The approach provides poor access to small laterally located intracanalicular tumours, unless careful drilling of the petrous bone is performed. It is the approach of choice when attempting hearing preservation.

Translabyrinthine approach

This is the shortest, most direct approach to the CP angle but always results in a dead ear. It is the approach of choice for laterally located intracanalicular tumours where hearing preservation is not required as well as for large tumours minimising cerebellar retraction.⁹ It involves an extended mastoidectomy and labyrinthectomy. The facial nerve is exposed at the fundus of the internal auditory canal along with the canalicular portion of the tumour. The brainstem end of the facial nerve is then identified enabling vigilant protection during resection of the tumour bulk using a cavitating ultrasonic surgical aspirator (CUSA).

Middle fossa approach

This approach has not been universally adopted. It is reported to be useful for small intracanalicular tumours where hearing preservation is desired. It involves an extradural approach in the floor of the middle fossa with retraction of the temporal lobe to expose the petrous temporal bone.¹⁰ Drawbacks of this approach are increased risk of epilepsy from temporal lobe retraction, poor access to the posterior fossa and risk of injury to the facial nerve at the level of the geniculate ganglion.

Results of microsurgery

The object of vestibular schwannoma surgery is the total removal of the neoplastic lesion with minimal morbidity and mortality. Objective recordings of cranial nerve function, CSF leak rates, meningitis, and quality of life assessments can be used to assess morbidity. Extent of tumour removal can be determined intraoperatively, and recurrence can be monitored with MRI scans.

Review of data from over 5000 patients in 16 studies who underwent surgical tumour removal between 1972 and 1999 revealed an average of 96% (93% - 100%) total tumour removal with a

recurrence rate of 1.8%.⁵

A series of 179 patients who underwent microsurgery reports the rates of facial nerve preservation with respect to the size of tumour. Excellent results occurred in 96% of small tumours (<2 cm), 74% of medium tumours (2.0 – 3.9 cm) and 38% of large tumours (4 cm). Serviceable hearing was achieved in 48% of small tumours and 25% of medium tumours.¹² Hearing preservation is rarely an objective in patients with large tumours.

Facial Nerve Function

Facial Nerve Function is assessed using the House-Brackmann Scale.¹¹ This grades facial weakness from normal (I) through to total paralysis (VI) (Table 2). The extracapsular dissection of the tumour capsule from the surrounding neurovascular structures should be done along the tumour capsule-arachnoid interface and not the interface between the arachnoid and neurovascular structures.¹ This ensures protection of the neurovascular structures, especially the facial nerve, by a layer of arachnoid. Some surgeons advocate incomplete resection of large tumours with adjuvant stereotactic radiosurgery to attempt reduced facial nerve morbidity. Loss of the facial nerve can be repaired by use of an interposition cable graft using the great auricular or sural nerve. Facial reanimation techniques can be performed at a later stage if considered appropriate. Decreased lacrimation and corneal exposure both predispose to keratitis. Eye lubrication, taping the eye shut at night, Botulinum injection, tarsorrhaphy and gold eyelid weights are all techniques worthy of consideration in patients with facial weakness where the cornea is at risk.

Summary

The management of patients with vestibular schwannomas is by no means clear-cut and many factors need to be taken into account. Microsurgery offers the best tumour control but has a considerable complication rate. The size, site and aim for hearing preservation would determine the route taken. Over the past 4 decades, radiosurgery has become a viable alternative for small to medium sized tumours and offers effective tumour control. Tumour surveil-

lance with targeted intervention has a role to play in elderly patients and some patients with asymptomatic lesions. The frequency of repeat imaging is empirical. At our institution, patients have six monthly scans for the first year decreasing to annually or even longer depending on the rate of growth with a low threshold to rescan if new symptoms arise prevails.

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13. Gardner G, Robertson JH. *Hearing preservation in unilateral acoustic neuroma surgery*. Ann Otol Rhinol Laryngol. 1988 Jan-Feb;97(1):55-66.

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2005

September

Biomechanics of the Lower Limb in Health, Disease and Rehabilitation
5-7 September, 2005; Manchester, UK
E. j.fletcher@salford.ac.uk

Encephalitis Explored: Assessment, Rehabilitation and Therapies
6-7 September, 2005; York, UK
T. 01653 692583,
E. mail@encephalitis.info
www.encephalitis.info

Event Processing by the Human Prefrontal Cortex. A seminar with Professor Jordan Grafman
7 September, 2005; Cardiff, UK
E. Halliganpw@cardiff.ac.uk

Joint ABN/SBNS meeting
7 - 9 September, 2005; Torquay, UK
T. 020 7405 4060, E. info@theabn.org

4th International Symposium on RLS and PD
8-9 September, 2005; Stresa, Italy
T. +33 1 42 53 03 03,
E. fchristory@lms-group.com

Symposium: Genetics in Modern Medicine
9 September, 2005; Edinburgh, UK
T. 0131 225 7324, E. h.olaez@rcpe.ac.uk

The Neurorehabilitation of Children and Young Adults
9 September, 2005; Ely, UK
www.easternrehabgroup.org.uk,
E. marlena.judd@addenbrookes.nhs.uk/
lloyd.bradley@addenbrookes.nhs.uk

European Paediatric Neurology Society
14-17 September, 2005; Goteborg, Sweden
T. +46-31-708 60 00, F. +46-31-708 60 25,
E. epsn2005@gbg.congrex.se

Behavioural Experiments in the rehabilitation of Acquired Brain Injury
16 September, 2005; Ely, UK
E. alison.gamble@ozc.nhs.uk

8th Congress of the European Federation of Neurological Societies
17-20 September, 2005; Athens, Greece
T. 0041 22 908 0488, F. 0041 22 732 2850,
E. efns05@kenes.com, www.efns.org/efns2005

World Congress on Huntington's Disease
10-13 September, 2005; Manchester, UK
E. david.craufurd@man.ac.uk, F. 0161 276 6145,
www.hda.org.uk/congress/index.html

33rd Annual Meeting of the International Society for Pediatric Neurosurgery
11-15 September, 2005; Vancouver, BC, Canada
www.venuewest.com/2005/ispn/

Methods in Mind, BPPS Meeting
12-16th September, 2005; Aston University, UK
www.hop.man.ac.uk/bpps/, E. events@acnr.co.uk

fMRI experience VII
15-16 September, 2005 Birmingham, UK
www.fmriexp.com/7

Behaviour Experiments in the Neuro Rehabilitation of Acquired Brain Injury
16 September, 2005; Ely, UK
T. 01353 652173

9th Congress of the European Federation of Neurological Societies (EFNS)
17-20 September, 2005; Athens, Greece
E. efns05@kenes.com

Attention - Advanced Cognitive Rehabilitation Workshop
17 September, 2005; Gatwick, UK
T. 01276 472369,
E. enquiries@braintreertraining.co.uk

Treatment of neurological diseases-an evidence-based approach. Cochrane Neurological Network workshop
18 September, 2005; Athens, Greece
E. cochrane.neuronet@unimi.it

An International Educational Course: Pharmacological Treatment of Epilepsy
18-25 September, 2005; Eilat, Israel
E. eilatedu@targetconf.com, F. 97-235-175-155

International Psychogeriatric Association Annual Meeting
20-24 September, 2005; Stockholm, Sweden
E. stockholm2005@ipa-online.org

78th Congress of the German Neurological Society
21-23 September, 2005; Wiesbaden, Germany
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Kongress Der Deutschen Gesellschaft Fur Neurologie
21-24 September, 2005; Wiesbaden, Germany
T. +49 7621 98330, E. info@akmcongress.com

Stewarts 5th Annual Legal Seminar for Brain Injury Professionals (in conjunction with BISWG - Brain Injury Social Work Group)
22 September, 2005; London, UK
T. 020 7242 6462,
E. braininjury@stewarts-solicitors.co.uk

1st European Conference on Child & Adolescent Mental Health in Educational Settings
22-23 September, 2005; Paris, France
T. 020 7447 3829, E. events@tavi-port.org

European Brain & Behaviour Society (EBBS) 37th Meeting
24-28 September, 2005; Dublin, Ireland
E. info@EBBS2005.com, www.ebbs-science.org

The second IBRO/FENS Summer School 'Development and Plasticity of the Human Cerebral Cortex'
24 September-1 October, 2005; Croatia
E. school@hiim.hr,
www.hiim.hr/english/index.html

Scientific Symposium of the Multiple Sclerosis International Federation (MSIF) and 7th Greek Conference
25-27 September, 2005; Thessaloniki, Greece
E. ms@artion.com.gr, T. 302 310 250 927.

6th Meeting of the International Society for NeuroImmunoModulation
25-28 September, 2005; Athens, Greece
T. +30 210 7257693, E. info@erasmus.gr

130th Annual Meeting of the American Neurological Association
25-28 September, 2005; San Diego, US
www.aneuroa.org/index.html,
E. tanyahehs@llmsi.com

Epilepsy Study Day
28 September, 2005; Glasgow, UK
E. camilla.young@nhs.net, T. 0141 201 2423

10th International Congress of the World Muscle Society
28 September-1 October, 2005;
Iguassu Falls, Brazil
www.wms2005.com/

34th Annual Meeting of the Child Neurology Society
28 September-1 October, 2005; Los Angeles, US
www.childneurologysociety.org/events/
evt_001.asp

ECTRIMS-ACTRIMS 2005
28 September-1 October, 2005;
Thessaloniki, Greece
www.akm.ch/ectrims2005, E. info@akm.ch

21st International Conference of Alzheimers Disease International (ADI)
28 September - 1 October, 2005; Istanbul, Turkey
www.adi2005.org

19th National Congress of the Italian Society for the Study of Headache
29 September - 2 October, 2005; Venice, Italy
E. info@nicongress.it

Primary Care Neurology Conference
29 September, 2005; Manchester, UK
E. stuart@innervate.co.uk, T. 01483 243335.

American Congress of Rehabilitation Medicine, Achieving, Evidence-Based Rehabilitation
29 September - 2 October, 2005; Chicago, US
T. 001 317 915-2250, E. acrm@acrm.org,
www.acrm.org

The Conversation: MS Professional Network Conference in Scotland
30 September, 2005; Stirling, UK
E. h.maunder@msscocietyscotland.org.uk, or
T. 0131 335 4050.

October

Regional Symposium on Alzheimer's Disease in the Middle East
1-2 October, 2005; Istanbul, Turkey
www.worldeventsforum.com/alz.htm

ESF Research Conference on Brain Development and Cognition in Human Infants
1 - 6 October, 2005; Naples, Italy
www.esf.org/conferences/mc05118

British Geriatric Society Autumn Meeting
4-7 October, 2005; Harrogate, UK
T. 020 7608 1369

1st Annual Meeting of the International Spine Society
6-8 October, 2005; London, UK
E. contact@spineinternational.org,
F. 32 38 214 532.

