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Significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia. Severe active infection until resolution. Severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group. Severe hypoproteinaemia, e.g. in nephrotic syndrome. **EDUCATIONAL GUIDANCE**: Prior to prescribing AUBAGIO, physicians must familiarise themselves with educational materials which consist of a *Healthcare Professional Education/Discussion guide* and they should provide their patients with a *Patient Card* and *Patient Leaflet*. **WARNINGS AND PRECAUTIONS:** ***Monitoring***: *Before starting treatment* the following should be assessed: blood pressure, alanine aminotransferase (ALT/SGPT), complete blood cell count (CBC) including differential white blood cell (WBC) and platelet count. Exclude pregnancy. *During treatment* the following should be monitored: blood pressure, ALT/SGPT. A CBC should be performed based on signs and symptoms. ***Accelerated elimination procedure:*** Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide. (For further information, please refer to the SmPC). ***Hepatic effects:*** Assess liver enzymes before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. Teriflunomide therapy should be discontinued if liver injury is suspected and discontinuation should be considered if liver enzymes are confirmed as >3x ULN. Patients with pre-existing liver disease may be at increased risk of developing elevated liver enzymes when taking teriflunomide and should be closely monitored for signals of liver disease. AUBAGIO should be used with caution in patients who consume substantial quantities of alcohol. ***Blood pressure***: Must be checked before the start of teriflunomide treatment and periodically thereafter. ***Infections:*** Patients receiving AUBAGIO should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with AUBAGIO until the infection(s) is resolved. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with teriflunomide. ***Haematological effects***: A mean decrease of less than 15% from baseline affecting white blood cell counts have been observed. 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In cases of severe haematological reactions, including pancytopenia, AUBAGIO and all concomitant myelosuppressive treatment must be discontinued and the accelerated elimination procedure be considered. ***Respiratory reactions***: Due to the potential risk of interstitial lung disease, pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. ***Skin reactions:*** In case of ulcerative stomatitis, or if skin and /or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions, teriflunomide must be discontinued and an accelerated procedure initiated immediately. ***Immunosuppressive/Immunomodulating therapies:*** Co-administration with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. ***Peripheral neuropathy***: Confirmed peripheral neuropathy, consider discontinuing AUBAGIO therapy and performing the accelerated elimination procedure. ***Vaccination***: Live attenuated vaccines should be avoided. **SWITCHING to or from AUBAGIO**: No waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate. Due to the risk of concomitant immune effects for up to 2-3 months, caution is required when switching patients immediately from natalizumab to teriflunomide. To avoid concomitant immune effects when switching from fingolimod, 10-14 weeks is needed for lymphocytes to return to the normal range. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months, although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO. This may lead to an additive effect on the immune system and caution is, therefore, indicated. **CONCOMITANT USE AND DRUG INTERACTION:** Co-administration of teriflunomide with leflunomide is not recommended. Co-administration with antineoplastic or immunosuppressive therapies has not been evaluated. Rifampicin and other known potent CYP and transporter inducers, medicinal products metabolised by CYP2C8, oral contraceptives, medicinal products metabolised by CYP1A2, OAT3 substrates, BCRP substrates and OATP substrates should be used with caution during treatment with teriflunomide. For patients receiving teriflunomide treatment with cholestyramine or activated charcoal is not recommended. For co-administration of warfarin with teriflunomide, close INR follow-up and monitoring is recommended. **PREGNANCY AND LACTATION:** ***Pregnancy:*** Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. In case of suspicion of pregnancy, patient must notify the physician. In case of pregnancy, the physician and patient must discuss the risk to the pregnancy and the accelerated elimination procedure. In women wishing to become pregnant, teriflunomide should be stopped and an accelerated elimination procedure is recommended (Please refer to the SmPC for further information). Both cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens during the accelerated elimination procedure. Use of alternative contraceptive methods is recommended. ***Lactation***: Breast-feeding women must not receive teriflunomide. **UNDESIRABLE EFFECTS:** Based on placebo-controlled studies the most commonly reported adverse reactions in the teriflunomide treated patients were: influenza, upper respiratory tract infection, urinary tract infection, paraesthesia, diarrhoea, increased ALT, nausea, and alopecia. ***Very common (≥ 1/10)*** Influenza, upper respiratory tract infection, urinary tract infection, paresthesia, diarrhoea, nausea, alopecia, ALT increase. ***Common (≥ 1/100 to < 1/10):*** Bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis, neutropenia, mild allergic reactions, anxiety, sciatica, carpal tunnel syndrome, hyperaesthesia, neuralgia, peripheral neuropathy, hypertension, vomiting, toothache, rash, acne, musculoskeletal pain, myalgia, pollakiuria, menorrhagia, pain, GGT increase, AST increase, weight decrease, neutrophil count decrease, WBC decrease, post-traumatic pain. For listings and further information on adverse reactions, please refer to the SmPC. **Legal Classification:** POM (Prescription Only Medicine). **List Price:** £1037.84 per 28 day pack. **MARKETING AUTORISATION NUMBER** : EU/1/13/838/001-005. **MARKETING AUTHORISATION HOLDER:** Sanofi-Aventis Groupe. 54, Rue La Boétie. F-75008 Paris. France. **FULL PRESCRIBING INFORMATION AVAILABLE FROM** Genzyme Therapeutics Ltd, 4620 Kingsgate, Cascade Way, Oxford Business Park South, Oxford OX4 2SU. **DATE OF PREPARATION:** October 2013.

