ISSN 1473-9348 Volume 5 Issue 2 May/June 2005

ACNR

Advances in Clinical Neuroscience & Rehabilitation

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

Alasdair Coles is co-editor of ACNR. He has recently been appointed to the new position of University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

Stephen Kirker is the editor of the Rehabilitation section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.

David J Burn is the editor of our conference news section and Consultant and Reader in Movement Disorder Neurology at the Regional Neurosciences Centre, Newcastle upon Tyne. He runs Movement Disorders clinics in Newcastle upon Tyne. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

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

Alastair Wilkins is our Case Report Co-ordinator. He is Specialist Registrar in Neurology in Cambridge. His main research interests are the study of axon loss in multiple sclerosis and the molecular biology of axon-glia interactions in the central nervous system.

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

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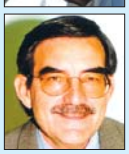


Professor Hermann Stefan, Germany: Professor of Neurology / Epileptology in the Department of Neurology, University Erlangen-Nürnberg, andspecialises in the treatment of epilepsies, especially difficult to treat types of epilepsy and presurgical evaluation, including Magnetic source imaging (MEG/EEG)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

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

This issue of ACNR contains review articles on inflammatory neuropathies by Michael Lunn, and the intracellular processes underlying neurodegenerative disorders by Sarah Tabrizi and Mark Kristiansen. In his clinical review article, Michael Lunn concentrates on GBS and discusses the variants of this disease and their possible aetiologies, including immunopathogenesis. In particular he discusses the relative contributions of antibodies and T-cells in these different types of GBS and concludes with a section on treatment. This succinct account by Michael is based on his extensive research and is complimented by a recent case report of an unusual case of GBS, which can be found on ACNR's website.

In the second review article, Sarah Tabrizi and Mark Kristiansen give us a state of the art account of the mechanisms that underlie cell death in neurodegenerative disorders. They focus on prion diseases, Huntington's and Parkinson's disease and make the valuable point that whilst mechanisms of cell death in these diseases may have similarities they may also be multifactorial, and that these factors may be different in each of the conditions. Furthermore they tackle the thorny issue of the role of the UPS in neurodegeneration and in particular discuss whether dysfunction of this pathway is a primary pathogenic process, or a consequence of a cell loaded with misfolded abnormal proteins.

Peter Whitfield, in his series on neurosurgery, leads us through modern developments in frameless stereotactic techniques for tackling brain lesions. This is a clear account of an emerging technology that may be familiar to those involved in surgery, but is certainly a real education to those outside this discipline.

The link between art and neurology is a strong one, both historically and in the present age. Thus I review Ian McEwans latest novel, whilst Andrew Larner takes us back to the novels of Jane Austen and the plays of Anton Chekhov. Once more Andrew displays his impressive literary knowledge in another unique account, which has clearly involved a close reading of the text. Whilst we are discussing this, don't forget the competition we advertised in the last issue of ACNR, which invites you to contribute to this fascinating area, by writing about a novel which deals with some aspect of neuroscience.

In the neuropathology article, Federico Roncaroli takes us on an extensive tour of MS pathology, touching on pathogenic mechanisms and different types of this disease. This includes discussing curious entities such as Balo's concentric sclerosis and Schilder's disease. These are conditions with which we are familiar, although in reality I have often struggled to know how they relate to MS.

Thomas Bak engages with the issue of aphasia or dysphasia in the Cognitive Primer series. We are very fortunate to have such an expert discuss this aspect of language, and the article is a real education in the problems and issues underlying the different types/forms of dysphasia. This article highlights not only areas of contention but is of immense practical help to everyone involved in the neurological assessment of patients with language deficits.

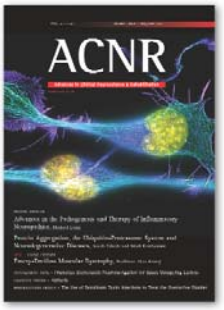
In the rehabilitation section of the journal, Clare Fowler and colleagues have written a very interesting account on the novel use of botulinum toxin in treating bladder detrusor overactivity. This is not only very practical in its content, but it shares with us the very latest data on this innovative technique from the leading Uro-neurological service in the UK.

The conference reports in this issue of the ACNR have a heavy PD influence but together they provide an excellent update on the recent advances in this disease - especially as there is also a sponsored article on somnolence in PD by Doug McMahon. Furthermore, we have an entertaining account of the latest ABN meeting from Chris Allen and Andrew Larner.

Finally we have our journal reviews and the first in a new series on famous names in neurology by Professor Alan Emery. This account is a very personal one, reliving how he first came across and described the muscular dystrophy that is named after him and Dreifuss. This is a fascinating, inspiring and yet human account and in many ways encapsulates the very essence of what ACNR hopes to convey in its articles and approach to neurology and neuroscience.

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

ACNR is published by Whitehouse Publishing, 7 Alderbank Terrace, Edinburgh EH11 1SX.
Tel: 0131 477 2335 / 07989 470278, **Fax:** 0131 313 1110, **Email:** Rachael@acnr.co.uk
Publisher: Rachael Hansford, **Design & Production Email:** production@acnr.co.uk
Printed by: Warners Midlands PLC, Tel. 01778 391000.



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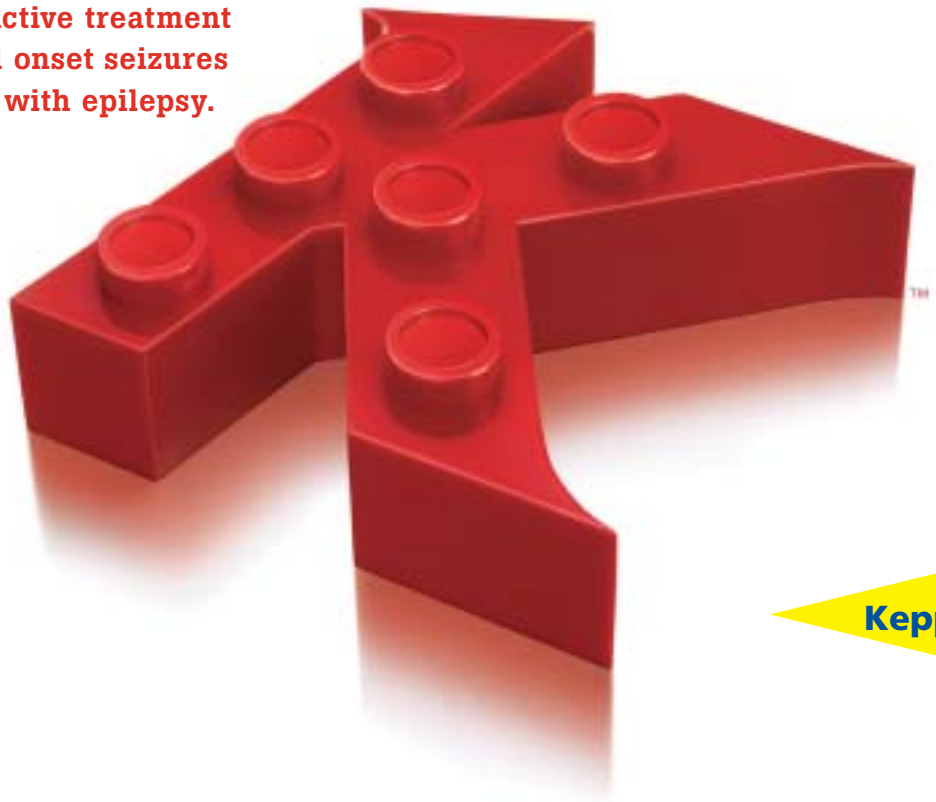

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Date of preparation: September 2004.

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Protein Aggregation, the Ubiquitin-Proteasome System and Neurodegenerative Diseases

Protein aggregation is thought to be the pathological driving force responsible for neurodegenerative disorders such as Alzheimer's, Parkinson's, Huntington's and prion diseases.[1] However, it is not yet clear whether, or to what extent, the misfolded proteins are the cause of the disease rather than the consequence. The aggregated proteins that are characteristic of these diseases have in common the ability to undergo conformational changes and often form fibrillar structures (Figure 1). It is postulated that these proteins may share similar pathways of aggregation. Degradation of intracellular proteins via the ubiquitin-proteasome system (UPS) is a highly complex, temporally controlled and tightly regulated process that plays major roles in a variety of cellular processes and aberrations in this system have been implicated, either as a primary cause or secondary consequence, in the pathogenesis of neurodegenerative disease.[2] This review will give a brief overview of the possible role of proteasome dysfunction and protein aggregation in neurodegeneration.

Prion diseases

Transmissible spongiform encephalopathies (TSEs) or prion disorders are rare fatal neurodegenerative disorders which include Creutzfeldt-Jakob disease (CJD) in humans, bovine spongiform encephalopathy (BSE) in cattle and scrapie in sheep. A hallmark of these disorders is the accumulation of abnormal prion protein (PrP^{Sc}) which is a misfolded form of the normal cellular host prion protein (PrP^{C}). The key pathological features of prion disorders are spongiform degeneration of the brain, massive neuronal loss, astrogliosis, and the accumulation in the CNS of PrP^{Sc}. However the precise cause of neurodegeneration in these disorders is not well understood, and a major gap exists in our understanding of how the conformational conversion of PrP^{C} to PrP^{Sc} ultimately kills neurons.

Lindquist and colleagues have suggested a novel mechanism involving inhibition of the UPS and altered trafficking of PrP^{C} that may account for prion-associated toxicity.[3] They propose that in neurones misfolded PrP^{C} is retrogradely transported to the cytoplasm via ER-associated degradation (ERAD). Whereas normally PrP^{C} reaching the cytosol would be rapidly degraded, they demonstrated using inhibition of the UPS with high-dose proteasome inhibitors in mouse neuroblastoma N2a cells that cytoplasmic accumulation of large quantities of PrP^{C} resulted in aggregates in the cytoplasm, which acquired properties of partial protease-resistance with self-sustaining properties of replication,[3] thereby inducing neuronal cell death. However other reports argue against this potential neurotoxic species by suggesting that PrP^{C} does not undergo ERAD.[4] Paradoxically one group found retro-translocated cytoplasmic PrP^{C} was actually neuroprotective in primary cultured

Table 1. Neurodegenerative diseases: aggregation in disease

Disease	*Protein deposit – major composition*	*Characteristic pathology*
Prion disease	*Prion protein*	*Extracellular amyloid plaques, intracellular deposits, and occasional synaptic and axonal deposits*
Huntington's disease	*Mutant Huntingtin*	*Intranuclear neuronal inclusions, cytoplasmic aggregates and fibrillar huntingtin fragments*
Parkinson's disease	*α-synuclein*	*Intracellular Lewy bodies, Lewy neurites, fibrillar α-synuclein*
Alzheimer's disease	*Aβ or tau*	*Extracellular neuritic plaques, intracellular neurofibrillary tangles of hyperphosphorylated tau*
Amyotrophic lateral sclerosis	*SOD-1*	*Intraneuronal inclusions, insoluble SOD*

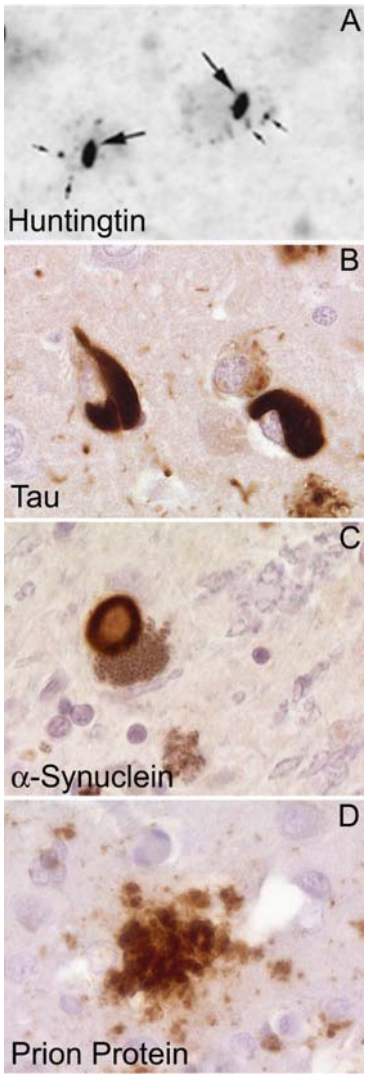

Figure 1: Aggregation in neurodegenerative diseases (A) Immunoreactive aggregates in neuronal nuclei (long arrows) and perikarya (short arrows) localised in Huntington's disease cortex (with permission from Gutekunst et al)[16] (B) Hyperphosphorylated tau forms neurofibrillary tangles in neuronal cell bodies (Hippocampus of Alzheimer's disease brain) (C) Halo immunostaining of Lewy bodies in Parkinson's disease that predominantly comprises α-synuclein. The lighter granular material beside the Lewy body represents the neuromelanin of dopaminergic neurons of the substantia nigra (D) Extracellular plaque in sporadic prion disease stained with anti-PrP monoclonal antibody.

Figure 1

Sarah J Tabrizi studied Biochemistry and Medicine in Edinburgh and then Trained in Neurology at the National Hospital, Queen Square and the Royal Free Hospital, London. She did her PhD, as an MRC Clinical Training Fellow, with Tony Schapira in London studying mitochondrial dysfunction, excitotoxicity and oxidative stress in neurodegeneration. She is currently a Department of Health National Clinician Scientist and Clinical Senior Lecturer in the Dept of Neurodegenerative Disease at the Institute of Neurology. Her laboratory research interests are cellular mechanisms of neurodegeneration, and her clinical interests are in neurogenetics and particularly Huntington's disease.

Mark Kristiansen studied Biomedicine in Liverpool and is currently a final year PhD student in the Department of Neurodegenerative Disease at the Institute of Neurology, University College London. His main research concerns the cellular mechanisms of neuronal cell death in prion disease.

Correspondence to:
Dr Sarah J Tabrizi,
Honorary Consultant Neurologist,
National Hospital for Neurology and Neurosurgery,
Queen Square,
London, WC1N 3BG.
Tel: 0207 837 3611 Ext 4434
Fax: 0207 676 2180
Email: sarah.tabrizi@prion.ucl.ac.uk

Acknowledgements
We are grateful to Professor Sebastian Brandner for Figures B to D.

human neurons by protecting against Bax-mediated cell death.[5] It seems likely that some proportion of misfolded PrP^C undergoes ERAD-proteasome mediated degradation,[6] but is likely to be rapidly degraded and a short-lived species;[7] there is still clearly debate as to whether accumulation of this species is neurotoxic to the cell. It has been reported that proteasome dysfunction occurs *in vivo* in the brains of prion scrapie-infected mice; in this study they found that the level of ubiquitin protein conjugates increased significantly ~144 days post infection when clinical signs first became apparent and that this elevation correlated with a decline in proteasome function.[8] It is likely therefore that proteasome impairment may be important in the pathogenesis of prion disease, but may be unrelated to the accumulation of the wild-type prion protein, and work is ongoing in our laboratory to address this question.

Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease with a prevalence of 4-10 per 100,000 in populations of Western European descent. In 1993, the gene defect associated with HD was identified as a CAG repeat expansion, encoding polyglutamine repeats, within a novel protein *huntingtin*. This highly polymorphic CAG repeat encoding polyglutamine is located in exon 1 and has been shown to range between 10 and 29 copies on normal chromosomes, whereas it is expanded to a range of 36-121 on HD chromosomes. HD is characterised by selective loss of neurons in the striatum and cerebral cortex, and by nuclear and cytoplasmic inclusion bodies of aggregated fragments of N-terminal mutant huntingtin, but it is not clear what role these aggregates play in the pathogenesis of HD. However, there is a striking correlation between the threshold for aggregation *in vitro* and the threshold for disease in humans, consistent with the idea that aggregation is related to pathogenesis.[9] This supports the argument that self-association or aggregation of expanded polyglutamine underlies a toxic gain of function. Bence and colleagues found that mutant huntingtin fragments inhibited proteasome function in intact cells, and the formation of intracellular aggregated inclusions was associated with a further decline in UPS function resulting in a positive feedback mechanism that may explain the rapid loss of neuronal function in many neurodegenerative diseases.[10] Whether a decline in UPS dysfunction alone is sufficient to induce striatal neuronal damage in HD was recently investigated by Seo and colleagues, who found inhibition of the UPS in various brain regions from early and late-stage HD patients and also interestingly in their skin fibroblasts.[11] However, they report that UPS dysfunction is associated with neuronal pathology only when it occurs in parallel with other neurodegenerative pathways involving decreases in brain derived neurotrophic factor levels and defects in mitochondrial respiratory chain complex II, both of which are found in HD brains. A novel method of trying to ascertain whether HD inclusion bodies are pathogenic, incidental or a beneficial coping response has been reported recently by Arrasate and colleagues who developed an automated robotic microscope that returns to precisely the same neuron after arbitrary intervals.[12] They found by studying neurons expressing mutant huntingtin fragments that inclusion bodies were not essential for neuronal death. They argue that inclusion body formation can lead to decreased levels of mutant huntingtin and thus improve survival, and suggest that the toxic species may, in fact, be an intermediate soluble form of the protein.

Parkinson's disease

Parkinson's disease (PD) is a common age-related neurodegenerative disease that is characterised pathologically by extensive selective and progressive neurodegeneration in the substantia nigra (SN) of the midbrain with resultant loss of dopamine in the striatum, and formation of Lewy bodies in the remaining neurons in the SN as well as in a few other brain regions. As well as mitochondrial dysfunction and oxidative stress in sporadic PD, UPS impairment may also contribute to SN dopaminergic pathology. Lewy bodies are cytoplasmic inclusion bodies of fibrillar, misfolded proteins containing ubiquitinated α-synuclein and parkin as the major constituents although proteasome components are often found. Sporadic PD has been shown to be associated with impaired 26/20S proteasomal function and in 2002, McNaught and colleagues showed that inhibition of 26/20S proteasome function resulted in the specific accumulation of α-synuclein and ubiquitin, with the formation of cytoplasmic inclusions that were immunoreactive for these proteins, in dopaminergic neurons in culture.[13] More recently, they showed that proteasome inhibition alone is sufficient to produce a clinical syndrome in rats that closely recapitulates key features of PD and not more widespread neuronal damage.[14] Whether such inclusions contribute to neuronal death or protect cells from the toxic effects of misfolded proteins remains controversial.[15] Genetic defects in UPS protein components have been found linked to familial forms of PD. These cases, although rare, have yielded important information on basic pathogenetic mechanisms in PD[2] and suggest that failure of the UPS to degrade abnormal proteins may underlie nigral degeneration and Lewy body formation that occur in PD. For example, mutations in the gene encoding parkin, which is a ubiquitin protein ligase, have been found to inactivate its ubiquitin ligating activity whereas mutations in the gene encoding UCH-L1 have been shown to lead to a decrease in ubiquitin hydrolytic activity causing a shortage of free ubiquitin resulting in a general impairment of UPS function. α-synuclein has been implicated in both sporadic and familial forms of PD but whilst a direct link between α-synuclein and the UPS has not been firmly established, impairment of α-synuclein function via mutations may disturb ubiquitination of α-synuclein associated proteins that may lead to a disturbance in neuronal homeostasis. It has also been shown that the mutant form of α-synculein is less susceptible to degradation by the proteasome and subsequent aggregation may lead to secondary neuronal damage by inhibiting the UPS.[2]

Conclusion

Several lines of evidence argue for a common mechanism of toxicity based on protein aggregation and the impairment of the UPS in neurodegeneration. However, it is still unclear whether protein aggregation and dysfunction of the UPS is the cause or consequence of neuronal loss in these disorders, and is still a subject of speculation and intense research interest. It may well be that proteasome inhibition occurs in these diseases but the pathophysiology of the neurodegenerative process per se in each disorder is likely to be multifactorial, and not a one-hit phenomenon. Therefore a key challenge in the development of disease-modifying treatments for this group of diseases is the design of therapeutic strategies that target many different cellular pathways.

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Advances in the Pathogenesis and Therapy of Inflammatory Neuropathies

The inflammatory neuropathies are a diverse group of peripheral nerve disorders presumed to have an immune mediated pathogenesis. They are characterised pathologically by inflammatory infiltration of the peripheral nerves associated with destruction of myelin and/or axons. The inflammatory neuropathies are typified by the idiopathic demyelinating neuropathies, both chronic and acute, and the closely related neuropathies associated with paraproteinaemia. However, vasculitic, infectious and parainfectious, paraneoplastic neuropathies and more recently diabetic plexopathy[1] are included. Some of these may be thought of as primary disorders of the peripheral nervous system (e.g. Guillain-Barré Syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)) and others secondary to a systemic immune process with subsequent involvement of the peripheral nerves (e.g. the neuropathy associated with vasculitis and the connective tissue diseases). Even some neuropathies with a known inherited pathogenesis (e.g. the hereditary motor and sensory neuropathies (HMSN)) may have an inflammatory element.[2,3]

Increased understanding of the pathogenesis of the inflammatory neuropathies from disease induction to cell damage is informing developments in treatment. These will be the exciting advances of the near future. The acute inflammatory neuropathies are an excellent example of the progress in clinically directed research in this area.

Guillain-Barré Syndrome

Guillain-Barré Syndrome is the commonest cause of acute neuromuscular paralysis in the developed world. It affects about 2 per 100 000 population per year. It is now recognised that the syndrome is an umbrella term for disease variants including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN) and the Miller Fisher syndrome. The mortality of GBS remains about 5-10% despite the almost routine use of intravenous immunoglobulin (IVIG) or plasma exchange (PEx).

The subtypes of GBS are probably specified by the pathogenic mechanisms predominant in any one case and emerging evidence is helping to clarify these. Pathogenic mechanisms may be complicated by geographical and genetic susceptibility factors in populations and the agents to which they are exposed. For instance in Europe and the USA more than 90% of patients have the AIDP sub-type and *Campylobacter jejuni* infection precedes onset of the GBS in 26% of cases.[4] In China and Japan, where AMAN accounts for more than 60% of GBS cases, preceding *C jejuni* infection may occur in 2/3 of patients[5] and seems to be exclusively associated with AMAN.[6]

Campylobacter jejuni, cytomegalovirus, Epstein Barr virus, *Mycoplasma pneumoniae* and more recently unencapsulated *Haemophilus influenzae*[7] are all associated with GBS. All of these organisms have been shown to have ganglioside-like epitopes in their surface coat. Furthermore *Campylobacter jejuni* possesses a very similar protein glycosylation mechanism to eukaryotic cells.[8] Similarity between neural gangliosides and pathogen borne molecules is the basis of molecular mimicry which remains the major theory explaining how an infectious organism can drive an autoimmune response.

The exclusive involvement of B-cells, T-cells, cytokines or complement in a subtype of inflammatory neuropathy is unlikely. The role of the individual facets of the immune system is becoming increasingly clear.

Antibodies and B-cells

Antibody targeting of specific neural epitopes is responsible for the pathogenic phenotype of several inflammatory neuropathies, best illustrated by the Miller Fisher Syndrome and its variants, AMAN and possibly multifocal motor neuropathy with conduction block (MMNCB). Limited evidence exists for the pathogenesis of anti-MAG and other chronic neuropathies and remains less convincing for AIDP.

Fisher Syndrome (ataxia, ophthalmoplegia and areflexia)[9] is associated with serum IgG antibodies to the ganglioside GQ1b (see Figure 1) in 90% of cases. These antibodies may cross-react with similar gangliosides, commonly GT1a, which may extend the phenotype to bulbar muscles. Ganglioside GQ1b is found in greatest concentration in cranial nerves II, III, IV and VI.[10] In an *ex vivo* model these antibodies bind to nerve at the nodes of Ranvier and the neuromuscular junction where they fix complement (see below), disrupt cell structure and cause neuromuscular conduction failure similar to the spider venom α-latrotoxin.[11]

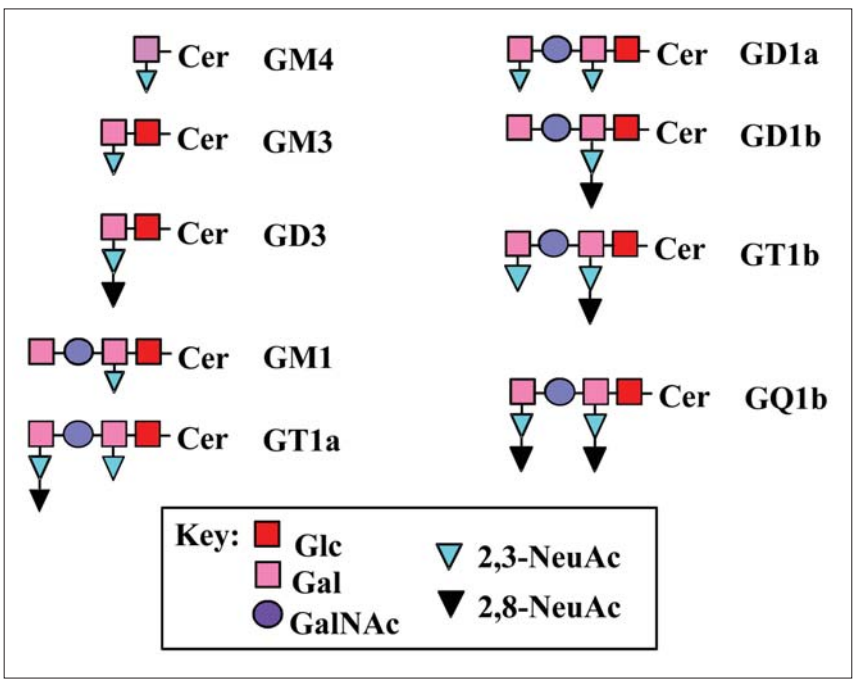
The AMAN variant of GBS is associated with antibodies to GM1, GD1a, GalNAc-GD1a and GD1b. Although unusual in the western hemisphere, AMAN accounts for the majority of GBS patients in China. It is often more clinically devastating than AIDP but can be followed by remarkable recovery. A complement-dependent antibody-mediated attack has been demonstrated in the motor nerves and roots. Some monoclonal IgG anti-GD1a antibodies specifically bind motor nerves (see Figure 2) giving explanation to the motor phenotype. An animal model of IgG anti-GD1a neuropathy has recently been described[12] in which an axonal neuropathy was induced by implanting mouse anti-GD1a producing hybridomas to host mice. This strengthens the evidence for the pathogenesis of anti-GD1a antibodies in AMAN.

Michael Lunn is a Specialist Registrar in Neurology. He trained in Cambridge and London. His PhD, on the pathogenesis of inflammatory neuropathies, was researched within King's College London and at the Johns Hopkins Hospital, Baltimore, USA.

Correspondence to:
Michael Lunn,
Specialist Registrar Neurology,
Department of Neurology,
3rd Floor Lambeth Wing
Guy's and St Thomas' Hospitals,
Lambeth Palace Road,
London SE1 7EH.
Tel: 020 7188 3962,
Fax: 020 7188 3952,
Email: michael.lunn@kcl.ac.uk

Figure 1: Structures of the common complex gangliosides found in peripheral nerves. All are derived from a common backbone. Structural similarities are apparent explaining cross-reactivities of serum anti-ganglioside antibodies.

Cer = ceramide, Glc = glucose, Gal = galactose, GalNAc = N-acetylgalactosamine, 2,3-NeuAc = 2,3-linked N-acetylneuraminic acid (sialic acid), 2,8-NeuAc = 2,8-linked N-acetylneuraminic acid



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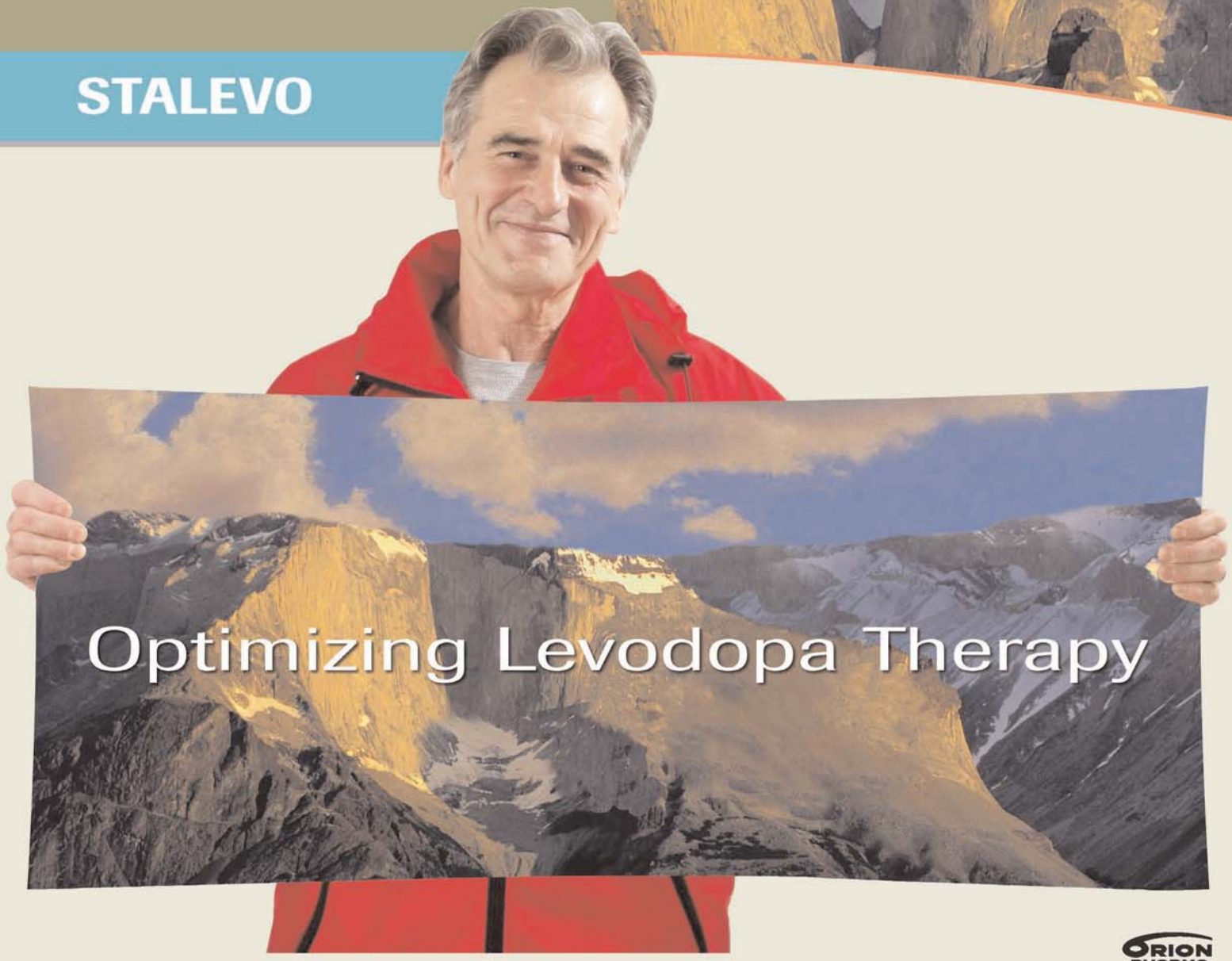

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STA1295

T-cells

Experimental autoimmune neuritis (EAN) is a T-cell mediated disease and is the prototypic animal model for inflammatory neuropathy. The endoneurium is infiltrated with lymphocytes under the guidance of leucocyte and endothelial adhesion molecules and chemokines and their receptors.[13] Myelin is stripped by activated macrophages which, at least early on, are endogenous. However the role of T-lymphocytes in GBS remains elusive. Chemokines and receptors have been shown to be upregulated in human specimens and T-cells are certainly activated and present in damaged nerve. Of four T-cell lines isolated from GBS patient nerve specimens two had γδ-T-cell receptors illustrating the importance of the immune reaction to non-protein antigens.[14] Proof of the specific role of the T-cell in GBS pathogenesis although not far away is still lacking.