The 16th International Symposium on the Autonomic Nervous System
6-9 October, 2005; Los Cabos, Mexico
Anita Zeller, AAS Executive Secretary,
T. +1 952-469-5837, E. zeller.anita@mayo.edu,
www.americanautonomicsociety.org

British Society of Neuroradiologists Annual Meeting
7-8 October, 2005; Edinburgh, UK
E. john@bsnr.co.uk

Congress of Neurological Surgeons Annual Meeting
7-12 October, 2005; Boston, US
T. 001 630 323 5144, F. 001 630 323 6989,
E. info@1CNS.org

The 6th Euroyapmeet - conference for Younger People with Parkinson's
7-9 October, 2005; Ireland
E. lizzie@epda.eu.com

The National Tremor Foundation Annual Conference
8 October, 2005; Durham, UK
T 01708 386399, E. tremorfoundation@aol.com

Society for Neuropsychology National Conference
9 October, 2005; Bremen, Germany
www.neuropsychologie.de

12th Congress of the International Headache Society
9-12 October, 2005; Kyoto, Japan
www.ihc2005.com, E. ihc2005@convention.co.jp

Overview of the Assessment, Treatment and Management of the Vegetative State (VS) and Minimally Conscious State (MCS) Patient
10 October, 2005; London, UK
E. institute@rhn.org.uk

5th Meeting of British Society of Neuro-Otology
10 October, 2005; London, UK
E. neuro-otology@imperial.ac.uk,
T. 0208 8467285 (Janet Mills).

Sensory Modality & Assessment Rehabilitation Technique (SMART) 5 Day Assessor Training
10-14 October, 2005; London, UK
E. institute@rhn.org.uk

RCP Live - Epilepsy
11 October, 2005; online
See www.rcp-live.ac to register

'Neuropathic Pain' Annual Meeting of the Hellenic Pain Society (IASP Chapter)
14-15 October, 2005, Athens, Greece
Hellenic Pain Society,
T. 30-210-64-44-174, E. pain@internet.gr,
www.hps-pain.gr

Practical Management of Motor Complications in Parkinson's Disease
14 October, 2005; Lisbon, Portugal
Lisa Seidl, T. +1 414-276-2145,
E. lseidl@movementdisorders.org
www.movementdisorders.org

1st Congress of the World Association of Sleep Medicine
15-18 October, 2005; Berlin, Germany
www.wasm2005.org, E.info@wasm2005.org

2nd International Congress on Brain and Behaviour (2nd ICBB)
17-20 October, 2005, Thessaloniki, Greece
Dr. KN Fountoulakis E. kfount@med.auth.gr,
www.psychiatry.gr/intro_brain2_eng.html

Epilepsy Masterclass
18 October, 2005; Coventry, UK
E. d.sidwick@stac-consultancy.co.uk,
T. 01202 201580.

Sex, Relationships and Physically Disabled People
19 October, 2005; Leeds, UK
E. adele.archer@nhs.net, T. 0113 3055086.

Parkinson's Disease Masterclass
19-21 October, 2005; Stortford, UK
E. doug.macmahon@cornwall.nhs.uk,
T. 01209 881631

1st International Symposium on Brain, Vision & Artificial Intelligence
19-21 October, 2005; Naples, Italy
E. contact@bvai.cib.na.cnr.it
<http://bvai.cib.na.cnr.it/BVAI2005>

National Academy of Neuropsychology (NAN)
19 - 22 October, 2005; Tampa, Florida, USA
www.nanonline.org/conferences.shtm

4th International Congress on Vascular Dementia
20-23 October, 2005; Porto, Portugal
T. +41 22 9080488, E. vascular@kenes.com

Dopamine Transporter Imaging in Neurological Practice
October 21, 2005; Leipzig, Germany
Lisa Seidl, T. +1 414-276-2145,
E. lseidl@movementdisorders.org
www.movementdisorders.org

Cognitive Development Society 2005 Meeting
21-22 October, 2005; San Diego, US
www.cogdevsoc.org

Attention and Executive Skills
20-21 October, 2005; Ely, UK
Oliver Zangwill Centre, Ely, UK
E. alison.gamble@ozc.nhs.uk

XVII Annual Technical Workshop of Institute Guttmann - A Window to the Future of Neurorehabilitation
20-21 October, 2005; Barcelona, Spain
www.guttmann.com

4th International Congress on Vascular Dementia
20-23 October, 2005; Porto, Portugal
E. vascular@kenes.com, T. +41 22 908 0488.

18th Congress of the European College of Neuropsychopharmacology
22-26 October, 2005; Amsterdam,
The Netherlands
E. secretariat@ecnp.nl


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

Academy of Aphasia
23 - 25 October, 2005; Amsterdam,
The Netherlands
www.academyofaphasia.org

Understanding Brain Injury, Headway Training Services
26 October, 2005; Altringham, UK
Steve Shears, T. 0115 924 0800.

Learning Disability Annual Meeting
27 October, 2005; Jersey, UK
E. ecocook@rcpsyh.ac.uk, T. 0207 2352351 ext 145

British Association of Neuroscience Nurses Annual Conference
28-30 October, 2005; Edinburgh, UK
Shanne McNamara, Edinburgh Centre for Neuro-Oncology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.

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For a report on the 6th World Congress on Brain Injury, see www.acnr.co.uk/conferences.htm



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CONTROVERSIES IN THE MANAGEMENT OF TRAUMATIC SPINAL CORD INJURY

Tuesday 29 November 2005

A one day conference organised by

Royal College of Physicians and
British Society of Rehabilitation Medicine

at the Royal College of Physicians, 11 St Andrews Place,
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This conference aims to provide an opportunity to debate some of the more controversial areas in the management of people with traumatic spinal cord injury. Whilst the UK has an excellent range of spinal injury centres, there is not yet a complete consensus on management of the injury and some of the more common complications. The speakers, each eminent in their subject, will address these more controversial areas and the programme will allow plenty of time for debate and discussion.

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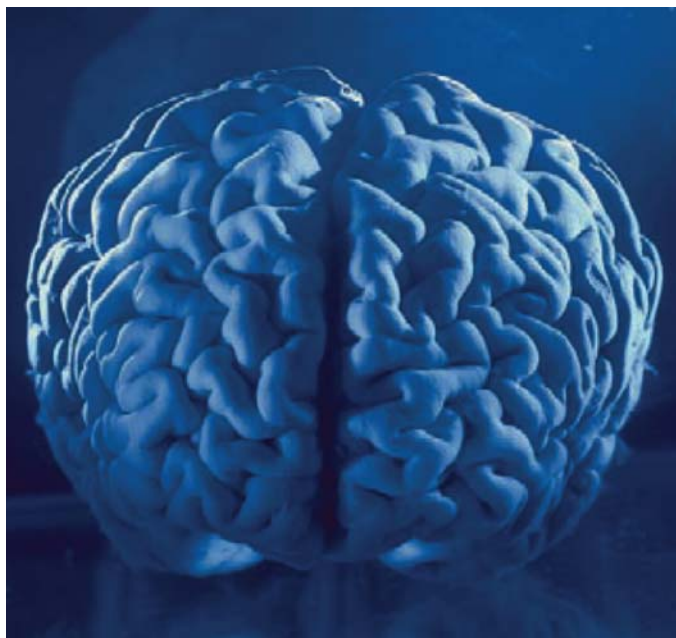
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Jean-Martin Charcot on 'Sclérose en plaques' (Multiple Sclerosis)

Although not the first to describe multiple sclerosis, Charcot formulated ideas on the clinical features and pathology so effectively that Julius Althaus (1877) suggested naming the condition after him. Charcot first encountered three patients whose symptoms had begun in 1855. In that year Alexandrine C. became aware during pregnancy of difficulty in using her legs although she may have had symptoms for the previous two years. The diagnosis was established clinically at the Salpêtrière in 1863. Later, Charcot realised that a maid employed in his house had sclérose en plaques and not, as he first thought, Parkinson's disease. He presented three cases to the Société Médicale des Hôpitaux on March 8th 1865 (Vulpian 1866) and published four original papers at around that time (Charcot 1865; 1868a; 1868b; 1868c). But Charcot's observations on sclérose en plaques are best known through his published lectures (Charcot 1872; 1875) and clinical demonstrations (Charcot 1887), the early volumes of his collected works (Charcot 1886) and the English translations of these lectures published by the New Sydenham Society (Charcot 1877). Charcot left a brilliant account of the clinical features, delineating the cerebral, spinal and mixed cerebrospinal forms. He formulated views on the pathogenesis and pathophysiology, provided the first attempts at clinical measurement, and threw down a therapeutic gauntlet to his successors. His clinical descriptions were vivid and, with access to pathological material (Figure 1), he was clearly thinking about disease mechanisms. On visual involvement, he wrote:

"Amblyopia is a persistent and frequent symptom of cerebro-spinal disseminated sclerosis but it rarely issues in complete blindness ... patches of sclerosis have been found after death occupying the whole thickness ... of the optic nerve, in cases where during life an enfeeblement of sight simply had been noted. This discrepancy between symptom and lesion constitutes one of the most powerful arguments to show that the functional continuity of the nerve tubes is not absolutely interrupted although these, in their course through the sclerosed patches, have been despoiled of their medullary sheaths and reduced to axis cylinders."



Figure 1. The pathological anatomy of sclérose en plaques (Charcot 1886).

On cognitive manifestations of multiple sclerosis, and pathological laughter and crying:

"Most of the patients affected by multilocular sclerosis, whom I have had occasion to observe, have presented at a certain stage of the disease a truly peculiar facies. ... there is marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality. ... it is not rare to see them give way to foolish laughter for no cause, and sometimes, on the contrary, melt into tears without reason."

Charcot described the triad of nystagmus, dysarthria and ataxia resulting from involvement of brainstem-

cerebellar connections:

"When the patient wishes to lift a glass full of water to her lips, the rhythmical agitation of the hand and forearm is scarcely noticeable when taking hold of the object; ... but ... at the moment when the goal is being attained, the glass is ... dashed with violence against the teeth, and the water is flung out to a distance."

On spinal disease, Charcot described the characteristic weakness, spasticity, ankle clonus (spinal epilepsy) and loss of function resulting from de-afferentation:

"Some of the symptoms of ataxia are found ... when the sclerosed islets in certain regions of the cord spread over a certain height of the posterior columns ... In order to grasp and use a pin [the patient] is required to have her eyes open, otherwise the pin drops from her fingers."

We can admire Charcot for the attempt to measure deficits, and to explain their origins in terms of disordered physiological mechanisms (Figure 2). On pathophysiology he wrote:

"transmission of voluntary impulses would still proceed by means of the denuded axis cylinder ... deprived of medullary sheathing in the midst of the foci of sclerosis .. but it would be carried on irregularly in a broken or jerky manner and would thus produce the oscillations which disturb the due execution of voluntary movement."

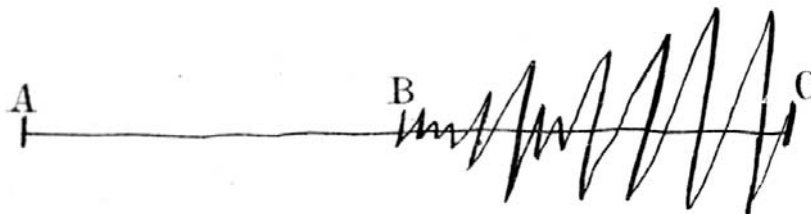
Many of Charcot's students were also put to work on the disorder. In his thesis, Leopold Ordenstein first depicts the lesions of sclérose en plaques using material from Charcot's laboratory (Ordenstein 1868). Désiré-Magloire Bourneville and Louis Guerard (1869) completed the clinical description and provided additional illustrations. Joseph Babinski emphasised hemiplegia as a manifestation of multiple sclerosis (Babinski 1885). The work also contains an elaborate depiction of early multiple sclerosis lesions, showing the interaction of macrophages with demyelinated and remyelinated nerve fibres. Babinski is the young physician catching the swooning Blanche Wittmann in the much reproduced painting by Pierre Brouillet of Charcot demonstrating hysteria at La Salpêtrière during one of his Tuesday lectures. Gilles de la Tourette (1886) described the gait in neurological disease and depicted the footprints of ataxic patients with sclérose en plaques. The last of Charcot's pupils to write at length on multiple sclerosis was Pierre Marie who sought to classify and record the typical gait disturbance - distinguishing spastic from cerebellar components. He was no less thorough in his descriptions of upper limb tremor and sensation, dealing at length with the special senses, hearing and vision, and distinguishing disorders of acuity and colour vision from those of eye movements. He was awarded the Civrieux prize of the Academy of Medicine in 1885 for his account of disordered bladder, bowel and sexual function in multiple sclerosis. Marie recognised the variable symptoms at onset, delineating a number of stereotyped presenting syndromes and documenting the subsequent clinical course, including the category of benign multiple sclerosis. He made the distinction between progression from



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Figure 2. Measurement of tremor at rest and on attempted movement (Charcot 1887).



onset and its development later in the course of the illness - in fact, his account of primary progressive multiple sclerosis is faultless, noting the later age of onset, the worse prognosis, the relative absence of histological (or clinical) involvement of the cerebrum, and the more frequent axon degeneration.