▼AUBAGIO is subject to additional monitoring. This will allow quick identification of new safety information. Adverse Events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard Adverse events should also be reported to Genzyme Tel: 01865 405 200

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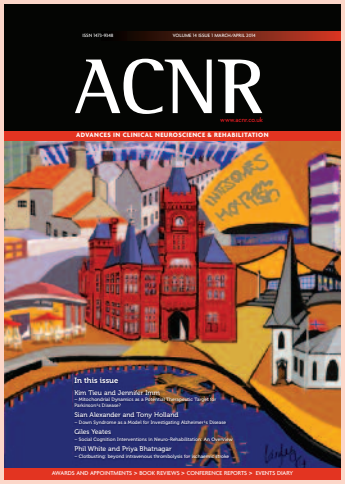

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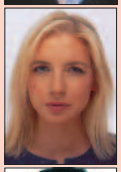

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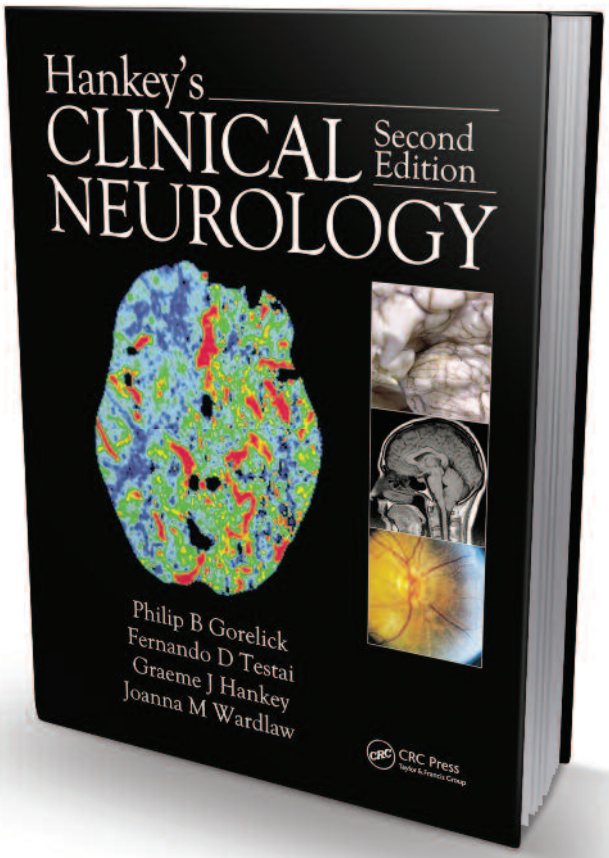

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Mitochondrial Dynamics as a Potential Therapeutic Target for Parkinson's Disease?