Complement

Complement has been visualised in biopsy specimens from inflammatory neuropathies for more than 30 years. It is only recently that the role of complement has been more clearly defined in an *ex vivo* model.[11] Pore-forming membrane attack complex was visualised at the neuromuscular junction in conjunction with GQ1b antibodies and correlated to structural neurofilament disruption at the nerve terminal. This was worsened in mice lacking the complement regulating molecule CD59. Complement is a key weapon delivering antibody directed damage to the target.

Treatment

The long awaited trial of intravenous methyl prednisolone and IVIG in the treatment of GBS has now been published[15] and provoked some controversy. In a pilot study this combination seemed to be more effective than IVIG alone. In the randomised controlled trial of 233 patients a positive effect of steroids just reached statistical significance on the primary but none of the secondary outcome measures. The biological significance of this effect is negligible. Since previous trials, and a Cochrane meta-analysis, have shown steroids to be at best ineffective, and in some cases harmful, there is no indication for their use in GBS.

The effectiveness of other immunotherapy for GBS is supported by good evidence.[16] Two to five sessions of PEx hastens recovery in non-ambulant patients preferably started within two weeks of disease onset. Intravenous immunoglobulin is as effective as PEx and is still probably the intervention of choice. The concern about possible contamination of IVIG with prions means that written informed consent is essential before administration. The drive to search for new, more effective and safer therapies is stronger than ever.

Increased understanding of disease mechanisms is informing the development of new treatment. Complement inhibitors are already available and clinical trials in the treatment of GBS are being planned. Specific, targeted immunoadsorption of pathogenic anti-ganglioside antibodies by glycoforms conjugated within haemofilters is being developed for possible clinical use.[17] As T-cell mechanisms become better understood appropriate inhibitors may be developed. The choice of therapy may then be less simple but potentially more effective.

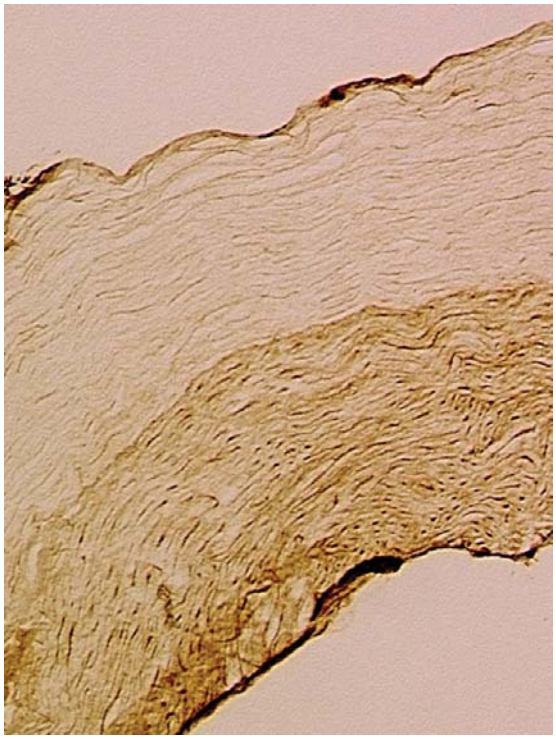

Figure 2: Fresh frozen unfixed nerve root stained with monoclonal IgG monospecific anti-GD1a antibody. Axons of the motor root (below) stain much more strongly than those in the sensory root (above).

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Jane Austen on Memory; Anton Chekhov on Agnosia

The observations and insights which artists and writers may have concerning neurological phenomena have previously been discussed.[1,2] Two further examples, of possible relevance to the discipline of neuropsychology, are presented here.

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

Correspondence to:
AJ Larner,
Consultant Neurologist,
Cognitive Function Clinic,
Walton Centre for Neurology and Neurosurgery,
Lower Lane,
Fazakerley,
Liverpool,
L9 7LJ.
Fax: 0151 529 5513,
Email: a.larner@thewaltoncentre.nhs.uk

Jane Austen on Memory

Jane Austen (1775-1817) remains one of the most popular novelists in the English language nearly 200 years after her death, but the author and her works seem to have attracted relatively little interest from members of the medical profession. One exception relates to the cause of her death: based on her correspondence, Cope believes her to be the first recorded case of Addison's disease of the adrenal glands.[3] However, a reading of her novels suggests various insights into the human condition, for example memory.

It has been argued that Jane Austen's "tenacious memory" was crucial to her art, allowing her to draw on the works of authors she knew well, such as John Locke, himself a physician as well as a philosopher (*Northanger Abbey*), Richardson and Milton (*Sense and Sensibility, Pride and Prejudice, Mansfield Park*), Shakespeare (*Emma*) and Chaucer (*Persuasion*).[4] Perhaps the most striking comment on the nature of memory in Jane Austen's oeuvre is given to Fanny Price in *Mansfield Park* (1814), a character of whom it has been said that memory is "her personal identity, her lifeline", in a work described as "the book of Memory":[5]

> If any one faculty of our nature may be called more wonderful than the rest, I do think it is memory. There seems something more speakingly incomprehensible in the powers, the failures, the inequalities of memory, than in any other of our intelligences. The memory is sometimes so retentive, so serviceable, so obedient - at others, so bewildered and so weak - and at others again, so tyrannic, so beyond controul [*sic*]! - … our powers of recollecting and of forgetting, do seem peculiarly past finding out.

To a neurologist with an interest in cognitive disorders, this passage, written before neuropsychology as a discipline came into existence, seems prescient in various ways. It seems to recognise memory as a faculty of variable efficiency, and also to anticipate ("inequalities") its characterisation as a non-uniform distributed cognitive function, fractionated into various domains or subtypes (e.g. immediate, long-term; explicit, implicit; episodic, semantic), selective impairments of which may occur. The difficulty of dissecting out the various capacities of memory is also recognised.

Although we are rightly discouraged from trying to intuit mental processes in favour of an experimental methodology,[6] nonetheless Jane Austen's understanding of memory, as in so many other spheres, seems pertinent even today.

Anton Chekhov on Agnosia

2004 marked the 100th anniversary of the death of Dr Anton Pavlovich Chekhov (1860-1904).[7] Although best known for his plays in the realist genre, Chekhov also performed significant medical work, not least his 1890 visit to the island of Sakhalin whence he reported on the social and medical conditions of the penal colonies located there.[8]

Chekhov's plays often feature a doctor, and in most there is also a character who looks forward to a bright future destined not for himself but for the generations to come. It has been suggested that Doctor Astrov in the play *Uncle Vania* (first performed 1899) voices some of Chekhov's personal thoughts.[9,10] Although Chekhov once famously stated that "medicine is my lawful wife"[11] and that he never regretted his choice of career, nonetheless Astrov states of medicine:

> The life itself is tedious, stupid, squalid …. This sort of life drags you down. You're surrounded by queer people – they're a queer lot, all of them – and after you've lived with them for a year or two, you gradually become queer yourself, without noticing it. That's inevitable.

A century on, Chekhov might be interested to see what remarkable progress has been made in medical life.

With his medical training,[10] Chekhov was perhaps alert to defects in human cognitive function. In the short story *The Kiss*, first published in 1887, this passage appears:

> When he first entered the dining room and sat down to tea, he found it impossible to concentrate on any one face or object. All those faces, dresses, cut-glass decanters, steaming glasses, moulded cornices, merged into one composite sensation, making Ryabovich feel ill-at-ease, and he longed to bury his head somewhere. Like a lecturer at his first appearance in public, he could see everything in front of him well enough, but at the same time he could make little sense of it (physicians call this condition, when someone sees without understanding, "psychic blindness").

Although when we consider the history of agnosia, we typically think of Lissauer's distinction of apperceptive and associative types, drawn in 1890, he in fact talked of *Seelenblindheit*,[12] literally "soul-blindness" but technically "psychic blindness" (a term also used by Munk in 1877).[13] It was not until the following year that Sigmund Freud, previously a pupil of Charcot, coined the term "agnosia" ("not knowing" or "without knowledge").[14] There were other, earlier, descriptions relevant to these phenomena which Chekhov might possibly have been aware of: Bastian described "visual perceptive centres" in 1869, Finkelnburg "asymbolia" in 1870, and Hughlings Jackson "imperceptions" in 1876.[13]

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Presentation: White to off-white tablets containing modafinil 100 mg or modafinil 200 mg (debossed with "Provigil" on one side and "100 mg" or "200 mg" on the other). **Indication:** Excessive sleepiness associated with chronic pathological conditions, including narcolepsy, obstructive sleep apnoea/hypopnoea syndrome and moderate to severe chronic shift work sleep disorder. **Dosage:** *Adults: Narcolepsy and Obstructive Sleep Apnoea/Hypopnoea Syndrome:* 200 – 400 mg daily either as two divided doses in the morning and at noon or as a single morning dose according to response; *Shift Work Sleep Disorder:* 200 mg daily taken as a single dose approximately 1 hour prior to the start of the work shift. *Elderly:* Treatment should start at 100 mg daily, which may be increased subsequently to the maximum adult daily dose in the absence of renal or hepatic impairment. *Severe renal or hepatic impairment:* Reduce dose by half (100 – 200 mg daily). *Children:* Not recommended. **Contra-indications:** Use in pregnancy and lactation, uncontrolled moderate to severe hypertension, arrhythmia, hypersensitivity to modafinil or any excipients used in Provigil. **Warnings and precautions:** Patients with major anxiety should only receive Provigil treatment in a specialist unit. Sexually active women of child-bearing potential should be established on a contraceptive programme before taking Provigil. Blood pressure and heart rate should be monitored in hypertensive patients. In patients with obstructive sleep apnoea, the underlying condition (and any associated cardiovascular pathology) should be monitored. Patients should be advised that Provigil is not a replacement for sleep and good sleep hygiene should be maintained. Provigil is not recommended in patients with a history of left ventricular hypertrophy, cor pulmonale, or in patients who have experienced mitral valve prolapse syndrome when previously receiving CNS stimulants. This syndrome may present with ischaemic ECG changes, chest pain or arrhythmia. Studies of modafinil have demonstrated a low potential for dependence, although the possibility of this occurring with long - term use cannot be entirely excluded. Provigil tablets contain lactose and therefore should not be used in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption. **Drug interactions:** Modafinil is known to induce CYP3A4/5 (and to a lesser extent, other) enzymes and so may cause clinically significant effects on other drugs metabolised via the same pathways. 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. **Legal category:** POM. **Date of preparation:** March 2004. Provigil and Cephalon are registered trademarks. Full prescribing information, including SmPC, is available from **Cephalon UK Limited**, 11/13 Frederick Sanger Road, Surrey Research Park, Guildford, Surrey UK GU2 7YD, Medical Information Freefone 0800 783 4869 (ukmedinfo@cephalon.com). PRO809/Mar 04

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Neuropathology of Multiple Sclerosis

Since the first clinico-pathological descriptions of multiple sclerosis (MS), neuropathologists, neurologists, immunologists, geneticists and scientists have worked together in an attempt to clarify the pathogenesis of this enigmatic disease. Multiple sclerosis is a complex condition and there is no consensus as to whether it represents a single disease or a series of diseases with a common final pathway. For this reason systematic pathological analysis of brains affected by demyelination is still important to provide new insight into the pathogenesis of the disease. This review is the result of experience gained from examining brains donated by patients with MS to the UK Multiple Sclerosis Tissue Bank (UKMSTB) at the Imperial College of London.

Brief historical overview

Descriptions of cases of putative MS date back as early as the Middle Ages but it was in the 19th century when doctors definitively recognised MS as a distinct disease. The first pathological report was published by Jean-Martin Charcot, Professor of Neurology at the University of Paris in 1868 in the *Leçons du mardi*.[2] He examined a young woman who presented with tremor, slurred speech and abnormal eye movements. When she died, Charcot had the chance to study her brain and document the characteristic scars he termed 'plaques' coining the definition of '*la sclerose en plaques*'. He also delineated the clinical diagnostic criteria with the triad of nystagmus, intention tremor and scanning speech which, though not specific, are still helpful in recognising the disease. In 1916 James Dawson at the University of Edinburgh wrote the first detailed microscopic description of the brains of MS patients, documenting perivascular inflammation and myelin disruption. Since this time, MS research has grown relentlessly with the discovery of abnormalities in spinal fluid in 1919, the discovery of oligodendrocytes made by Ranvier in 1928 and with the observation in animal models in 1935 that injection of brain tissue produces an MS-like illness, called experimental allergic encephalomyelitis.

Definition of multiple sclerosis

Multiple sclerosis belongs to the complex group of disorders of the central nervous system characterised by destruction of myelin (Table 1). Given the clinical and pathological heterogeneity of MS, there is no conclusive definition of the disease and the one suggested by Poser[11] of an "inflammatory demyelinating disease of the central nervous system in which the particular myelinoclastic sequence, regardless of the clinical course and the phenotypic manifestation is determined by the individual endowment and which results in a pathognomonically unique lesion, the sharp-edge plaque" emphasises the fact that we can only be descriptive. As stated, multiple sclerosis is a heterogeneous pathological condition and the different variants reported so far (Table 2) most likely represent separate entities rather than different phenotypic expressions of the same disease.

Epidemiology and clinical features

Multiple sclerosis is a common disease worldwide and one of the leading causes of disability in Western Europe and the United States. It has been estimated that it affects more than 2.5 million individuals with a prevalence varying between 5 and 119 per 100,000 in the United States. In the United Kingdom, MS affects about 85,000 individuals. The age of onset is broad and ranges between 10 and 60 years, with a peak between 20 and 40 years and a mean of 32 years. There is a predominance in females with a ratio of female/males of almost 2 to 1. Incidence of MS varies by geographical location, the more industrialised countries showing the highest figures. It remains unclear whether this altered incidence represents an environmental influence, genetic difference or simply is the result of variable surveillance. The natural history of MS is usually characterised by progressive neurological deterioration. Physical disability is the rule. A considerable number of affected individuals also experience cognitive dysfunction in the course of the disease although cognitive disability at onset is rare. Patients with MS exhibit different patterns of disease activity. About 80-85% have a relapsing–remitting course and a considerable number develop secondary progression with or without occasional relapses. About 10% of patients exhibit primary progressive MS. The least common form is progressive relapsing MS, a variant where the disease is progressive from the onset with acute relapses.

Neuropathology

Macroscopic findings: At external examination, brains affected by MS can look normal or show variable degrees of atrophy. In many cases, plaques are visible on the external surface of the optic pathways, brainstem and spinal cord. In atrophic brains, the lateral ventricles in particular appear dilated due to loss of volume of the centrum semiovale. Severe hydrocephalus is observed in 5-10% of cases. On sections, plaques appear as sharply demarcated and slightly depressed areas varying in colour. Fresh plaques are pink due to hyperaemia induced by inflammation or white to yellowish due to lipid breakdown; chronic

Federico Roncaroli qualified as a Histopathologist in Italy and is now Clinical Senior Lecturer in Neuropathology at the Department of Neuropathology, Imperial College of London. He is one of the referring neuropathologists of the UK Multiple Sclerosis Tissue Bank.

Correspondence to:
Federico Roncaroli, MD,
University Department of Neuropathology,
Division of Neuroscience and Mental Health,
Imperial College of London,
Charing Cross Campus,
St. Dunstans Road,
London, W6 8RP.
Email: f.roncaroli@imperial.ac.uk

Table 1: Spectrum of Demyelinating Diseases

Demyelination due to infectious agents
- Progressive multifocal leukoencephalopathy
- Subacute sclerosing panencephalitis
Metabolic disorders of myelin
- Metachromatic leukodystrophy
- Globoid cell leukodystrophy
- Pelizaeus-Merzbacher disease
Peroxisomal disorders affecting myelin
- Generalised peroxisomal disorders
- Cerebrohepatorenal (Zellweger) syndrome
- Infantile Refsum disease (phytanic acid storage)
- Neonatal adrenoleukodystrophy
- Hyperpipecolic acidemia
Single peroxisomal enzyme deficiencies with widespread pathology
- Thiolase deficiency
- Acyl-CoA oxidase deficiency
- Rhizomelic chondrodysplasia
- Single peroxisomal enzyme deficiencies with more restricted pathology
- Adrenoleukodystrophy complex
.- Diseases of unknown aetiology
Multiple sclerosis
Acute disseminated encephalomyelitis
Fibrinoid leukodystrophy (Alexander disease)

Table 2: Clinicopathological Variants of Multiple Sclerosis

Relapsing remitting course/Secondary progressive
Primary progressive
Progressive relapsing
Acute Multiple Sclerosis or Marburg Variant
Neuromyelitis Optica or Devic's Disease
Balo's Concentric Sclerosis
Myelinoclastic Diffuse Sclerosis or Schilder's Disease

plaques are grey–tan and firm in consistency due to marked gliosis. The number and distribution of plaques vary from cases to case but in at least two-thirds of brains there is an equal distribution of demyelination in the cerebral hemispheres, spinal cord and optic pathways (Figure 1). As a rule, plaques are not restricted to any anatomical zone, do not follow specific vascular territories, are not related to any neuroanatomical tract or system, and are not associated with any defined neurotransmitter (Figure 2a).[5] In the cerebral hemispheres, lesions usually involve the white matter around the lateral ventricles and often the lesions show continuity from the frontal to the occipital lobes. The borders of the areas of myelin loss are convex at the beginning of the process and become finger-like as demyelination proceeds following parenchymal and sub-ependymal veins (Dawson's fingers). Juxta-cortical plaques are also commonly seen. They appear smaller than white matter plaques and often extend to the lower part of the cortical ribbon. Isolated cortical plaques are rare and difficult to see on macroscopic inspection. Demyelinating areas in the brainstem are often subpial and visible on the anterior aspect of pons (Figure 2b) and medulla or subependymal affecting the floor of the fourth ventricle. In sections of the brain stem, plaques are rounded and often cross the midline. Cerebellar involvement is less frequent and at gross examination, plaques involving folia are not recognisable. In the spinal cord, areas of myelin loss can be peripheral or central. Plaques usually do not exceed 1.5 cm and often appear to be subpial. In cases with long duration, the spinal cord is atrophic and on cross section the architecture is effaced in that there is no clear distinction between white and grey matter.

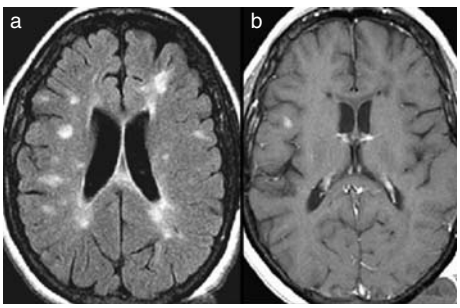
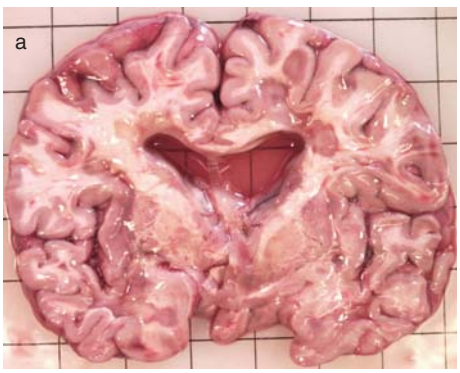


Fig 1: This axial T1-weighted MR-scan shows several brightly hyperintense periventricular and white matter plaques (a). One subcortical plaque is seen after administration of paramagnetic contrast (b).



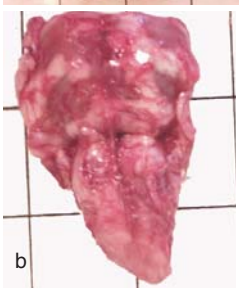


Fig 2: Plaques appear as grey-pink and yellow irregular lesions (a).

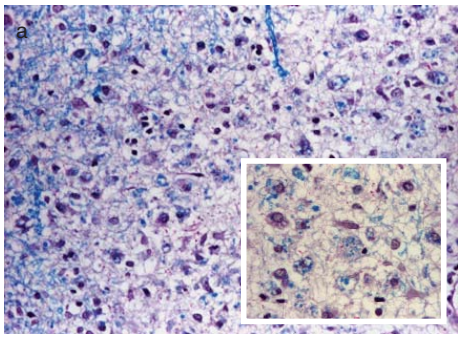
The anterior aspect of the pons shows several confluent plaques (b).

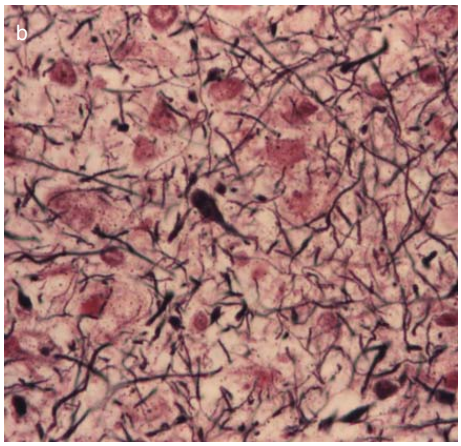
General histological features: The vast majority of cases of MS show a mild non-specific leptomeningeal inflammatory infiltrate composed of mature lymphocytes and often plasma cells. Histological features of plaques vary according to the stage of demyelination and degree of activity. Commonly, plaques are classified as acute, chronic active, inactive and, when remyelination occurs they are termed shadow plaques. At the UKMSTB, we have adopted a slightly different terminology to define active plaques and we prefer to distinguish those with early activity from those with late changes based on the number of macrophages, distribution and extent of microglial activation, degree of reactive astrocytosis and severity of demyelination. Criteria are essentially those suggested by the consensus meeting held in Vienna in 1998.[7]

Chronic active and inactive plaques: Activity is determined by the presence of foamy macrophages containing fragments of myelin. Staining properties of myelin debris change with time and become PAS-positive. Active plaques are characterised by progressive destruction of myelin which appears to be stripped off by macrophages (Figure 3a), variable perivascular inflammatory infiltrate mostly composed of T-lymphocytes, prominent reactive astrocytosis, and a variable degree of activation of microglial cells. Axons are often swollen and wavy indicating damage and sometimes appear interrupted with the formation of spheroids (Figure 3b). Active myelin destruction can occur in normal white matter or in remyelinated lesion as in Figure 3c. Oligodendrocytes are usually preserved or slightly reduced in newly demyelinating lesions whereas they often appear to be increased in number when demyelination involves a remyelinated plaque. As mentioned before, we consider as early active plaques those lesions in which myelin loss is still incomplete, myelin debris can be seen within macrophages when stained using Luxol fast blue (LFB) and in which reactive astrocytosis predominates. In these plaques, reactive astrocytes feature atypical nuclei and sometimes undergo mitotic division. In contrast, late active plaques are those with nearly complete disappearance of myelin sheaths, PAS-positive myelin debris and less prominent reactive astrocytosis (Figure 4). Chronic inactive plaques are easily seen in conventional haematoxylin-eosin and Luxol-fast blue stains. They appear as sharply demarcated areas of discolouration with dense fibrillary gliosis, loss of oligodendrocytes and few microglial cells (Figure 5a). A few macrophages containing PAS-positive old products of myelin degradation can also be seen, particularly at the edge of the lesion. Vessels typically are surrounded by an empty space and their walls appear to be damaged. Chronic inactive plaques are also characterised by marked reduction of axonal density (Figure 5b-5c).

Consensus of classification of plaques

The structural pathology and immunopathology of MS was discussed in an interdisciplinary forum held in Vienna in 1998 under the patronage of the International Federation of Multiple Sclerosis





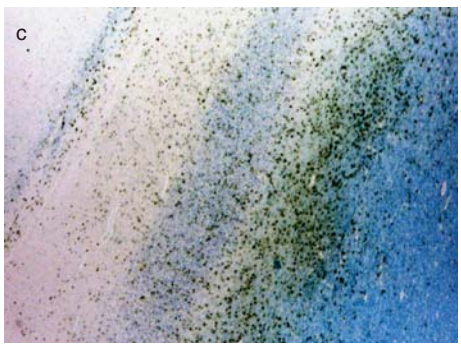


Fig 3: Early active demyelination with many macrophages and reactive astrocytes (a, LFB/PAS), the inset shows macrophages with cytoplasm filled with myelin debris (LFB/PAS); Bielschowsky stain demonstrates axonal spheroids within the same plaque (b, Bielschowsky); reactivation is seen at the edge of this plaque (c, LFB/PAS-MHC class II antigen).

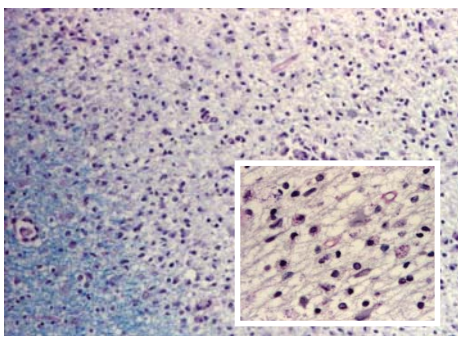


Fig 4: A late active plaque with complete loss of myelin and several macrophages containing PAS-positive products of myelin degradation (LFB/PAS).

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therapy needed. Monitor renal function carefully as there are no data on patients with renal impairment. CNS-related adverse events might affect ability to drive and use machines in susceptible patients. Injection site necrosis has been reported which may result in scar formation. Debridement or skin grafting required occasionally. With multiple lesions, stop therapy until healing occurs. With single lesions therapy may be continued. Advise patients to use an aseptic injection technique and rotate injection sites. Periodically review patients' self-injection procedures. *Drug interactions:* 28 days of corticosteroid or ACTH treatment has been well tolerated. Use of other immunomodulators is not recommended. A down regulation of hepatic cytochrome P450 has been reported with interferons. Exercise caution when administering with drugs that have a narrow therapeutic index and are dependent on the hepatic cytochrome P450 system for clearance. Caution with any drugs affecting the haematopoetic system. **Side effects:** The following adverse events collected as spontaneous reports are classified as : very common ≥ 10%, common <10% - ≥1% , uncommon < 1% - ≥0.1% , rare <0.1% - ≥ 0.01%, very rare < 0.01%. *Very common:* flu-like symptom complex, chills, fever, injection site reaction, inflammation, injection site pain. *Common:* necrosis. *Uncommon:* anaemia, thrombocytopenia, leucopenia, increase in ALT, AST, hypertonia, depression, hypertension, nausea, vomiting, alopecia, urticaria, pruritus, rash, myalgia. *Rare*: lymphadenopathy, thyroid dysfunction, γ-GT and triglyceride increase, convulsion, confusion, anxiety, emotional lability, cardiomyopathy, tachycardia, palpitation, bronchospasm, dyspnoea, pancreatitis, hepatitis, skin discoloration, sweating, menstrual disorder, suicide attempt, anaphylactic reactions, malaise, chest pain. *Very rare:* hypocalcaemia, hypercalcaemia, depersonalisation. Other adverse events reported during clinical trials are: lymphopenia, neutropenia, altered laboratory tests for glucose and urinary proteins, peripheral oedema, dizziness, insomnia, conjunctivitis, ear pain, migraine, vasodilatation, sinusitis, increased cough, diarrhoea, constipation, skin disorder, myasthenia, urinary disorders, impotence, pain in various sites, asthenia, infection, abscess. The incidence rate of injection site reactions decreases over time. If breaks in the skin occur advise patients to contact their physician before continuing with injections. For further information please refer to the SmPC. **Legal category:** POM **Basic NHS price:** £596.63 for 15 x 3ml Betaferon vials with diluent. **PL numbers:** EU/1/95/003/001, EU/1/95/003/002 **PL holder:** Schering Akteingessellschaft, D-13353 Berlin, Germany. **Date of preparation:** 24 January / 03. ® **Betaferon is a registered trademark of Schering AG.**

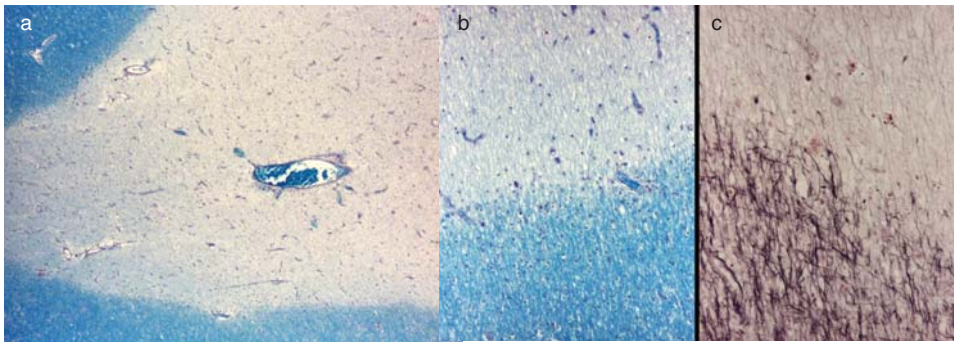


Fig 5: Inactive plaques are characterised by sharp margins and low celllularity (a, LFB/PAS). There is considerable reduction of axons (b, LFB/PAS – c, Bielschowsky).

Societies and the National Multiple Sclerosis Societies of the United States and Canada. Fully aware of the heterogeneity of MS, neuropathologists, clinical neurologists, neuroradiologists and immunologists attempted to clarify pathological changes seen in MS. Observations gathered in this multidisciplinary review and the conclusions were published in a review article[7] and now represent a sort of guideline for the pathological diagnosis.