Charcot described axon loss in some lesions of sclérose en plaques (Charcot 1868b) and linked these to clinical disability:

"The paresis advances with extreme slowness ... but at last the day comes when ... they may be confined to bed ... this resistance of the axis cylinders ... may account for the slowness with which the paretic symptoms advance in disseminated sclerosis and for the long space of time which elapses before they give place to complete paralysis and permanent contracture."

He suggested that the naked axis cylinders might again clothe themselves with myelin and thus effect a "restituto ad integrum". Neither he nor Babinski realised that this is what they had already depicted (Babinski 1885). For Charcot, sclérose en plaques was a toxin- or microorganism-induced condition in which overgrowth of glia strangles the myelin sheath, sometimes leading to degeneration of the axis cylinders and with secondary changes in blood vessels (Figure 3).

"undoubtedly, the multiplication of nuclei and the concomitant hyperplasia of the reticulated fibres of the neuroglia constitutes the initial, fundamental fact, and necessary antecedent; the degenerative atrophy of the nerve elements, is consecutive and secondary."



Figure 3. The 'primary' glial overgrowth that is the basis for sclérose en plaques (Charcot 186 8b).

On treatment, Charcot came straight to the point:

"After what precedes, need I detain you long over the question of treatment? The time has not yet come when such a subject can be seriously considered."

Charcot only saw 30 cases of sclérose en plaques during his working lifetime but he observed most of the cardinal clinical and pathological features and showed great intuition in thinking about the clinical science of what is now recognised to be the commonest potentially disabling neurological disease of young adults in the western world.

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Azilect in Parkinson's Disease

LEVODOPA has been the mainstay of treatment for patients with Parkinson's disease (PD) for the past 30 years and is still often used as first line treatment. In the long-term, however, levodopa-sparing strategies, such as using dopamine agonists, COMT inhibitors and monoamine oxidase-B inhibitors (MAO-B inhibitors), are necessary because of levodopa motor complications. Within a few years of levodopa treatment, many patients experience 'end of dose' fluctuations, off-periods and drug-induced dyskinesia. These may respond to treatment with adjunct dopamine agonists or COMT inhibitors, but these are not always effective or tolerated so we continue to need new treatments for PD.

The availability of the second generation MAO-B inhibitor – rasagiline – offers clinicians a promising new treatment for idiopathic Parkinson's disease. Rasagiline can be used both as monotherapy and as an adjunct to levodopa to alleviate motor fluctuations. It is more potent than selegiline and has the benefit of absence of amphetamine metabolites.¹ Moreover, the extension of the TEMPO trial² hints that the drug may offer a disease-modifying effect in addition to its conventional activity as a MAO-B inhibitor, however this does warrant further investigation.

This article reviews the pharmacodynamics of rasagiline, the evidence from clinical trials and comments on the place of this new treatment in clinical practice.

Goals of treatment

The current aims of treating Parkinson's disease are to alleviate the motor symptoms and, if possible, slow progression of the disease whilst improving quality of life for the patient and their carers.

Despite the initial considerable benefit obtained by most PD patients, long-term levodopa does not solve all of the problems faced by PD patients. In the more advanced stages of the disease, it does not improve many disabling motor and non-motor parkinsonian features.³ Managing motor complications such as fluctuating treatment responses, dyskinesias and dystonias, becomes a key objective in advanced disease. Around 40–60% develop such motor fluctuations within just four to six years of levodopa therapy.⁴ These problems tend to be more noticeable in patients with young-onset PD than in those who develop the disease in later years.⁵

Goals of PD treatment:

- Improve mobility
- Maintain function and quality of life
- Have minimal side effects
- Manage levodopa associated fluctuations and dyskinesias so decreasing daily 'off' time

The most common presentation of motor fluctuations is the wearing-off effect.⁴ This can manifest as early morning akinesia or each levodopa dose having a noticeable period of efficacy which appears to fade before the next dose is due. Patients may also develop 'delayed-on', 'on-off' or 'no-on' fluctuations and peak-dose or biphasic dyskinesias.⁴

Monoamine oxidase-B inhibitors

Dopamine agonists (pergolide, pramipexole, ropinirole, cabergoline) and COMT inhibitors (entacapone and tolcapon) have been combined with levodopa to help manage motor fluctuations. However, adjunct use of these drugs produces only partial improvement as PD progresses, leaving patients with clinically significant off-periods, while adding complexity to their treatment schedule. Inhibition of monoamine oxidase-B (MAO-B) activity provides an alternative option for the treatment of levodopa-associated motor fluctuations. A meta-analysis of all published trials (17 randomised trials involving 3,525 patients) concluded

that MAO-B inhibitors reduce disability, the need for levodopa, and the incidence of motor fluctuations without substantial side effects or increased mortality.⁶ Rasagiline is a newly available, second generation treatment for Parkinson's disease with potent, selective, irreversible monoamine oxidase-B inhibitor properties.

Rasagiline pharmacodynamics

Rasagiline (N-propargyl-1-R-aminoindan) is more potent than selegiline, the only other MAO-B inhibitor on the current UK market. A 1mg dose of rasagiline almost fully inhibits platelet MAO-B activity in humans. Rasagiline and its metabolite, aminoindan, show a linear, dose-proportional increase in maximum blood concentration (C_{max}) and area under the concentration time curve (AUC). The time to reach the maximum concentration (T_{max}) is between 0.5 and 0.7 hours.¹

Unlike selegiline, rasagiline is not degraded to amphetamine-like metabolites which have been associated with side effects such as raised blood pressure or increases in heart rate.⁷ Preclinical studies confirmed that rasagiline does not induce the alterations in blood pressure or heart rate observed with selegiline.⁷

Rasagiline has been shown to protect neurons against hypoxic injury, oxidative stress, cerebral trauma and N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced neurotoxicity in animal models. The major metabolite of rasagiline, aminoindan, also shows dose-dependent inhibition of apoptosis in cell culture models. It is also possible that rasagiline promotes better function of surviving dopaminergic neurons, improves the connectivity of these neurons, or acts through another unidentified mechanism.² The combination of rasagiline's MAO-B inhibitory activity and potential disease-modifying action raises the spectre of offering clinicians and patients a significant new treatment for Parkinson's disease.

Clinical trials

The safety, tolerability and clinical efficacy of rasagiline as adjunctive therapy to levodopa was tested in a multicentre, double-blind, randomised, placebo-controlled, parallel group study conducted for 12 weeks in 70 patients with PD (mean age 57.4; 32 patients had fluctuating PD).¹ A beneficial clinical effect was observed in fluctuating patients treated with 0.5mg, 1mg or 2mg once daily. This was expressed as a decrease in total Unified Parkinson's Disease Rating Scale (UPDRS) (23.0% in the rasagiline groups versus 8.5% in the placebo group). The treatment effect was still evident six weeks after drug discontinuation and the authors reported that the incidence and type of adverse experiences reported by patients receiving rasagiline were indistinguishable from those reported by patients receiving placebo. Interestingly, 15% of patients taking rasagiline had abolition of their off-periods.

In a 10-week, randomised, placebo-controlled phase II study of rasagiline in patients with early, untreated PD, the treatment was well tolerated.⁸ There were no occurrences of hypertension, bradycardia or other cardiovascular adverse experiences.

The TEMPO study ([TVP-1012] as Early Monotherapy for Parkinson's disease Outpatients) was a 26-week, randomised, double-blind, placebo-controlled study in Canadian and US centres.⁹ It assessed the safety and efficacy of 1mg and 2mg rasagiline once daily in patients with early PD not requiring dopaminergic therapy (1mg n=134; mean age 61.6 years; mean disease duration 0.92 years; 2mg n=132; mean age 60.4 years; mean disease duration 1.15 years) against placebo (n=138; mean age 60.5 years; mean disease duration 0.94 years). Eligible patients included those older than 35 years



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who had the presence of at least two of the cardinal signs of PD and whose disease severity was not greater than Hoehn and Yahr stage III.

The primary pre-specified measure of efficacy was the change in the total Unified Parkinson's Disease Rating Scale (UPDRS) score between baseline and 26 weeks. The results showed that monotherapy with both doses of rasagiline was effective: the adjusted effect size for the total UPDRS was -4.20 units comparing 1mg and placebo (95% confidence interval, -5.66 to -2.73; $p < 0.001$). Of the 138 subjects in the placebo group, 16.7% ($n=23$) reached the secondary end point of requiring levodopa therapy compared with 11.2% ($n=15$) of the 134 subjects treated with 1mg rasagiline. The latter group showed significant improvements in Parkinson's Disease Quality of Life scale (PDQUALIF) compared with the placebo group. The benefit occurred primarily in the subscale measuring self-image/sexuality, with borderline effects on the social role subscale. Overall, adverse events were no more frequent in the treated group compared to placebo. Rasagiline was not associated with hallucinations, oedema and somnolence, potentially dose-limiting side effects that can emerge with other PD drugs.

The magnitude of the symptomatic benefit observed in this trial is comparable to that for selegiline over a comparable six-month period. Although the symptomatic effect observed with rasagiline monotherapy in this study is more modest than the effects observed with dopamine agonists as monotherapy for PD, the difference between these effects is relatively small. The reported incidence of adverse events is higher with dopamine agonists than was observed for rasagiline in the TEMPO trial. Rasagiline's simple once daily dosage and no titration led to a high level of compliance: 91.8% of patients taking the 1mg dose took 95% of their scheduled doses, compared with 89.4% taking the 2mg and 92% taking placebo.

The PRESTO¹⁰ (Parkinson's Rasagiline: Efficacy and Safety in the Treatment of 'Off') trial was a multicentre, randomised, placebo-controlled, double-blind, parallel group study of 472 people with PD who experienced at least 2.5 hours off-time a day, despite receiving optimal therapy with other drugs. Patients were randomised to rasagiline 1mg or 0.5mg once daily or placebo. They had a modified Hoehn and Yahr stage of less than 5 in the 'off' state, were 30 years or older and experienced at least 2.5 hours in the off-state daily, as confirmed by a three-day home diary. The main outcome measures were change from baseline in total daily off-time measured by patients' home diaries during 26 weeks of treatment and percentage of patients completing 26 weeks of treatment. Off-time decreased by 1.85 hours (29%) in patients treated with 1.0mg rasagiline once daily, 1.41 hours (23%) with 0.5mg rasagiline once daily and 0.91 hour (15%) with placebo. Patients on rasagiline had an improved daily on-time without troublesome dyskinesias compared to placebo; 0.51 hours in patients treated with 0.5mg rasagiline once daily, 0.78 hours with 1mg rasagiline once daily.