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Summary

- Mitochondrial dysfunction is a pathogenic mechanism in Parkinson's disease.
- Mitochondrial dynamics (refers to fission, fusion and movement of mitochondria) can highly affect mitochondrial function and hence, neuronal activity and viability.
- In recent years imbalances in mitochondrial dynamics have been reported in a wide range of experimental models of Parkinson's disease. Targeting this pathway has emerged as a potential novel therapeutic avenue for Parkinson's disease.

Parkinson's disease

Parkinson's disease (PD) is the most common neurodegenerative movement disorder. Motor features such as resting tremor, bradykinesia, rigidity and postural instability, can be attributed to the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Because extra-nigrostriatal regions are also affected in PD, non-motor symptoms, including but not limited to depression, cognitive deficits and dementia, and some autonomic impairments are also commonly observed in these patients. Together, these motor and non-motor featuress cause significant disability and drastically reduce quality of life in the afflicted patients.

It has been estimated that up to 10 million people worldwide are affected by PD and approximately 100,000 people in the UK are living with this disease.[1] This prevalence will increase dramatically with the ageing population. PD also causes an enormous economic burden. Combining both the direct costs (medication and healthcare resources use) and indirect costs (loss of productivity, unemployment, and mortality costs), PD is estimated to have a staggering economic burden of £3.3 billion annually in the UK.[2] Additional effective treatments for this devastating disease are urgently needed. To achieve this goal, it is critical to understand the aetiology and underlying mechanisms of neuronal dysfunction and degeneration in PD.

The cause(s) of the majority of PD cases remains unknown. Epidemiological studies indicate that both the environment and genetic susceptibility most likely play a role in sporadic PD. Significant strides, however, have been made in familial PD studies in the past decade. Although currently less than 10% of PD cases can be directly linked to monogenic mutations, studies from these autosomal dominant (*SNCA, LRRK2*) and recessive (*Parkin, DJ1, PINK1 and ATP13A2*) genes have provided significant insights into potential mechanisms of neuronal dysfunction and degeneration in PD. These non-mutually exclusive mechanisms include mitochondrial dysfunction, oxidative stress, neuroinflammation, protein misfolding, and insufficient autophagic or proteasomal protein degradation.

Mitochondrial dysfunction in PD

The initial proposal of mitochondrial dysfunction as a pathogenic mechanism in PD originated from the discoveries that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism in humans and subsequently in various laboratory animal species. Because the active metabolite of MPTP blocks the mitochondrial complex I function, many investigators have actively searched for mitochondrial defects in PD patients and develop therapeutic strategies targeting the electron transport chain. However, accumulating studies from recent years show that other innovative strategies aimed at restoring mitochondrial function have considerable beneficial potential with wide applicability to other diseases. These studies, led initially by the observations of mutations in PTEN-induced putative kinase-1 (PINK1) and parkin, not only have affirmed the critical role of mitochondria in PD but also have uncovered mitochondrial dynamics (fission / fusion / movement) as a potential therapeutic target for PD.[3,4]

Impact of mitochondrial dynamics on neuronal function and survival

Mitochondria are "dynamic" organelles. They constantly undergo changes in shape, size, number and location. These alterations can