All participants emphasised the importance of combining neuropathology with neuroimmunology and neuroimaging in elucidating the pathogenesis, dynamics and mechanisms of demyelination. It was agreed that: pathogenesis of lesions in MS is complex and not merely a T-cell mediated response. Axonal degeneration occurs to a significant extent and is clinically relevant; the regenerative potential is more pronounced than previously recognised, with abundant spontaneous remyelination in early stages of the disease and some oligodendrocyte progenitor cells remaining in chronic sclerotic lesions. All participants finally agreed that neuropathological studies should be performed on well-staged and defined material because this will give the essential basis for defining the mechanisms of tissue damage and the structural correlates of MRI abnormalities. This latter is also the remit of the UKMSTB. Most important was the attempt of a more precise definition of ongoing demyelinating activity based on the presence within macrophages of degradation products of minor myelin proteins rather than on the activity of the inflammatory process. The following different stages have therefore been delineated: i) Plaques with inflammation and macrophages containing early myelin debris identified by their reactivity for LFB or myelin proteins; ii) Plaques with inflammation in the absence of early myelin degradation products in macrophages; iii) Plaques with early myelin degradation products in the absence of perivascular infiltrates and iv) Plaques without inflammatory infiltrates and absent early myelin degradation products.

Patterns of demyelination

In a seminal study published in 2000,[8] Lucchinetti et al. proposed a new approach to MS that substantially changed the current interpretation of the disease. Their pathological examination of active lesions led to the recognition of four different patterns of demyelination, all sharing a qualitatively and quantitatively similar response of T-lymphocytes and macrophages. Each pattern appeared to be the same in all of the lesions examined in a single patient and only conversion from pattern I into pattern II was seen to be possible.

Pattern I: This pattern is characterised by T-lymphocytes and microglia and macrophages alone without deposition of immunoglobulins throughout the lesion and no deposition of complement components. Demyelination is perivenular and there is loss of all types of myelin protein. Pathological changes occur simultaneously in all plaques. It has been suggested that demyelination and tissue injury is mediated by the cytotoxic effect of T-lymphocytes and activated phagocytes.

Pattern II: This is the most common pattern. Pathologically similar to pattern I, it shows plaques with well-defined margins, perivascular cuffs of lymphocytes and simultaneous loss of myelin with myelin degradation products in macrophages. Dissolving myelin sheaths are coated with immunoglobulins and activated complement and antibodies against components of the myelin sheath appear to be involved in demyelination. This pattern is associated with shadow plaques indicating that remyelination may occur.

Pattern III: Activation of macrophages and microglia is less pronounced than in patterns I and II and the destruction of myelin sheaths does not strictly follow the distribution of inflammatory cells. Plaques are not centred on veins and venules and are characterised by ill-defined margins, preferential loss of myelin-associated glycoprotein relative to other myelin proteins such as MBP and proteolipid protein and no deposition of IgG. Preservation of a rim of myelin around inflamed vessels is common. Typically, there is marked loss of oligodendrocytes at the border of demyelination.

Pattern IV: The inflammatory reaction of pattern IV is similar to that described for pattern I but it is associated with a more extensive demyelination, and death of oligodendroglial cells. Tissue damage is likely to be determined by a genetic susceptibility of the target tissue for immune mediated injury.

The acute plaques

The definition of an acute plaque is challenging because it implies a definition of early stages of demyelination. The terminology appears confusing because the term 'acute' is used to describe subtle lesions of the white matter characterised by oedema and initial myelin fragmentation and lesions in which the inflammatory component, active myelin phagocytosis and reactive astrocytes are already present and prominent. Aware that the process of demyelination is a continuum and classifications are always artificial, we prefer to designate as acute plaques only those white matter changes with mild activation of microglia, ie. a few activated microglial cells but lacking definite activation of the immune system. Our position is in keeping with the interesting observation published by Barnett and Prineas on the early white matter changes in a case of relapsing-remitting MS.[1] This study suggested that the inflammatory response is secondary to the initial event of apoptotic death of oligodendrocytes. Oligodendrocyte death causes a series of tissue responses including activation of resident microglia that remove the dying oligodendrocytes before frank myelin pathology. As part of the apoptotic pathway, activated complement is deposited on myelin sheaths and, within days, myelin appears vacuolated. The vacuolated and complement-positive myelin attracts monocytes that begin phagocytosis. When phagocytosis takes place, foamy macrophages dominate the pathological picture.

The issue of axonal damage

Although early observations by Charcot and Marburg mentioned axonal damage as a relevant component of MS pathology, for decades plaques have generally been considered to be areas of demyelination with preservation or little disruption of neuropil.[4] Features of damage such as wavy axons and axonal spheroids were known to occur in MS plaques but have usually been dismissed as an epiphenomenon of demyelination with no clinical relevance. It was only recently that axonal damage and axonal loss emerged as important for explaining permanent irreversible neurological disability of patients with MS. Recent studies have indicated that small fibres are more vulnerable and that significant axonal loss occurs not only within plaques but also around demyelinating areas and even in histologically normal white matter.[5,13] Long pathways such as the pyramidal tracts and the dorsal columns of the spinal cord are those most heavily affected. Multiple episodes of demyelination over the course of the disease and subclinical attacks may cause permanent injury that leads to progressive axonal destruction and eventually to neuron loss due to Wallerian degeneration. Damage of nerve fibres appears to be more extensive during the first year from onset and the number of acutely injured axons decreases with disease duration longer than 10 years. The anatomical correlate of axon loss is atrophy, which increases along with disease progression and involves white and grey matter of the cerebral hemispheres, brain stem and posterior sensory tracts and corticospinal tracts of the spinal cord. Atrophy is most severe in primary and secondary progressive disease and may indicate the conversion from a relapsing remitting course into secondary progression. The irreversible secondary progressive stage begins when axonal injury reaches a threshold. The mechanisms of axonal degeneration are incompletely understood. It seems that axonal loss might depend on several causes including direct effects through the loss of trophic influ-

ences from oligodendrocytes, as a consequence of sustained demyelination-induced conduction block, and indirectly through the increased vulnerability of the exposed axons to noxious agents.

Cortical involvement

Multiple sclerosis is not only a disease of the white matter. It is not uncommon to find juxtacortical plaques with extension to the lower layers of the grey matter. Some cases show isolated cortical plaques and are characterised by predominant cortical involvement.[5,12] Cortical plaques are hardly recognisable at macroscopic examination particularly when the brains are fixed. Cortical demyelination can occur anywhere and plaques usually range in size between a few millimetres and 1 cm. Grey matter involvement can be hardly visible at microscopic examination using histochemical stains because the cortex contains much less myelin and inflammatory cells and microglia are much less abundant in cortical demyelination than the white matter counterpart (Figures 6a-6b). Immunohistochemical stains to identify gliosis, macrophages and microglial infiltrates, and anti-myelin antibodies are therefore helpful for a correct assessment of cortical pathology. Cortical pathology in MS has been carefully investigated in recent studies by Kidd et al[3] and Peterson et al.[10] These authors studied 112 cortical lesions identified in 50 patients with MS and suggested a classification of cortical plaques, the type 1 being contiguous with subcortical lesions, type 2 small, usually perivascular lesions confined to the cortex, and type 3 extending from the cortical surface to layer 3 or 4 of the cortex. In grey matter plaques, demyelination is accompanied by mild microglial activation. Cortical pathology seems to play an important role in MS and cortical lesions may account for many of the cognitive changes occurring in the later stages of the disease.

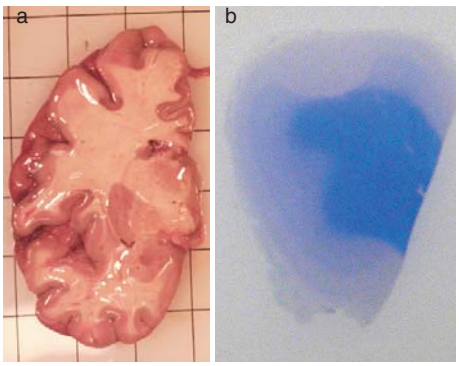


Fig 6: This coronal cut shows a cortical plaque at the base of the superior frontal sulcus (a); A cortical plaque is seen with LFB/PAS (b).

Remyelination

Remyelination is commonly seen in cases of relapsing-remitting MS. Defined as shadow plaques, areas of myelin recovery appear as plaque-like lesions where myelin stains weakly, cellularity is increased due to an increased number of oligodendrocytes and progenitor cells and myelin sheaths appear to be thinner than normal and of relatively uniform thickness. Less commonly, recovery of myelin is nearly complete and shadow plaques are indistinguishable from normal white matter. In these cases, the presence of mild gliosis, corpora amylacea and a few macrophages containing products of myelin breakdown at the periphery of the lesion may be helpful. Regeneration of central myelin is sometimes accompanied by invasion of Schwann cells migrating from the root entry or exit zones of peripheral nerves. In many instances, recurrent demyelination may occur at the edge of shadow plaques causing enlargement of the lesion. Episodes of myelin breakdown in shadow plaques eventually lead to gliosis with tissue scarring so that further remyelination can no longer occur. For this reason, recovery of myelin becomes less effective with disease progression so that post-mortem examination of brains from patients with long standing disease hardly ever reveals shadow plaques.

Clinico-Pathological variants of multiple sclerosis

Relapsing remitting type: Relapsing remitting type is the commonest variant of MS. It is characterised by periods of exacerbation with a variable amount of improvement between attacks. The pathology of typical relapsing remitting MS consists of disseminated plaques of different ages. Plaques can be found wherever there is central myelin. Lesions range from acute plaques to early and late active and chronic inactive plaques. Although plaques can appear anywhere, the periventricular white matter, optic nerves, spinal cord, and juxtacortical areas are the commonest sites. The majority of patients then develop secondary progressive MS.

Secondary progressive: Change from relapsing remitting to secondary progressive MS usually occurs in patients in their 40s or early 50s after many years of disease. Clinically, the secondary progressive course is marked by slowly ascending paralysis or rarely by progressive ataxia. Pathological examination demonstrates loss of axons in the spinal cord with cord atrophy. Many plaques are chronic inactive and only a few appear to be active plaques. A feature of secondary progressive MS is also degeneration of multiple individual nerve fibres, which is likely to be the result of inadequate supply of transported materials. Demyelination of individual fibres could be the substrate for the slowly progressive ascending paralysis.

Primary progressive: The primary progressive form of the disease accounts for about 10% of cases of MS and usually occurs in older patients. Onset is insidious and progression is constant. Disability affects primarily the spinal cord without exacerbations or remissions. Pathologically, lesions in primary progressive MS feature T-lymphocytes and macrophages but there is no deposition of IgG and complement. A hallmark of this variant is death of oligodendrocytes, which occurs in the white matter adjacent to areas of demyelination with the simultaneous loss of various myelin proteins.

Marburg's type: This disease was first described by Otto Marburg in 1906. Marburg documented a few cases presenting with a short and fulminant course and showing extensive myelin destruction. Clinically, Marburg disease is an acute, severe and progressive condition with no relapsing–remitting course. The illness progresses relentlessly and often leads to death within months from onset. Such an acute course may be evident from the beginning or develop in the setting of otherwise classical chronic MS. The few patients that survive the acute phase then show a relapsing remitting course. In Marburg disease, demyelination usually begins in the hemispheres or in the brainstem. Distribution of the lesions is indistinguishable from classical MS, but unlike classical MS, myelin loss occurs simultaneously in all affected areas. On histological grounds, lesions are similar to those of classical MS although they may contain more inflammatory infiltrates and appear more destructive. The margins of the lesions are often indistinct and myelin breakdown may be patchy or incomplete. Reactive astrocytes are scattered; oligodendroglial cells usually appear to be considerably reduced in the acute lesions although there is no evidence of their death and they increase in older lesions, indicating regeneration. Axonal damage is prominent.

Balo-type concentric sclerosis: Described by Joseph Balo in 1928 as 'Encephalitis periaxialis concentrica' and then characterised by Courville in 1970, this disease is aggressive and often leads to death in weeks to months. The age of onset ranges between the first and the fifth decade and there are no clinical findings that distinguish this variant from other types of MS. Some cases with Balo-type lesions may improve and develop a typical relapsing remitting MS. The striking and diagnostic pathological feature is the presence of alternating bands of demyelinated white matter with bands of preserved or regenerated myelin. These concentric lesions always involve the cerebral hemispheres, most commonly the frontal lobe, and may range from one to several centimetres in diameter. They can be spherical or irregular. Histological examination suggests that the lesions expand over weeks or months by progressive addition of bands of myelin breakdown. The demyelinated areas exhibit axonal preservation, absence of oligodendroglial cells, and variable inflammatory infiltrates. There is currently no anatomical, immunohistochemical, vascular or immunological explanation for the remarkable development of concentric, alternating bands of demyelination and white matter preservation.

Neuromyelitis optica of Devic: In 1894, Eugene Devic reported the case of a 45-year-old woman who presented with intractable headache, depression and generalised weakness. The illness progressed with urinary retention and complete paraplegia and eventually with complete bilateral blindness whereas the depression and headache resolved with time. Pathological examination demonstrated demyelinating and necrotising lesions of both white and grey matter limited to the spinal cord and optic nerves. This patient and another 16 reported in Europe and the United States were studied in the doctoral thesis of Fernand Gault 'De la neuromyélite optique aiguë' in the same year and published by Devic. In his paper, Devic named the disorder 'neuro-myélite optique' or 'neuroptico-myélite' as a clinical type, or rather a syndrome and suggested a relationship with an acute form of MS. It was Acchiote who proposed in 1907 to define neuromyelitis optica as Devic's disease. Devic's type MS is an acute illness characterised by optic neuritis and transverse myelitis, which occur within a short time of each other and with little or no involvement of other

parts of the central nervous system. Unlike chronic MS, this variant appears to be common in Asians and Africans. It is usually monophasic although several cases have developed a relapsing remitting course. In these instances, residual lesions after attacks are more severe and more necrotic than classical MS. On pathological grounds, Devic's lesions are composed of isolated or confluent areas of demyelination with tissue destruction. Perivascular cuffing by T-lymphocytes is present in many cases. When the episode of demyelination resolves, marked atrophy and even cystic changes may follow. Interestingly, the few plaques found in the cerebral hemispheres of patients with Devic's disease are histologically similar to plaques of classical MS. Whether Devic's disease represents a variant of MS or a distinct entity remains unclear and questions that Devic asked at the end of his study on the reasons for such a peculiar distribution of lesions and its pathogenesis still remain unanswered.

Myelinoclastic diffuse sclerosis or Schilder's disease: Schilder's disease is a controversial entity and for a long time it has been unclear whether this condition fitted into the classification of MS variants. The reason for this controversy was the fact that the second and third case described by Paul Schilder himself respectively in 1913 and 1924 were most likely adrenoleukodystrophy and subacute sclerosing panencephalitis. It is now accepted that the 14-year old female patient reported in 1912 was an example of MS.[11] The designation of Schilder's disease is nowadays applied to cases with acute bilateral demyelination of cerebral hemispheres. Patients may present with hemiparesis, seizures, changes in their behaviour and signs of increased intracranial pressure. The course is typically progressive and neurological dysfunction widespread. Pathologically, the cases diagnosed as Schilder's disease demonstrate asymmetrical sharp areas of extensive myelin loss predominantly affecting the cerebral hemispheres. Involvement is often bilateral. A peculiar feature is preservation of the subcortical 'U' fibres although this finding is not invariable. At the microscopic level, changes in acute lesions are similar to those observed in classical MS but unlike the classical variant cavitation or multiple cysts are common. Older demyelinated areas feature little or no lymphocytic inflammation. Axonal damage is always present and seems more severe in older parts of the lesions.

Diagnosis of MS on surgical samples

Rarely, plaques may present as a single space-occupying lesion and mimic an intrinsic brain tumour. In these instances, the differential diagnosis with diffuse astrocytomas or oligodendrogliomas is difficult if not impossible using neuroimaging studies (Figure 7a) and a biopsy is often necessary. Histological examination of surgical biopsies in patients with MS is challenging and poses considerable problems of interpretation. Active plaques are always hypercellular and reactive astrocytes may show severe nuclear atypia and mitotic activity (Figure 7b). Also, macrophages may mimic neoplastic cells, and particularly neoplastic oligodendrocytes because during the first stages of their activation they feature little cytoplasm and a centrally placed round nucleus. Histochemical stains for myelin and immunohistochemistry are mandatory in these cases and complete clinical information needs to be taken into consideration before issuing the final diagnosis.

The issue of pathogenesis

The pathogenesis of MS is obscure and the history of the disease is also the history of the many hypotheses on the causative mechanisms underlying myelin destruction. Despite the enormous body of results achieved so far, there are several questions that require an urgent answer if we are to achieve the result of a cure for patients with MS. We are all clear that the immune system is somehow tricked into destroying central myelin but the processes that sustain such immune-mediated damage in humans remain uncertain and the key question as to whether the immune response to myelin is primary or secondary to another disease mechanism is still unanswered. The other, perhaps more speculative question is about whether the cause of MS is genuinely enigmatic or rather that we are merely incapable of understanding what is in front of our eyes. We entirely agree on the comment by Trapp that our eyes see only what our mind is prepared to comprehend.[13]

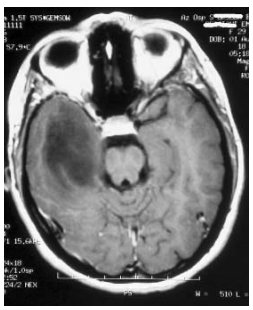
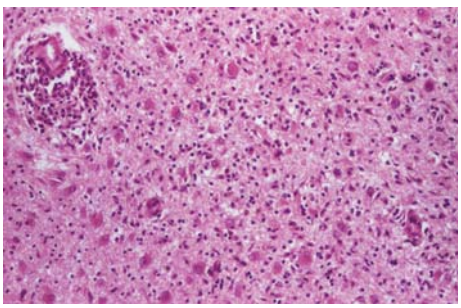


Fig 7: Single plaques may mimic intrinsic tumours. This axial T1-weighted MR-scan after gadolinium administration demonstrates a right temporal hypointense lesion with no contrast uptake (a). Histologically, the lesion features high cellularity and nuclear atypia that can be misinterpreted as an astrocytoma (b, Haematoxylin-eosin).



Conclusion

As a conclusion of this brief review, I would like to mention two recent studies that suggest intriguing explanations of the pathogenesis of MS and give hope that the real cause will be revealed soon. In the first study, published in the Annals of Neurology by Barnett and Prineas[1] the authors observed the initial stages of demyelination in a young patient with relapsing-remitting MS and suggested that formation of plaques begins with apoptotic death of oligodendrocytes and that death of oligodendroglial cells is the primary cause of inflammation. Activation of the immune system comes later, only when complement and immunoglobulins begin accumulating on myelin sheaths. The other study published by Mastronardi and Moscarello[9] suggests an interesting and innovative pathogenetic hypothesis. The authors propose that the initial degenerative process results from a failure to maintain adult compact myelin which becomes more easily degradable. The decreased stability of myelin seems to depend on metabolic causes such as the loss of positive charges on myelin basic protein and changes in the microtubular network of oligodendrocytes. Interestingly, the authors show that white and grey matter distant from areas of demyelination are also affected.

Given the lack of a clear understanding of MS, we should be open to all interpretations and be ready to go beyond the dogma of MS being primarily an inflammatory disease. Although there is no doubt that the immune system plays a key role, these two hypotheses seem intriguing and it will be important to determine if a structural impairment of myelin can trigger oligodendrocyte death with subsequent activation of the immune response and whether this can help explain the clinicopathological heterogeneity of MS.

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Acknowledgements:

Dr SM Gentleman PhD – Reader in Experimental Neuropathology, Department of Neuropathology
Prof R Reynolds BSc PhD – Professor of Cellular Neurobiology, Scientific Director of the UKMSTB
Dr O Malik MD – Consultant Neurologist, Clinical Director of the UKMSTB
Dr R Nicholas MD – Consultant Neurologist, referring Neurologist of the UKMSTB
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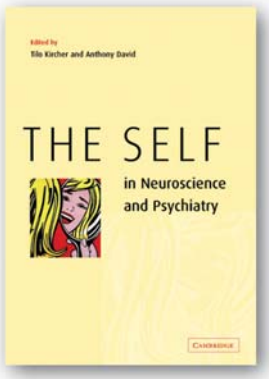
The Self in Neuroscience and Psychiatry



Edited by: Kircher T, David A, eds
Published by: Cambridge University Press
ISBN: 0521533503
Price: £24.95

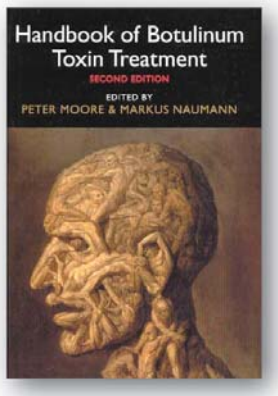
Like our perceived world, our self is a construction of our mind. But self appears to be a particular perception, with particular properties. Unlike perceptions of the external world it cannot readily be shared, and unlike perceptions of the external world it generally has a quality of continuity and changelessness over time that can be remarkably robust to changes in (our perceptions of) the external world. Yet the perception of self can change, and such phenomena are recognised both as a consequence of focal brain injury, and are the level at which some conceptions of schizophrenia are framed. This book is a wonderfully wide-ranging, and demanding, *tour de force*. It synthesises accounts of self from a variety of perspectives: psychological, philosophical, historical, linguistic, social, psychiatric, computing and basic neuroscience. The editors are to be commended for ensuring that such authors from such diverse backgrounds have managed to convey their insights in generally accessible language. The "problem" of self is clearly closely related to the "problem" of consciousness, at its highest, most fascinating level. Inevitably, there is no overall reconciliation of these perspectives yet, but it's a fascinating overview of work under way in these areas. Some surprisingly clear and consistent themes do emerge (such as the necessity, if not sufficiency, of right frontotemporal structures for access to self-awareness and episodic memory) and the promise of significant progress is palpable.

The clinical relevance is to situations where that "continuous" quality of the self is lost, and the perception of self fundamentally changes. Perhaps inevitably, given that the editors and many authors are psychiatrists, the clinical emphasis is on schizophrenia, although the neurology of focal acquired brain injury is used to inform models of self-awareness. There are certainly many insights into consciousness and self to be gained from the "natural experiments" of both schizophrenia and focal brain injury. Both give rise to observations that suggest that (self-)consciousness may be a multiple, "multi-track", rather than unitary phenomenon: the phenomenon of thought insertion, a thought that the thinker does not "own", suggests a dissociability of thought and "ownership". Zeki's model of "multiple microconsciousnesses" in the context of visual awareness is compatible. The fact that we generally have a unitary perception of our self may ultimately relate to a general tendency for temporally near-coincident coherence of perceptions across modalities: I plan to type an "a" on the computer keyboard, make a movement of my left little finger, hear a click and see an "a" appear on the screen all in a coherent way.

This is a fascinating and highly recommended read.

Rob Forsyth, Newcastle.

Handbook of Botulinum Toxin Treatment



Editors: Peter Moore and Marcus Naumann
Published by: Blackwell Science
ISBN: 0632059575
Price: £79.50

The journey of botulinum toxin from an experimental treatment for strabismus to its current ever-expanding list of indications and prominent public profile has been an astounding one. It is therefore of great importance for practising neurologists to have a guide to the uses of botulinum toxin, and in particular a text which can separate fact from hyperbole. Peter Moore and Marcus Naumann as editors have, in the second edition of their book, provided just such a text. Their book gives readers unfamiliar with the uses of botulinum toxin, those learning how to use it, and experienced practicioners an excellent book to use as a reference and practical guide.

The book starts with a good historical introduction, followed by in-depth information on the mechanisms of action of botulinum toxin. There then follows a practical guide to an approach to treating a patient with botulinum toxin, in particular negotiating the different types of toxin and their differing potency, how to counsel the potential patient regarding risks and benefits, and how to manage follow-up. Specific attention is paid to EMG guided injection technique.

The subsequent chapters deal with each indication of botulinum toxin from dystonia to spasticity, including more unusual or emerging indications such as hyperhidrosis, urinary dysfunction and pain. A section on the cosmetic use of botulinum toxin is also provided. In each of these sections, practical guidance is given regarding patient selection, injection sites and dosage, with equivalent dose information provided for each of the three available toxins. Each section is well referenced, giving the reader up to date information regarding the level of evidence available to support each indication for the use of botulinum toxin. Excellent diagrams are provided throughout to indicate injection sites and to remind readers of the relevant anatomy.

In all this is an excellent book, and one that clearly fills a gap in the market currently. Its practical nature will, I am sure, appeal to many who are learning injection technique, and its comprehensiveness makes it an excellent reference book for those who are already familiar with botulinum toxin injections.

Mark Edwards, London.

Neurosurgery Oral Board Review

Jonathan Stuart Citow, Lydia M Johns
Published by: Thieme
ISBN: 3131357711, **Price:** €44,95

The introduction of this book states that it was compiled from notes scribbled down while studying for the Neurosurgery Oral Board examination. The manual is designed to act as a supplement to the knowledge gained during training. The book addresses these objectives in a systematic, structured fashion. As a result, this manual is full of information, with very few wasted words. It is the nature of such small revision aids that numerous lists of key points are detailed. This, therefore, makes the book difficult to assimilate in other than short doses.

Overall, I think that the book is a useful read for all Neurosurgical trainees, in the mid to latter stages of their training. It provides a comprehensive, focused summary of nearly all conditions that a Neurosurgical trainee is likely to encounter. For example, the one page dedicated to thoracic disc disease precisely describes a variety of operative approaches with clarity as an aide memoire.

In summary, the book is comprehensive and concise. It is well illustrated and is likely to be found helpful in the run-up to specialist examination.

Peter C Whitfield, Plymouth.

Saturday - Ian McEwan

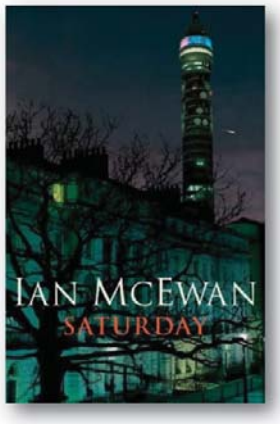
"There were three thousand six hundred and fifty three days like that in his stretch. From the first clang of the rail to the last clang of the rail. The three extra days were for leap years"

So wrote Alexander Solzhenitsyn about a day in the life of Ivan Denisovich, a day that was exactly like the rest of his days in the harsh Gulag to which he had been sentenced to 3653 days, an outcast for disagreeing with government thinking. Ian McEwan's latest book on the other hand, follows one Saturday in the life of Henry Perowne, a Saturday unlike any other day, a day played out against mass protests against the government.

Henry is a very successful London neurosurgeon who lives in an expensive house close to his hospital of work in Bloomsbury – presumably the National Hospital for Neurology and Neurosurgery at Queen Square. He enjoys the trappings of success, his tastes are expensive, his family both beautiful and gifted.

As the Saturday that temporally frames this novel begins, Henry is suffering from insomnia and watches from his bedroom a flaming plane streak across the sky en route to Heathrow. It ends as he shuts this same bedroom window on a waking London some 24 odd hours later. During this Saturday the lives of Henry and those closest to him oscillate from normal routine to unique experiences, against the backdrop of the anti-Iraqi protests of the 15th February 2003. We learn of his skills as a surgeon and clinician and of the various talents of his family as they all converge for a memorable reunion and evening meal. We see Henry in the comfortable surroundings of his work, home and family whilst also having to confront the unpredictable street life of London and the minds of those with neurodegenerative disorders. An accidental encounter with Baxter, a patient with Huntington's Disease, serves to destabilise the world of Henry, the mutant gene causing a disorder that extends beyond the confines of Baxter's failing brain. Thus we see Henry as surgeon, father, husband, martyr, educated clinician but appallingly ignorant of art and confused about his views on life and family, exemplified in his difficulty in resolving his attitude towards the impending war in Iraq. The decisive surgeon finds himself full of indecision in a world that seems to have made its mind up about the validity of the war. In contrast, his wife Rosalind whilst being wise is also passionate, affectionate and wholly beholden to Henry who in turn is almost childishly dependent on her. Into this day comes Daisy, the poet daughter who shares none of her father's ambiguities on the war and Theo, the-blues-playing son, who lives in a world dominated by music. Intellectually superior to them all is Grammaticus, Rosalind's father, a poet of international repute with whom Henry shares little other than their mutual pride in their own work. We are drawn into this small family and their part of London – the microcosm of individual lives played out on the background of the macrocosm of mass protest. So it is that this book sets out its themes of relationships and reactions – what should be the response to injustice? When does inequality become injustice? What is our responsibility to the less privileged, abused people in society? What is our role in life and within the family? And how does our work impinge on our families and those around us?

In this book we learn a lot about Henry and his family and Baxter. We learn a lot about neurosurgical procedures and neurology – indeed it is everywhere, such that even the aged mother of Henry has multi-infarct dementia. We learn a lot about families but fundamentally what we really learn is that we will all have to face questions of identity – what constitutes "us" and how we are constructed and deconstructed by life and disease. It is a book that leaves us feeling self conscious and that challenges our value system, both as individuals in our private worlds and as a member of a democratic society. There are of course many different ways of seeking a sense of worth and peace in life, and this book tackles many of them with a secular emphasis….whether you agree with this is a matter of opinion, but Ian McEwan's book will challenge you to re-evaluate the life you lead…. *Roger Barker, Cambridge.*



Author: Ian McEwan
Published by: Jonathan Cape
ISBN: 0224072994
Price: £17.99

An Early Account of Brain Transplantation

AJ Larner,[1] RA Barker[2]
1. Walton Centre for Neurology and Neurosurgery, Liverpool.
2. Brain Repair Centre, Cambridge.

Correspondence to:
Dr Larner,
Email: a.larner@thewaltoncentre.nhs.uk

The accounts with which the surgeon Lemuel Gulliver returned from his various travels in the late 17th and early 18th century were often treated with considerable scepticism if not frank incredulity and ridicule. Nonetheless, as someone with some medical training, we should perhaps look carefully at his reports of medical practice in other lands. Amongst these, there appears to be an early account of brain transplantation surgery, originating from the Academy at Lagado on the island of Balnibarbi:

> When Parties in a State are violent, [the Ingenious Doctor] offered a wonderful Contrivance to reconcile them. The Method is this. You take an Hundred Leaders of each Party, you dispose them into Couples of such whose Heads are nearest of a size; then let two nice Operators saw off the *Occiput* of each Couple at the same time, in such a manner that the Brain may be equally divided. Let the Occiputs thus cut off be interchanged, applying each to the head of his opposite Party-man. It seems indeed to be a Work that requireth some exactness, but the Professor assured us, that if it were dextrously performed, the Cure would be infallible. For he argued thus; that the two half Brains being left to debate the Matter between themselves within the space of one Skull, would soon come to a good Understanding, and produce that Moderation as well as Regularity of thinking, so much to be wished for in the Heads of those, who imagine they come into the World only to watch and govern its Motion.