Pre-specified secondary endpoints also improved during rasagiline treatment, including scores on an investigator-related clinical global impression scale and the UPDRS.

CLINICAL PRACTICE

Rasagiline is taken as a single, oral, daily dose with no need for titration and is thus easier to use for both patients and clinicians than most other adjunct therapies. This, plus its favourable tolerability profile should make it a useful addition to current treatments available for Parkinson's disease.

As monotherapy, rasagiline significantly improves tremor and bradykinesia and overall motor function in de novo patients. In addition, the drug improves activities of daily living and is well tolerated. Starting patients with Parkinson's disease with rasagiline is a rational management strategy, given its efficacy, good tolerability profile and the avoidance of titration regimes.

In adjunct therapy, rasagiline is an effective and simple treatment when used in combination with levodopa. It is a well tolerated adjunct in younger and older patients. Rasagiline effectively reduced the time spent in the off state and increased useful on-time, making it a favourable candidate for the adjunct treatment of Parkinson's disease.

The number of patients discontinuing for any reason or because of an adverse event was not significantly different between treatment groups ($p=0.85$). High patient acceptability was demonstrated by the high compliance rates in this trial: 95% of patients taking 90% of their scheduled doses. Adverse events mainly involved the gastrointestinal system (weight loss, vomiting and anorexia) and were significantly more common in patients treated with either dosage of rasagiline compared with placebo. These appeared to be dose related.

The LARGO (Lasting effect in Adjunct therapy with Rasagiline Given Once daily) trial was an 18-week, double-blind, multicentre study in which 687 patients were randomly assigned to 1mg once daily rasagiline ($n=231$), 200mg entacapone with every levodopa dose ($n=227$) or placebo ($n=229$).¹¹ Over a quarter of patients were ≥ 70 years (26%, 26% and 31%, respectively). Eligible patients had a modified Hoehn and Yahr stage of less than 5 in the off-state. They had to have received optimum levodopa therapy and been stable for at least 14 days before baseline and have had motor fluctuations for at least 1 hour every day in the off-state during waking hours, not including early morning akinesia. The primary outcome was change in total daily off-time.

Rasagiline and entacapone equivalently reduced mean off-time by 1.18 ($p=0.0001$) and 1.2 hours, respectively ($p < 0.0001$) compared to placebo (0.4 hours). The daily on-time without troublesome dyskinesia increased by 0.85 hours in both arms, compared to 0.03 hours in patients treated with placebo ($p=0.0005$).

Changes in UPDRS scores also significantly improved for activities of daily living during off-time (-1.71 and -1.38 versus placebo, $p < 0.0001$ and $p=0.0006$, respectively) and motor function during on-time (-2.94 and -2.73, versus placebo, both $p < 0.0001$) in the rasagiline and entacapone arms, respectively. The trial also looked at the effects of rasagiline, entacapone and placebo on Postural Instability and Gait Disorder (PIGD) and freezing. These symptoms are, generally, poorly responsive to PD therapy. Rasagiline-treated patients experienced a significantly greater

improvement in PIGD and in the UPDRS subscore for freezing than placebo-treated patients ($p < 0.05$). In contrast patients treated with entacapone showed no significant improvement compared to placebo though a trend was evident. In an ancillary study rasagiline added to levodopa also significantly improved freezing of gait (FOG) compared to placebo.¹²

A smaller proportion of patients withdrew from the rasagiline (10%) arm than either the entacapone (13%) or placebo (15%) arms though these differences were not significant. Rasagiline was as equally efficacious and as well tolerated in patients above and below the age of 70 years and also equally efficacious and well tolerated in patients taking or not taking concomitant dopamine agonists.¹¹

An important feature for patients noted in this trial was that rasagiline significantly improved motor symptoms before first morning drug administration compared to placebo, meaning that patients did not have to wait for their drug to work before they could move first thing in the morning.¹¹ In the UK, Azilect is currently available as a 1mg tablet for use as monotherapy and adjunct therapy.¹³

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

Vision in Alzheimer's Disease - (Interdisciplinary topics in gerontology, vol. 34)

Any neurologist who has encountered patients with the visual variant of Alzheimer's disease (AD), also known as posterior cortical atrophy, will be aware of the profound disability caused by this condition, even when memory function is relatively intact. Lesser degrees of visual agnosia and/or impairment of visuospatial functions are common in typical AD presenting with memory problems, although often undiagnosed. This volume gives an overview of the visual problems of AD. These include impairments of: contrast sensitivity, especially at low spatial frequencies; motion, shape and colour perception; pupil reaction; face discrimination; and reading.

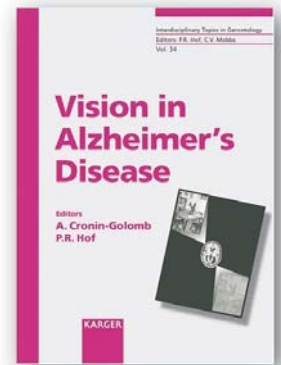
The 16 chapters are arranged into four sections. The first of these deals with "structure and function", describing changes in the retinal ganglion cells, suprachiasmatic nucleus (which may impact on circadian function, perhaps relevant to the clinical phenomenon of "sundowning"), lateral geniculate nucleus, primary visual cortex, and corticocortical association pathways. These findings are complemented by the experimental findings in the third section ("Visual perception and cognition", challenging reading for the non-research clinician), indicating that both the magnocellular and parvocellular (dorsal/ventral,

where/what) visual pathways may be affected in AD. Impairments of visual attention are the topic of the fourth section, specifically reductions in the window of visual attention, processing speed, and ability to divide attention, with obvious implications for tasks such as driving.

For the clinical reader, the second section will perhaps be of greatest interest, detailing the heterogeneity of visual presentations in AD, the visual variant of AD, and visual hallucinations. How to tackle these problems is difficult. Clinical experience suggests that, whatever their benefits for memory, behaviour and function, cholinesterase inhibitors have little to offer for the visual problems of AD (although cholinergic mechanisms may be relevant to visual attention). The final chapter offers some practical advice about visual interventions, particularly enhancing contrast, with evidence that this may impact beneficially on bathing, dressing, toileting and eating function.

Overall, this is a stimulating volume, although the potential market may be limited.

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Edited by: A Cronin-Golomb, PR Hof
Published by: Karger
Price: €141.50
ISBN: 3-8055-7757-5

Cognitive Neuropsychology of Alzheimer's Disease (2nd edition)

This book is the expanded and updated successor to The Cognitive Neuropsychology of Alzheimer-type dementia published in 1996. As before, the majority of the book is devoted to neuropsychological function in AD, with chapters devoted to attention, executive function, memory (episodic, remote, implicit, semantic), language, and calculation. It is odd however that, unlike the first edition, this volume has no chapter devoted to visuospatial function, visual agnosia gaining only brief mentions in the chapters addressing reading and spelling, and motor functioning (alongside extrapyramidal signs, myoclonus and seizures, and apraxia). A welcome addition is a chapter on the loss of "awareness" of, or "insight" into, cognitive function, also known as cognitive anosognosia: it is perplexing how some AD patients are acutely aware of and appropriately worried by their cognitive decline whereas others are seemingly able to "paper over the cracks" and deny any problems at all, often to the incredulity of their exasperated relatives.

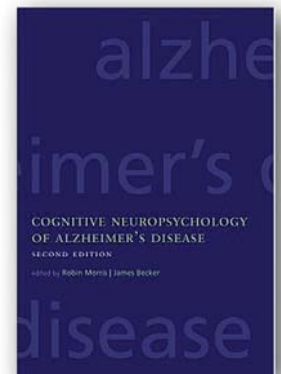
This neuropsychological core is sandwiched between sections on: background issues, with new chapters on the natural history of AD and preclinical AD; neurobiological correlates of cognitive dysfunction; and the treatment and management of AD. The 1996 chapter on genetic subtypes

of AD in the neurobiological correlates section is another omission in this updated edition, which is perhaps peculiar in light of the increase knowledge of genetic mutations, particularly in the presenilin 1 gene, causing AD, and the desirability of attempting genotype-phenotype correlations.

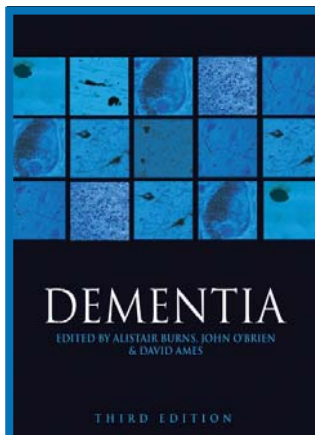
There is much more information here than will be needed by the practising clinician. I particularly enjoyed the chapter by Edgar Miller ("The assessment of dementia") as it seemed to me the only one obviously suffused with clinical lore, as opposed to knowledge of theoretical underpinnings and research findings.

I don't know if the book was prepared as "camera ready copy" but if not the proof reading in places left something to be desired (how about "DA" for "AD", p 19; and numerous text references not in the bibliography in chapter 18?). For me, this did detract from an otherwise useful book. Nonetheless, most clinicians with an interest in AD will wish to have this book available, in the departmental library if not on their own bookshelves.

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Edited by: RG Morris, JT Becker
Published by: Oxford University Press
Price: £60.00
ISBN: 0-19-850830-1



DEMENTIA

Third edition - Alistair Burns, John O'Brien, David Ames

0 340 81203 6 / August 2005 / Hardback / 1040 pages / 115 b/w & 24 col illus / £145.00

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EDITOR'S CHOICE

Friends in high places

The process by which the visual image is built up in the brain has been an area of controversy for many years. Simplistically this consists of two main opposing views. One is serial processing leading to hierarchy of processing areas/units culminating in a grandmother cell versus a parallel processing of information about different attributes of the image leading to object recognition via co-ordinated patterns / rhythms of activity. The former should predict cells/areas of high visual specificity such as 'face' recognition so that damage to it should lead to a selective deficit such as prosopagnosia. Experimentally, in non human primates, 'face specific neurons' have been recorded in the infero temporal cortex. This recording of single units has now been extended to humans in this recent study by Quiroga et al. A group of patients with intractable epilepsy had single unit recordings made from their medial temporal lobe. The recordings were made in response to a series of images of famous people viewed in different contexts. By so doing they were able to demonstrate that a number of units had very high specificity for that image irrespective of the context in which it was seen. So for example one cell could recognise different images of Jennifer Aniston out of nearly 100 different images, whilst others recognised Halle Berry again in the context of several different profiles and image presentations. This seemed to be a relatively consistent response and suggest that these cells recognise that person's face as a whole and not the combination of features that make up any old face. Of course whether these cells were involved in the perception or recognition and naming of that person's face is not clear, as opposed to simply representing a memory trace for that individual. However it does show that the specificity of stimuli stored in individual cells in the human brain is extraordinary. Of course it does make one worry about how much of one's own brain is cluttered up with irrelevant non-significant images. - *RAB*

Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I.

Invariant visual representation by single neurons in the human brain.