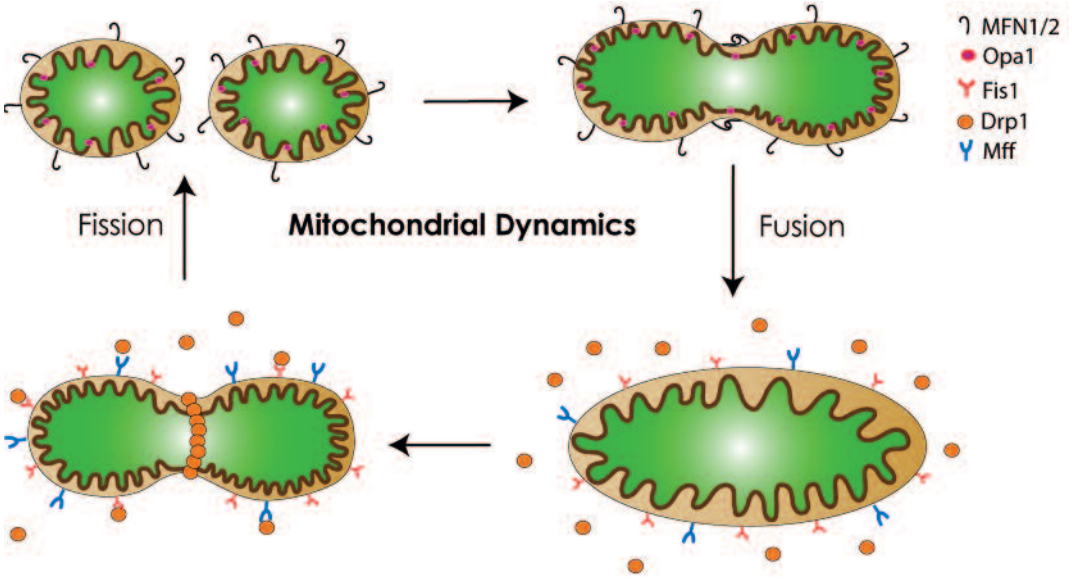

Figure 1: Mitochondrial dynamics is controlled by mitochondrial fission and fusion proteins. Mitochondrial fusion is a highly regulated process that requires the coordination of both the inner mitochondrial membrane (IMM) and the outer mitochondrial membrane (OMM). The OMM uses proteins such as mitofusin 1 and mitofusin 2 (mfn1/2), which are GTPase proteins, whereas the IMM uses optic atrophy 1 (Opa1) to coordinate the joining of the membrane. Mitochondrial fission factor (Mff) and Fission-1 (Fis1) are anchored to the outer mitochondrial membrane where they recruit cytosolic Drp1, which then oligomerises and forms a ring-like structure around the mitochondria to constrict and divide them into multiple smaller mitochondria. Imbalanced mitochondrial fission/fusion negatively impact neuronal function and viability.

be affected by mitochondrial morphology, which in turn, is controlled mainly by the processes of fission and fusion. As illustrated in Figure 1, in mammals, the outer mitochondrial proteins mitofusins (Mfn1 and Mfn2) and the inner mitochondrial protein optic atrophy 1 (OPA1) are responsible for mitochondrial fusion. Fission on the other hand requires the recruitment of dynamin-related protein 1 (Drp1) from the cytosol to the outer mitochondrial membrane by Fission-1 (Fis1) and mitochondrial fission factor (Mff).