Mr Lemuel Gulliver, from 'Gulliver's Travels' as illustrated by Luis Quintanilla. www.lqart.org

Dean Jonathan Swift (1667-1745), Gulliver's creator, suffered from cognitive decline probably due to a dementing disorder, possibly Alzheimer's disease, in later life.[1,2] In this context, it is perhaps ironic that attempts to transplant brain tissue have been explored for the treatment of dementing disorders such as Alzheimer's disease.[3]

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Frameless Stereotactic Neuronavigation for Space Occupying Lesions

Introduction

Prior to the widespread advent of frameless stereotaxy, intracranial tumour surgery relied upon a 3-D conceptualisation of anatomy from pre-operative imaging. External anatomical landmarks such as the coronal suture and auricle helped guide the placement of a craniotomy. Bone flaps were often planned with a margin for error, particularly when locating non-lobar tumours. The choice of an appropriate trajectory for a burr hole biopsy was frequently suboptimal with negative biopsies and significant associated morbidity. For less accessible lesions a frame-based stereotactic craniotomy was performed. This entailed placement of a stereotactic frame, acquisition of pre-operative images and calculation of tri-planar coordinates. Such procedures, although cumbersome and to some extent restrictive in the access they provide, remain part of the armamentarium for small deep targets. However, the evolution of sophisticated, accurate frameless stereotaxy has significantly changed the surgical approach to the majority of patients with space occupying lesions.[1] Application of stereotactic technology can also be used to locate other lesions such as cavernomas and abscesses. Neuronavigation is also used to facilitate rigid endoscopic procedures. This paper aims to outline the principles of neuronavigation for neuro-oncology.

System Components

Several manufacturers supply serviceable neuronavigation systems. The fundamental components include:

- Computer workstation (pre-operative and intra-operative) with neuronavigation software and computer monitor
- Medical imaging input (either through a DICOM link or a portable digital data format)
- Optical digitiser with infrared emitters and two infrared cameras
- Reference frame (secured to a head clamp)
- Registration stars (frames) for surgical instruments.
- Passive infrared reflectors (aluminium impregnated glass spheres)

Understanding the Basics

The principal concepts that underpin neuronavigation are simple:

- Pre-operative imaging. This must comprise sequential, non-overlapping volumetric slices without interspacing. Most commonly MRI slices of 1-3 mm are used to provide this 'image dataset'.
- Accurate registration of the 'image dataset' with the 'real time surgical space'.
- A triangulation based system (analogous to Satellite navigation) to track operative instruments.
- A dynamic referencing system to maintain the validity of registration during the operative procedure.

Pre-operative Imaging

The mainstay of pre-operative diagnostic imaging in patients with intracranial mass lesions is the MRI scan. If each slice represents a known thickness of brain tissue (e.g. 2 mm) and the slices are contiguous without overlaps or spaces, the summation of the slices creates a 3-D reconstruction of the brain. This digital imaging dataset is then transferred to the workstation. Software enables the imaging dataset to be viewed in multiple planes and as a 3-D reconstruction, permitting pre-operative planning to be undertaken (Figure 1). The target lesion is identified and the surgical approach planned. Image fusion software can now fuse digitised information from other modalities such as CT and PET with the MRI scan at this stage.[2] Although functional imaging is not yet widely available preliminary experience indicates that delineation of elo-

Peter Whitfield is a Consultant Neurosurgeon at the South West Neurosurgical Centre in Plymouth. He has previously worked in Glasgow and Aberdeen in addition to his higher surgical training in Cambridge. Peter has a PhD in the molecular biology of cerebral ischaemia. His clinical interests include vascular neurosurgery, image guided tumour surgery and microsurgical spinal surgery. He has a practical interest in medical education and is involved in implementation of the Phase 2 teaching in neurosciences at the Peninsula Medical School.

Correspondence to:
Peter Whitfield,
South West Neurosurgery Centre,
Derriford Hospital,
Plymouth PL6 8DH.
Email:
Peter.whitfield@phnt.swest.nhs.uk

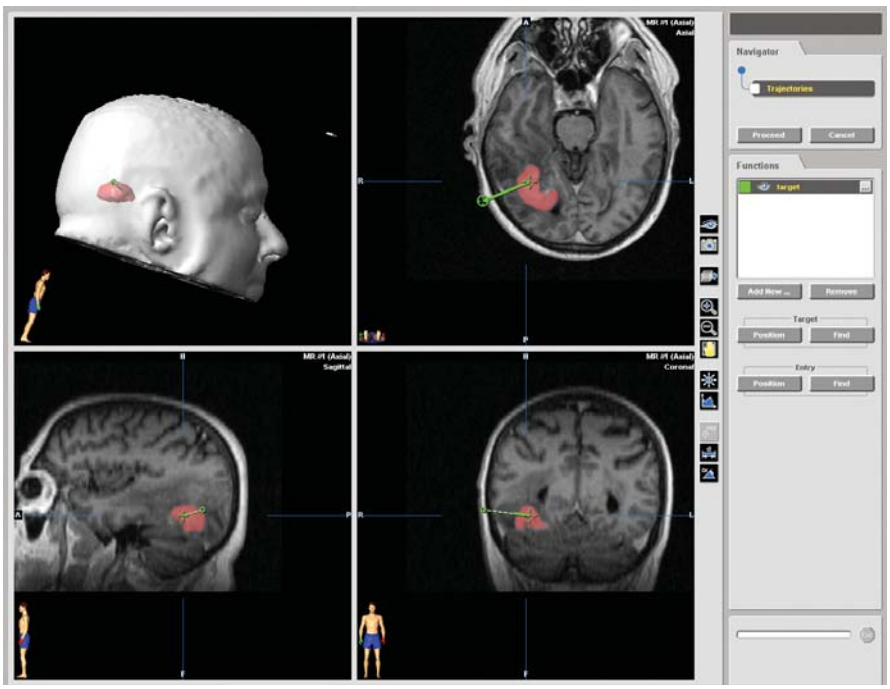

Figure 1: Navigation software enables the target lesion to be examined in multiple planes. Fiducials were utilised to perform point registration in this case. The surgical approach can be planned pre-operatively, taking into account anatomical factors.

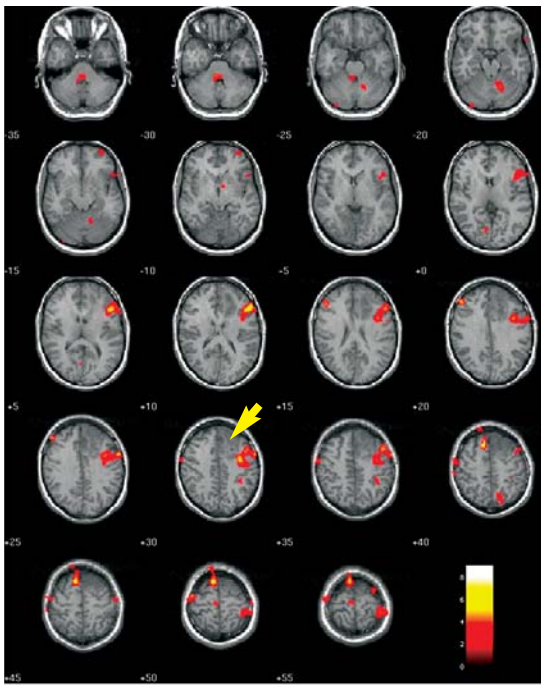

Figure 2: Positron Emission Tomograph demonstrating regional cerebral blood flow in a comprehension language paradigm in a patient with a low grade glioma. Note the proximity of the speech cortex to the tumour. The incorporation of functional information into the navigation system is of immense potential benefit.

quent cortex will assist surgical planning (Figure 2). The planning software has now reached a level of sophistication whereby the tumour and other structures (e.g. cranial nerves, vessels, eloquent cortex) can be independently outlined and shaded to facilitate surgery.

Registration

Registration is the process by which the pre-operative image dataset is aligned with the real-time anatomy of the surgical space in the operating theatre (Figure 3).[3] To prevent movement the patient's head is held in a Mayfield Clamp in view of the Optical Digitiser. Registration is then performed using either a point or surface alignment technique. The workstation/optical digitiser recognises a default surgical pointer instrument within the field of view. The tip of this tool is then used to identify the real-time location of widely spaced, non-collinear fiducials (surface markers) placed on the surface of the head prior to the pre-operative image dataset acquisition. The co-alignment of these image dataset points with the surgical field achieves registration. Alternatively, anatomical landmarks identifiable on the imaging and in the surgical field (e.g. nasion, external auditory canal, orbital margins) can be co-aligned for registration. Registration using surface alignment uses complex mathematical algorithms to co-align the surface of the patient's head in the operating theatre with the surface of the image dataset. A Laser beam is used within sight of the optical digitiser to delineate the peri-orbital and forehead regions of the scalp. Co-alignment of the thousands of surface points identified by the Laser and the surface contours of the image dataset enables registration. The manual addition of another 10 or so points from all quadrants of the scalp using the default pointer further refines the accuracy of this technique.

The accuracy of registration must be confirmed with visual checks. The computer monitor shows the pre-operative image dataset (usually in axial, coronal and sagittal planes with a 3D reconstruction view). Known landmarks on this dataset are identified in the surgical space using the default pointer tool (e.g. globes, orbits, external auditory meatus, tragus). The radiological and real-time anatomical landmarks should coincide exactly. If there are discrepancies the registration process should be repeated.

Triangulation Based Instrument Tracking

If 3 or 4 passive infrared reflectors are clamped via a star shaped reference frame to a surgical instrument, and the tip of the instrument is registered with a known location, intraoperative tracking can be performed. A triangulation principle is used to achieve this aim. Infrared light emitted by the optical digitiser is reflected from the passive reflectors to the 2 cameras. The position of the instrument can then be calculated and transcribed onto the imaging dataset enabling intraoperative tracking on the navigation system monitor.

Dynamic Referencing

Microsurgical approaches demand a straight corridor of access to permit illumination of the target area. To facilitate access and to provide manoeuvrability around the circumference of a tumour, frequent adjustments in operating table position are necessary during a resection procedure. Each movement alters the spatial relationship between the real-time surgical space and the previously registered position of the imaging dataset. To prevent such adjustments from invalidating registration, an optical reference frame with passive infrared reflectors is secured to the Mayfield head clamp. The optical digitisers recognise the fixed relationship between the reference frame and the patient's head. Any movement of the operating table therefore moves not only the patient but also the dynamic reference frame, maintaining valid registration. Similarly, if the optical digitiser is moved, the constant spatial relationship between the reference frame and the surgical space maintains registration.

Figure 3: Neuronavigation equipment. The optical digitiser comprises LED emitters and infrared cameras. The touch screen monitor provides the surgeon with readily accessible software access.

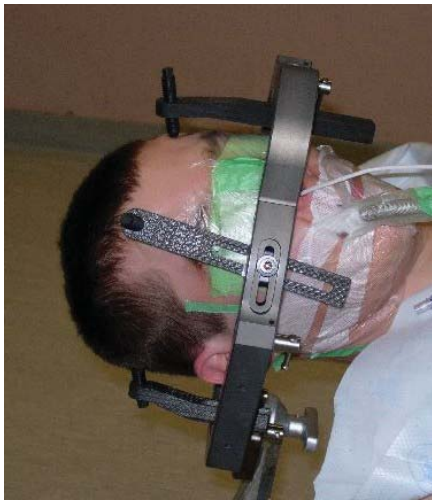

Figure 4: This patient had a small cavernoma just beneath the motor strip. The lesion could not be located with frameless stereotaxy. Image fusion utilising MRI and CT scans was performed to maximise the quality of the imaging dataset prior to a frame-based stereotactic procedure. This technique enabled accurate identification of the lesion that was resected without incurring any neurological deficit.

Intra-Operative Navigation

Craniotomy

Following registration, neuronavigation can be performed. Initially the pointer can be used to map out the site of a craniotomy flap. For small convexity meningiomas the bone flap can be accurately sited minimising the size of the flap. Care needs to be exercised when drawing a flap to account for parallax-type errors. These are minimised by planning a bone flap perpendicular, rather than oblique, to the bone. When working intracranially it is convenient to register familiar surgical instruments that can then be tracked as described above. The operating microscope can also be used as a surgical tool. The microscope has a passive reflector star secured in the line of sight from the optical digitiser. This permits the focal point of the microscope to be tracked in the surgical space and observed in the image space. The previously outlined target lesion (from pre-operative planning) can also be visualised in a "head-up" display to help direct both the dissection to the target and to guide resection margins during the procedure.

Burrhole Biopsy

Neuronavigation can be used to perform biopsies with minimal trauma to the brain. A lockable trajectory arm is secured to the Mayfield clamp. A 2.0 mm drill guide with a registration star attached is then used in conjunction with a concentric ring target view that enables the required trajectory to be determined. The addition of a virtual tip extension to the drill guide confirms that the target is at the centre of the trajectory. The drill guide is then secured in the lockable trajectory arm and a small twist drill hole performed through the guide. After opening the dura and keeping the position of the trajectory arm constant a disposable double lumen side cutting sedan needle is inserted through the drill guide to perform the biopsy at the appropriate depth. Registration of the needle can be undertaken to allow real-time visualisa-

tion of the biopsy on the pre-operative image dataset. The outer sheath of the needle remains in situ whilst samples are taken at 12, 4 and 8 o'clock. The needle can then be withdrawn a few millimetres to permit repeat sampling, minimising sampling errors.

Neuronavigation Errors

Errors can occur at any stage during the neuronavigation process. These can seriously compromise the accuracy of neuronavigation. Diligence therefore needs to be observed at all stages to minimise, recognise and avoid errors (Figure 4). Some of these are shown in Table 1. The use of intraoperative MRI scanning with all its associated inherent problems aims to recognise brainshift and enable an up to date imaging dataset to be used. Whilst time consuming and expensive such technology may have a role to play, particularly during resective procedures for low-grade gliomas.

Summary

The rapid evolution of neuronavigation over the past decade has led to numerous publications describing the application and advancement of such technology. In this era of evidence-based medicine most of the literature supporting the use of neuronavigation comprises single centre case series. However, the confidence instilled by this technology in the surgical fraternity is such that randomised trials of efficacy are considered by most as inappropriate and unethical. Future developments are likely to be targeted at circumventing neuronavigation errors and providing up to date image sets during surgery.

Table 1: A summary of errors that the operator should recognise when undertaking image guided neurosurgery

Error Domain	*Types of Error*	*Methods to minimise errors*
Image dataset acquisition	• *Overlapping or interspacing slices.* • *Variable slice thickness due to mechanical factors* • *Resolution errors and limitations* • *Errors associated with image fusion algorithms*	• *Careful planning on well maintained equipment*
Registration	• *Adverse skin mobility* • *Poor delineation of occipital region in surface mapping models* • *Fiducial movement*	• *Careful placement of Mayfield clamp* • *Combination of surface and point registration techniques* • *Inclusion of the whole head during registration*
Intra-operative errors	• *Brainshift* • *Parallax type error when planning craniotomy* • *Head movement causing loss of registration* • *Small errors in trajectory angle are magnified at the tip of a biopsy needle*	• *Careful positioning* • *Prudent use of mannitol* • *Plan flap perpendicular to skull* • *Ensure head secure in Mayfield clamp* • *Use a rigid biopsy needle* • *Use the largest registration star possible when tracking instruments*

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Erratum

We are fans of ACNR and regularly use it for our journal club. Recently we looked at the article on Subarachnoid Haemorrhage on page 14 of Vol 4, Number 3, 2004. We enjoyed it very much but questioned a statement towards the end of paragraph 2 under diagnosis and grading where it is suggested that uniformly blood stained CSF supports a diagnosis of a Sylvian Fissure Haematoma. Is this correct?

– Tom Hughes, on behalf of the Neurosciences Journal Club, University Hospital of Wales, Cardiff.

You have spotted an error! The paragraph should read "...uniformly blood stained CSF supports a diagnosis of subarachnoid haemorrhage and warrants further investigation..."

– Peter Whitfield, Plymouth.

Aphasia

Introduction

The term "aphasia" refers to an acquired disorder of language function caused by brain damage. It was introduced in 1864 by Trousseau to replace the term "aphemia", used in the classical 1861 description of the syndrome by Broca. However, the term "aphemia" continues to be used, referring usually to severely impaired, non-fluent speech output, considered by some as an independent phenomenon, by others as a form of aphasia. Some authors prefer the term "dysphasia" to "aphasia", to stress that the syndrome is usually associated with a dysfunction rather than a complete loss of language abilities. Aphasia is often accompanied by disorders of reading and writing. A disorder of reading is referred to as "alexia" or "dyslexia" (some authors use the first term for an acquired, the second for a developmental disorder). A disorder of writing can be described as "agraphia" or "dysgraphia".

Aphasia can be distinguished on the one hand from peripheral disorders of speech and articulation, such as dysarthria, speech ataxia and speech apraxia, on the other hand from other central deficits affecting memory, attention or executive function. The distinction is, however, not always straightforward. Firstly, different deficits can co-occur, e.g. aphasia and dysarthria. Secondly, given the close interaction between language and other cognitive functions, the same clinical picture, such as semantic dementia, can be interpreted either as a form of aphasia or as a semantic memory disorder with linguistic ramifications. Another problematic distinction is that between aphasia and language abnormalities seen in psychiatric patients, such as "schizophasia". It is still a matter of considerable debate to what extent abstract thinking can be independent of language and hence, not affected by aphasia.

History

Aphasia is one of the earliest documented neurological disorders and has played a central role in advancing our knowledge of brain function. A description of a language disorder following an injury to the temple by the Egyptian surgeon Imhotep (2800 BC) is possibly the earliest recorded case of a localised brain lesion causing a neurological deficit. Descriptions of a sudden loss of language can also be found in the Bible as well as in the medical treatises of ancient Greece and Rome. The observation of dissociations between different aspects of language (e.g. loss of speech with preserved singing, selective noun and verb impairment) in the 18th century prepared the ground for the idea of the dissociability of mental faculties, which, in the next century, lead to the first elaborated models of brain function based on clinico-pathological correlation studies. In the 20th century the study of aphasia influenced the development of many scientific theories, from the modularity of mind to connectionist modelling and it continues to play an important role in the current debates on innateness, functional specialisation, neuronal plasticity.

Etiology

By far the most common cause of aphasia is stroke and the majority of studies of aphasia have been conducted in stroke patients.[1,2] Other common causes include space occupying lesions and head injury. Aphasia also occurs in neurodegenerative diseases, such as Alzheimer's disease (AD), frontal (fv) and semantic dementia (SD) variants of Frontotemporal Dementia (FTD), Parkinson's disease (PD) and Huntington's disease (HD). It is the defining characteristic of Primary Progressive Aphasia (PPA) and can be a prominent and even presenting feature in diseases traditionally considered to affect mainly the motor system, such as Corticobasal Degeneration (CBD), Progressive Supranuclear Palsy (PSP) and Motor Neurone Disease (MND).[3]

Classification

Based on the observation of different forms of aphasia Wernicke and Lichtheim constructed what was to become the most influential model in cognitive neurology. It assumed the existence of two language centres, a sensory and a motor one, connected by a direct and an indirect pathway, the latter connecting both centres with a putative conceptual centre. The model predicted different forms of aphasia on the basis of lesion location (Table 1). Broca's and Wernicke's aphasia were due to direct damage of the motor and sensory centre respectively. A disruption of the direct pathway between the motor and the sensory centre lead to conduction aphasia, while a disconnection between either of them and the conceptual centre produced transcortical-motor and transcortical-sensory aphasia. Extensive damage to different parts of the system resulted in global aphasia, affecting all aspects of language.

Dr Thomas Bak is a Research Associate at the Neurology Department of Addenbrooke's Hospital, MRC Cognition and Brain Sciences Unit and Corpus Christi College, Cambridge. He wrote his thesis on the classification of acute aphasia and is currently working on language dysfunction in disorders traditionally considered as affecting mainly the motor system, in particular PSP, CBD and MND. He is also involved in a cross-linguistic study comparing aphasia in Polish and English speakers.

Correspondence to:
Thomas Bak,
MRC - Cognition and Brain Sciences Unit,
15 Chaucer Road,
Cambridge CB2 2EF.
Tel: 01223 355294, ext 358,
Email: thomas.bak@mrc-cbu.cam.ac.uk

Table 1: The classical forms of aphasia

Diagnosis:	Main characteristics:	Associated deficits:	Localisation (all left hemisphere):
Broca's aphasia	slow, non-fluent, laboured speech, telegraphic speech, agrammatism*	right-sided hemiparesis, dysarthria	medial cerebral artery territory (anterior branch
Wernicke's aphasia	fluent speech, paragrammatism** paraphasias, comprehension deficit	right-sided hemianopia, dyslexia	medial cerebral artery territory (posterior branch)
Conduction aphasia	fluent speech with phonemic paraphasias good comprehension, repetition deficit	right-sided hemisensory deficits	arcuate fasciculus (inferior parietal lobe) supramarginal gyrus
Transcortical-motor aphasia	reduced, dysarthric speech output preserved comprehension & repetition	mutism	frontal lobes (supplementary motor area) deep subcortical
Transcortical-sensory aphasia	fluent, semantic paraphasias, impaired comprehension, preserved repetition	variable	typically temporo-parietal junction, but also anterior perisylvian and deep subcortical areas

* agrammatism – loss of grammatical morphemes (e.g. the third person marker "s" in words like "he runs") and function words (e.g. "at", "also", "because").
** paragrammatism - blending of different sentence structures.

Table 2: Aphasia examination

What to test?	How to test?	What to look for?
Spontaneous speech	asking the patient questions (e.g. the history of the disease etc.), asking to describe a picture	decreased fluency and speed of speech, dysprosody, slurred articulation semantic and phonemic paraphasias, self-correction, conduit d'approche*
Naming	naming of real objects, pictures, drawings naming to description (e.g. What do you call an African animal with a very long neck?)	word finding difficulty, semantic and phonemic naming paraphasias, substitutions, use of superordinate category ("animal" for "giraffe"), neologisms, circumlocutions, perseverations
Repetition	asking the patient to repeat words and sentences	paraphasias, incomplete sentences, breaking up in the middle
Comprehension	asking the patient to answer questions, perform actions or point to objects, people or pictures	failure to follow commands, incorrect answers, performing incorrect actions or performing correct actions in a wrong order
Sentence completion	asking the patient to complete a phrase (e.g. he posted a letter without a….)	facilitates speech production in patients with dynamic aphasia, particularly in sentences with only one plausible answer (… stamp)
Definition	asking the patient to define a concept (e.g. what is an elephant? a violin?)	particularly sensitive to deficits in semantic knowledge, e.g in patients with semantic dementia with otherwise fluent and grammatically correct speech
Phonological processing	asking the patient to judge whether two words start with the same sound, if they rhyme etc.	a useful way to distinguish central phonological deficits (inability to process phonological information) from pure speech output deficits (e.g. dysarthria)

* repeated attempts to articulate the word, getting closer and closer to the target

It is a remarkable achievement of Wernicke and Lichtheim that the terms they introduced are still widely used today[4,1] and that the basic assumption of their model, that of a direct and indirect route between the two language areas, has been recently confirmed using the modern technique of tractography.[5] However, despite the use of the same terms different authors interpret the basic syndromes in very different ways. The agrammatism of Broca's aphasia, a phenomenon which has attracted particular attention of researchers, has been interpreted among others as a selective loss of a particular syntactic module, a breakdown of automatic speech processing, an impairment of rule-based grammar (as opposed to memory-based lexicon) or a compensation strategy. Each interpretation focuses on a particular aspect of the phenomenon but none succeeds in capturing the full range of the observed symptoms. To minimise the theoretical bias many aphasiologists prefer, therefore, to divide aphasia into two broad, descriptive categories: "non-fluent" vs. "fluent".

Since the traditional classification of aphasia is based mainly on the study of chronic stroke patients[6] it is less appropriate for describing acute aphasia, aphasia recovery or aphasias of non-vascular origin. Anomic aphasia is a relatively pure word-finding difficulty, seen in recovery from stroke as well as in neurodegeneration. Dynamic aphasia, originally described by Luria in patients with traumatic brain injury, is also observed in patients with tumours and neurodegenerative processes affecting the frontal lobes. Patients with this form of aphasia have difficulty producing spontaneous speech but are much better on constrained tasks such as naming or sentence completion.

The most extreme form of fluent aphasia is jargon aphasia, in which the speech production is characterised by frequent paraphasias, neologisms, perseverations, non-sense syllables and different words run together into one. This form of aphasia has been observed in patients with subcortical lesions. Despite its dramatic appearance it can be associated with a good recovery.

Localisation

Although generally speaking anterior lesions tend to produce a non-fluent, posterior lesions a fluent aphasia, Broca's and Wernicke's aphasia cannot always be identified with lesions to Broca's (posterior inferior frontal gyrus) and Wernicke's (superior temporal gyrus) area respectively.[7] Broca's aphasia has been observed in patients with intact Broca's area while lesions in Broca's area do not automatically lead to Broca's aphasia. The same applies to Wernicke's aphasia and area. Many other brain regions have been implicated in different forms of aphasia: inferior parietal cortex and supramarginal gyrus (BA 40) have been implicated in conduction aphasia, angular gyrus (BA 39) in written language, supplementary motor cortex (BA 6) in transcortical motor aphasia, the region anterior to Broca's area (BA 45) in dynamic aphasia, anterior insula in non-fluent progressive aphasia.[8] The role of the right hemisphere, cerebellum and basal ganglia in the pathogenesis of aphasia are topics of intense debate.[9]

Aphasia – a language specific phenomenon?

The majority of studies of aphasia has been conducted in a comparatively small number of related languages such as German, French and English. It is questionable, however, that the observations made in a particular language can be generalised to others.[10] The use of free stems (words without grammatical endings), for example, considered to be a hallmark of agrammatism in English, does not occur to the same extent in highly inflected languages such as Greek or Polish. Language-related differences are of particular importance in multilingual patients. The same aphasic process can affect differently the different languages spoken by the same person. The native tongue is often better preserved than languages learned later in life, but the opposite pattern has also been reported.[11] A new and fascinating area of cross-linguistic research is aphasia in sign language, where clinical pictures analogous to Broca's and Wernicke's aphasia have been described.[12]

Assessment

A brief conversation with a patient can provide a lot of valuable information about the language function: speech rate (fluent/non-fluent distinction), pronunciation (articulation, phonology), choice of words (semantics), use of past and present tense (syntax), self-correction of aphasic errors (awareness of the deficit). Table 2 lists simple tests that can easily be performed at the patient's bedside. Table 3 gives examples of some standardised tests for a more comprehensive aphasia assessment. The individual test batteries differ greatly in their length, composition and focus and the choice of an appropriate test depends on the relevant questions. Diagnostic tests (BDAE, WAB, CAT) provide a measure of the severity of aphasia and classify the patients into the main syndromes. They can be useful in the initial assessment and help to chose the right treatment strategy. The tests of communicative abilities (PICA, ANELT), in contrast, focus on practical communication skills, which reflect not only the underlying linguistic deficit but also the compensation strategies as well as an interaction with motor, cognitive and behavioural symptoms, such as depression, apraxia or anosognosia. They are particularly useful in assessing the results of aphasia treatment.

Table 3: Examples of standardised aphasia tests (BDAE, WAB, CAT), a comprehensive test battery (PALPA), tests of communicative abilities (PICA, ANELT), aphasia screening test (TT), and tests of specific language functions such as comprehension (TROG) and semantic processing (PPT, KDT).

Name of the test & its authors:	Structure:	Scope:
Boston Diagnostic Aphasia Examination (BDAE) H. Goodglass & E. Kaplan	34 subtests examining different components of language as well as aspects of perception and problem solving	well known and comprehensive but also long (180 mins) provides a profile of impairment and severity rating
Western Aphasia Battery (WAB) A. Kertesz	contains 10 subtests examining different aspects of language, such as naming, repetition, comprehension	shorter than BDAE (60 mins), determines severity and allows taxonomic categorisation into the main syndromes
Comprehensive Aphasia Test (CAT) K. Swinburn, G.Porter, D.Howard	34 subtests, including a cognitive screening, a language battery (21 subtests) and a disability questionnaire	a new test designed to be completed in 90-120 mins can also be used in the early stages of aphasia
Psycholinguistic Assessment of Language Processing (PALPA) Kay et al	a selection of different individual aphasia tests e.g. phonological processing, reading, writing etc.	individual subtests can be selected and used separately depending on the specific questions in each case
Porch Index of Communicative Ability (PICA), B.E. Porch	18 verbal, gestural and graphic subtests, using 10 common items (e.g. pen, key); 16 point scoring system	a sensitive measure of the ability to communicate and of changes in performance, useful in monitoring treatment
Amesterdam-Nijmegen Everyday Language Test (ANELT), Blomert et al	10 situations in which the patient has to demonstrate practical communication skills, 5 point rating scale	ecologically valid but the rating can be difficult frequently used to evaluate aphasia treatment
Token Test (TT) E. De Renzi & L. Vignolo	a set of geometric tokens of different size and colour patient asked to perform actions (e.g. touch the squares)	used for aphasia screening, quantitative but not qualitative influenced by motor symptoms e.g. apraxia, bradykinesia
Test of the Reception of Grammar (TROG) D. Bishop	20 blocks examining syntactic structures of growing complexity, from single words to embedded phrases	qualitative assessment of comprehension (15-20 mins) applied in language acquisition as well as in aphasia
Pyramids & Palmtrees Test (PPT) D. Howard & K. Patterson	52 pages with triplets of pictures depicting objects and the same number of pages with corresponding words	examines separately picture and word association, assesses verbal and non-verbal semantic knowledge
Kissing and Dancing Test (KDT) T. Bak & J. Hodges	an extension of the PPT, containing the same number of pictures/words in the same format, but depicting actions	assesses specifically the knowledge of actions/verbs, which can dissociate from that of objects/nouns

One of the most important yet often neglected parts of language examination is the assessment of comprehension. The extent of comprehension deficit is easily underestimated, particularly if the patient has a chance to rely on non-verbal cues, the context or the mimic and gestures of the examiner. Many commands widely used to test comprehension, such as "close your eyes" require only understanding of a single word: there is not much more that the patient can do with his/her eyes than to close them. Commands and questions used to test comprehension should be, therefore, more complex and less obvious, e.g. "point to the window after touching the bed" or "how many people in this room are not standing?" There is also the opposite danger: to underestimate the patient's communicative ability. Patients with MND-associated aphasia might still be able to write full sentences at a time when they are virtually mute. Patients with dynamic aphasia or bradykinesia might have little spontaneous speech and be extremely slow in answering open questions. Giving the right tasks, however, such as sentence completion or object naming, one might exhibit a remarkably intact language function.