NATURE

2005 Jun 23;435(7045):1102-7.

Panel of Reviewers

Roger A Barker	Honorary Consultant in Neurology, Cambridge Centre of Brain Repair
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MIGRAINE: a new channelopathy

Clues that help to unravel the pathogenesis of any disease, and present opportunities to discover novel drug therapies, are always interesting. When the disease is as common as migraine, the interest generated is obviously heightened. In this paper, Dichgans et al. report a mutation in the SCN1A sodium channel, which causes familial hemiplegic migraine in three related families. The mutation inherits in an autosomal dominant manner and may cause the voltage-gated sodium channel to recover too quickly from fast inactivation leading to excessive neuronal firing. The authors speculate that this initiates the cortical spreading depression, considered the underlying mechanism behind migraine aura. However some important functional data has yet to be provided, owing to technical difficulties in introducing the mutation into SCN1A cDNA. SCN1A is now the third gene for migraine, joining the calcium channel gene CACNA1A (1996) and a Na⁺/K⁺ pump ATP1A2 gene (2003). The mutations in all three genes affect ion channel function, a fact in itself highly suggestive that more common forms of migraine also share an 'ionopathic' basis. It is worth noting however, that based on data from other linkage studies, further potentially novel migraine genes are expected in the future. At this early stage there are no clinical features that discriminate this gene from other hemiplegic migraineurs and the authors describe the phenotype as 'clear cut familial hemiplegic migraine'. An interesting quirk to the familial hemiplegic migraine story is the excess of co-morbid epilepsy in all three of the migraine genes, including three patients in this study that had infantile seizures. Furthermore, in familial forms of epilepsy, mutations have already been found in the SCN1A gene albeit that the causative mutations may have different functional consequences. These include 'generalised epilepsy and febrile seizures plus' and 'severe myoclonic epilepsy of infancy'. A common pathogenesis between these two paroxysmal disorders is likely, which may explain the efficacy of some anticonvulsants in migraine prophylaxis. Finally, one major dilemma facing medicine is the critical translational step from rare mendelian discoveries to relevance for common disease. This is not specific to migraine and a similar dilemma faces other common disorders like Parkinson's and Alzheimer's disease. Doubtless a plethora of association studies will follow the discovery of this gene; all searching for population-based genetic susceptibility factors. However if previous mendelian genes are to go by, this will be a harder nut to crack. - *DGH*

Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, Ferrari MD, Herzog J, van den Maagdenberg AM, Pusch M, Strom TM.

Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine.

LANCET

2005;366:371-7.

PARANEOPLASTIC: what is the anti-amphiphysin syndrome?

*** RECOMMENDED

Very few laboratories could do this study... with the possible exception of Angela Vincent's laboratory in Oxford, none could beat the through-put of serum samples of the Mayo's Neuroimmunology Laboratory, run by Vanda Lennon (she of the NMO-Ig antibody associated with Devic's disease, reported last year in the Lancet). Over the last 15 years, they have handled samples from approximately 120,000 patients with suspected paraneoplastic neurological syndromes. So, think of an antibody; screen the samples; pull the notes; et voila! The biggest series ever. The Mayo have now done this job for antibodies against amphiphysin, a lowly cytoplasmic molecule whose job it is to retrieve spent synaptic vesicles from the axon terminal's plasma membrane. They found 71 positive samples, of which they could recover clinical information from 63 patients. Most (79%) turned out to have a neoplasm, mainly lung cancer; and the majority (74%) also had positive serology for other autoantibodies associated with neurological disease. After six months of a subacute multifocal neurological syndrome most patients were in a wheelchair. A handful of patients responded either to treatment of the tumour or to immunotherapy (steroids and IVIG, but plasma exchange did not work!). So what is characteristic of the anti-amphiphysin syndrome? Of the 19 patients with only this antibody present in their serum, there were more women, who tended to have breast cancer, and who presented with a progressive myelopathy (53%) or stiff-person syndrome (58%). And in the one patient of these who went to post-mortem, inflammatory cells (CD8+ and macrophages especially) were found in their brainstem and spinal cord. So: anti-amphiphysin antibodies are very uncommon, usually found with other

paraneoplastic antibodies and we have probably overestimated their relationship with stiff-person syndrome. Now to start my collection of 120,000 patient samples... - *AJC*

Pittock SJ, Lucchinetti CF, Parisi JE, Benarroch EE, Mokri B, Stephan CL, Kim KK, Kilimann MW, Lennon VA.

Amphiphysin autoimmunity: Paraneoplastic accompaniments.

ANNALS OF NEUROLOGY

2005;Jul;58(1):96-107.

STROKE: The familial risk of subarachnoid haemorrhage

*** RECOMMENDED

All clinical neurologists, I suspect, have been faced with the situation of an apparently healthy individual attending the clinic because of a family history of a 'cerebral bleed'. Anxiety levels are usually high, and information about the relative's precise clinical diagnosis (was it a subarachnoid haemorrhage [SAH], or an intracerebral or extradural or subdural haemorrhage?) correspondingly scarce. Any study which might assist clinicians in these tricky circumstances would therefore be welcome. This paper reports two samples of relatives of patients with SAH; one covers the whole of Scotland for SAH occurring in the years 1994-5; the other relates to admissions to the West of Scotland neurosurgical unit in Glasgow in 1986-7. Hence, large samples, and long follow-up. The epidemiological contortions required to extract and obtain the data seem to have been formidable, and one must commend the investigators for their fortitude (bloody mindedness?) in pursuing the study to a meaningful conclusion, despite the obstruction of the Data Protection Act. The overall finding, common to both cohorts, was a low absolute risk of SAH among relatives of patients with SAH (2%), although this is about 10 times the risk in the general population. As might have been expected, risk is higher for first-degree relatives compared to second-degree relatives; and is highest with two first-degree relatives affected, and lowest with one second-degree relative affected. Hence, on the thorny issue of screening, this would seem inappropriate except for families in which two or more first-degree relatives are affected. Hence, this may be that oddity, the Brain paper which is of use to the common-or-garden clinical neurologist in the face-to-face outpatient clinic encounter. Whether patients, apprised of this data, will be happy in some cases to be reassured that doing nothing is appropriate, remains to be seen. Most of those I have seen want 'a scan'. - *AJL*

Teasdale GM, Wardlaw JM, White PM, Murray G, Teasdale EM, Easton V; Davie.

Cooper Scottish Aneurysm Study Group.

The familial risk of subarachnoid haemorrhage.

BRAIN

2005;128(7):1677-85.

EPILEPSY: focal lesions cause febrile seizures

It has long been known that there is a clinical association between complex febrile seizures and temporal lobe epilepsy (TLE) due to hippocampal sclerosis, conferring a risk up to 8 times higher than the background risk, whereas the common brief febrile seizures carry virtually no additional risk of later epilepsy. Some (not all) pathological studies of human temporal lobe resections for TLE have shown dysplastic neurons within the neocortex of the temporal lobe, leading to the suggestion that there may be a developmental abnormality predating the febrile seizures. In this experimental study the authors used freezing probes to produce tiny lesions on the fronto-parietal neocortex of neonatal rats. This creates a lesion which has the histological appearance of focal microgyria. The rats were then rendered hyperthermic in a chamber attached to a hairdryer. They were heated until they had a convulsion and then moved to room temperature. Following this they were observed for any clinical evidence of seizure activity and underwent regular EEG monitoring. They were also tested on a water maze task of learning and memory. Control groups included naive controls (9 animals), rats with just lesions (9 animals) and rats with just hyperthermic seizures (17 rats). Four of 11 rats with lesions and hyperthermia were observed to have clinical temporal lobe seizures, sometimes with secondary generalisation, without EEG recording. Seven had EEGs recorded from the amygdala and six of these had spontaneous electrographic seizures – an average of 11 per rat. All EEG recorded seizures were associated with behavioural arrest, typical of TLE. Abnormal EEGs were recorded in 2 of 6 rats with hyperthermic seizures alone but in

no control rats or those with just lesions. No seizures were observed in these 3 groups or recorded on EEG. In the experimental animals with seizures there was an associated learning and memory deficit on the maze task. Pathological examination of the brains of these animals demonstrated the freeze lesions of the cortex but showed no evidence of cell loss in the hippocampus. This model shows the interaction of a pre-existing cortical lesion and febrile seizures in the development of TLE. Clinically and electrographically this looks like human epilepsy but the absence of hippocampal damage raises questions about the applicability of the model. It is nevertheless interesting how the same phenotype can be produced without obvious hippocampal damage. The authors argue that this may be related to the age of the animals. It is important to remember the differences in scale between the rat and human brains - the cortical freeze lesions were only about 100µm from the hippocampus but do seem to be histologically distinct. If this represents a valid model of TLE, it may be useful in the development of drugs that are effective in preventing the development of TLE rather than just those for seizure control, which could be applied to high risk febrile seizure patients. - *MRAM*

Scantlebury MH, Gibbs SA, Foadjo B, Lema P, Psarropoulou C, Carmant L.
Febrile seizures in the predisposed brain: a new model of temporal lobe epilepsy.

ANNALS OF NEUROLOGY

2005;58:41-9.

STROKE: and virtual reality games

*** RECOMMENDED

Task specific practice is considered important for recovery of function after stroke. In the best conditions for motor learning, practice should be varied and feedback or knowledge of results should be accurate. In clinical practice time is short for therapists to provide much good quality practice. And speaking from personal experience, practice can also be boring, and therapists are often side tracked by aspects of treatment that may be more interesting to them. Several groups have tried to resolve this problem by interfacing exercises with computer games that can of course be played repeatedly and can be tailored to give accurate performance information. Now also virtual reality is receiving interest in the literature. An article in the June edition of Stroke caught my attention because it assessed both behavioural and functional brain changes resulting from practice using virtual reality (VR) games. Ten stroke patients, aged between 45 and 66 and all over a year post stroke were randomly assigned to control group or to VR training. The control group received no intervention. The VR group practised for 60 minutes a day, five times a week for four weeks. The training included a stepping exercise game, a Sharkbait game in which players have to shift weight, step and squat to avoid sharks and a snow boarding game in which like real snow boarding the weight has to be shifted laterally to control motion. Locomotor function was assessed using the Functional Ambulation Category and the Walking items of the Modified Motor Assessment Scale. And since it's not possible to walk in a fMRI scanner cortical activity during a knee flexion and extension task was captured. Although the training tasks were not exactly like walking, in that they were more static, the VR group showed significantly better gains in walking than the control group. Alongside this improvement the VR group's cortical activity showed a reorganisation from ipsilateral sensorimotor cortex activity before VR to a more normal pattern of activation in contralateral sensorimotor cortex after VR. The technology used in the VR training and in imaging places constraints on training real locomotion and assessing task specific cortical reorganisation. The results of this study can demonstrate only a relationship between brain and lower limb performance in simpler exercises. However it's exciting to see neural changes that are approaching normal that parallel improved function. Therapists will find encouragement for the value of high quality practice from these results. It is just a shame expensive therapeutic tools, such as VR, are unlikely to be seen in many NHS rehabilitation settings in the UK. - *AT*

You SH, Jang SH, Kim Y-H, Hallett M, Ahn SH, Kwon Y-H, Kim JH, Lee MY.
Virtual reality-induced cortical reorganisation and associated locomotor recovery in chronic stroke.

STROKE

2005;36:1166-71.