Fission produces multiple smaller mitochondria which are more motile within the cell and therefore facilitating mitochondrial trafficking to neuronal dendrites and axons.[5] Fission is also important for segregating dysfunctional mitochondria from healthy counterparts.[6] Through this segregation, damaged mitochondria are subsequently removed by autophagy (known as mitophagy). Fission, therefore, also plays a role in quality control for the maintenance of a healthy pool of mitochondria. However, as discussed later, the in vivo significance of this mechanism remains to be established. In contrast to fission, fusion results in larger and highly interconnected networks of mitochondria, which could offer a larger ATP supply. Furthermore, it has been established that within a single cell, wild type mitochondrial DNA (mtDNA) and mutant variants can co-exist (a scenario known as heteroplasmy) and when the damaged load exceeds a threshold of >60%, mitochondrial dysfunction occurs.[7] By promoting exchanges of mtDNA between functional and defective mitochondria in heteroplasmic cells, mitochondrial fusion can dilute defective mitochondria and attenuate the negative impact of damaged mtDNA through functional complementation.[3,8] Damages or mutations in mtDNA of nigral dopaminergic neurons have been detected in experimental models of PD as well as in patients with sporadic PD.[7,9] Lastly, mitochondrial fusion prevents cell death by blocking the release of the pro-apoptotic protein cytochrome c.[3] In short, a balance of fusion and fission is crucial not only to mitochondrial morphology, but also to function and survival of cells. Thus, it does not come as a surprise that imbalances in this pathway have been linked to various human diseases,[10] including PD.

Potential clinical relevance of impaired mitochondrial dynamics in PD

Imbalances in mitochondrial fission/fusion have been linked to several prominent genetic mutations in PD. Mutations in *LRRK2* are the most common cause of familial PD. In mammalian cell culture models, pathogenic LRRK2 mutations induce excessive mitochondrial fragmentation in a Drp1-dependent mechanism. Blocking mitochondrial fission or promoting mitochondrial fusion improves mitochondrial morphology, function and cell viability.[11] *SNCA*, which encodes α-synuclein, is another prominent autosomal dominant PD gene. The discoveries of mutations in this gene have revolutionised PD research in the past two decades. Recent genome-wide association studies have identified both *SNCA* and LRRK2 as major genes linked to sporadic PD. Like LRRK2, α-synuclein has been reported in cultured cells to induce severe mitochondrial fragmentation.[12-15] Although it is still a topic of debate regarding the mechanisms by which this excessive mitochondrial fission occurs, α-synuclein has been reported to increase Drp1 function[13] and to reduce OPA1 expression,[15] leading to an overall enhanced fission effect. Imbalanced mitochondrial fission/fusion has also been widely observed in recessive genes (*PINK1, parkin and DJ1*) causing PD. PINK1 and parkin are most extensively studied (see review[16] for a more detailed discussion of various PINK1/parkin studies). Overall, based on most mammalian cell culture models, loss of PINK1 and parkin function has been demonstrated to tip the balance of mitochondrial fission/fusion to an overall enhanced pathogenic fission. Either blocking fission or promoting fusion confers protection in these studies. However, these results are not consistent primarily with those obtained from the *drosophila* models.[16] In addition to PD genes, neurotoxic molecules capable of damaging the nigrostriatal pathway such as rotenone, MPTP, methamphetamine and 6-hydroxydopamine, have been reported to cause mitochondrial fission and neurotoxicity that can be attenuated by promoting fusion or blocking fission. Perturbed mitochondrial dynamics may, therefore, represent a shared mechanism that underlies both genetic and toxin-induced related PD.

Conclusion

The link between mitochondrial dysfunction and PD has been proposed since the discovery of parkinsonism in humans caused by MPTP-contaminated synthetic meperidine in the early 1980s. Advances in the genetics of PD have now established a strong genetic link between this neurological disorder and mitochondria. Furthermore, these genetic studies

Perturbed mitochondrial dynamics may, therefore, represent a shared mechanism that underlies both genetic and toxin-induced related PD