Treatment and Recovery

The growing recognition of neural plasticity and the functional reorganisation of the brain after injury has had profound impact on our understanding of aphasia. Aphasic syndromes believed to result from specific damage to well-defined parts of the language system became reinterpreted as compensation strategies. These theoretical developments have also increased the interest in aphasia therapy. Some treatments, like constraint-induced aphasia therapy, build explicitly on the experiences of physiotherapy in the rehabilitation of stroke patients. Others make use of the facilitation of language production through association with singing or chanting (Melodic Intonation Therapy MIT) or focus on practical strategies to cope with everyday requirements (Promoting aphasic's communicative effectiveness PACE). In many cases the treatment combines elements from different techniques to adjust to the needs of an individual patient. Despite practical difficulties in evaluating aphasia therapy, a number of meta-analyses could establish their utility in aphasia treatment.[13] Transcranial magnetic stimulation (TMS) has been proposed as a complementary treatment, based on the assumption that the overactivation of the right hemisphere constitutes a maladaptive strategy interfering with recovery.[14] Growing experience with the pharmacotherapy of aphasia suggests that the efficacy of each drug (Piracetam, Dopamine, Bromocriptine, Dexamfetamine, Donepezil) might depend on the stage of aphasia (acute vs. chronic) as well as on its type (fluent vs. non–fluent).[2]

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To list your event in this diary, e-mail brief details to: Rachael@acnr.co.uk

2005

May

Short Courses : Neuro-Medical / Surgical Nursing
May, 2005; Cambridge, UK
E. wood@health-homerton.ac.uk

6th World Congress on Brain Injury
1 - 4 May, 2005; Melbourne, Australia
E. braininjury@icms.com.au

Aspects of the Neurological Examination - RSM Clinical Neurosciences Section
Tel. 20 7290 2984/2982, E. cns@rsm.ac.uk

Annual Meeting of the German, Austrian, Swiss section of the International League Against Epilepsy
5-7 May, 2005; Innsbruck, Austria
Tel. +43 512 5043879,
E: iris.unterberger@uibk.ac.at

2nd quadrennial meeting of the World Federation of Neuro-Oncology EANO VI
5-7 May, 2005; Edinburgh, UK
E. EANO6@fecs.be, Tel. 32 27 750 205,
Fax. 32 27 750 200.

4th BASP Thrombolysis Training Day
6 May, 2005; Nottingham, UK
Pamela Nicholson, sec to Professor Lees,
E. pcn1w@clinmed.gla.ac.uk, Tel. 0141 211 2176.

Neurochirurgie 2005
7-11 May, 2005; Strasbourg, France
Fax. +49 3 028 449 911,
E. nch2005@porstmann-kongresse.de

12th European Congress of Clinical Neurophysiology
8-12 May, 2005; Stockholm, Sweden
E. secretary@ec-ifcn.org /weerd@ipe.nl

Tone Deafness: Neural Correlates, Hereditability and Plasticity
A seminar with Professor Isabelle Peretz
10 May, 2005; Cardiff, UK
E. halliganpw@cardiff.ac.uk

How Musical is the Human Brain?
A seminar with Professor Isabelle Peretz
10 May, 2005; Cardiff, UK
E. halliganpw@cardiff.ac.uk

Inaugural Meeting of the Vocational Rehabilitation Special Interest Group
13 May, 2005; London, UK
E. admin@bsrm.co.uk

Alzheimer's Disease: Update on Research, Treatment, & Care
19-20 May, 2005; San Diego, US
E. jcollier@ucsd.edu

Carotid and Transcranial Doppler
13-15 May, 2005; Las Vegas, USA
E. info@iame.com

7th European Federation of Autonomic Societies (EFAS) Meeting
18-21 May, 2005; Bled, Slovenia
http://efas.over.net/index.htm

XIXth Conference on Epilepsy for Polish Society of Epilepsy
19-21 May, 2005; Warsaw, Poland
E. fundacja@epilepsy.org.pl

Annual Meeting of the German Section of the International League Against Epilepsy
20-22 May, 2005; Freiburg, Germany
www.ctw-congress.de/liga

10th Meeting of the European Society of Neurosonology and Cerebral Hemodynamics
21-24 May, 2005; Padova, Italy
www.neurosonology2005.it

ASNR 43rd Annual Meeting
21-27 May, 2005; Toronto, Canada
www.asnr.org/2005/

Freedom Evolves: A seminar with Professor Daniel C Dennett
24 May, 2005; Cardiff, UK
E. halliganpw@cardiff.ac.uk

14th European Stroke Conference
25-28 May, 2005; Bologna, Italy
E. m.g@eurostroke.org or
daffertshofer@eurostroke.org

MS Frontiers
25-26 May, 2005; Edinburgh, UK
E. CBray@mssociety.org.uk

Explaining the 'Magic' of Consciousness. A Seminar with Professor Daniel C Dennett
26 May, 2005; Cardiff, UK
E. halliganpw@cardiff.ac.uk

The Second Meeting of the AEP Section of Neuroimaging
26-27 May, 2005; Berlin, Germany
Tel. 01159 692 016, Fax. 01159 692 017,
E. rp@rpa.bz

International Society of Posture and Gait Research 2005 – ISPGR XVIIth Conference
29 May -2 June, 2005; Marseilles, France
E. assaiant@dpm.cnrs-mrs.fr or
ispgr2005@atout-org.com

13th International Symposium on Brain Edema and Conference on Intracerebral Hemorrhage
31 May-4 June, 2005; Ann Arbor, US
www2.med.umich.edu/neurosurgery/
brainedema/ website/index.cfm

June

The Past, Present & Future of Neurosciences - RSM
2 June, 2005; London, UK
Tel. 20 7290 2984/2982, E. cns@rsm.ac.uk

Complex Neurological Disabilities
3 June, 2005; London, UK
E. sarah.rsidon@rsm.ac.uk, www.rsm.ac

16th International Congress on Parkinson's Disease & Allied Disorders
5-9 June, 2005; Berlin, Germany
Tel. 0049 30 300 6690, Fax. 0049 30 305 7391,
E. Berlin@cpo-hanser.de, www.cpo-hanser.de

28th International Congress of Clinical Neurophysiology
5-9 June, 2005; Berlin, Germany
Fax. 001 507 288 1225; E. aaem@aaem.net

Neurological Assessment Short Course for Nurses
6 June, 2005; London, UK
Tel. 020 7836 5454, E. sue.woodward@kcl.ac.uk

1st International Conference on Applied Technologies in Medicine and Neuroscience
6-10 June, 2005; Basel, Switzerland
www.alma-advice.com/seiten/ATMN.html

Autism and Asperger Syndrome
8 June, 2005; Manchester, UK
E. Anke.muller@rsm.ac.uk

VAS-COG 2005
8-12 June, 2005; Florence, Italy
www.vas-cog.org/vas-cog-2005-link.html

7th Annual Neurology SpR Study Weekend
10-12 June, 2005; Coventry, UK
Tel. 01462 811239, Fax. 01462 819338,
E. lucie.flint@btinternet.com

Organisation for Human Brain Mapping 11th Annual Meeting
12-16 June, 2005; Toronto, Canada
E. tanyahess@llmsi.com

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

The Cognitive Neuroscience of Socioeconomic Status. A Seminar with Professor Martha Farah
13 June, 2005; Cardiff, UK
E. halliganpw@cardiff.ac.uk

Neuroethics: A Guide for the Perplexed. A Seminar with Professor Martha Farah
14 June, 2005; Cardiff, UK
E. halliganpw@cardiff.ac.uk

2nd Quadrennial Meeting of the World Federation of NeuroOncology
13-16 June, 2005; Edinburgh, UK
Tel. +32 0 27 750 201, Fax. 32 0 27 750 200,
E. eano6@fecs.be

Sensory Modality & Assessment Rehabilitation Technique (SMART) 5 Day Assessor Training
13-17 June; 2005; London, UK
E. institute@rhn.org.uk

International League Against Epilepsy
15-17 June, 2005; Belfast, UK
Tel. 01691 650290, Fax. 01691 670302,
E. denise@conference2k.com

American Academy of Clinical Neuropsychology (AACN) Workshops and Annual Meeting
15-18 June, 2005; Minneapolis, USA
www.theaacn.org

Understanding and Dealing with Behavioural Problems following Brain Injury. A Workshop
17-18 June, 2005; Gatwick, UK
Tel. 01276 472369.

Alzheimer's Association International Conference on Prevention and Dementia
18-21 June, 2005; Washington, US
Tel. +1 312 335 5790, E. info@alz.org
www.alz.org/preventionconference/
pc2005/overview.asp

15th ENS Meeting
18-22 June, 2005; Vienna, Austria
www.ensinfo.com/

13th World Congress of Neurological Surgery 19-24 June, 2005; Marrakesh, Morocco
www.marrakesh2005.org/default.cfm

Neuroscience Nursing - Moving Ahead 2005
20 June, 2005; London, UK
Pat Anslow, Tel. 02920 546492,
E. pat.anslow@rcn.org.uk

16th International Bethel-Cleveland Clinic Epilepsy Symposium
20-22 June, 2005; Bielefeld, Germany
www.bethel-cleveland-epilepsy-symposium.de/

RCN Neurosciences Nurses Forum Conference and Exhibition
21 June; 2005; UK
Tel. 029 2054 6492, Fax. 029 2054 6495,
E. neurosciences@rcn.org.uk

2nd Quadrennial meeting of the World Federation of NeuroOncology & 6th Congress of the European Association for Neuro-Oncology EANO VI
23-26 June, 2005; Edinburgh, UK
E. EANO6@fecs.be

Muscular Dystrophies: Advances in Diagnosis and Management
23 June, 2005; Leeds, UK
Tel. 0113 3055086, E. adele.archer@nhs.net

International Symposium on Epileptogenesis and Therapeutic Strategies: Rational Therapy
23-25 June, 2005; Erlangen, Germany
Fax. +49 9131 8536469,
E. hermann.stefan@neuro.imed.uni-erlangen.de

8th European Congress of Neuropathology
25-28 June, 2005; Amsterdam, The Netherlands
Tel. +31 (0) 20 566 8585, Fax. +31 206 960 389,
E. a.vanschendel@amc.uva.nl or
i.m.uhang@amc.uva.nl

World Congress of Gerontology
26-30 June, 2005; Rio de Janeiro, Brazil
Fax. 55 11 3081 6247, Tel. 55 11 3081 6247,
E. iag2005@unicamp.br

9th International Conference on Rehabilitation Robotics, Frontiers of the Human-Machine Interface
28 June-1 July, 2005; Chicago, US
E. m-devitt@northwestern.edu

Sleep Disorders & Restless Legs Syndrome
28 June, 2005; London, UK
E. sharan.gallagher@rsm.ac.uk

49th Annual Scientific Meeting of the Society for Research into Hydrocephalus and Spina Bifida
29 June-2 July, 2005; Barcelona, Spain
www.drcubittandpartners.org.uk/srhsb/h05.htm

Working With Families After Acquired Brain Injury
30 June-1 July, 2005; Ely, UK
E.alison.gamble@ozc.nhs.uk

Cochrane Systematic Reviews in Practice: Epilepsy
30 June - 1 July, 2005; London, UK
E. cochrane.neuronet@unimi.it

July

International Society for the History of the Neurosciences, 10th Annual Meeting
5-9 July, 2005; St Andrews, UK
www.ishn.org/, Russell A. Johnson
Tel. 001 310 825 6940, 001 310 825 3191
Fax. 001 310 206 5855,
E. rjohnson@library.ucla.edu

International Neuropsychological Society Joint Mid Year Meeting
6-9 July, 2005; Dublin, Ireland
E. ins@osu.edu

MS Professional Network
7 July, 2005; Bristol, UK
E. CBray@mssociety.org.uk

Society for Research in Rehabilitation
7-8 July, 2005; Southampton, UK
E. angela.webster@manchester.ac.uk

Conference on Neuropsychological Rehabilitation
11-12 July, 2005; Galway, Ireland
www.conference.ie

Multidisciplinary Care in Parkinson's Disease: from science to practice
12 July, 2005; London, UK
E. info@mepltd.co.uk, www.mepltd.co.uk

4th Congress of the International for Autonomic Neuroscience
12-16 July, 2005; Marseille, France
www.atout-org.com/isan2005/

PSIGE Conference 2005
13-15 July, 2005; Chester, UK
E. PSIGE2005@bps.org.uk
Tel. 0116 252 9555, Fax. 0116 252 7123

12th Meeting of the Neurosonology Research Group of the World Federation of Neurology
13-15 July, 2005; Osaka, Japan
www.congre.co.jp/nsrg/

The Use of Botulinum Toxin Injections to Treat the Overactive Bladder

Botulinum toxin, the most lethal poison known to mankind, has through research, been transformed from a dangerous and feared entity to a novel drug able to help and sometimes cure conditions previously difficult to treat. Such a challenge was posed by the treatment of patients with detrusor overactivity (DO), resulting in an overactive bladder syndrome with its distressing symptoms of urinary frequency, urgency, incontinence and nocturia.[1] Until recently, there have been limited options available to patients with DO, who have failed to respond to established first line oral therapies and clean intermittent self catheterisation (CISC), and a therapeutic chasm existed between these non-invasive treatments and surgery namely augmentation cystoplasty. The advent of intradetrusor injection of botulinum neurotoxin A (BoNT/A) is fast filling this void, and has revolutionised the management of DO. As further research into this exciting treatment modality proceeds, other indications of its use in urological practice including in children, patients with painful bladders, and indwelling catheters is being evaluated.

There are seven serotypes of BoNT, designated A to G, each with a different antigenic profile and biochemical action, however with the same pharmacological effect. BoNT's are metalloproteases specific for the three proteins that form the core of the neuroexocytosis machinery. They work by binding to and entering inside peripheral cholinergic terminals, causing a sustained block of acetylcholine (ACh) release at the neuromuscular junction and in cholinergic autonomic nerves, with ensuing flaccid paralysis.[2]

Background

It has long been known that an area in the dorsal tegmentum of the pons, the pontine micturition centre (PMC), is central to bladder storage and appropriate voiding. Intact projections from the PMC to the sacral spinal cord (S2 – S4) determine parasympathetic outflow to the detrusor and reciprocal activity of the motor neurones innervating the striated urethral sphincter. Synergistic activity between the detrusor and the sphincter depends on the integrity of the connections with the pontine region. A condition known as 'detrusor sphincter dyssynergia' (DSD) results from interruption or damage to these pathways, however the most marked abnormality occurring as a consequence from disconnection from the PMC is a segmental reflex that causes a detrusor contraction in response to bladder distension. Following any form of spinal cord lesion, previously quiescent unmyelinated C fibres become mechanosensitive and respond to bladder stretch.[3] Detrusor contractions are caused by this afferent activity, through synaptic activity in the sacral spinal cord.[4] It is this that is responsible for the emergence of DO. DO is defined as a urodynamic observation characterised by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked.[1]

An attempt to block the efferent limb of the detrusor segmental reflex arc, in the hope of relieving the symptoms caused by DO was originally carried out in 1998 at a rehabilitation centre in Switzerland. Schurch et al injected patients with complete spinal cord injury suffering from intractable neurogenic detrusor overactivity and incontinence, and demonstrated striking improvements in urodynamic and clinical parameters lasting up to nine months.[5]

Minimally invasive Intradetrusor injection of BoNT/A

The original technique used a rigid cystoscope and a wide diameter injection needle. Patients with spinal lesions above T5 had 40mls of 2% lignocaine instilled to anaesthetise the bladder. The bladder was then injected with 200-400 units of BoNT/A (Botox®), in 20-30 points avoiding the trigone. It was concluded that 300 units of Botox® might be the most effective dose.

Standard practice in the UK for performing a rigid cystoscopy would require either regional or general anaesthesia. This would mean even though a procedure such as intradetrusor BoNT/A injections could be done as a day case, recovery facilities would still be required. The minimally invasive outpatient technique developed in the Department of Uro-Neurology, at the National Hospital for Neurology and Neurosurgery,[6] allows for the treatment to be carried out under local anaesthetic, as an outpatient, obviating the need for any recovery ward or inpatient stay.

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Pre-operative work-up

The main indication for intrdetrusor BoNT/A is intractable urodynamically proven DO. Patients are made aware that this is as yet an unlicensed indication for the use of BoNT/A, and full informed consent is taken. As there is a tendency for the post void residual volume to increase following treatment, patients should be willing and able to perform CISC should the need arise.

Prior to injection urinalysis is performed to rule out any urinary tract infection (UTI). UTI at the time of planned injection is an absolute contraindication to the procedure. Other exclusion criteria include: bladder malignancy, bleeding disorders, anticoagulation therapy, neurotransmission disorders or drugs affecting neuromuscular transmission (e.g. aminoglycosides), pregnancy or planning a family.

The minimally invasive injection technique

There are no specific pre-operative preparation instructions and the patient comes to the clinic immediately before the procedure is planned. Following oral antibiotic prophylaxis, the unsedated patient is positioned supine, adequately prepared and draped. Local anaesthetic gel is applied to the urethra and the bladder is accessed using a standard flexible cystoscope. The cystoscope should have a 2.2mm working channel that can accommodate a 27 G, 4mm needle which locks into a reusable sheath to protect the scope and facilitate the injections (Figure 1).

If at cystoscopy the bladder mucosa is free of any inflammation and lesions (Figure 2), the BoNT/A is then reconstituted and the bladder injected. Of the formulations of BoNT/A available, Botox® (Allergan Ltd., UK) is used in our department. This is available as single use vials of 100 units of the neurotoxin complex which is diluted using 10mls of 0.9% normal saline without preservative (10U/ml). Care should be taken when reconstituting the drug, as vigorous agitation will denature the compound. The bladder is filled to 100mls and injected over 20-30 equidistant sites over the bladder wall and the dome of the bladder. Patients with neurogenic DO (NDO) receive 300U of Botox®, and those with idiopathic DO (IDO) receive 200U. The injections are mapped out using 6 rows of 5 injections for patients with NDO and 4 rows of 5 for IDO patients (Figure 3). The trigone is not injected for the reasons of tolerability, access using a flexible cystoscope and the potential of vesico-ureteric reflux by paralysing the ureteric ostia.

Post-operative patient follow-up

A 3-day antibiotic course is completed, and the patient is reviewed at 4 weeks post injection to check if they are emp-

Vinay Kalsi, MRCS is a Registrar in Uro-Neurology at the National Hospital for Neurology and Neurosurgery, Queen Square, London. He is currently undertaking research into the mechanisms of action of botulinum toxin in the treatment of the overactive bladder.

Clare Fowler is a Consultant at the National Hospital for Neurology and Neurosurgery and Professor of Uro-Neurology. Her special interest is in the investigation and management of patients with neurogenic bladder disorders.

Mr Prokar Dasgupta MSc (Urol), MD, DLS, FRCS (Urol), FEBU is a Consultant Urological Surgeon at Guy's & St Thomas' Hospitals, and an Honorary Consultant Urologist at the National Hospital for Neurology and Neurosurgery. His specialist interest is in Endourology including Laparoscopic Urological Surgery and Robotics.

Mr Vinay Kalsi,
Clinical Research Fellow to Professor Clare J Fowler,
Department of Uro-Neurology,
Box 71,
National Hospital of Neurology and Neurosurgery,
Queen Square,
London, WC1N 3BG.
Tel: 020 7837 3611 ext 3139
Fax: 020 7813 4587
Email: v.kalsi@ion.ucl.ac.uk

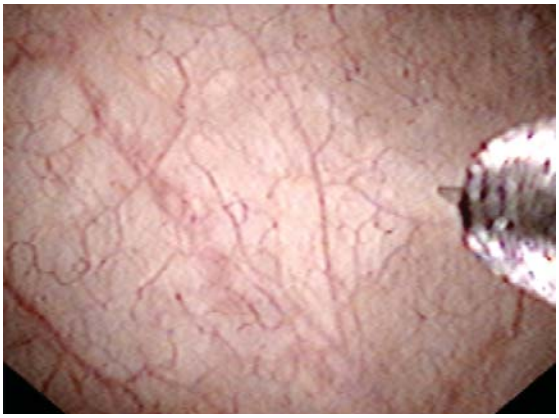

Figure 1: View inside the bladder showing bladder ready for injection. The needle and sheath are visible.

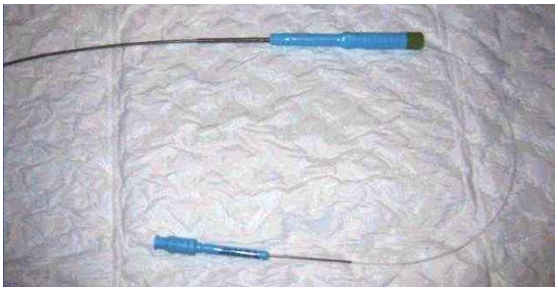

Figure 2: Flexible sheath containing needle.

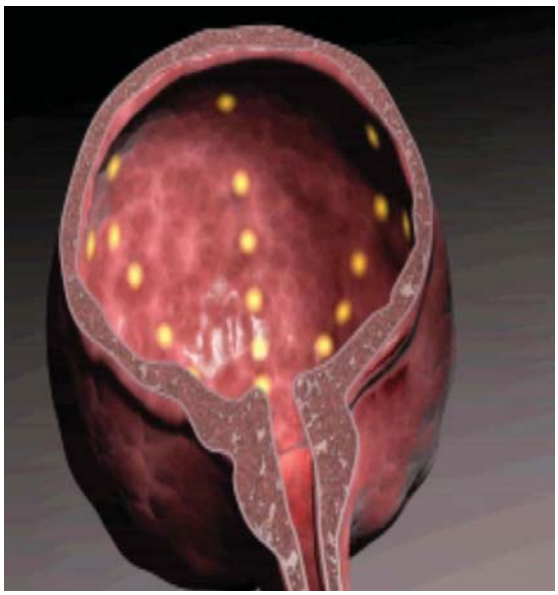

Figure 3: Illustration of the bladder with the injection points mapped out.

tying to completion. This is done by a simple handheld ultrasound bladder scanner, however as a part of our research protocol, urodynamics is performed at 4 and 16 weeks post treatment. If the post void residual volume is greater than 100mls and the patient is symptomatic, with no reduction in frequency, urgency and incontinence, and/or suffering from repeated UTI's, they are instructed how to perform CISC.

The effects of the injections are generally noticed within a week, and the patients are advised to cut back, and eventually stop concurrent anticholinergic treatment. When the effects of BoNT/A start to wear off, they may then need to reintroduce their anticholinergics.

Results

Efficacy data from cohort studies report a success rate of 89-100% in patients with spinal NDO.[5,7] A retrospective multicentre study demonstrated a success rate of 96%, with clinical and urodynamic improvement at 12 and 36 weeks post treatment; 73% of patients who were previously incontinent were 'dry' at 12 weeks follow up.[8] These findings have been confirmed in a randomised placebo controlled trial.[9]

In our own series of 44 patients with spinal NDO and 31 with IDO treated with minimally invasive outpatient intradetrusor Botox®, we found significant improvements in urinary urgency, frequency, incontinence, bladder capacity and end-filling detrusor pressures,[7] in all patients. A success was defined as a greater than 25% improvement in 2 parameters, clinical and/or urodynamic. Ameliorations of symptoms were reflected in the observed improvement in the quality of life data, complementing previous publications.[10]

Of the patients who were not already performing CISC, 69.2% of patients with NDO required CISC post-treatment compared with 19.3% of those with IDO. The procedure is quick (approximately 15 minutes) and well-tolerated, the average discomfort score on a 0-10 verbal pain scale being 3.2. This duration of effect was maintained after repeat treatment (mean 10.7 months, range 7- 12). These findings are similar to results from other studies.[11] The side-effects have been minor following treatment and include macroscopic haematuria in 2 patients, urinary tract infection in 3, and 1 patient experienced transient flu-like symptoms. Generalised adverse events such as muscle weakness that have been rarely reported[12] have been not encountered in our experience.

Conclusions

Minimally invasive outpatient intradetrusor BoNT/A is shown to be a safe, effective, and well-tolerated treatment for patients with intractable detrusor overactivity. This simple yet innovative technique is easily reproducible and may be performed by any practitioner who is trained to carry out diagnostic flexible cystoscopy.

As yet unlicensed, intradetrusor BoNT/A is being adopted by increasing numbers of centres throughout the UK and worldwide. This treatment option is known to have a significant positive impact on patients' quality of life, and is now emerging as an important modality in the management of refractory lower urinary tract symptoms, independent of aetiology, challenging the future place of invasive surgical measures such as augmentation cystoplasty.

Our project is funded by a grant from the Multiple Sclerosis Society, and one of the aims is to make this treatment widely available for patients with MS. We therefore encourage visits from other centres of urologists, uro-gynaecologists, neurologists and rehabilitation doctors who wish to learn the technique and assist them by providing supporting paperwork for them to obtain local ethical approval. To date we have had 35 visitors and to our knowledge we are the only centre in the UK that provides this service. For more information contact Vinay Kalsi.

References

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5. Schurch B, et al. *Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results.* J Urol 2000;164:692-7.
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7. Popat R, et al. *A comparison between the response of patients with idiopathic detrusor overactivity (IDO) and neurogenic detrusor overactivity (NDO) to the first intradetrusor injection of botulinum A toxin.* J Urol, 2005. In press.
8. Reitz A, et al. *European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity.* Eur Urol 2004;45(4):510-5.
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12. De Laet K, and Wyndaele J. *Adverse events after botulinum A toxin injection for neurogenic voiding disorders.* Spinal Cord, 2005. doi:10.1038/sj.sc.3101736(advance online publication 1 March 2005).

Emery-Dreifuss Muscular Dystrophy (EDMD or EMD)

We are planning a new series of articles in which we ask famous neurologists to describe neurological disorders that they have either discovered or to which they have made a major contribution. In this, the first of the series, we invited Professor Alan Emery to describe the story leading to the first description of Emery-Dreifuss muscular dystrophy. His account combines the scientific and human side of neurological research and acts as an inspiration to all those embarking on or involved with such research. - Roger Barker

'As good luck would have it!'
Shakespeare. The Merry Wives of Windsor

I qualified in medicine rather late in life at the age of 32, having first served in the Army and then having taught for several years. Thus to me career opportunities in medicine at my age seemed a little restricted. I therefore seized an offer in 1961 of a travelling Fellowship to go to Johns Hopkins University to study the then burgeoning new specialty of Medical Genetics. I registered for a PhD degree with the aim of researching the clinical and biochemical aspects of muscular dystrophy.

This decision had been partly influenced by advice when I attended a demobilisation course just before leaving the army for civilian life. Most attending the course wanted help about possible future careers. The lecturer repeatedly emphasised, in a rather cynical way we thought at the time, that it would be best to choose an unpopular field because there would then be less competition! I'm not certain how true this is in general, but certainly in my case it proved good advice. I was attracted to muscle disease because there seemed very little interest in the subject among most clinicians at the time yet a lot of patients with these diseases were attending the neurology clinic where I worked. Furthermore muscle diseases were already recognised to be usually genetic but little else was known about them. It therefore seemed from all points of view to be attractive to someone who wanted a career in research and in medical genetics. It's also possible that I may have been somewhat influenced by having had osteomyelitis in my leg in early childhood, in the days before antibiotics, and spent more than two years wearing a calliper - or 'irons' as they were then called

I became particularly interested in Duchenne, the commonest form of muscular dystrophy. In order to identify genetic factors in the disease however it was necessary to study extensive families with several affected males. But such families are very rare because affected boys rarely survived beyond adolescence and therefore did not transmit the disease. I was therefore very excited when I read in a scientific paper published at the time of an extensive family in Virginia affected with what the authors considered to be merely a mild form of Duchenne muscular dystrophy.[1] Some of the affected males in the family had survived to middle age and had had children! I wrote to the senior author of the paper, Dr. Fritz Dreifuss in Virginia, and asked if he would have any objection to my driving down to see the family. He was delighted to find someone so interested in the disease. All the family members, except one, lived within easy driving distance of each other and Dr. Dreifuss said he would arrange for them all to meet me in the local school house where the senior affected member of the family was a teacher. I could see the various members of the family, examine them and as he said 'do whatever else you like!'

In those Elysian days it was still possible to carry out an entire research project on one's own. So I put together in my station-wagon all the equipment I would need. This included the usual instruments for doing a clinical examination such as a stethoscope, tendon hammer, and ophthalmoscope. I also took along my camera, books of colour plates used to assess colour blindness, equipment for blood sampling for the determination of blood groups back in the hospital, a centrifuge for spinning the blood samples, a small electrocardiogram (ECG) machine for monitoring cardiac activity and finally a rather old-fashioned spectrophotometer and the necessary chemicals in order to measure creatine kinase levels in blood. The latter had just been introduced by Japanese scientists as a valuable diagnostic test for muscular dystrophy and I was keen to use it on the various members of the family. The car was so full that there was hardly room for my personal belongings - and I spent some time carefully checking and re-checking the equipment. This was going to involve a round-trip of over a thousand miles and there might only be this one opportunity. I also needed good maps as the family lived in a remote area of the Appalachian Mountains close to the borders of Virginia, Kentucky and West Virginia, a part of America with which I was not at all familiar.

The small community in which the family lived turned out to be very remote indeed and it took me a day and a half to locate it. Fortunately I'd left plenty of time and arrived on the Friday afternoon, which I spent with the school teacher. What a very delightful man he was. He had obviously been on the lookout for my arrival and as I parked on the grass in front of the small schoolhouse he came out to shake hands. I shall always remember his greeting because as he walked toward me he exhibited a gait which is almost diagnostic of the disease. He was in his 50s and walked with a waddling gait. But apart from lordosis, he also walked with both elbows bent. He gave every appearance of a cowboy in a Western movie, who strolls out with both hands resting on his revolvers! I came to refer to this as the 'cowboy gait' and it seemed even with my limited experience, to be unique to this disease.

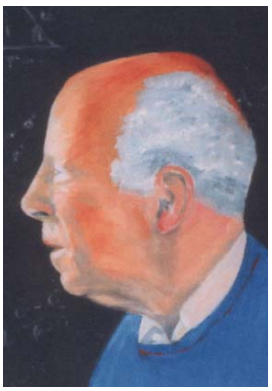
He invited me to his home for an evening meal and so we could get to know each other better. One of the great attractions of medical genetics was to visit families in their own homes. Unfortunately this is nowadays not done so much. As we sat and drank coffee, and later a glass of 'Wild Turkey', our talk turned to the family's origins. They were very proud of their ancestry having descended directly from early English and French settlers. At the time a hobby of mine was recording old folk songs and one of the family members obliged by singing an old song, passed down through the generations with a refrain about 'good Queen Bess'. They had no idea who this referred to, but from the lyrics it seemed to me to refer to Queen Elizabeth I of England. I still cherish these recordings but unfortunately the quality is poor. I'm sure this region of the US is a wonderful source of folk songs just waiting to be researched - or perhaps it has, and I've no doubt missed it....