MULTIPLE SCLEROSIS: Conserving energy and self-help

A 'managing fatigue' programme has recently been investigated within an Occupational Therapy-led randomised controlled trial. Involving people with M.S. in face-to-face community education sessions, the aim of the

programme is to promote energy conservation. Mathiowetz et al (in press) report efficacy in terms of increased use of strategies to conserve energy, and reduced severity and impact of fatigue among participants. The findings are encouraging as fatigue is often a debilitating symptom of the disease. This paper discusses whether there were any differences between the outcomes of people with multiple sclerosis who completed six sessions of the "managing fatigue" programme (n=46) compared to individuals who for one reason or another did not attend all six face-to-face sessions, and received a module to self-study whenever they missed a session (n=49). The authors make a retrospective comparison of how these two naturally occurring groups of patients fared with respect to the same outcome measures. After taking account of multiple comparisons, it was found that there were no significant differences between the two groups in outcome. This suggests that self-study is a useful means of educating patients if they miss part of the community based program. As the authors suggest, further investigations may establish whether self-study alone could provide a suitable alternative to group based study. Self-study through distance learning (sometimes, including elements of group work) has become a popular enabling tool within education. To some individuals, a group situation may fulfil social support needs whereas for others, self-help could be more empowering. Interesting further studies could look at psychological and social factors influencing an individual's choice of health study method. - LAJ

Lamb AL, Finlayson M, Mathiowetz V.

The outcomes of using self-study modules in energy conservation education for people with multiple sclerosis.

CLINICAL REHABILITATION
2005;19:475-81.

PARKINSON'S DISEASE: A shot in the arm

The treatment of chronic neurodegenerative disorders of the CNS has always been a subject of much research and many different strategies. This could involve reducing pathology by either targeting the pathogenic pathway or the pathogenic product. Alternatively one can try to restore function by enhancing plasticity or replacing the lost cells. In PD all these approaches have been undertaken with the exception of trying to get rid of the pathogenic proteinaceous mediator of the disease, in part because we are not quite sure what this is. However over recent years a central role for alpha synuclein and the Lewy body in this process seems probable (Harrover et al, *Experimental Neurology* 2005; July 13th epub), and thus one strategy is to get rid of the abnormal alpha synuclein. Obviously this is easier said than done, given that alpha synuclein in its normal state must fulfil an important role in the CNS. Ways to achieve this might be using interfering RNAs or immunising against alpha synuclein as has been tried for amyloid in Alzheimer's disease. It is this later approach that Masliah et al have tried in a recent paper in *Neuron*. In this study they immunised a transgenic synuclein mouse model of Parkinson's disease and demonstrated that this immunisation induced variable antibody responses. In those mice that produced high levels of antibodies there was less alpha synuclein present, presumably because of its increased clearance via a lysosomal pathway. There was no behavioural aspect to the study and it was not clear what this means in terms of disease progression and expression, nor is it clear how the antibody could actually get inside cells to remove the alpha synuclein. What it does do however is suggest that immunisation strategies may have a role to play in the treatment of neurodegenerative conditions and where there is widespread pathology coupled to a core pathogenic protein. - RAB

Masliah E, Rockenstein E, Adame A, Alford M, Crews L, Hashimoto M, Seubert P, Lee M, Goldstein J, Chilcote T, Games D, Schenk D.

Effects of alpha-synuclein immunization in a mouse model of Parkinson's disease.

NEURON

Jun16;46(6):857-68.

APHASIA: measuring outcome

Assessment of the outcome of intervention is generally deemed a good thing, in theory at least. The practice in many areas of healthcare is rather less straightforward as a result of what the authors of this article term 'the complexity and multidimensionality of clinical outcomes measurement'. The challenge of outcome measurement in aphasia therapy, where meaningful initial assessment can take several hours, is the focus of this American survey. The authors distributed the survey electronically to mailing lists of therapists working in aphasia, an approach which reached a fairly large number of potential participants (roughly 1000), of whom about 100 responded. The

results, while not entirely surprising, highlight ongoing tensions between well-recognised theory and limitations on full implementation of the theory. Somewhat unexpectedly, only 85% of respondents reported that they undertook outcome measurement in aphasia. One wonders what the other 15% are thinking. Be that as it may, the most frequently reported barrier to measuring outcome in individual clients was time constraints, occasioned particularly by caseload and other administrative issues. Interestingly, in this American context several respondents reported that re-evaluations were not funded. The focus of the majority of outcome assessment was reported to be re-evaluation of abilities in individual clients (as opposed to group/cohort/population outcomes), with none of the respondents interpreting outcome in terms of cost or amount of therapy associated with specific language improvement. A high proportion of therapists used a combination of both formal linguistic reassessment and social participation measures. Having said this, only a small proportion (12%) cited the WHO framework as philosophical background to their approach. The authors' interpretation of the survey results focuses on the continuing need for 'a coherent model of outcome assessment to guide the choice of outcome assessment tools and the management of outcome data'. They argue that the WHO International Classification of Functioning, Disability and Health, while in need of expansion to accommodate issues specific to communication, provides the most logical platform for just such a coherent model. - RB

Simmons-Mackie N, Threats TT, and Kagan A.

Outcome assessment in aphasia: a survey.

JOURNAL OF COMMUNICATION DISORDERS
2005;38:1-27.

EPILEPSY: new drugs safe to OD?

Depression is common in epilepsy and attempted suicide flows from this accounting for 13% of epilepsy-related deaths over several studies. From 1979-1985 one study reported that 18% of antiepileptic drug (AED) overdoses had a fatal outcome (however this was done before the new AEDs appeared). Now we have data on non-accidental overdoses of the newer AEDs from Ireland from 1996-2000. Nearly all patients took more than one drug (these are often prescribed as add-on therapy). The number of cases for each drug was Gabapentin 33; Lamotrigine 97; Levetiracetam 1; Tiagabine 5; Topiramate 7; and Vigabatrin 21. None of these overdoses had a fatal outcome. It is probably easier to kill a rat by suffocating it in a vat of gabapentin pills than by trying to give it an overdose and one human has taken 100g of topiramate and survived. Fatalities have been reported with lamotrigine but overall this group of drugs seems safer than older ones and might influence choice of drug in patients with a significant suicide risk. By contrast, as little as 6g of Phenobarbital can be fatal. - MRAM

Sukumaran S, Herbert J, Tracey J, Delanty N.

Safety of newer generation anti-epileptic drugs in non-accidental overdose: an Irish population study.

SEIZURE

2005;14:151-6.

HUNTINGTON'S DISEASE p53 is linked pathogenesis

*** RECOMMENDED

A recent study in *Neuron* reveals a specific role for p53 in Huntington's disease (HD) pathogenesis. The work carried out by Bae et al. provides compelling evidence that p53 is the molecular link between the nuclear pathology and mitochondrial abnormalities associated with Huntington's disease. The tumour suppressor function of p53 is well established but Bae et al. hypothesised its involvement in HD pathogenesis for several reasons. First, it is a nuclear transcription factor that plays a central role in cellular stress response. HD is an autosomal dominantly inherited disease, which is characterised by nuclear pathology. The disease-causing mutation results in an expansion of the polyglutamine repeat region of the Huntingtin protein (Htt), which causes the mutant protein to misfold and aggregate as intranuclear inclusion bodies. Second, p53 regulates mitochondrial genes; the net result of its actions is to alter the permeability of the outer mitochondrial membrane. Multiple lines of evidence have implicated mitochondrial dysfunction in HD pathogenesis. Third, elevated levels of p53 have been detected in brain tissue of several neurodegenerative diseases, including Alzheimer's disease, and p53 overexpression elicits cell death in primary cortical cultures. This study demonstrated an upregulation of nuclear p53 protein levels in mutant Htt-expressing cells, a transgenic HD model and also in cerebral cortical and striatal tissue of HD patients. The increase in

p53 was proposed to be due mainly to post-translational stabilisation of p53 by mutant Htt, rather than transcriptional upregulation. This increase in p53 levels resulted in more p53 transcriptional activity, so that downstream targets of p53 including the apoptotic effector, Bax, were also detected at elevated levels. Functionally, augmented p53 was demonstrated to mediate mitochondrial dysfunction in HD cells and HD transgenic animals. Enhanced mitochondrial membrane depolarisation in HD lymphoblasts and mutant Htt-expressing cells was reversed by a specific p53 inhibitor (pifithrin), RNA interference targeted against p53 and p53 gene deletion. In the HD transgenic mice, impaired mitochondrial complex IV activity was also partially rescued by inhibiting p53 pharmacologically and genetically. Interestingly, p53 was shown not to be involved in nuclear aggregation of mutant Htt. It was also shown that p53 mediates mutant Htt-induced neurotoxicity in vivo. By crossing HD animal models onto a p53 null genetic background the neurodegenerative phenotype was improved. For example, in HD transgenic mice, neurobehavioural deficits characteristic of this HD model, including hind limb dyskinesia, were normalised by genetic deletion of p53. These findings suggest that p53 mediates mitochondrial dysfunction, cell death and behavioural abnormalities associated with HD in vivo. In contrast to its anti-cancer function, this work also identifies p53 as a molecular mechanism that links nuclear transcriptional dysregulation and mitochondrial abnormalities specific to HD. This study demonstrated a direct interaction between mutant Huntingtin and p53 in vitro, which suggests that identification of protein domains that mediate binding between these two proteins may provide important targets for HD therapeutics. - *LMS & SJT*

Bae B, Xu H, Igarashi S, Fujimuro M, Agrawal N, Taya Y, Hayward SD, Moran T, Montell C, Ross CA, Snyder SH, Sawa A.

p53 mediates cellular dysfunction and behavioural abnormalities in Huntington's Disease.

NEURON

2005;47:29-41.

REHABILITATION: Sing, sing a song...to improve expression of emotion after TBI

Impaired intonation (defined here as the rise and fall in pitch over time within a spoken phrase) in voice production can be one residual impairment affecting quality of life after traumatic brain injury (TBI). Individuals with reduced intonation can be at risk of being misunderstood, being unable to engage and maintain conversations and thus at risk of social isolation. There is some research to support the benefit of music therapy for a range of neurological disorders but studies in this area are limited. This small study of four individuals after severe TBI looked at short and long-term change in characteristics of intonation, which can be recorded and analysed digitally (the pitch control, F0, F0 variability and F0 range), as well as influences of change of mood on these characteristics. Each subject received 15 sessions of 40-50 minutes over 5-8 weeks with a music therapist who sang along and accompanied on guitar – though it is not clear if with the same therapist. Individuals could pick their own three songs that were used for all sessions. The study did show some long-term benefit in intonation and reduced feeling of tension but there was considerable variability between individuals. However in the short term, there was an unexpected drop in post-session mood and intonation scores compared to pre-session scores. They attribute the mood changes to the themes of the lyrics and advise of the need for emotional support for individuals after their sessions. There was no comment on whether individuals practiced singing on their own or with family/carers outside of the sessions or the possibility of using these resources in practice. It is an interesting theme that needs some more development and research evidence before considering it as a valid part of a rehabilitation programme. - *JMCF*

Baker F, Wigram T, Gold C.

The effects of song-singing programme on the affective speaking intonation of people with traumatic brain injury.

BRAIN INJURY

2005;19(7):519-28.