have highlighted mitochondrial dynamics with a tremendous potential to restore mitochondrial function. Moving forward, to make this target one step closer to "from bench to bedside", first, the in vivo significance of manipulating mitochondrial dynamics in animal models of PD must be vigorously evaluated. Second, given that both fission and fusion are important physiologically, it is critical to determine whether and to what extent mitochondrial fission or fusion should be promoted in PD. This answer should become clearer based on future studies of animal models of PD and brain samples of PD patients. Based on an animal study using a mouse model with a conditional deletion of *Mfn2* in dopaminergic neurons,[17] the loss of this mitochondrial fusion gene results in progressive retrograde neurodegeneration and L-DOPA responsive locomotor deficits. Simultaneous deletion of *Mfn2* in dopaminergic neurons in the ventral tegmental area further reveals that nigral dopaminergic neurons are most vulnerable to enhanced mitochondrial fission. Combined with other in vitro studies, this animal study supports promoting mitochondrial fusion as a strategy for PD. One potential concern with this approach is that mitochondrial fission is important for mitophagy. However, a recent study points out that mitophagy might not occur in the mammalian brain.[18] In short, manipulating mitochondrial dynamics pathway, perhaps by blocking mitochondrial fission or promoting fusion, represents a high potential for novel therapeutic strategy for PD. ◆

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Down Syndrome as a Model for Investigating Alzheimer's Disease

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Summary

- Individuals with Down syndrome are at high risk of developing Alzheimer's disease (AD)
- Multiple levels of evidence (genetic, histopathological, imaging and clinical) suggest that the study of AD in Down syndrome will inform our understanding of sporadic AD.
- Key areas for research of AD in Down syndrome include (i) better identification and study of pre-symptomatic AD and (ii) improving predictive validity in models of AD
- New initiatives to research AD in Down syndrome offer exciting opportunities for the benefits of detailed clinical studies and robust trials, performed almost exclusively on AD in the general population to date, to be brought to the DS population.

Abbreviations: Aβ: amyloid-beta protein; AD: Alzheimer's disease; APP: amyloid precursor protein; DS: Down syndrome

Introduction

Individuals with Down syndrome (DS) have a high risk of developing Alzheimer neuropathology which, in later life, gives rise to the symptoms of Alzheimer's disease (AD).[1,2,3] In the context of the improving life expectancy of people with DS, new research initiatives have been launched with the specific remit of investigating this relationship (Box 1). However, the research investment into DS also reflects the aspiration that the study of AD in DS will bring benefit to patients with AD whether or not they have DS. In this article we discuss the rationale for this and whether such research can inform about AD more widely.

Comparison of AD in people with and without Down syndrome

There is convincing evidence at multiple levels that the study of AD in people with DS could inform our understanding of sporadic AD.

i. Histopathology

Historical studies of Alzheimer pathology in people with DS were complicated by selection bias, often limited clinical information and without karyotypic confirmation of DS. Since these early studies, detailed neuropathological accounts have described and quantified neuropathology in DS and conclusively demonstrated the same pathological hallmarks of amyloid plaques and neurofibrillary tangles as in sporadic AD.[1] Alzheimer pathology is virtually ubiquitous in the DS population ≥30 years, but time to onset of clinical features is highly variable.[7] The disparity between AD neuropathology and clinical symptoms is also seen in the general population, but is particularly striking in the DS population, and this is the subject of planned research in the LonDownS project (see Box 1).

ii. Genetics

The observation that individuals with complete trisomy 21 (accounting for the vast majority of people with DS) developed early-onset Alzheimer pathology led to studies that localised the amyloid precursor protein (APP) on chromosome 21.[4] In addition, in later studies disomic individuals with AD were found with three copies of the APP gene due to a de novo interstitial chromosomal duplication and, in other cases, mutations were observed in the APP gene in kindreds with early-onset autosomal dominant AD. [see reference 5] Such inherited mutations affect the processing of amyloid beta in vitro and, it is hypothesised, this abnormal processing leads to accumulation of pathogenic oligomers. Together these various observations both in DS and in the general population led to the amyloid cascade hypothesis of AD.[6] Experimental models of trisomy 21, overproduction of APP and accumulation of Aβ species each convincingly recapitulate patterns of in vitro protein pathophysiology seen with autosomal-dominant forms of AD.[2] However, these autosomal dominant causes only represent a small minority (<1%) of all cases of AD and it is considered unlikely that they represent the extent of the heterogeneity of disease mechanisms in the full spectrum of sporadic AD. In contrast, support for common pathophysiological mechanisms comes from recent genome-wide association studies. These have demonstrated shared genetic risk factors for sporadic AD and early disease progression of AD in DS.[5]