I soon fell asleep that night, probably aided by the Wild Turkey, and the following morning turned up at the school house all ready to start. The entire family had already been marshalled there and in some ways the scene resembled a church fete run by the Women's Voluntary Service back home. Screens had been brought as well as a couch, a desk

Professor Alan Emery

Correspondence to:
Fax. 01395 443855.

The late Dr. Fritz Dreifuss.



Emery Self Portrait

for me to write at and various tables for the equipment. I began by drawing up the family tree in chalk on the blackboard. We would use felt pens and a special laminated board nowadays. It was a great help to have everyone there so all the facts could be checked. A few details were added but it was essentially the same as the published pedigree. Then began the laborious job of meticulously examining everybody in the family including the unaffected females who, from the pedigree, clearly carried the abnormal gene. The blood samples were each placed on one side to be analysed later that night.

Eventually in the late afternoon I had finally made notes on everyone. This included information on eight affected males (one of whom had died some time previously) ranging in age from 11 to 55, and some eleven female carriers. The disorder was clearly inherited as an X-linked recessive trait. I had a hasty meal at one of the family member's homes and then returned to start analysing the blood samples for the enzyme creatine kinase.

These were good, kind and hospitable people and they wanted me to delay my return so they could show me something more of the countryside. However I was anxious to get home and study the results of my efforts but promised to return later. In fact a few months later I did return to fill in some gaps in the information I had gathered on my first visit. And returned again some 25 years later to a great family welcome, when they made me feel almost as if I had come home!

When I returned to the department I began to put together all the information I had collected and it slowly dawned on me that, for various reasons, this disease was perhaps a clinically distinct condition and may not have been described previously. It was clearly not Duchenne muscular dystrophy or for that matter any of the other forms of muscle disease I had seen or read about. I decided to present the results at one of our research seminars. I had expected, with the naiveté of youth and inexperience, that the findings would be greeted with great excitement. But I was disappointed. There was of course polite interest but that was all. In retrospect I think it was largely because perhaps I was the only one in the Department at all interested in muscle diseases! In fact it was several years later when I had returned to England that I had the courage to submit the details for publication in a journal specialising in neurological and neuromuscular disorders.[2] A little interest was shown and a few people wrote to me for reprints, but that was all. However in my medical work I kept a watchful eye open for other affected families and gradually my files on the disease increased. But it was not until 20 years after my first foray into the Appalachians that the reality of the disease as a distinct entity began to be accepted. This resulted from a scientific paper written by the eminent New York neurologist, Lewis Rowland, in 1979 in which he described a case and drew attention to our first description of the disease, and suggested the eponymous name Emery-Dreifuss muscular dystrophy.[3] An autosomal dominant form is now also recognised[4] and though some slight clinical differences have been suggested, both forms of the disease are characterised by:

1. *early* contractures, often *before* there is any significant weakness, of the elbows, Achilles tendons and postcervical muscles (with limitation of neck flexion but later forward flexion of the spine becomes limited);

2. slowly progressive relatively mild muscle wasting and weakness with a humeroperoneal distribution (i.e., proximal in the upper limbs and distal in the lower limbs) early in the course of the disease. Later weakness also affects the proximal limb girdle musculature;

3. most importantly a cardiomyopathy usually presenting as cardiac conduction defects ranging from sinus bradycardia, prolongation of the PR interval to complete heart block (Figure 1).

The genes and their products for both forms of EDMD have now been identified. The STA gene at Xq28 encodes for a nuclear membrane protein designated 'emerin',[5] and the gene LMNA at 1q21 encodes other nuclear membrane proteins, lamins A/C.[6] Mutations of the latter gene are now also associated with at least seven other disorders as well (Table 1).[7] How the STA and LMNA genes regulate cardiac conduction, the most important aspect of the disease, is as yet completely unknown. Yet this could have far-ranging implications in cardiology in general.

Some time ago I began to search the old medical literature to see if this disease had ever been described previously. I had almost convinced myself that our description was unique when my attention was drawn to an obscure publication in French in 1902. In this report from the Salpêtrière Hospital in Paris, two brothers were described who, though there was no mention of muscle pathology or heart involvement, which is a very important manifestation of this form of muscular dystrophy, may have had the same disease we had described.[8] Nevertheless as the French might say: Quoi de neuf? Rien de neuf!

Table 1: Clinical disorders resulting from different mutations of the LMNA gene

EMERY-DREIFUSS MD	*(AD)*
LIMB GIRDLE MD TYPE 1B	*(AD)*
DILATED CARDIOMYOPATHY & CONDUCTION DEFECTS	*(AD)*
ATRIAL FIBRILLATION ± DILATED CARDIOMYOPATHY	*(AD)*
PARTIAL LIPODYSTROPHY	*(AD)*
CHARCOT-MARIE-TOOTH TYPE 2	*(AR)*
MANDIBULOACRAL DYSPLASIA	*(AR)*
PROGERIA (?WERNER'S SYNDROME)	*(AR)*

(MD: MUSCULAR DYSTROPHY; AD: AUTOSOMAL DOMINANT; AR: AUTOSOMAL RECESSIVE)

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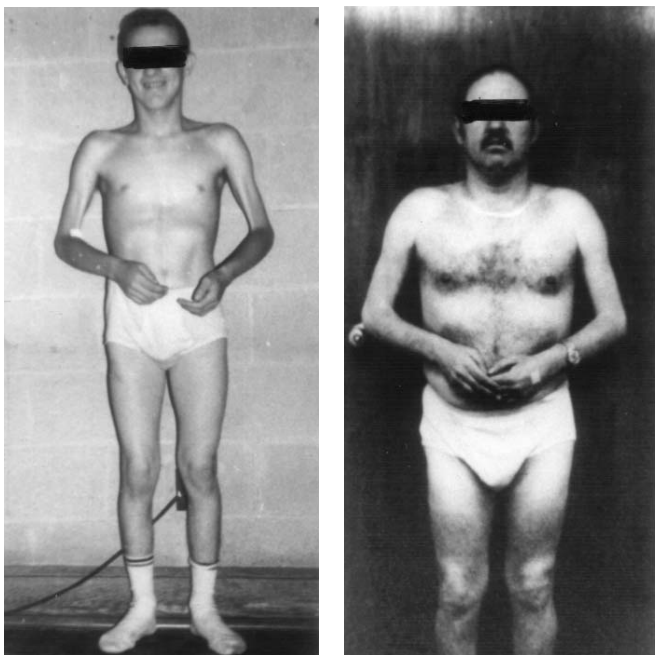
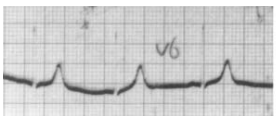
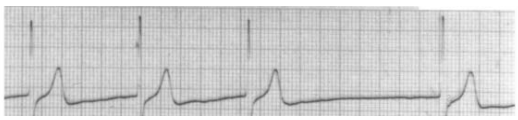


Figure 1: An original family member age 18 and again at 45. Note evidence of heart block at the later age.





*"Rage, rage against the dying of the light"**

There's a treatment that could shed light on the desolation of Parkinson's disease.

There's the UK's first and only NMDA antagonist for PD[1,2] which alleviates parkinsonian symptoms.[3-6]

There's a treatment that provides up to 60% reduction in motor fluctuations like dyskinesia,[3-5] while also offering possible neuroprotection.[1,7]

There's Symmetrel – because *"old age should burn and rave at close of day."*

*Taken from: *Do not go gentle into that good night* by Dylan Thomas; published by: Dent.

Symmetrel®
amantadine

The only NMDA antagonist for PD

Abbreviated prescribing information. Symmetrel (amantadine hydrochloride). **Presentation:** Capsules containing 100 mg of amantadine hydrochloride PhEur. Syrup containing 50mg/5ml of amantadine hydrochloride PhEur. **Indications:** Parkinson's disease. **Dosage:** Initially 100mg daily for the first week, increasing to 100mg twice daily. The dose can be titrated against signs and symptoms. Doses exceeding 200mg daily may provide some additional relief, but should not exceed 400mg. The dose should be increased gradually, at intervals of not less than 1 week. Amantadine acts within a few days, but may appear to lose efficacy within a few months of continuous treatment. Its effectiveness may be prolonged by withdrawal for three to four weeks, which seems to restore activity. Any antiparkinson drug already in use should be continued during initial Symmetrel treatment. It may then be possible to reduce the other drug gradually. Symmetrel withdrawal should be gradual, e.g. half the dose at weekly intervals. ***Renal impairment*:** Reduce daily dose, or increase the dosage interval (see full prescribing information). **Contra-indications:** Hypersensitivity to amantadine or excipients. Individuals subject to convulsions. A history of gastric ulceration. Severe renal disease. Pregnancy. **Precautions:** Confusional or hallucinatory states or psychiatric disorders. Liver, kidney or cardiovascular disorders. Congestive heart failure. Concurrent administration with anticholinergics, levodopa, neuroleptic medication, drugs or substances (e.g. alcohol) acting on the CNS, combination diuretics (hydrochlorothiazide + potassium sparing diuretics). Withdrawal of amantadine in patients taking neuroleptic agents may cause or aggravate neuroleptic malignant syndrome. Lactation. Driving or operating machinery (blurred vision). **Side effects:** The most commonly reported effects were gastro-intestinal disturbances (anorexia, nausea), CNS effects (loss of concentration, dizziness, agitation, nervousness, depression, insomnia, fatigue, weakness), or myalgia. Side effects after higher doses or chronic use, in addition to above include: Anxiety, elevation of mood, lightheadedness, headache, lethargy, hallucinations, nightmares, ataxia, slurred speech, blurred vision. Confusion, disorientation, psychosis, tremor, dyskinesia, convulsions. Delirium, hypomanic state and mania have been reported but their incidence is not known. Oedema of ankles, livedo reticularis (usually after very high doses or use over many months). Palpitations, orthostatic hypotension. Heart insufficiency/failure. Leucopenia, reversible elevation of liver enzymes. Dry mouth, anorexia, nausea, vomiting, constipation. Diarrhoea. Diaphoresis. Exanthema. Photosensitisation. Corneal lesions, e.g. punctate subepithelial opacities which might be associated with superficial punctate keratitis, corneal epithelial oedema, and markedly reduced visual acuity. Urinary retention, urinary incontinence. **Legal category:** POM. **Product licence number:** Symmetrel Capsules PL16853/0015. Symmetrel Syrup PL16853/0016. **Packs:** Blister packs of 56 capsules. 150ml bottle. **Basic NHS price:** Symmetrel Capsules £15.35. Symmetrel Syrup £5.05. Full prescribing information is available from: Alliance Pharmaceuticals Ltd, Avonbridge House, Bath Road, Chippenham, Wiltshire SN15 2BB, www.alliancepharma.co.uk. **Date of preparation:** September 2003. **References:** 1. Kornhuber J *et al. J Neural Transm* 1994;**43**(Suppl):91-104. 2. Blanchet PJ *et al. Adv Neurol* 2003; **91**:251-257. 3. Verhagen Metman L *et al. Neurology* 1998; **50**(5):1323-1326. 4. Luginger E *et al. Mov Disord* 2000; **15**(5):873-878. 5. Verhagen Metman L *et al. Arch Neurol* 1999; **56**(11):1383-1386. 6. Ruzicka E *et al. J Neural Transm* 2000; **107**(11):1297-1306. 7. Uitti RJ *et al. Neurology* 1996; **46**:1551-1556.

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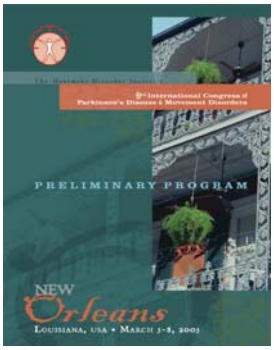
ALLIANCE

9th International Congress of Parkinson's Disease and Movement Disorders

5-8 March, 2005; New Orleans, US



The 9th International Congress of Parkinson's disease and Movement Disorders was located on the banks of the Mississippi in New Orleans in Louisiana. Several members of the ACNR team were to be found in the French Quarter after the sun had set exchanging notes on the day whilst supping a Hurricane cocktail and listening to jazz! The main findings from this hugely popular event are perhaps best presented as a series of points:

- **PD pathogenesis:** One recurring theme in both the plenary and parallel sessions was the key issue of the pathogenesis of Parkinson's disease, and in particular the likely importance of an interaction between genetic and environmental influences. The final common pathway probably involves three major areas of biochemical abnormality in the PD brain: mitochondrial dysfunction, oxidative free radical damage and proteosomal inhibition. Both the known environmental risk factors for PD and known genetic mutations act via these biochemical pathways to cause cell death, perhaps as follows: Mitochondrial complex 1, the activity of which has been shown to be reduced in the substantia nigra in PD brains, is inhibited by environmental toxins associated with PD risk, including annonacin (a toxin found in the tropical fruit soursop) and MPTP. PD patients with Parkin mutations are also known to have a specific reduction in peripheral complex 1 activity, and Parkin deficient mice have a striatal respiratory chain defect. Complex 1 deficiency appears to mediate cell death via reduced cell respiration, increased superoxide generation, proteosomal inhibition and a reduced threshold for apoptosis. Both annonacin and MPTP, as well as pesticides such as rotenone and paraquat, also cause direct free radical mediated oxidative damage to the cell. Furthermore, there is increasing evidence that Park gene products have a role to play in this pathway: oxidative stress increases α-synuclein expression and promotes the interaction of DJ-1 and Parkin. Other environmental toxins known to be associated with PD risk are naturally occurring proteosomal inhibitors. Dysfunction of the ubiquitin-proteosome system is a good candidate for a pathogenic pathway in PD, given that the Lewy body, a protein aggregate containing ubiquitin, is central to the pathology of PD. At least some of the park genetic mutations may feed into this pathway: parkin encodes a ubiquitin ligase, and α-synuclein is, of course a key component of the Lewy body. Indeed the recent proteosome inhibitor model of PD, created by systemically administering proteosome inhibitors to rodents for a two week period, was discussed with respect to providing a better model of the clinical condition. This model, particularly if replicated by other groups, may provide a very useful tool for investigating the biochemical basis of PD and for testing putative neuroprotective agents.
- **PD genetics:** This featured heavily at this meeting with an emerging consensus on pathogenic pathways that may link the autosomal dominant forms of PD (PARK 1,5 and 8 = α-synuclein, UCHL1 and LRRK2) and autosomal recessive forms of PD (PARK 2,6 and 7 = parkin, PINK-1 and DJ-1). Furthermore the potential role for heterozygous mutations in recessively inherited forms of PD increasing the risk of developing PD was explored. There was also much discussion about the clinical features and pathology in the latest genetic form of PD, as well as the molecular pathogenesis of the LRRK2 mutations in the PARK 8 families reported in Neuron in the autumn of last year (ACNR 4(6)). This 144kilobase gene, contains 51 exons and is a member of the ROCO gene family, and appears to be ubiquitously expressed in the brain. There is speculation that its effects lie through a cascade of kinase activity, perhaps ultimately influencing the phosphorylation of α-synuclein.
- **PD drug therapies:** The new MAOI, rasagiline, appears to improve the control of moderately advanced PD (LARGO study recently reported in the Lancet) as well as having a possible neuroprotective role in early PD. Furthermore there was much discussion about the future of GDNF in PD. Although shown to be safe in an open label trial in Bristol (Nature Medicine 2003 and Annals of Neurology 2005) in five patients, the efficacy has not been replicated in a double blind placebo controlled trial sponsored by Amgen, the company that make the drug. This negative clinical outcome at 6 months, coupled to reports of cerebellar pathology in monkeys treated with high levels of this drug and the presence of anti-GDNF antibodies in some patients has led to the trial being abandoned. This has dashed the hopes of many for the use of growth factors in PD, but it was emphasised that the trial used different parameters (catheter size, dose of GDNF infused etc) to the open label study which has reported post-mortem evidence of GDNF efficacy in one of their patients. In particular they have shown that in one of their patients there was dopaminergic fibre sprouting around the site of GDNF infusion, which correlated well with the F-dopa PET findings in this patient. Undaunted, other groups are continuing to explore this therapeutic avenue using viral vector delivery systems, an approach that is currently being explored clinically in PD using virally delivered GAD to the subthalamic nucleus.
- A pilot study of six patients showed impressive improvements in their UPDRS following implantation of retinal pigment epithelial cells on the surface of gelatin microcarriers (spheramines) into the striatum. A sham control study is underway.
- **PD surgical therapies:** Deep brain stimulation continues to be a very active area in the treatment of PD as well as a range of other movement disorders, most notably essential tremor and primary generalised dystonia. However there is also an emerging story on side effects with this treatment, especially speech as well as some unpredictable psychiatric complications.
- **PD clinical features:** Another major development in PD discussed at this meeting was the new UPDRS, which takes into account the non-motor features of PD to a much greater extent. This often-neglected aspect of PD is now emerging as a major research theme with much work looking at the cognitive, autonomic and psychiatric features of PD and how they are best recognised and treated.
- **PD pathology:** Braak presented his thorough, but controversial work on the staging of pathology in this condition. This painstaking work involving many dozens of brains defines six stages of PD, with the earliest abnormalities being seen in the medulla and olfactory bulb, and disease then spreading rostrally up the brainstem such that the nigra is only involved in stage 3 disease. Thereafter the disease focus switches to the transitional and then neocortex. This beautiful work raises many questions, not least what constitutes the first clinical features of PD, and perhaps even more fundamentally how PD is actually defined.
- **Other movement disorders:** Mark Hallett presented an interesting account on apraxia (see also ACNR 5(1)) whilst Stan Fahn discussed dystonia, and a workshop on HD was presented by Flint Beal and Kathleen Shannon. In the session on MSA, Wenning discussed the existence of neuronal inclusions (that stain positively for α-synuclein and ubiquitin) in addition to the well described glial cell inclusions. Electron microscopy of these neuronal inclusions reveal subtle differences from the Lewy bodies seen in PD.

Concerns that, coming so soon after the meeting in Rome, there might not be much new data presented in New Orleans proved to be largely unfounded. The new style of the meeting brought a freshness to the format and conference fatigue was not a major issue. There are already plans afoot to stick to a similar format for the next conference in Kyoto, 2006.

Roger Barker, Caroline Williams-Gray, Tom Foltynie, Andy Michell and David Burn.

SPRING Meeting 2005

7 February, 2005; London, UK.

An audience of scientists, clinicians, patients and their carers gathered to hear an exceptional day of lectures and discussion at this year's SPRING conference (the research-promoting arm of the UK Parkinson's disease Society). Professor Nicholas Wood presented work examining the role of single gene mutations in familial cases of PD, in particular two recently identified genes; PARK6 and PARK 8, and discussed the role of common variation in such genes in the commoner idiopathic form of PD.

Neuronal death in PD is thought to be characterised by such mechanisms as oxidative stress, excitotoxicity and mitochondrial dysfunction – mechanisms which are undeniably interlinked. Professor Peter Jenner presented work examining proteasomal dysfunction in PD as a way of identifying a single event upstream of the cycle of oxidative stress and cellular dysfunction in order to discover novel therapeutic targets with the potential to halt the progression of neuronal death and clinical impairment in PD. Data from brain tissue of PD patients showed a remarkable 40-50% downregulation of the α subunit of the proteasome in the substantia nigra pars compacta compared to controls; a finding specific to this brain region. Other components of the proteasome such as the PA700 regulatory cap were also downregulated in the PD SNc, but were also upregulated throughout other brain regions, suggesting a change in the protein handling of the whole CNS in PD.

Professor Moussa Youdim argued that since neurodegenerative diseases such as PD and Alzheimer's disease have complex and distributed pathology with alterations in several neurotransmitter systems, multifunctional drugs which can target several of these pathways at once will prove superior to monofunctional drugs both in symptomatic relief and slowing disease progression. Dr Philip Robinson discussed the merits of a proteomics approach to identify the interacting partners of the protein products of genes associated with PD such as α-synuclein and Parkin. Overexpression of α-synuclein leads to a decreased expression of the proteasome α-subunit and lactate dehydrogenase and an increased expression of mitochondrial transport protein, hinting at roles of α-synuclein in the proteasome pathway and in mitochondrial function.

Michel Goedert discussed the role of α-synuclein in PD and current efforts towards the generation of a transgenic mouse expressing the human form of this protein as a model of PD progression. Lewy bodies, the pathological hallmark of idiopathic PD, are constructed mainly from abnormal filamentous protein aggregates consisting of α-synuclein. It seems that some pathological pathway exists in which the natively soluble unfolded α-synuclein is converted to these insoluble filamentous aggregates. Mutations leading to familial PD have been identified in the α-synuclein gene and are essentially of two types; missense mutations which render the gene product more liable to form filaments, or gene duplications/triplications. Thus even a simple gene dosage effect, i.e. expressing more of the wild-type α-synuclein, is sufficient to lead to aggregate formation and clinical disease.

The use of cell line models to manipulate the expression of PD associated genes, with a view to providing a better understanding of the mechanisms leading to their damaging effects on cells and ultimately ways in which to minimise this damage, was discussed by Professor David Latchman. Using this approach Prof. Latchman has analysed the effects of overexpression of α-synuclein (WT and mutant forms) and PINK1, as well as reducing the expression of Parkin, on cell death when exposed to a variety of exogenous stressors such as dopamine, staurosporine and hydrogen peroxide. Whilst mutant forms of α-synuclein are damaging regardless of which stress the cells encounter the wild-type form can be either protective or damaging in different circumstances. Of particular interest is a protective effect of WT α-synuclein (and a damaging effect of mutant forms) when cells are exposed to dopamine. The introduction of a Parkin antisense plasmid into cells in order to reduce Parkin expression levels resulted in increased cell death in response to stress, an effect which was reversed by caspase inhibitors, thus suggesting that the death seen in the absence of Parkin is mediated through the apopototic pathway. Recent work in collaboration with Professor Nick Wood lead to the identification of the protein kinase PINK1 as having a protective function against collapse of the mitochondrial membrane potential in response to proteasome inhibitors. Further characterisation of the mechanisms through which these single gene mutations lead to cellular dysfunction, death, and ultimately clinically apparent disease is likely to identify novel therapeutic targets which may be more broadly applicable to sporadic cases of the disease.

Transcriptome analysis, the establishment of a microarray-based expression profile of the parkinsonian substantia nigra as a method of providing a novel molecular pathology based set of diagnostic criteria for PD, was presented by Professor Maneul Graeber of Imperial College, London. The sophisticated mathematical analyses employed in these studies are providing a picture of the different molecular pathways disturbed in PD, with the ubiquitin-proteasome pathway and mitochondrial dysfunction featuring prominently.

Work leading to the first clinical trial of gene transfer therapy in Parkinson's disease using adeno-associated viral vectors to transfer the glutamic acid decarboxylase (GAD) gene into subthalamic nucleus (STN) neurons, was presented by Professor Matthew During of Cornell University. The results of the initial phase one safety trial of this novel gene therapy approach to PD are due to be published later this year.

Another novel therapeutic approach to PD was presented by Professor Steven Gill, who, having

heard of preclinical trials using GDNF in animal models of PD at a SPRING meeting some 5 years ago, went on to use this neurotrophic factor in human PD patients in small scale phase 1 trials (see report from the 9th International Congress of Parkinson's Disease and Movement Disorders in this issue). Dr David Dexter presented results of experiments using antioxidant flavonoids found in fruit, vegetables, tea and wine as neuroprotective agents in the 6-OHDA rat model of PD. He demonstrated a significant reduction in TH+ cell death following 6-OHDA lesioning in animals treated with orally administered antioxidant tangeretin. Professor David Goldstein provided a discussion of the potential role of pharmacogenetics in optimising pharmacological therapies for PD based on patients' genotypes. The potential benefits would be able to predict particular groups of patients who would respond well or adversely to a given drug treatment and also to minimise the time spent trying to achieve optimal dosing through the traditional trial and error approach. This was illustrated with data from Prof. Goldstein's work on single nucleotide polymorphisms (SNPs) in genes known to influence the metabolism, and therefore required dose, of anti-epileptic drugs such as carbamazepine and phenytoin. There is as yet no systematic analysis of the effects of single gene polymorphisms on response to anti-parkinsonian drugs. The final speaker of the day, Dr Matthew Wood, discussed the potential of therapeutic gene silencing for Parkinson's disease using the relatively new technology of (short interfering RNA) siRNA. This highly conserved cellular pathway whereby short double stranded RNA leads to the destruction of homologous mRNA (i.e. post-transcriptional gene silencing) will be one possible future approach to PD therapy. As with all experimental forms of therapy there are problems to overcome; the major one here being the delivery of siRNA to specific target cells in the adult brain. The use of viral delivery systems may allow sufficient targeting, however, it may be possible through chemical modifications of the siRNA molecules to enhance stability of the naked RNA and to apply a certain degree of target specificity, thus avoiding the need for a viral delivery system. An alternative would be to use an ex-vivo technique, introducing the si-RNA into neural stem cells before transplanting them into the PD patient.

Any major advance in therapy is likely to involve a synthesis of several current major strands of research including genetic and cellular approaches, with the development of each of these individual strands driven by our ever-advancing understanding of the pathogenesis of this complex heterogeneous disease.

Mark Sayles,
Cambridge Centre for Brain Repair,
Cambridge.

Association of British Neurologists Spring Meeting

30th March-1st April 2005; Belfast

The Spring meeting of the ABN at the Queen's University campus in Belfast was a feast of 29 research presentations, 49 posters (the organisers clearly like odd numbers), four guest lectures, a clinicopathological conference and an educational symposium on stroke. The meeting was held a few yards from a library dedicated to Seamus Heaney, Nobel Prize winning poet who studied at Queen's; Philip Larkin was a former sub-librarian here, though seemingly not commemorated. Would these literary associations prompt the ABN to new poetic heights? As always it was a mixed bag, although the neurogossip was as good as ever.

A recurrent theme was 'the structure of neurological care', overviewed by Dr Victor Patterson, a pioneer of teleneurology in Northern Ireland, also demonstrating the "added value" of specialist opinions for distant patients with neurological problems. Future developments may include e-mail triage of new outpatient referrals which seems safe, effective, cost-effective and sustainable, as well as being acceptable to GPs and, more so, to patients. Loizou suggested that perhaps 50% of referrals may be dealt with through e-mail without the patient needing to attend clinic. A poster showed that e-mail teleneurology could bring neurological resources effectively to the developing world. Patterson had to travel to Brisbane (poor chap!) to show that modern technology (real-time telemedicine) also allows outsourcing of night time cover to a different (daytime) time zone. Worrying for those out-of-hours supplements!

With all the sophisticated techniques now at the disposal of the practising neurologist, what role remains for neurological examination? McNeill's comparison of the 1897 and 2002 editions of Hutchinson's Clinical Methods revealed an increased amount of text devoted to neurological examination over the 105-year period, whereas a reduction was noted in chapters on respiratory medicine and cardiology. Unfortunately, a similar analysis could not be performed for history taking.

The PRCP, Carol Black, spoke in her guest lecture of the modernisation of the Royal College ("Change, adjustment and redefinition") and discussed the challenges of the nascent specialty of "Acute medicine" and the changing pattern of chronic care (towards the community). It was good to hear elsewhere in this and previous meetings that neurologists are taking on the management of acute neurology (a sub-specialty of "Liaison Neurology"?). However it was fortunate that the PRCP didn't hear some of the less than enthusiastic opinions (widely reiterated over coffee) concerning the neurological competence of general physicians. GKT medical school (Ridsdale) showed that five weeks full time neurology teaching could reduce 'neurophobia' in students (and hence future acute medicine specialists?) and improve their interest and confidence in neurology… something for curriculum planners

to consider.

The cannabis story continues. Collin showed in a drug company sponsored trial that Sativex was well tolerated and superior to placebo for the relief of spasticity in multiple sclerosis, using a numerical rating scale as the primary end point (i.e. subjective evaluation by patient). Secondary endpoints were improved but not statistically so, possibly due to the strong placebo effect noted in the trial. Interestingly there was a trend to improvement in muscle strength rather than the anticipated weakness and the benefit seems to be sustained in an extension trial.

Serial volumetric imaging of low grade gliomas may allow prediction of malignant transformation (Rees). Annual tumour growth rate was greater in patients who subsequently transformed as compared to non-transformers. This may offer important opportunities for early intervention in a group of patients with poor prognosis.

The diagnosis of herpes simplex encephalitis is often considered in patients with an acute encephalopathy with seizures, but may be difficult to establish. An audit of all suspected cases seen at Queen Square over a five year period found that only 10 out of 222 had a definite diagnosis; an alternative diagnosis was established in 144. 20% of cases remained undiagnosed. Investigations used included PCR (31%), intrathecal antibodies (11%; relatively underused) and brain biopsy (8%) (Davies).

Two presentations audited the diagnostic use of brain biopsy. At Atkinson Morley Hospital, 186 biopsies performed over a 10-year period (1993-2002) were mostly done to confirm a diagnosis of tumour, with a high diagnostic yield (97%). Yield was lower for "white matter lesions", with cerebral vasculitis confirmed in only one of 13 patients referred for this indication, alternative diagnoses being established in seven (O'Riordan). Biopsies performed at Queen Square, for the investigation of dementia in the period 1989-2003, had a lower yield still (59% diagnostic). The most frequent finding was non-specific gliosis, possibly akin to the syndrome of progressive subcortical gliosis reported by Neumann in 1967. In only 11% of cases did information obtained at biopsy directly influence treatment; very few "reversible" dementias were identified (Schott).

Dementia was considered in three platform presentations (including the above audit of biopsy) and six posters (four concerning CJD). A Liverpool study showed that observing whether a patient, referred to a dementia clinic, followed instructions and brought a relative to the clinic was a test for the presence of dementia with 100% sensitivity but rather low specificity. Referrals to the dementia clinic from Liverpool neurologists were shown to have "added value" compared to those GPs and other clinicians (phew!). Steve Wroe reported that tonsillar biopsy achieved 100% specificity and sensitivity in the diagnosis of nvCJD, whilst a poster from Bristol demonstrated that some find it difficult to distinguish the EEG of CJD from non-convulsive status unresponsive to anticonvulsants.

Movement disorders were the subject of three platform and seven poster presentations. We heard from Gibson (Belfast) that simple non-invasive analysis of ocular fixation might improve the clinical differential diagnosis of parkinsonism. Molloy (Newcastle) showed that l-Dopa improved alertness in patients with Parkinson's disease but at the expense of increasing impulsivity (the speed of responses increased but the accuracy fell) in those with cognitive problems. Meanwhile in the MS section the Oxford group showed that modafinil improved the fatigue of patients with MS especially if they were also drowsy (perhaps when some patients say they are 'tired' they mean sleepy rather than fatigued?).