PARKINSON'S DISEASE: Post-mortem study of successful fetal grafts

Clinical trials for neural transplantation in Parkinson's disease (PD) began in 1987, with some positive results, and this led to two double-blind clinical trials (Freed et al, 2001; Olanow et al, 2003). In these studies, minimal benefit was reported, although younger patients did better and there were significant side effects such as off-state dyskinesias. There were, however, many method-

ological differences between these two trials and several open label trials including: amount of tissue used, storage time of tissue prior to grafting, use of solid grafts as opposed to cell suspension, little or no immuno-suppression and short follow-up. Post mortem examination has been performed on some of these patients (Olanow et al, 2003) and shown prominent inflammatory reactions around the graft. It has been proposed that the high levels of class I human leukocyte antigens present in the capillaries of the donor solid graft contribute to this immune reaction, which may in turn account for the poor clinical outcome. This study describes, for the first time, post mortem results of two patients grafted with a cell suspension, who died from a myocardial infarction (patient 1) and acute renal failure possibly due to renal cell carcinoma (patient 2), 3-4 years after surgery. Tissue from two to four donor 6-9 week old fetuses (2.6-3.2 million cells in patient 1 and 4.8 million cells in patient 2) was transplanted into the postcommisural putamen (patient 1) and striatum (two deposits from the caudate to putamen and four into the postcommisural putamen as for patient 1) and dorsostral SN (patient 2) with a dopaminergic cell survival rate of around 15-30%. Grafts were stored for 6 days, in glial cell derived neurotrophic factor (GDNF) prior to transplantation. These patients (aged 69 and 59) had a good clinical response to grafting, supported by 18F-DOPA PET. The patients received 6 months of immunosuppression (the same time course as the Tampa/Mount Sinai trial - Olanow et al, 2003). There was no inflammatory reaction around the graft (except for a small glial scar in patient 2), as measured by the microglial antigens CD45 and CD68 and astrocytic markers. The grafts were found to densely re-innervate the striatum. The authors found that substantia nigra pars compacta (SNpc) neurons (from region A9), which express the potassium channel protein, Girk2, made up 40-50% of the surviving tyrosine hydroxylase positive (TH+) neurons, and ventral tegmental area (VTA) neurons (region A10), expressing calbindin, comprised 10-20% of the total. Calbindin positive dopaminergic neurons project to the limbic nucleus accumbens and are relatively spared in PD, and animal studies have shown that only the SNpc subtype can re-innervate the striatum. SNpc neurons were expressed around the circumference of the graft, where they could make connections with the host striatum. Interestingly, the midbrain graft contained 4-8% surviving dopaminergic neurons and a lower ratio of SNpc/VTA neurons. The favourable clinical outcome post grafting, and 18F-DOPA PET appearance, was attributed to the good survival of the graft, and dense re-innervation of the target striatum by the higher proportion of area A9 SNpc neurones from the edge of the graft. This favourable outcome may have been due to the use of cell suspension, rather than solid grafts, and the handling of the tissue, such as incubation in GDNF. This post mortem study demonstrates that grafts can survive and appear to appropriately re-innervate the host striatum, and that specific methodological considerations can lead to favourable outcomes. - *WP*

Freed CR et al (2001) *N Engl J Med*, 344: 710-719.

Olanow CW (2003) *Ann Neurol*, 54: 403-414.

Mendez I, Sanchez-Pernaute R, Cooper O, Vinuela A, Ferrari D, Bjorklund L, Dagher A, Isacson O.

Cell type analysis of functional fetal dopamine cell suspension transplants in the striatum and substantia nigra of patients with Parkinson's disease.

BRAIN

2005;128:1498-1510.

DEMENTIA: tau deposition irrelevant?

Transgenic mice expressing the P301L variant of human tau have previously been described: they develop progressive age-related neurofibrillary tangles (aggregates of tau phosphoprotein), neuronal loss and behavioural impairment. This paper reports a new mouse model characterised by a suppressible transgene with a doxycycline-responsive element placed upstream of P301L tau. The authors observe that suppression of the transgenic tau (by doxycycline) results in improved memory function (water maze performance) and in stabilisation of neuronal numbers. Their key finding is that histopathological examination of brains from mice that show memory recovery following tau suppression revealed as much abnormal tau deposition as in the unsuppressed tau animals. The latter, by contrast, showed severe memory impairment and had marked brain atrophy. Neurofibrillary tangles are among the commonest pathological lesions found in the brains of patients with neurodegenerative disease. They have been implicated in neuronal death and cognitive dysfunction. This elegant study by Santacruz and colleagues shows, however, that tangles in themselves may be insufficient to cause cognitive decline or neuronal death. A criticism of the paper is that, perhaps because of limited space, the clinical background is focused on Alzheimer's disease (AD). Human kindreds with the P301L tau mutation, however, do not show clinical features of AD

but rather frontotemporal dementia (FTD) with parkinsonism. Neither is there mention of beta amyloid plaques, which are as much a feature of AD pathology as neurofibrillary tangles (or of the continuing challenge of producing a mouse model manifesting both plaque and tangle pathology). The point is that tau involvement in the pathogenesis of FTD, the disease most closely resembled by the new mouse, may differ from that in AD. Tangle 'load' correlates with cognitive impairment in AD but familial AD is caused by genes in the amyloid-beta system. Thus, abnormalities of soluble tau are likely to be important early in the pathogenesis of FTD while tau aggregates may be relevant later in the pathogenesis of AD. Though much can be learnt from transgenic animals, care must always be taken when extrapolating to human diseases. - RD

Santacruz K, Lewis J, Spire T, Paulson J, Kotilinek L, Ingelsson M, Guimaraes A, DeTure M, Ramsden M, McGowan E, Forster C, Yue M, Orne J, Janus C, Mariash A, Kuskowski M, Hyman B, Hutton M, Ashe KH.

Tau suppression in a neurodegenerative mouse model improves memory function.

SCIENCE

2005;309(5733):476-81.

TREMOR: Alcohol for ataxia in Essential Tremor?

The beneficial effects of alcohol on upper limb tremor in essential tremor (ET) are already well recognized by patients and clinicians. Klebe and colleagues, from Germany, looked at the effects of alcohol on tremor and ataxia of 16 patients with ET and 11 matched controls. Clinical measures of tremor and ataxia, as well as instrumental measures (using gait analysis) were taken before and 30 mins after ingestion of 0.25mL of 10% alcohol (a typo? – presumably 0.25L, a large glass of table wine). In the patient group, the ataxia score during tandem gait declined significantly ($p < 0.05$), from a mean of 24.7 to 18.2 while worsening slightly but not significantly in the controls (12.6 to 15.1). The rate of missteps during tandem gait was significantly reduced from 8.8 per minute to 5.6 per minute among patients and increased (non-significantly) from 0.4 to 0.7 among controls. They also note the lack of correlation between the clinical and instrumental measures of ataxia, and the severity of leg tremor. In addition to this, they claim the lack of effect of alcohol on leg tremor (at variance with their data), supports the argument that ataxia is independent of tremor severity and alcohol does not improve ataxia through its effect on tremor. More credibly, they conclude their study does not support the 'neurodegeneration hypothesis' of ET. This paper is helpful in elucidating the pathogenesis of ET and the effects of alcohol, however we don't know if alcohol has any functional day-to-day benefit on ataxia as opposed to tremor symptoms for patients with ET. [And as the authors caution, higher doses of alcohol impairs cerebellar function and a dose-response study "was not practical". I don't think one would have too much difficulty recruiting subjects for such a study!] - JMCF

Klebe S, Stolze H, Gensing K, Volkman J, Wenzelburger R, Deuschl G.

Influence of alcohol on gait in patients with essential tremor.

NEUROLOGY

2005;Jul 12;65(1):96-101.

COGNITION: A case of vision-touch synaesthesia

Blakemore and colleagues are the first to describe a case of vision-touch synaesthesia, and they compared this subject with 12 controls in a functional MRI study. When the subject, C, observes someone being touched, she perceives the same touch on herself. Astonishingly, C was not aware that this was unusual. C has a cousin who also has vision-touch synaesthesia, and several female relatives with grapheme-colour synaesthesia. C herself had the more common grapheme-colour synaesthesia when she was younger, but no longer experiences this. The tendency for synaesthesia to run in families has been noted previously and it is interesting that different forms of synaesthesia appear in her family and change even in herself, raising the possibility that the tendency to synaesthesia may be general rather than modality specific. The authors aimed to investigate the neural activity to the observation of touch to the face and neck of a human or object and the somatosensory topography of any activation, both in C and in non-synaesthetic controls. Subjects were scanned while being touched on the face or neck by a piece of felt on the end of a stick; while watching images of a human face or neck being stroked by a finger, or watching objects with a 'face' and 'neck' (such as an electric fan) being stroked by a finger. Based on previous studies, the authors made several predictions: the somatosensory cortex would be activated by observing humans more than objects, this activation would be somatotopic, these activations would be higher in C and finally, additional areas would be activated

in C. When subjects were touched, the somatosensory regions SI and SII, the parietal cortex, the premotor cortex and the motor cortex were activated. In controls, the mere observation of touch resulted in activation of the superior temporal sulcus (STS) at the temporoparietal junction especially on the right, the fusiform gyrus, bilateral primary and secondary somatosensory cortices in a somatotopic fashion, and the premotor cortex. Activation was greater when observing humans versus inanimate objects, and in C. The anterior insula was also activated in the synaesthetic subject, C. It is known that the STS and fusiform gyrus are activated in response to faces and might form part of a mirror system (whereby neurons which execute a function are activated during the observation of the same function). The premotor cortex may also form part of a mirror system. It has been suggested previously that mirror systems are particularly sensitive to biological motion, and this study suggests that it is also sensitive to biological targets and as such, biased towards 'social' actions. Three main theories were mooted for C's pattern of activation. First, there could be increased activation in the normal 'mirror system'. Second, there could be direct connections between C's visual and somatosensory areas. Third, there may be hyperactivation of 'bimodal cells' in the STS, which respond to both vision and touch, and could be sufficient to produce the synaesthetic response. The first theory was deemed most likely, primarily due to the activation seen elsewhere, remote from the STS and somatosensory areas. The authors postulated that the normal mirror system allows us to understand the effect of tactile stimulation on others. When a threshold is reached, as in C, this activation results in conscious perception, explained also by activation in the anterior insula, which is associated with self-processing. The cynics among us, and in our journal club, might postulate that she perceives touch in response to observation of touch, along with the neural correlate simply by directing extra attention to the perception of touch. You decide! - WP

Blakemore SJ, Bristow D, Bird G, Frith C, Ward J.

Somatosensory activations during the observation of touch and a case of vision-touch synaesthesia.

BRAIN

2005;128:1571-83.

BRAIN INJURY: Who, when and how to screen and treat for pituitary deficiency after TBI

*** RECOMMENDED

Though figures vary, studies in recent years show that pituitary function is impaired in at least 20-30% of patients following traumatic brain injury (TBI). Yet for physicians (usually rehabilitation) caring for these individuals, there has been great uncertainty on what to do in practice. Limited evidence, the overlap of symptoms of hypopituitarism and TBI (e.g. fatigue, memory and concentration impairment) as highlighted in this paper, and until now, no published guidelines in this area have contributed. This group, comprising recognised neuroendocrinologists and rehabilitation physicians from around the Western World, met in 2003 to develop consensus guidelines and to raise awareness and education amongst professionals and patient groups. They review the evidence published so far in each area of screening, treating and follow-up with many references. Apart from clinical indications, they recommend prospective routine testing of pituitary function at 3 and 12 months in all patients hospitalised after TBI, as well as single retrospective evaluation and testing on those >12 months post (moderate or severe) injury. However they do acknowledge the need for further clarification on who is at most risk and the debate over classification of severity of TBI. Specific basal pituitary hormone tests are recommended but the need for collaboration at local level between endocrinologists and rehabilitation physicians is advocated. They discuss the issue of natural history and the controversies of hormone replacement, yet summarise practice recommendations in helpful flow charts. Although receiving an unrestricted grant from a pharmaceutical company, this paper is balanced in its discussion of the controversies, especially in relation to growth hormone replacement, and on the recommendations made in this area. For all clinicians treating individuals after a TBI, it's a worthwhile read and a challenge to become involved in the development and implementation of suitable outcome measures for efficacy studies. - JMCF

Ghigo E, Masel B, Aimaretti G, Leon-Carrion J, Casaneuva FF, Dominguez-Morales MR, Elovic E, Perrone K, Stalla G, Thompson C, Urban R.