iii. Imaging

A recent cross-sectional MRI study demonstrated smaller whole brain, temporal lobe and hippocampal volumes in DS individuals with AD compared with DS controls.[8] These findings are equivalent to those seen in studies of AD in the general population, in which early and significant volume reductions in medial temporal lobe structures are often seen, a finding supplemented by additional longitudinal data.[9,10] Following the completion of a proof of principle study[11] a neuroimaging study of people with DS over 30 years using PET imaging to detect cerebral amyloid binding combined with its cerebral localisation using structural MRI is being undertaken by the Cambridge DS group to investigate the relationship between cerebral amyloid deposition, cerebral atrophy and clinical symptoms.

iv. Clinical

Age-specific prevalence rates of AD in people with DS increase from a few percent in the 30's, to 40% or higher in the 50's and 60's.[3] However, the characteristic impairments in early stages of AD are important differences in DS. 'Forgetfulness' and episodic memory impairments occur early in AD in the general population, whereas changes in personality and behaviour, and objective impairments in executive function are often the earliest signs in DS.[3,6] Just as for the diagnosis of AD in the general population, the most valuable data often comes from informant or carer interviews, and in the absence of easily-applied bedside cognitive tests, such information contributes to a greater extent towards making diagnosis of AD in DS. One difficulty comparing across studies is that neuropsychological assessments used in the study of non-DS individuals cannot readily be applied to the DS population without significant adjustments. These differences in the clinical features of AD in DS and non-DS individuals are interesting topics for further investigation. For example, why does frontal dysfunction occur preferentially and early in DS individuals? Does this reflect different AD pathophysiology or, alternatively, an interaction with the developmentally-determined small reserve capacity of the frontal lobes in DS?

Why study AD in Down syndrome?

Clinical trials in AD have been uniformly disappointing and no disease-modifying therapies for AD are yet available. A series of monoclonal antibodies demonstrated to specifically and potently interfere with deposition of the pathological substrate amyloid-beta in vitro and in rodent models have failed to significantly alter disease progression or severity. These disappointing results demonstrate a critical need for novel experimental approaches to the study of AD with the aim of developing effective preventative therapeutic agents. For this to be possible two specific problems must be overcome. DS provides a means to address these and by doing so, effective treatments could be developed that would bring benefit to people with DS and inform our understanding of sporadic AD. We identify these problems as:

Box 1. Research initiatives into Alzheimer's disease in Down syndrome

Defeat Dementia in Down's Syndrome, University of Cambridge

www.psychiatry.cam.ac.uk/research/groups/ciddrg/dids/

Funding from: Medical Research Council; additional help and support from Down's Syndrome Association and Cambridgeshire and Peterborough NHS Foundation Trust.

Research remit: prospective neuroimaging (MRI and FDG-PET) study to evaluate the relationship between amyloid load and clinical features of Alzheimer's disease in the DS population, the identification of biomarkers, with Patrick Chinnery at the University of Newcastle studies of mitochondrial function, and with Rick Livesey at the Gurdon Institute, Cambridge the use of induced pluripotential stem cells .

LonDownS Consortium, University College London

www.ucl.ac.uk/londowns

Funding from: Wellcome Trust, Alzheimer's Research UK, Epilepsy Research UK

Research remit: Attempt to identify protective factors that prevent development of clinical features of Alzheimer's disease in the older Down syndrome population.

Techniques: detailed cognitive assessment; EEG; sleep monitoring; DNA analysis' generation of induced pluripotent stem cells, the use of animal models.

Down Syndrome Biomarker Initiative (DSBI), University of San Diego

http://neurosciences.ucsd.edu

Funding from: Janssen Research & Development, LLC

Research remit: Neuroimaging and biomarker measurements in DS individuals who are symptom-free, have mild cognitive impairment and those with early AD. The study is designed to align with a similar earlier ADNI study in the general population.