An impressive presentation from Schaeffer (Newcastle) showed that at the least the physiological parameters of patients with mitochondrial myopathies could be improved with exercise induced activation of muscle stem cells. Mark Wiles confirmed the clinical impression that patients with myotonic dystrophy fall a lot but we still don't know why or what to do about it. Farrugia (Oxford) considered the important point that the problem of muscle atrophy (especially tongue wasting) in MuSK positive myasthenia might be exacerbated by steroid therapy. Brian Lecky in presenting five cases of limb girdle dystrophy type 2I further emphasised the difficult task of identifying genotypes from phenotypes in muscle disease. He concluded that this dystrophy might be a more common cause of a proximal myopathy with a high CK than previously thought. The biopsies of some cases showed inflammatory cells which could be removed by steroids without helping the muscle disease.

Epilepsy problems were considered in four platform presentations and five posters. A

senior member of the ABN rather deflated the usefulness of Hitiris' presentation from Glasgow on the usefulness of investigation in a first seizure clinic by (correctly) pointing that there was "nothing new here". The same could be said of the poster which produced no surprises in showing that structural abnormalities of the brain were more likely to be found in patients referred to neurology outpatients with seizures than in those referred with headache.

There were only two platform presentations on cerebrovascular disease (and six posters), one about the IST-3 trial of outside the licence use of r-tpa in acute stroke which Peter Sandercock largely duplicated in his presentation on the same subject in the Stroke educational session. Rory Collins' data-packed guest lecture on cholesterol, statins and stroke made all of us over 45 feel uncomfortable about not taking a statin for breakfast in order to emulate the health of Chinese peasants. Unfortunately much of this was repeated in Ian Young's more austere talk in the Stroke educational session. Thus, by Friday, after two hotel breakfasts, we were all heartily fed up with cholesterol. In the final educational talk of the meeting, Rothwell, by teasing us with totally atypical presentations of posterior circulation TIAs, came some distance short of showing that the reliable diagnosis of TIAs requires a neurologist. However, of course, we all know that it does. Fortunately the expression "Brain Attack" was not to be heard in the whole three days.

The local Belfast expertise in Paramyxomaviruses was demonstrated in a perhaps over comprehensive review of these interesting beasts and how they enter the brain and cause diseases, possibly via CD46 and SLAM receptors on endothelial surfaces and elsewhere. Those working in rural areas will need to be on their guard to recognise the human equivalent of the Barking Pig Syndrome, if Nipah viruses are shown, like their relatives the Hendra viruses, to transfer to humans from their animal reservoirs. This talk was followed by a very entertaining performance by Brendan McLean as the discussant in a very difficult CPC. He predicted he would get it wrong and did, as we all would have done, except one member of the audience who told us, after the denouement, that it was a classic example of Enterovirus 71 encephalomyelitis!

Sydney Allison, the great Belfast neurologist who started the systematic study of MS in populations, was commemorated in a brilliant guest lecture by Stephan Waxman. He guided us through the numerical jungle of neuronal sodium channels in a fluent exposition of this area of neuroscience which holds so much promise in our search for effective treatments for axonal disease and degeneration. This, on its own, was worth the trip to a rather grey and damp Belfast.

Chris Allen, Addenbrooke's Hospital, Cambridge.
Andrew Larner, Walton Centre, Liverpool.

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Why Excessive Daytime Sleepiness is an Important Issue in Parkinson's Disease

Specialists are likely to see many patients with excessive daytime sleepiness (EDS) since disordered sleep is so common, especially with neurological conditions such as Parkinson's disease (PD), Alzheimer's disease and other types of dementia, other neurodegenerative conditions, peripheral neuropathy, neuromuscular disorders, depression, epilepsy and chronic pain syndromes.[1]

The corollary of impaired nocturnal sleep may be EDS. The issues related to excessive daytime sleepiness in PD attracted little attention until reports were published of patients treated with dopamine agonists falling asleep while driving.[2] These episodes of irresistible sleepiness - or 'sleep attacks' - initially were thought to be specifically related to dopamine agonists, but are now considered to be a class effect of all dopaminergic drugs and even of PD itself.[3] Much discussion has focused on the suddenness of their onset and whether they truly occur with no warning, and it has also been questioned whether the sleep attack is a distinct phenomenon or is indistinguishable from drug-induced somnolence or background levels of EDS.[3-5]

The consequence of this renewed interest in PD-related sleep pathology, and its effects on patients and their lives, has led to a greater focus on EDS yet the first systematic study of sleepiness in PD was published only a couple of years ago.[6] Given that excessive sleepiness can have profound, detrimental effects on an individual's day-to-day functioning, their safety and overall quality of life, as well as affecting the lives of their family and carers, it is now being appreciated that EDS in PD is a wide-reaching problem with important implications.

This article looks at the issue of EDS in patients with PD and explores the reasons why patients might suffer from daytime somnolence and what steps could be taken to manage it.

EDS in PD - a sizeable problem

Daytime sleepiness is common but often unrecognised[1] and appears to be a frequent complaint of PD patients: one community-based study indicated that around 15% of PD patients might be affected by EDS, compared to only 1% of elderly controls.[7] However, this could underestimate the size of the problem, as subsequent studies have reported much higher figures: Ondo et al[8] found "abnormally high" sleepiness scores in half of the PD patients they studied; similarly, an incidence of 51% was seen in a study of over 600, highly-functional PD patients without dementia;[5] and in another study of PD patients, being evaluated for quality of life, 72% showed symptoms of increased daytime somnolence.[9]

Table 1: Causes of excessive daytime sleepiness in PD
(Adapted from Olanow et al[4])

• *Disturbed nocturnal sleep resulting from PD-related motor symptoms, parasomnias, sleep disorders, coexisting medical conditions*
• *PD-related disturbance in sleep-wake regulation*
• *Age-related changes in sleep architecture and alterations in circadian rhythm*
• *Medications that can cause sedation, such as:* ◆ *dopaminergic drugs e.g. levodopa, dopamine agonists, selegiline* ◆ *other antiparkinsonian drugs e.g. anticholinergics, amantadine* ◆ *psychotropic drugs e.g. benzodiazepines, antidepressants, neuroleptics*
• *Endocrine dysfunction e.g. hypothyroidism*

EDS in PD patients - what causes the problem?

It would be logical to assume that a key reason why patients may suffer from excessive sleepiness during the day is because they are not getting enough good quality sleep at night. Whilst this is largely true, it does not give the full picture in PD: many factors can have an influence on PD patients' daytime alertness.[4]

PD patients may not get the right amount, or the right type, of sleep because of sleep disruption or disturbances (interference with getting to sleep and/or fragmentation of sleep during the night) and alterations of sleep architecture, where the patterns and relative amounts of REM and non-REM sleep change.

Sleep disturbances are very common in PD, affecting from 60% to 98% of patients[10] and can be caused by a wide range of factors (see Table 2). One frequent cause is sleep-disordered breathing: Arnulf et al detected moderate-to-severe obstructive sleep apnoea syndrome (OSAS) in 20% of PD patients, even though obesity was rare in this particular study.[6] However, although EDS has been attributed to sleep fragmentation, it can also be seen in patients with normal sleep efficiency who do get enough sleep at night.[11] PD patients may have daytime somnolence because of dysfunction of their sleep-wake mechanisms: in such patients, the underlying disease process is thought to affect the neuronal pathways and/or neurotransmitter functions that maintain the balance between the sleep and waking states, causing EDS.

Additional factors, such as sedating drugs, or comorbid disease e.g. thyroid disorders, must also be borne in mind when looking for causes of EDS.

Table 2: Factors contributing to sleep disturbance in PD
(Adapted from Comella, 2003[10]; Chaudhuri, 2003[12])

• *Nocturnal recurrence of PD symptoms e.g.*	*Tremor* *Akinesia (e.g. difficulty turning over in bed)* *Rigidity* *Painful cramps*
• *Conditions often associated with PD e.g.*	*Depression, anxiety* *Restless legs syndrome* *Periodic limb movement syndrome* *Dementia* *Sleep apnoea* *Nocturia* *Parasomnias e.g. nightmares, somnambulism*
• *Other comorbid disorders commonly seen in older people e.g*	*Arthritis and other painful conditions* *Cardiac disorders.* *Respiratory diseases*
• *Side-effects of medication (antiparkinsonian or other drugs)*	*Insomnia* *Changes in sleep architecture* *Sleep-related effects such as vivid dreams, nightmares, hallucinations* *Withdrawal effects*

Doug MacMahon is Consultant Physician with special responsibility for the elderly, Royal Cornwall Hospital NHS Trust. He has particular interests in PD, community care and rehabilitation. He has written extensively on PD, its management, and on healthcare policy for older people.

Correspondence to:
Dr Doug MacMahon,
Camborne-Redruth Hospital,
Redruth,
Cornwall,
TR15 3ER.
Tel: 01209 881634,
Email: Doug.MacMahon@cornwall.nhs.uk

We would like to thank Cephalon for their sponsorship of this article.

EDS in PD - an outcome of sleep-wake dysregulation?

Whilst much is still unknown, there have been great advances in sleep research recently that have helped define the multiple neural pathways, transmitters and cell groups involved in the regulation of sleep and wakefulness. This has provided a better understanding of the relationship between PD and daytime somnolence, and how new medications could offer improved treatment options for the symptom of EDS.

The neuropathology of PD can lead to structural changes of the sleep-wake centres causing insomnia, hypersomnia or circadian rhythm disturbances.[13] Similarly, it can cause neurochemical changes affecting not only dopamine, but a range of neurotransmitters now known to be involved in the modulation of the sleep-wake cycle. In the past, dopamine was not considered to be a modulator of the sleep-wake state, but discovery of the extensive striatal and thalamocortical connections of midbrain dopaminergic neurones suggests that dopamine does have such a role.[14]

Wakefulness and sleep (and the transition from one state to the other) are regulated by neuroanatomical, neurochemical and circadian systems, but no single brain centre is responsible for the whole sleep-wake cycle.[13] 'Being awake' involves two, parallel pathways that activate the cortex: one arises from neurones in the brainstem - the classical reticular activating system (RAS); the other a newly-characterised, neuronal projection from the hypothalamus that incorporates the sleep-wake 'switch'.[15,16] The latter involves three distinct hypothalamic structures that play a key role in promoting either sleep or wakefulness: the ventrolateral preoptic area (VLPO - sleep-promoting), the tuberomamillary nucleus (TMN - wake-promoting) and the suprachiasmatic nuclei (SCN - site of the 'internal clock' that regulates circadian rhythm).

The sleep-wake 'flip-flop' switch

One model of the normal sleep-wake cycle proposes that VLPO and TMN neurones inhibit each other, thus causing oscillations between wakefulness and sleep in a rhythm determined by the internal clock in the SCN. This is elegantly described by Saper et al[17] who discuss the concept of a reciprocal switching circuit - or 'flip-flop' switch - which means the brain can be either 'on' (calm wakefulness) or 'off' (asleep). The two halves of the flip-flop circuit, by each strongly inhibiting the other, create a feedback loop that is bi-stable, meaning there are two possible stable patterns of firing, with a tendency to avoid intermediate states (see Figure 1).

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

The relatively recent discovery of the neuropeptide, hypocretin (orexin), has thrown further light on how stability of this switch is maintained. It is now thought that hypocretin neurones might act as a 'finger', pressing the flip-flop switch into the 'wakeful' position, and preventing inappropriate switching into the 'sleep' position.

The Flip-Flop Switch

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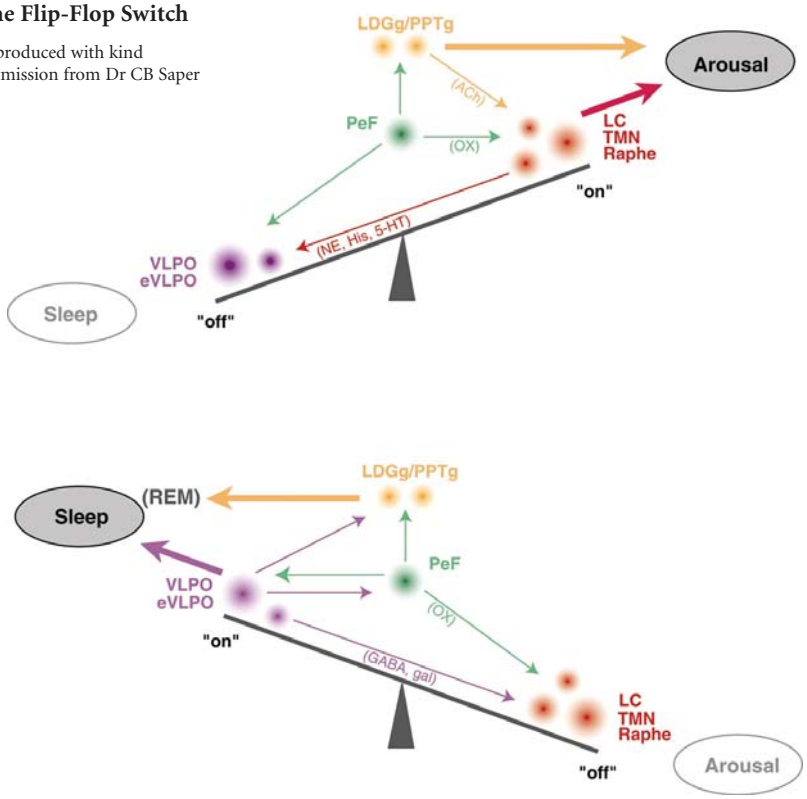

It would follow that an unstable switch could lead to insomnia or to unwanted, rapid transitions into sleep during wakefulness, e.g. as seen in narcolepsy.[16] Indeed, low levels of hypocretin have been implicated in the pathology of narcolepsy[18] and, more recently and relevantly, also in the pathogenesis of EDS in PD. [19]

EDS in PD - evaluating the problem

It is normal to experience bouts of daytime sleepiness from time to time, for instance, after a very late night, and the propensity for daytime somnolence and need for naps increases as part of the normal ageing process. These problems are accentuated in PD patients,[4] but when does sleepiness become 'excessive' or pathological? If there are episodes of overwhelming tiredness, extended daytime naps and unintended sleep episodes that interfere with patients' (and carers') day-to-day activities, then the sleepiness warrants further investigation.

Current PD scales, such as the United PD Rating Scale (UPDRS) and the PD Quality of Life Scale, are limited in terms of sleep-related questions. A Parkinson's Disease Sleep Scale (PDSS) has recently been developed for assessing the different factors contributing to sleep disturbances, particularly motor symptoms.[20] However,

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whilst frequency of falling asleep is included, it does not focus on daytime sleepiness.

A useful instrument for evaluating EDS, by assessing the likelihood of patients dozing off in a range of lifestyle situations, is the Epworth Sleepiness Scale (ESS) - a quick and easy-to-use questionnaire for the patient and/or carer that does not require technical measurements or the involvement of a sleep laboratory (see Figure 2).[21]

Objective confirmation of EDS - usually regarded as an Epworth score of 11 or more - can be obtained by the MSLT (Multiple Sleep Latency Test), but this may not be practicable for most cases as it requires the use of a sleep laboratory. Therefore, unless a primary sleep disorder (such as narcolepsy) is suspected, the ESS provides a useful evaluation tool.

Managing the PD patient with ES

A systematic approach will help build a picture of the patient and their EDS and enable identification of the possible cause - or causes :

- o establish the presence of EDS using the Epworth Sleepiness Scale
- o identify contributing medical or psychological factors - nocturnal PD-associated symptoms and comorbid complaints, including sleep disorders such as OSAHS (obstructive sleep apnoea/hypopnoea syndrome)
- o identify iatrogenic factors by reviewing all current medication

Useful measures to help overcome night-time sleep disturbances or their consequences include:[11]

Non-pharmacological interventions

- Improving sleep hygiene - making simple recommendations to help the patient create a mental / physical state and environment conducive to falling and staying asleep.

Pharmacological interventions

- Adjusting medication to ensure control of PD symptoms throughout the night. Slow-release L-dopa can help, but patients with advanced PD are particularly vulnerable to vivid dreams or sleep fragmentation by L-dopa. In these patients, sustained treatment with dopamine agonists such as nocturnal apomorphine, or an evening dose of cabergoline can be effective
- Avoiding excessive dosage of dopaminergic medication. Reducing the night-time dose or taking it earlier in the evening can reduce the risk of sleep onset insomnia, parasomnias and nocturnal myoclonus. Selegiline and amantadine can have stimulant effects which disturb sleep, so these drugs should not be taken later than noon.
- The use of stimulants such as dexamfetamine and methyphenidate could be considered in those cases where daytime sleepiness persists even when nocturnal symptoms and adverse effects from treatment are controlled. However, they are not licensed for such use and their drawbacks are well-known - high abuse potential, limitations in prescribing due to their Controlled Drug status, their tendency to interfere with sleep by decreasing total sleep time and REM sleep, as well as cardiovascular and other side effects.
- Use of a selective wakefulness-promoting agent, modafinil, which is chemically and pharmacologically unrelated to CNS stimulants. Whilst stimulants have a 'blanket' effect on both the RAS and hypothalamic sleep-wake system, modafinil is more selective - specifically affecting the latter - and thus avoiding the motor hyperactivity, hyperarousal and jitteriness often associated with amphetamines.[16]

Combating EDS in PD with a specific wakefulness-promoting agent - modafinil

Whilst its mode of action is yet to be clarified, modafinil appears to exert its effects specifically on the hypothalamic sleep-wake system: increasing wake-promoting neuronal activity in the TMN and decreasing sleep-promoting neuronal activity in the VLPO, thus inducing 'calm wakefulness'.[16] Modafinil is well-established as a first-

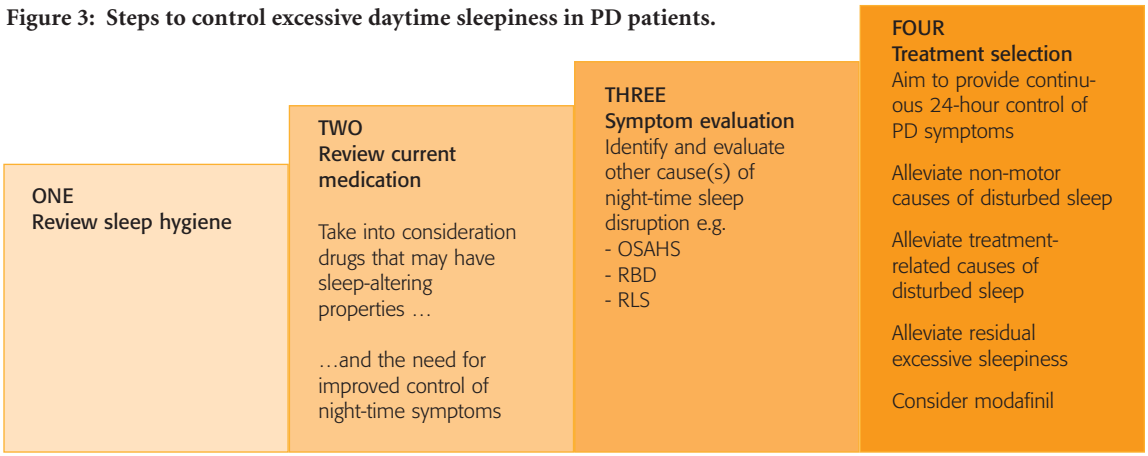
Figure 2: The Epworth Sleepiness Scale[21]

Questionnaire

Situation	Chance of dozing (0-3)			
1. Sitting and reading	0	1	2	3
2. Watching TV	0	1	2	3
3. Sitting, inactive in a public place e.g. a theatre or a meeting	0	1	2	3
4. As a passenger in a car for an hour without a break	0	1	2	3
5. Lying down to rest in the afternoon when circumstances permit	0	1	2	3
6. Sitting and talking to someone	0	1	2	3
7. Sitting quietly after a lunch without alcohol	0	1	2	3
8. In a car, while stopped for a few minutes in the traffic	0	1	2	3

Patients are asked to rate their chance of dozing off in each situation, giving them a ranking of between 0 (would never doze) and 3 (high chance of dozing).
Total scores range from 0 to 24
Scores > 10 indicate excessive sleepiness. Patients with scores > 15 should be referred to a specialist centre.

Figure 3: Steps to control excessive daytime sleepiness in PD patients.



OSAHS – obstructive sleep apnoea/hypopnoea syndrome, RBD - REM behaviour disorder and RLS - restless legs syndrome.

line, symptomatic treatment for EDS associated with narcolepsy and, more recently, is proving to be a useful agent in other medical conditions where EDS is a symptom.

The efficacy of modafinil in improving the symptom of EDS in patients with narcolepsy and other sleep disorders raised the question of whether it could resolve this troublesome and common symptom in other conditions, such as PD. A number of small studies and case reports using modafinil in single daily doses between 200 – 400 mg have shown it to be a well-tolerated addition to antiparkinsonian medication in patients with EDS, relieving excessive sleepiness with no detrimental effect on PD symptoms noted.[22-26]

The most extensive study was a 7-week, placebo-controlled, crossover study of modafinil 200 mg/day, followed (after a 1-week wash-out period) by a 4-week, open-label trial of modafinil 200 mg/day for the first week and 400mg/day for the remainder.[22,23] In both studies, Epworth Sleepiness Scale (ESS) scores were significantly improved in patients on modafinil ($p=0.039$[22]; $p=0.002$[23]) and, in the open-label extension, patient- and physician-rated Clinical Global Impression of Change (CGI-C) scores for improvement in wakefulness were also significant ($p=0.015$ and $p=0.003$, respectively). Modafinil was very well tolerated, with no significant changes in blood pressure or vital signs.

Importantly, modafinil does not appear to have a detrimental effect on the underlying disease as, when assessed, parkinsonian symptoms did not seem to be worsened in any of the studies. In fact, one study reported that some patients were able to tolerate the necessary increments in their dopamine agonist dosage only after receiving modafinil.[24]

Conclusions

Improving patients' quality of life is a key factor to consider when reviewing PD treatment plans. With up to 98% of PD patients reporting problems with sleep disturbances,[10,12] the management of these disturbances and any consequent excessive sleepiness should be a priority. By using the steps outlined above and simple evaluation tools, such as the Epworth Sleepiness Scale, the physician should be able to effectively manage and treat sleep disturbances and excessive daytime sleepiness in PD.

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26. Högl B, et al. *Modafinil for the Treatment of Daytime Sleepiness in Parkinson's Disease: A Double-blind, Randomized, Crossover, Placebo-controlled Polygraphic Trial.* Sleep 2002;25:62-66.

EDITOR'S CHOICE

SPEECH: Reinventing the Arch

A simplistic neural model of language consists of input at the superior temporal gyrus (Wernicke's area) and output at the inferior frontal gyrus (Broca's area) with a connecting tract, the arcuate fasciculus, arching from one to the other around the back of the Sylvian fissure. Receptive, expressive and conduction aphasia, respectively, by this model follow damage to Wernicke's, Broca's and the arcuate. Dejerine described the arcuate fasciculus itself in 1895 but even before this Lichtheim, on the basis of the myriad forms of conduction aphasia, had proposed an additional 'centre' in the network. Geschwind developed this argument and emphasised the role of the inferior parietal lobule (Brodmann areas 39 and 40). This beautifully illustrated paper describes the most interesting result yet from the technique of diffusion tensor magnetic resonance imaging. Diffusion tensor imaging (DTI) depends on the principle of anisotropy. In brief, water molecules diffuse more easily along myelin sheaths than across them and this property can be tracked from an initial 'seed' point, revealing the course of fibre bundles through white matter. Catani and colleagues use DTI in eleven healthy right-handed males to show the course of the arcuate fasciculus through the left hemisphere and also demonstrate the existence of two associated fibre bundles, one connecting Broca's area and the inferior parietal lobule and one connecting Wernicke's area to roughly the same location. They suggest, very plausibly, that relative damage to these tracts may correlate with the varied presentations of conduction aphasia. This study consolidates more than a century of work and shows the promise of DTI as complement to other imaging modalities. The spatial resolution of DTI will need to improve, however, if it is to reveal truly novel brain networks. - ***RRD***

Catani M, Jones DK, ffytche DK and DH.
Perisylvian language networks of the human brain.
ANNALS OF NEUROLOGY
2005;57:8-16.

NEUROINFLAMMATION: Antigen-presentation in EAE

★★★ RECOMMENDED

Microglia, mysterious little mites at the best of times, are classically considered as the antigen-presenting cells of the brain, responsible for bringing together the nasty autoaggressive cells and myelin antigens (doing the job of the "dendritic cells" of the systemic compartment which supposedly do not get into the brain). And, certainly, microglia are critical for inflammation in the brain, because getting rid of them abolishes EAE. However a couple of recent studies in Nature Medicine have thrown doubt on their antigen-presenting role. Although seemingly trivial, this issue is of critical importance for those who muse on immunotherapies designed to intervene in the process of antigen presentation (not, I admit, a large group of people, but an interesting bunch). Stephen Miller's group in Chicago examined the classical immunological phenomenon of "epitope spreading" whereby an immune response elicited against one antigen leads, in time, to immune responses against other related antigens (a process which may lead to the chronicity of some inflammatory diseases). They are especially interested in epitope spreading in EAE and, specifically, where this happens – in the periphery or in the brain? They use a beautiful model: following the proliferation of CFSE-dye labelled CD4+ T cells that recognise one PLP peptide (139-151) in the context of EAE induced by another PLP peptide (178-191). They showed that the first sign of activation of the CFSE-dye labelled cells (indicating spread of the epitope to the 139-151 peptide) occurred in the CNS, before they become activated in the systemic compartment. This proves what many have long suggested: that naïve cells can enter the intact brain, there to be activated locally by antigen presenting cells. But what antigen-presenting cells were doing this? Well, not microglia it turns out but some old-fashioned dendritic cells (CD11 positive for DC nerds), which, as I said, are not supposed to be in the brain... Burkhard Becher's team, from Zurich, follow this nicely with a study in MOG-induced EAE. They showed that encephalitogenic T cells could induce EAE when transferred to a naïve host, even when that host was completely devoid of a lymphoreticular system and spleen! They then developed, using a complex blend of transgenics and radiation, host animals with Class II restricted antigen-presenting cells restricted either to the CNS or the systemic compartment. Only the latter animals developed EAE on transfer of encephalitogenic T cells, implying that systemic antigen presenting cells are obligatory for the development of the disease. They further narrowed down the culprit antigen-presenting cells. By expressing class II under the CD11 promoter in otherwise class II deficient mice, they generated animals with only a few dendritic cells in the meninges and CNS blood vessels; yet these animals expressed EAE on transfer of encephalitogenic T cells. So it seems that the microglia are not needed for antigen presentation in EAE after all; a group of hitherto poorly recognised "systemic" antigen presenting cells, lurking in the meninges and CNS blood vessels, do the job rather well without them. Fascinating! ***-AJC***

McMahon EJ, Bailey SL, Castenada CV, Waldner H, Miller SD.
Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis.
NATURE MEDICINE
2005;Mar:11(3):335-9. Epub 2005 Feb 27.

Greter M, Heppner FL, Lemos MP, Odermatt BM, Goebels N, Laufer T, Noelle RJ, Becher B.
Dendritic cells permit immune invasion of the CNS in an animal model of multiple sclerosis.
NATURE MEDICINE
2005;Mar:11(3):328-34.

REHABILITATION: Improving outcomes through teamwork

One of the key factors in the benefit of stroke (and other rehabilitation) units has been identified as the multi-disciplinary (MDT) team-work, yet studies on what form this team-work should take are limited. This paper, though not a randomised controlled trial, does shed some light on how team-work can be improved to optimise patient care in a clinical setting. Perhaps not surprisingly, it showed that a MDT ward round (including a physician!) does significantly improve patient involvement and goal-setting over a standard MDT "chart round". The ward round also improved "team working" though did take twice as much staff time (and presumably, cost!). Though not "rocket science", it does add evidence to what many rehabilitation units practice on a routine basis and highlight how practical measures can improve patient care without scientific breakthrough. It also illustrates the type of practical studies that can be performed in the clinical setting to improve the evidence base for our practices. As the most expensive member of the MDT it does raise the question of how physician time should be best used? ***-JMcF***

Monaghan J, Channell K, McDowell D and Sharma AK.
Improving patient and carer communication, multidisciplinary team working and goal-setting in stroke rehabilitation.
CLINICAL REHABILITATION
2005;19:194-9.

PRION DISEASE: A meal fit for a monkey?

★★★ RECOMMENDED

When does feeding two macaques a meal, and watching what happens, get you a letter in the Lancet? When you have fed them brain homogenate from a BSE-affected cow, of course. One of the animals got variant CJD at 60 months, the other remained well at 76 months. The rest of the article examined the oral dose of brain homogenate required to cause CJD in primates, cattle, mice… and extrapolated to humans. In particular, the authors considered the risk of humans getting CJD from meat declared non-infected with PrPSc using the standard EU-approved testing kit (for which the authors' institution handily holds a patent but I am sure that had nothing to do with their desire to publish these data). The authors conclude that "If people were to eat CNS tissues from a cow with preclinical BSE with a concentration of PrPres just below the test detection limit of 1 in 300, they would need to ingest at least 1·5 kg to reach the degree of exposure equivalent to that in the 5 g of brain used for oral transmission to the macaque in the present study". Anyone for a BigMac? ***-AJC***

Lasmezas CI, Comoy E, Hawkins S, Herzog C, Mouthon F, Konold T, Auvre F, Correia E, Lescoutra-Etchegaray N, Sales N, Wells G, Brown P, Deslys JP.
Risk of oral infection with bovine spongiform encephalopathy agent in primates.
LANCET
2005;Feb 26:365(9461):781-3.