Consensus guidelines on screening for hypopituitarism following traumatic brain injury.

BRAIN INJURY

20 August 2005;19(9):711-24.

Biosensor enables breakthrough in the study of respiration control

A breakthrough study in the fields of neurophysiology and respiration, made possible by the sarissaprobe™-ATP from Sarissa Biomedical, was recently published in Nature. The experiment unveiled the exact location in the brain in which ATP mediates the breathing response. This major study also confirms the power of the sarissaprobe™-ATP biosensor to precisely measure purine production in real-time biochemical reactions in both in vitro and in vivo experiments.

With the sarissaprobe™-ATP, it is possible for researchers to obtain precise quantitative measurements on the amount of purines generated during biochemical reactions. More importantly, these micro-scale probes are



enabling researchers to pinpoint exactly where and when these substances are being produced in both in vitro experiments and in minimally invasive in vivo procedures. This is the first time scientists have been able to simultaneously obtain robust spatial, temporal, and quantitative measurements of purine produc-

tion – a crucial link in the process to gain full understanding of biochemical functions.

Dr Brian Stammers, CEO of Sarissa Biomedical, explains, “Being able to detect exactly where, when, and how much of a specific purine is produced during a biochemical reaction is of tremendous importance to the neuroscience community. The sarissaprobe™ line of biosensors will accelerate man’s ability to understand how chemical signalling in the brain mediates the central nervous system’s control over breathing, pain perception, blood glucose regulation, and many other internal state conditions.”

For more information
Email. b.m.stammers@sarissa-biomedical.com

Increased production of world’s fastest confocal microscope

In response to customer demand, Carl Zeiss has ramped up production of the LSM 5 LIVE confocal laser scanning microscope. This confocal system allows the visualisation of very fast processes in living cells at speeds up to 200 times faster than possible before and launched at a time of increasing focus on live cell imaging worldwide.



LSM 5 LIVE was premiered at the end of 2004 at the American Society of Cell Biology meeting in San Diego. Launched in Europe and the Far East just weeks later, the high speed imaging and fluorescence capabilities of the new instrument

have generated a plethora of interest. New production logistics and increased production capacities at Carl Zeiss are now being activated to cope.

“For the first time ever, scientists can capture dynamic processes in living specimens with a time resolution down to one millisecond. It is a major benefit and provides researchers with fundamentally new possibilities for experiments in biology and medicine,” says

Aubrey Lambert, Marketing Manager at Carl Zeiss UK.

For further information
Tel. 01707 871233, or
Email. a.lambert@zeiss.co.uk

Need more lab space?

The NeuroLog System provides researchers with a versatile and modular electrophysiology system ideally suited to a range of applications, such as intracellular and extracellular recording, isolated EEG or EMG amplification as well as pulse generation and signal conditioning tasks. However, the standard NeuroLog System Case & Power Unit (NL900D) has space for up to 13 modules and some of you may find your particular application only requires 3 or 4 modules.



As a result, Digitimer have recently designed a Compact Case & Power Unit (NL905) which will be ideal for applications requiring no more than 4 modules. The NL905 is fully compatible with existing NeuroLog System modules, incorporates many of the features included in the NL900D, but is a fraction of the size.

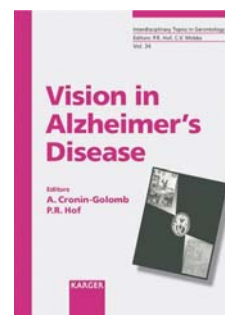
For more information on the NeuroLog System NL905 or any Digitimer products, Tel. 01707 328347 or
Email. sales@digitimer.com

New Volume of the Interdisciplinary Topics in Gerontology Series

Visual dysfunction is prevalent in Alzheimer’s disease and in related disorders such as posterior cortical atrophy and Down syndrome. The neuropathology of these disorders affects brain areas that process low-level vision as well as higher-order cognition and attention.

This volume spans the range of topics on vision, from structure (retinal and cortical) to function (cortical activation) to behaviour (perception, cognition, hallucinations, and everyday activities). The chapters together indicate that lower-level visual deficits can contribute to, or masquerade as, higher-order cognitive impairments. An emerging theme is that the study of variations in visual-system pathology, behaviour, and genetic risk will likely provide insights into typical Alzheimer’s disease as well as related conditions. The visual disorders of Alzheimer’s original case and its 21st century cousins have much to teach us about the changing visual system in ageing and age-related neurodegenerative disease.

For more information see www.karger.com/itoge



Expanding range from Quadragech

Quadragech distribute List Biological Laboratories exotoxins for cell stimulation and neurological research. This expanding range now includes new recombinant Type A and Type B light chains from Botulinum neurotoxin, and recombinant tetanus Toxin light chain. Recently List have also launched two unique products; SNAPtide™ quenched fluorogenic peptide substrate to detect SNARE protein cleavage by botulinum toxins and MAPKtide™ a synthetic peptide containing a cleavage site for anthrax lethal factor.

A full listing of products can be found through the website www.quadragech.co.uk, or
Tel. 0208 786 7811.



Elekta and Medical Intelligence form international distribution partnership

Elekta, a leading supplier of clinical solutions, comprehensive information systems and services for improved cancer care and management of brain disorders, has announced a global distribution agreement with Medical Intelligence (MI), a single-source supplier of high-precision patient fixation systems. Integrating key elements of MI's radiotherapy and patient positioning systems into its own product portfolio, the agreement reinforces Elekta's position as the world's most comprehensive provider of complete solutions for stereotactic radiation treatment throughout the body.

Among the products from MI is HexaPOD™



Elekta Synergy® S, courtesy of Elekta



Medical Intelligence HexaPOD

RTC, an image guided robotic patient positioning system that allows for sub millimetre patient positioning with six degrees of freedom (6D). 6D means that the system can correct rotational errors in patient positioning as well

as translational errors, making it ideal for the very high accuracy required for stereotactic radiosurgery (SRS) and stereotactic radiation therapy (SRT).

Integrating HexaPOD with Elekta Synergy® S for image-guided SRS and SRT will enable clinical staff to accurately position patients with a previously unattainable level of certainty. Elekta Synergy® S includes X-ray volume imaging,

the first system to allow three-dimensional imaging of the tumour and its surrounding soft tissues at the time of treatment.

For further information Tel. 01293 654413 or Email. amanda.deighton@elekta.com

2 out of 3 Universities prefer Carl Zeiss

In a recent tender and framework agreement, Carl Zeiss confocal microscopes were chosen by 9 out of the 13 British universities.

"The fact that more than 2 out of 3 Universities freely chose Carl Zeiss laser scanning microscopes underscores the technological leadership and customer service benefits associated



with our high performance systems," says Aubrey Lambert, Marketing Manager, Carl Zeiss UK.

Martin Lightbown, Head of Purchasing and Insurance at the University of Warwick, which managed the procurement process on behalf of the Higher Education Funding Council for England, commented,

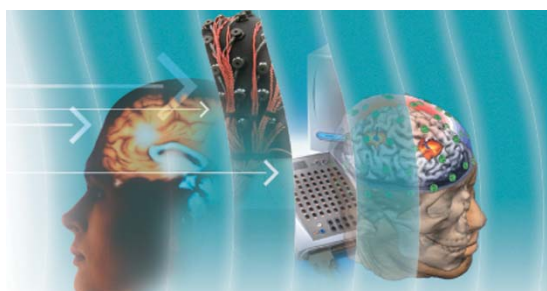
"The aim of the procurement exercise was to

offer participating institutions best value whilst meeting their high expectations. The relationship between Warwick and Zeiss played a major part in not only meeting those aims but in exceeding them."

Carl Zeiss' success in satisfying customer requirements comes hard on the heels of other much-coveted national and international awards, such as The R&D 100 Award, The Scientist's Choice, The Readers Choice Award and the Microsoft .NET Solutions Award.

For further information Tel. 01707 871233, or Email. a.lambert@zeiss.co.uk

EEG and MRI integration



Advanced Medical Equipment will be presenting the fMRI Boot Camp SCAN school in London from 19-23 September, 2005. This is a five day course for individuals with moderate to advanced levels of expertise with Neuroscan products, but with specific interest in simultaneous acquisition of EEG and fMRI. The course will be held at the Royal Holloway in Egham, Surrey. The last two days of this school will be focused on Curry5, the latest version of the most advanced software for Multimodal imaging and Source localisation.

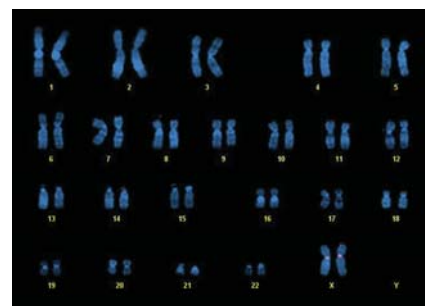
You can also meet with Advanced Medical Equipment at the British Association for Cognitive Neuroscience and fMRI experience, at Aston University, Birmingham, on 13th September. AME will be presenting a Workshop entitled 'Recording and Processing Data in Hostile Territory.' See www.fmriexp.com/7/

For more information on either of these events Tel. 01403 260156, or Email. admin@advancedmedicalequipment.com

Probing DNA with cytogenetic analysis software

Nikon Instruments Europe and HESP Technology have formed a collaborative partnership to provide powerful software for cytogenetic analysis. The Genikon system facilitates the acquisition and interpretation of results from manual and automated karyotyping and spot counting, fluorescence in situ hybridisation (FISH), multicolour fluorescence in situ hybridisation (mFISH), and comparative genomic hybridisation (CGH). In addition, its flexible archiving and database structure allows this system to be used in a true networking environment from a variety of locations, making it ideal for researchers, cytogeneticists, pathologists and haematologists working with chromosomes using DNA, Cancer and Leukaemia probes.

With the capacity for manual and automatic karyotyping (R, Q, and G bands), Genikon makes sense of the tangle of chromosomes from a metaphase spread. The karyotyping software module separates single or



An example screen shot of Genikon software's automatic karyotyping (R, Q and G bands) making sense of the tangle of chromosomes from a metaphase spread.

multiple overlapping chromosomes, aligns centromeres, and rotates chromosomes for easy quantification and ideogram comparison. Chromosome edges can be sharpened using an eraser tool and chromosomes may be zoomed up to 2X magnification. Contrast can be modified during and after acquisition using special filters, and annotations (text or arrows) can be added at any stage.

For more information Email. discover@nikon.co.uk

Help keep migraines and patients apart

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migraine frequency by:

- $\geq 50\%$ in 46%
of patients¹
- $\geq 75\%$ in over 25%
of patients¹



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 μ g 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:** PLM **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 4JH, UK. **Date of text revision:** August 2005. **APIVER150805.** **Reference:** 1. Bussone G, Diener H-G, Pfeil J *et al.* Topiramate 100mg/day in migraine prevention: a pooled analysis of double blind randomized controlled trials. *J Clin Prac* 2005; 58(8): 961-968.