ALZHEIMER'S DISEASE: Environmental enrichment in AD – an exercise in amyloid clearance

★★★ RECOMMENDED

The deposition of amyloid is a characteristic feature of Alzheimer's disease, the Aß amyloid peptide being cleaved from APP by the action of BACE1 and gamma-secretase. In this paper Lazarov et al propose the unusual hypothesis that Aß amyloidogenesis can be modulated by environmental experience, on the grounds that APP processing plus Aß production is modulated by synaptic activity which is known to be influenced by environmental factors. They therefore used a well established transgenic mouse model in which the familial Alzheimer disease linked APP Swedish mutation and the presenilin 1 E9 polypeptide variants are crossed to give a mouse which is known to produce Aß deposition throughout the hippocampus and cortex. These mice were then split into groups. One was brought up in a standard environment whilst the other was housed in an enriched environment. They demonstrated that the enriched environment reduced the amount of Aß deposition whilst increasing the degradating protease, neprilysin. Furthermore using Affymetrix gene chips microarray they demonstrated there was selective upregulation in a range of intermediate early gene (IEG) transcripts encoding polypeptides involved in endothelial and phospholipid metabolism as well as neurogenesis and cell survival pathways. However no behavioural tests were undertaken so it is not clear whether these molecular changes map onto any significant behavioural improvements. Furthermore other studies have not found this relationship; indeed some have even reported the opposite (*Jankowsky JL et al 2003, Experimental Neurology 62 1220 – 1227*). So what this really means is debatable, especially given the controversy over the role of mayloid in Alzheimer's pathogenesis. Nevertheless this fascinating study once more emphasises that an enriched environment can be good for the brain even in disease, although exactly how this influences the clinical condition is unknown. - ***RAB***

Lazarov O, Robinson J, Tang YP, Hairston IS, Korade-Mirnics Z, Lee VM, Hersh LB, Sapolsky RM, Mirnics K, Sisodia SS.
Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice.
CELL
2005;Mar11:120(5):701-13.

STEROID DEMENTIA: Can you remember the last time you took steroids?

There is a well known action of steroids within the brain which involves changes in mood and behaviour as well as a role in modulating inflammatory disease processes. However two new papers suggest that steroids may have a more profound, but transient, effect on cognitive functioning. In their case report, Sax and Schulman describe a patient with a dementia induced by high dose oral steroids for polymyalgia rheumatica which reversed on stopping this treatment. Whilst Brunner et al in their study looked at the effects of steroids on cognitive function in the context of acute optic neuritis (9 patients) and MS (21 patients) and found changes in some forms of memory whilst leaving untouched a range of other neuropsychological tests. These changes were all reversible. These short papers are interesting and raise many questions. Firstly how frequent are these side effects of steroids and to what extent does it impact on the patient and his quality of life. Secondly how do steroids produce this effect? In answer to the first question, more detailed studies are needed in larger numbers of patients using a range of measures. In terms of mechanisms, there has recently been a great deal of interest in the role of steroids on adult endogenous precursor cell turnover and survival, especially in the hippocampus, which is interesting given the memory deficits highlighted in these studies. Thus once more we are looking at the possibility that well established drugs may have unusual effects which may be mediated through these mysterious, newly discovered, population of adult neural cells. - ***RAB***

Brunner R, Schaefer D, Hess K, Parzer P, Resch F, Schwab S.
Effect of corticosteroids on short-term and long-term memory.
NEUROLOGY
2005;64:335-337.
Sacks O, Shulman M.
Steroid dementia: An overlooked diagnosis?
NEUROLOGY
2005;64:707-709.

PARKINSON'S DISEASE: Microglia in PD – an inflammatory topic?

The role of inflammation in the pathogenesis of neurodegenerative diseases is an area of intense interest, most notably in Alzheimer's disease. However in Parkinson's disease (PD) it has been known for over 20 years that there is increased microglia activity in post mortem tissue around the midbrain dopaminergic neurons. Furthermore a couple of years ago it was reported that the use of anti-inflammatory drugs may actually impact on the risk of developing Parkinson's disease. However the unresolved problem has always been the extent to which any inflammatory abnormalities are secondary to the cell loss rather than a primary mover in the disease process. Now Ouchi et al have shown, using PET-PK11195 PET, that there is microglia activation with dopamine loss in early Parkinson's disease. On the basis of temporal expression of microglial markers with dopaminergic terminal loss, the authors conclude causality. However this is not the strongest of arguments, especially as other groups using similar approaches have failed to replicate this relationship. The group did not attempt to intervene and assess the impact of modifying the inflammatory response. Nevertheless it does raise intriguing questions on PD pathogenesis as well as the role of inflammation in neurodegenerative disorders. In addition it may provide a useful biomarker of PD or at least serve as a surrogate marker for investigating neuroprotective therapies in this common condition. - RAB

Ouchi Y, Yoshikawa E, Sekine Y et al.
Microglial activation and dopamine terminal loss in early Parkinson's disease.
ANNALS OF NEUROLOGY
2005;57:168-175.

ALZHEIMER'S DISEASE: Effects of cognitive-communication stimulation for AD patients treated with Donepezil

This study is representative of a growing field of research in which drug treatments are investigated in combination with cognitive rehabilitation programmes (traumatic brain injury being another field undergoing this sort of investigation). The authors conclude that this study "adds to the growing evidence that active cognitive stimulation may slow the rate of verbal and functional decline in Alzheimer's Disease (AD) when combined with acetylcholinesterase inhibitors". The combination of cognitive stimulation and donepezil was administered to 26 participants with mild to moderate AD, while a further 28 received the drug treatment alone. The stimulation programme was delivered in groups, covered a period of 8 weeks and involved a total of 12 hours contact time for each participant. Performance was measured in terms of relevance of discourse, performance of functional activities, emotional symptoms, quality of life and global functioning. Follow-up measures were taken 4 and 8 months after intervention. Slower rates of decline in the areas of discourse, functional abilities, emotional wellbeing and global functioning were found for the group receiving both forms of treatment. Though the gains (or more accurately the slower rates of decline) were relatively modest, the authors point out that they were achieved with fairly short-

term (and low cost) group intervention and that they persisted until the end of the study. Having said this, they also acknowledge that the study design did not allow them to differentiate between specific cognitive therapy and the possible effects of general stimulation by increased contact between participants and professionals. - ***RB***

Chapman SB, Weiner MF, Rackley A, Hynan LS & Zientz J.
Effects of cognitive-communication stimulation for Alzheimer's Disease patients treated with Donepezil.
JOURNAL OF SPEECH, LANGUAGE, AND HEARING RESEARCH
2004;47:1149-63.

ALZHEIMER'S DISEASE: Effects of Alzheimer's disease in a creative writer

★★★ RECOMMENDED

The novelist Dame Iris Murdoch is perhaps the most high profile individual to have suffered from Alzheimer's disease in the UK, largely as a consequence of her husband John Bayley's book about her illness and the subsequent film of the book. Her literary output over many years has provided the opportunity to undertake a retrospective examination of certain cognitive operations during the presymptomatic period of the disease. A systematic comparison of three of her novels was undertaken: *Under the net* (1954), her first published novel; *The sea, the sea* (1978) which won the Booker prize; and *Jackson's dilemma* (1995), her last published work, which received a lukewarm response from the critics. Retrospectively, it seems likely she was in the preclinical phase of AD when writing this. Texts were analysed using a variety of methods, both automated and manual. The final novel was found to have a more restricted vocabulary, implying greater repetition, than the earlier works. Although this was also the least syntactically complex of the three books, nonetheless syntactic structures were relatively unchanged. The fact that Iris Murdoch resisted all editorial suggestions to alter her submitted texts (imagine such a situation in neurology: referees and editors could be done away with entirely!) gives the analytical approach used here some validity. It is interesting to read AN Wilson's accompanying editorial (*Brain 2005;128:237-8*) suggesting that, as an author, Murdoch was "extremely careless and none of her books really contains a simple or perfectly organised plot". The paper is also testament to the fact that education and creativity per se are not necessarily guarantees against the development of AD (the author of Gulliver's travels, Dean Jonathan Swift, also developed dementia, probably AD, in later life). - ***AJL***

Garrard P, Maloney LM, Hodges JR, Patterson K.
The effects of very early Alzheimer's disease on the characteristics of writing by a renowned author.
BRAIN
2005;128(2):250-60.

EPILEPSY: Magnetoencephalography and surgery for seizures

Brain surgery is sometimes used to control seizures when people living with epilepsy do not respond sufficiently to medication. The idea is to remove the tissues prone to epileptic activity, thus controlling seizures, while preserving tissues most important for cognitive function. Presurgical evaluation involves physiological, functional and cognitive tests and integrating results to determine how to proceed. Magnetoencephalography (MEG) is a non-invasive method for measuring neuronal activity directly. Sophisticated analysis methods are able to detect small changes in magnetic fields that accompany neuronal activity. MEG has excellent temporal and spatial resolution. There is the potential for better localisation accuracy than EEG especially when using simplistic spherical models of the head. There is faster temporal resolution than fMRI because the technique is not dependent on comparatively slow changes in blood oxygenation levels. Patients (n=33) whose pre-surgical MEG registered epileptic activity were examined pre- and post-operatively to see whether surgical outcome related to their presurgical MEG findings. The authors developed a novel method of combining groups of individual MEG source localisations into an ellipsoidal volume. The position and size of this volume was then compared with the resection volume generated using pre- and post-operative MRI data. A small distance between the MEG localisation volume and the resection volume correlated with favourable outcome measured using Engel's classification scheme. A high coverage of the MEG results ellipsoid by the resection volume also correlated with a favourable outcome. It seems that MEG will help surgeons decide which tissues to remove and which to preserve, but only when used in conjunction with other techniques. The authors highlight the need for further research into the clinical evaluation of this method. – ***LAJ & DJL***

Fischer MJM, Scheler G and Stefan H.
Utilization of magnetoencephalography results to obtain favourable outcomes in epilepsy surgery.
BRAIN
2005:128:153-7.

MULTIPLE SCLEROSIS: Winter sunshine to reduce risk of multiple sclerosis?

Patients with multiple sclerosis (MS) are more likely to be born in May, and less likely to be born in November, reported a large population based study earlier this year. The study compared the birth dates of individuals affected with MS with two control groups; a population-based control group and unaffected siblings. A total of 42,045 affected individuals from Canada, Denmark, Great Britain and Sweden, were used. The result was obtained by comparing the observed birth frequency for each month in the affected group with the expected frequency based on the two control groups. The May/November risk was seen in individual countries, and also increased in significance with the prevalence of MS in each country, suggesting both are dictated by the same factor. The significance increased further when unaffected sibs were used as controls, excluding ethnic differences in seasonal birth patterns or survival being influenced by month of birth as potential confounders. Among affected people with a family history of MS they found 16.2% fewer were born in November relative to population controls compared with 3.0% fewer in those with no family history of MS, suggesting that the as yet unidentified environmental factor interacts with genetic risk factors. The authors go on to speculate whether maternal vitamin D levels may be responsible for the observed results, particularly during the second and third trimesters of pregnancy. - ***ALC***

Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Murray TJ, Ebers GC; Canadian Collaborative Study Group.
Timing of birth and risk of multiple sclerosis: population based study.
BRITISH MEDICAL JOURNAL
2005;Jan15:330(7483):120.

ALZHEIMER'S DISEASE: In vivo Imaging

★★★ RECOMMENDED

A novel brain scanning technique to detect amyloid in the living brain may eventually provide a safe, cost-effective way of screening patients for Alzheimer's disease. Senile plaques, composed of amyloid-β peptide (Aβ), are a defining neuropathological feature of Alzheimer's disease and develop many years prior to disease onset. The magnetic resonance imaging (MRI)-based technology was developed at the RIKEN Brain Science Institute in Japan utilising the amyloid precursor protein (APP) transgenic mouse model of Alzheimer's disease. Saido and colleagues found that regular 1H MRI failed to detect the smaller diffuse amyloid-β plaques in vivo. They enhanced the sensitivity of this technique using a modified amyloidophilic probe (FSB), which incorporated a fluorine atom (19F) that is not normally encountered in biological tissues. The probe was administered intravenously to the mice where it bound to Aβ-plaques and allowed them to be captured by 19F and 1H MRI. Experimentally, this technique will be useful for assessing the effectiveness of novel therapeutic agents on halting disease progression and for the identification of potential biomarkers of Aβ-pathology. For ante-mortem non-invasive imaging of Aβ-plaques in Alzheimer's disease 19F and 1H MRI using FSB offers several advantages over positron emission tomography (PET), a technique which is currently in clinical trials: it is cheaper, safer and offers higher spatial resolution. This approach would allow much earlier pre-symptomatic diagnosis and preventative treatment of Alzheimer's disease. Before this technology can be of use in the clinic, probe design and safety issues need to be further investigated. - ***LMS & SJT***

Higuchi M, Iwata N, Matsuba Y, Sato K, Sasamoto, Saido T.
19F and 1H MRI detection of amyloid _ plaques in vivo.
NATURE NEUROSCIENCE
2005:online publication:doi:10.1038/nn1422

EPILEPSY: Ethnic bias in surgery

The number of patients in ethnic minorities with epilepsy in the USA is what one would expect for their proportions in the community; around 26% of residents of Alabama are African Americans and they represent 25% of 432 patients with TLE seen at the University Hospital in Birmingham. 130 had mesial temporal sclerosis (MTS) based on MRI findings. But only 9% who

underwent surgery were African American. The difference remained between ethnic groups, even after adjustment for socio-economic factors. Possible reasons include a greater tendency for African Americans to decline invasive treatments, which has been documented in cardiology studies, differences in family support, and a poor relationship with health-care staff. The authors note that none of the treating clinicians was African American. Who knows how we perform in the UK? This study is easy to do where ethnic minorities are relatively large but in most UK population centres they are small and the confidence intervals of the statistics would be so wide as to be difficult to assess. - ***MRAM***

Burneo JG, Black L, Knowlton RC, Faught E, Morawetz R, Kuzniecky R.
Racial disparities in the use of surgical treatment for intractable temporal lobe epilepsy.
NEUROLOGY
2005;64:50-54.

EPILEPSY: Does it damage the brain?

A central debate in epilepsy circles and a common question from patients is: "Does epilepsy damage the brain?" In this study, 103 patients were recruited from 1993-2000 with newly diagnosed focal epilepsy based on clinical pattern EEG or MRI. Patients' treatment was by inclusion into randomised drug trials of carbamazepine versus vigabatrin or tiagabine. There was a broad spectrum of causes of epilepsy. Volumetric studies of the hippocampus were obtained. In 8 cases there was some evidence of hippocampal asymmetry at diagnosis. In 13 patients hippocampal volume declined more than 12% over 2-3 years. All but one of these patients was seizure-free after starting medication but they tended to have had a longer seizure history with more attacks before the start of treatment. There was no control group in this study and there are well recognised changes in hippocampal volume from just ageing alone, so the significance of this finding, which is related to historical controls, is uncertain. In any event, for the majority of patients with newly diagnosed focal epilepsy in adulthood, there was no significant change in hippocampal volume in 2-3 years after diagnosis. There was no development of hippocampal sclerosis during follow-up. The question remains unanswered as longer follow-up may be needed; there may be different subgroups; and the effects of seizures in children remains to be established. - ***MRAM***

Könönen M, Roberts N, Vanninen R, Pitkänen A, Kälviäinen R.
Hippocampal damage in newly diagnosed focal epilepsy. A prospective MRI study. Salenperä T.
NEUROLOGY
2005;64:62-68.

REHABILITATION: Non-invasive motor cortex stimulation improves hand function in stroke patients

★★★ RECOMMENDED

Interest in using cortical stimulation as a tool for rehabilitation after stroke is increasing. A successful outcome was reported in a stroke patient stimulated with implanted electrodes. Now results from a study using non-invasive cortical stimulation on six stroke patients shows that it may used to improve recovery of hand function without surgery. In a double blind, sham controlled cross-over study, six chronic stroke patients with subcortical lesions, were treated with transcranial direct current (tDC) stimulation over the hand area of motor cortex. The stimulation site was found by co-registration with each individual's MRI. Performance on an ecologically valid hand function test (Jebson –Taylor hand function test) improved significantly after twenty minutes of tDC stimulation but not with sham stimulation. The effect lasted for as long as the 25 minute follow up period after stimulation, but had disappeared by the time of a subsequent test ~10 days later. All six patients showed a small improvement of ~12% associated with increased excitability in the affected hemisphere. The subjects were asked to rate discomfort from the procedure and their feelings of fatigue and attention during the experiment. They were unable to tell the difference between real and sham tDC stimulation and there were no significant differences in fatigue or attention. Reports of discomfort were low (level 1 on a scale of 1 to 10 for five subjects and level 2 in the remaining subject). The small beneficial effect on patients who were over one year post stroke together with the lack of discomfort holds promise that non-invasive stimulation may be a useful adjunct to hand function training in rehabilitation. – ***AJT***

Hummel F, Celnik P, Giraux P, Floel A, Wu W-H, Gerloff C, Cohen LG.
Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke.
BRAIN
2005:128:490-99.

DOCTOR-PATIENT RELATIONSHIP: Forensic Psychiatry for chronic illness?

Having come across this article in the BMJ recently it did strike me of how much I have focused my reading on the "specialist" journals, and am reminded of a Richard Asher quote " …a doctor should be a jack of all trades and a master of one". And no, not as the heading might suggest, forensic psychiatrists are not offering to involuntarily admit all patients with chronic illness (or their doctors for that matter!). These two forensic psychiatrists do however offer some useful insights from the vantage of their speciality that may well have relevance to all of us dealing with patients with chronic illness. How many of us actually regularly reflect on our own feelings and reactions to "chronic" patients? Yet, this can very much affect the therapeutic relationship with the patient and their cooperation and compliance with whatever treatments we may be offering. Do we discuss with our teams how we as a group react to certain patients? Although the article does focus on the importance of these issues in the wider context of undergraduate medical education, it does offer some gems to those of us at a later stage of medical education. It reminds me of the importance of the first part of that old cliché "…the art and science of medicine". – ***JMcF***

Campbell C, McGauley G.
Doctor-patient relationships in chronic illness: insights from forensic psychiatry.
BRITISH MEDICAL JOURNAL
2005:330:667-70.

NEUROSURGERY: Head injury: craniectomy for ICP reduction

Management of raised intracranial pressure (ICP) following severe head injuries continues to be of major concern for neurosurgeons and intensivists. Brain oedema may continue to progress for hours or days after the initial insult and various strategies have been explored in an endeavour to control the resultant rise in ICP. Head elevation, osmotic diuretics, CSF drainage and hyperventilation have been employed to reduce the volume of the intracranial contents; attempts have been made to reduce cerebral metabolism by inducing hypothermia or by barbiturate administration; in addition to removal of extra-cerebral or intra-parenchymal haematomas some surgeons have performed 'internal decompression' in which a significant volume of brain parenchyma is excised, thereby providing space which swollen brain may occupy. Despite these various attempts to influence the natural history of the condition the outcome from serious head injury remains a major cause of death and serious morbidity in children and young adults. With this background it is unsurprising that even more radical approaches to the management of raised ICP have been explored, including decompressive craniectomy, a procedure which is now gaining momentum in some centres. The procedure (both unilateral and bilateral craniectomy) is described in great detail and with clear illustrations in a recent issue of Operative Techniques in Neurosurgery. Careful description is made of the incisions required to preserve a good blood supply when resecting the scalp in order to expose large areas of cranium and of pitfalls to be avoided so as not to cause the swollen brain to sustain further injury on sharp craniectomy margins. The problem of postoperative hygroma formation is described, as is the method of storage of the bone flap in the anterior abdominal wall. The authors concede that evidence for the efficacy of the procedure is anecdotal and present no date of their own to justify its use but do provide a suggested list of indications which include "mechanisms of injury, age, degree of underlying cerebral swelling atrophy, or both; and the surgeon's estimation of the likelihood that the patient will develop severe intracranial hypertension" – and this is really the nub of the problem. Until such time as a properly controlled study is conducted we will remain in the dark as to whether or not this invasive procedure has any part to play in the management of severe head injuries. If, however, it does find a regular and justified place in the surgical repertoire I shall probably turn to this article to learn the tricks of the trade. – ***RR***

Holland M, Nakaji P.
Craniectomy: Surgical Indications and Technique.
OPERATIVE TECHNIQUES IN NEUROSURGERY
2004;7(1):10-15.

Information Leaflets for People with Dystonia

A new series of information leaflets are available from The Dystonia Society entitled: 'Dystonia explained: Your questions answered'; 'Making living with cervical dystonia easier'; and 'Making living with blepharospasm easier'.

The leaflets detail the causes of the dystonia, the treatment and provide advice about how to live with the condition. "It is extremely important that The Society provides an up to date information service for our members and we are grateful to Ipsen for sponsoring this project" said Mr Philip Eckstein, Chief Executive of The Dystonia Society.

Dystonia is a term used to describe a group of conditions characterised by uncontrollable muscle spasms affecting one or several parts of the body. The condition is thought to affect over 40,000 people in the UK. The Dystonia Society is dedicated to the support of all people affected by dystonia.

For further information contact The Dystonia Society, Tel.020 7490 5671, Email. info@dystonia.org.uk, Web. www.dystonia.org.uk

A New Entry Level for Confocal Microscopy

Responding to demand for basic, affordable, yet high quality confocal microscopy, Nikon Instruments have introduced the new e-C1 Confocal Microscope System. Entry-level buyers can now generate confocal fluorescence images with unsurpassed resolution and contrast. Using dual-channel simultaneous detection, the new e-C1 supports almost any imaging technique required, including simultaneous dual-channel fluorescence, DIC, time-lapse recording, and spatial analysis.

Nikon's continual development of optical and electronic technology ensures images are of the highest resolution, contrast, and brightness. To remove problems with crosstalk between channels when using simultaneous imaging, the e-C1 can be configured to capture sequential channel images frame by frame. Changing the filter to match fluorescent dyes is quick and simple.

Live 3D images can be captured effortlessly as the settings and procedures required can be viewed in a single window. Furthermore, using the simple and intuitive Graphical User Interface (GUI), experimental set-up, image analysis and processing can all be carried out by the click of a mouse.

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

Results of the Tutankhamen Scan Revealed

Inside King Tutankhamun's tomb, Zahi Hawass, head of the Egyptian Supreme Council of Antiquities, and a team of Egyptian researchers examine the 3,300-year-old mummy as it is removed from its sarcophagus prior to being CT-scanned.

Images generated by Siemens' mobile CT scanner enabled Egyptian experts to examine the cause of King Tutankhamen's death some 3,000 years ago. The mummy of Tutankhamen was discovered in 1922. An initial X-ray analysis in 1968 revealed a bone splinter embedded in the pharaoh's skull. This fact – coupled with the body's obviously hasty mummification and burial – led to speculation that Tutankhamen had died from head injuries, and possibly been murdered.

The completed analysis of the CT examination, based on images generated from a total of 1,700 slices, found no evidence for this theory. But the Pharaoh may have suffered from a broken thigh shortly before his death at the age of 19. Some members of the examination team say the Pharaoh may have died from an infection of this wound, because CT images revealed embalming resin inside it and there was no sign of a healing process. Other scientists on the team doubt that the injury was the cause of the king's death.

This examination is part of a research project being conducted by Egypt's Supreme Council of Antiquities. The project also includes meticulous CT scans of a large number of other Egyptian mummies. Siemens has provided a special CT system, installed on a trailer for ease of transport, allowing the fragile remains of Egypt's ancient people to be studied with minimum disturbance.

For more information see www.siemens.co.uk/medical, or Tel. 01344 396317.

Images courtesy of National Geographic.

The 3,300-year-old mummy is prepared for scanning on January 5, 2005.

New Titles from Cambridge University Press

Cambridge University Press has published Clinical MR Neuroimaging edited by Jonathan H. Gillard. This book provides the reader with a thorough review of the underlying physical principles of diffusion imaging, perfusion imaging and spectroscopy, as well as comprehensive coverage of their clinical applications.

Also new is Neurodegenerative Diseases edited by Flint Beal. This major reference reviews the rapidly advancing knowledge of pathogenesis and treatment of neurodegenerative diseases in the context of a comprehensive survey of each disease and its clinical features. Covering basic science, diagnostic tools and therapeutic approaches, the book focuses on all aspects of neurodegenerative disease, including the normal ageing process. The dementias, prion diseases, Parkinson's disease and atypical parkinsonisms, neurodegenerative ataxias, motor neuron diseases, degenerative diseases with chorea, iron and copper disorders, and mitochondrial diseases, are all methodically discussed. In each case the underlying genetics, neuropathological and clinical issues are fully reviewed, making this the most complete as well as the most authoritative reference available to clinicians and neuroscientists. A special introductory price of £195.00 is on offer.

For more information contact Cambridge University Press on Tel. 01223 312393 or see www.cambridge.org/uk/

Carl Zeiss wins Life Science Industry Award

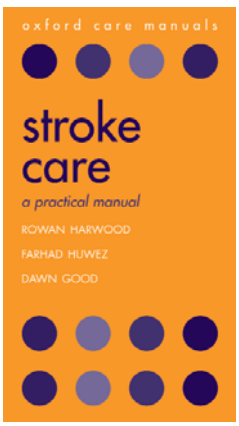
Carl Zeiss has won an award in the Image Analysis category at the Life Science Industry Awards – The Scientist's Choice. Carl Zeiss was a finalist in two of the Award's categories of excellence – Cell Biology Instrumentation and Image Analysis systems. They won the Image Analysis category and were runners-up in Cell Biology Instrumentation.

"The Scientists Choice is the ultimate accolade for any instrument manufacturer," says Aubrey Lambert, marketing manager at Carl Zeiss UK. "This is not an award for a single instrument, but recognition of the whole company's attributes across the board, from R&D and manufacturing to service and support. It demonstrates our commitment to innovation and excellence and our leadership in features and performance."

Carl Zeiss won the Readers' Choice Awards, the predecessor to the Life Science Industry Awards, in 2002 and 2003. Explaining the company's continuing success, Lambert says, "In other microscope companies it's still the physicists and engineers in the development team who decide what goes into the product. At Zeiss we have a multi-discipline approach. Our biologists, the people with the application edge, determine feature sets from the market-leading options given to them by the engineering team."

More details can be found at www.lifescienceindustryawards.com or Tel. 01707 871233.

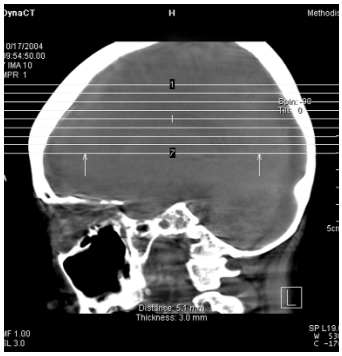
Stroke Care: A practical manual



Oxford University Press has just published Stroke Care: A practical manual, by Rowan Harwood, Farhad Huwez and Dawn Good. It provides guidance on the management of stroke patients from initial diagnosis, through acute care, long term care and rehabilitation, to outcomes and secondary prevention. It is written in a clear how-to-do-it style and is produced in a portable pocketbook format so it can always be close at hand. The authors have all worked in stroke units and base their guidelines on the best available evidence and extensive experience. Subjects covered include the essential neurological aspects of stroke care, decision making and terminal care, psychological issues and much more.

Available in paperback at £19.95 (ISBN 0198529732). To order your copy, please telephone Oxford University Press on 01536 741727.

Siemens Enhanced Angiography Suite Applications



Neurological image acquired using DynaCT.

Siemens Medical Solutions has received 510K clearance from the FDA of DynaCT, an enhancement for C-arm angiography systems that allows soft tissue imaging in the angio suite. DynaCT is the first application that enables clinicians to perform Angiographic Computed Tomography (ACT) with the AXIOM Artis Flat Panel Detector (FD) technology systems, increasing diagnostic capabilities in the angiography laboratory.

Available as an enhancement to the AXIOM Artis dFA, dTA and dBA systems, DynaCT allows clinicians to perform ACT directly in the angio suite, therefore supporting more informed decision-making capabilities and treatment planning.

Additionally, with the ability to perform ACT directly on the AXIOM Artis FD system, DynaCT virtually eliminates patient transfers to other modalities for follow-up procedures. This reduces the need to move the patient out of the sterile environment, delivering a full "one-stop-shopping" capability.

DynaCT delivers soft tissue images that enable visualisation of tissue differentiation in the range of 10 HU (Hounsfield Units), giving the ability to visualise soft tissue abnormalities such as abdominal tumours as well as cerebral hemorrhaging.

For more information see www.siemens.co.uk/medical, or Tel. 01344 396317.

New Brain and Tissue Research Bank

In March the MRC-funded Edinburgh Brain and Tissue Bank for Investigation of Sudden Death was launched, run by Jeanne Bell, Professor of Neuropathology at Edinburgh University.

The project aims to build a brain and tissue bank over the next two years as a resource for researchers. The bank will also collect disease-free tissues and organs – an essential part of the research process into conditions such as Multiple Sclerosis, Alzheimer's and Parkinson's disease.

A crucial feature is the appointment of full time staff to ensure good communications with families of sudden death victims. A dedicated Research Nurse will liaise with families asking for their approval and consent for the collection of tissue at the time of autopsy. It is claimed that research into sudden death has suffered in recent years after organ retention controversies in the UK. New rules mean doctors need to seek more informed consent from relatives. It is hoped that tissue can be taken from up to 1,000 post mortems conducted at the hospital each year.

For more information contact the MRC on Tel. 020 7636 5422.

Carl Zeiss wins Microsoft Competition

Carl Zeiss has won first place in Microsoft's 2004 .NET Solutions Competition. The Light Microscopy division of Carl Zeiss AG, Goettingen, together with the Sohard AG, Fürth Software Company, won the "Best .NET Project" in the .NET Solutions Competition organised by Microsoft.

The winning firmware and operational software were designed for a new generation of Carl Zeiss microscopes launched in 2004. Axio Imager is a modular system for digital fluorescence microscopy, featuring IC2S objectives (Infinity Contrast & Colour Corrected System) that optimise image quality and maximise contrast in all techniques and special fluorescence filters that increase excitation intensity and reduce exposure times. Axio Imager systems range from entry-level system to high-end multi-user systems and are fully configurable depending on user requirements.

In making the award, Microsoft recognised the achievement in developing software that enables flexibility whilst meeting the increasing scientific challenges of providing brilliant images, excellent 3D quality, precision and ease of use.

For further information Tel. 01707 871233 or see www.zeiss.co.uk

DR. ALOIS ALZHEIMER

Aricept Significantly Improves Behavioural Symptoms[1-3]

Compared to untreated AD patients

Aricept® donepezil hydrochloride

BEFORE HIM,
THE DISEASE DIDN'T HAVE A NAME

BEFORE ARICEPT,
IT DIDN'T HAVE A REALISTIC TREATMENT

Aricept® donepezil hydrochloride

CONTINUING COMMITMENT TO ALZHEIMER'S

ABBREVIATED PRESCRIBING INFORMATION
ARICEPT® (donepezil hydrochloride)
Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** ***Pregnancy.*** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. ***Lactation:*** Excretion into breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering 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, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £68.32. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £95.76. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM
Date of preparation: January 2002.

References: 1. Gauthier S, Feldman H, Hecker J, *et al. Curr Med Res Opin* 2002; **18** (6): 347-354. **2.** Holmes C, Wilkinson D, Dean C, *et al. Neurology* 2004; **63**: 214-219. **3.** Cummings JL, Donohue JA, Brooks RL. *Am J Geriatr Psychiatry* 2000; **8:2:** 134-140.

Eisai Pfizer

A735-ARI572-09-04