Also see: comment on NIA-funded initiatives at www.nia.nih.gov/alzheimers/features/researchers-seek-alzheimers-clues-people-down-syndrome

i. The identification and study of pre-symptomatic AD

Accurate identification of pre-symptomatic individuals, either with AD pathology or before, is relevant to understanding the natural course of disease progression, for the identification of risk factors for progression to clinical symptoms, and for the early application of potential disease-modifying agents. Although AD is common, it is by no means ubiquitous and there is good evidence for healthy ageing without AD. Some studies have addressed this issue of early identification by using individuals with mild cognitive impairment, in which there is objective evidence of limited cognitive (usually memory) impairment but without meeting criteria for the diagnosis of AD. However, not all individuals with MCI go on to develop AD, and better understanding of predictors of MCI-AD disease progression will be important.[12] Clinical manifestations of AD correlate to a disease process as evidenced initially by pre-symptomatic regional cerebral hypometabolism and later when structural imaging and neuropathology demonstrate significant and widespread atrophy. The pre-symptomatic hypometabolism is considered to be an indication of synaptic abnormalities and attributed to toxic effects of abnormal proteins or oligomers. In the absence of established atrophy, the hope is that neuronal physiology may be restored if the offending 'toxic material' can be removed or rendered inactive.

We propose that prospective studies of AD in DS are more feasible due to the higher incidence of Alzheimer pathology and AD in this population and the likely homogeneity of causation, arguably linked to APP on chromosome 21. Such an approach provides the opportunity to prospectively study the biomarkers of disease, including neuroimaging or CSF biomarkers, alongside clinical measures. This would then enable proof-of-principle studies of whether earlier administration of disease-modifying treatments, including those already developed, such as anti-amyloid monoclonal antibodies, are efficacious.

ii. The need to improve predictive validity in models of AD

Research using DS-derived clinical, radiological or biological substrates may have advantages over existing animal and cellular disease models. Animal models critically require, for the most part, overexpression or alteration of a hypothesised 'culprit gene' and behavioural measures of the effect. This is a problematic approach as it requires a priori identification of a gene of interest and limits this approach to genetic abnormalities that are either monogenic or have high penetrance. A second problem with this approach is the quality of the outcome measures: developing specific and sensitive tests that capture 'Alzheimer' qualities in non-human subjects is a significant challenge. Nevertheless, these animal models have been heavily used in the development and testing of potential disease-modifying therapies.

An area of great interest at the moment is that of inducible pluripotent stem cells, and the potential for patient-derived cells to be 'reprogrammed' into neurons. In the context of DS, for example, skin cells taken by a simple skin biopsy have been used to generate neurons with the same genetic propensity for

Alzheimer type pathology.[13] This is a potentially powerful tool for the identification of pathways of cell dysfunction preceding cell death and molecules that may interfere with these pathways.

Critics would appropriately question the assumption that AD in DS resembles sporadic disease, and indeed, the differences discussed above demonstrate that there are limitations to this approach. Similar criticisms are applicable to the in-depth study of rare monogenic causes of AD. AD is a heterogeneous disease entity, as reflected by the multitude of genetic and non-genetic factors implicated in its pathogenesis, variation in clinical manifestations of pathological burden, and differing rates of disease progression. Therefore, a well-defined and more homogenously affected population, such as DS individuals with AD, may offer a useful initial study cohort, even though subsequent validation of treatment approaches in a broader population is necessary.

Discussion

Novel methods for investigating AD and developing therapeutic strategies are clearly necessary. It is exciting to see the enthusiasm of funding agencies for studies in DS as a way to better understand AD in DS and non-DS populations alike. It is equally good to see the many opportunities for detailed clinical studies, and robust trials that have been performed almost exclusively on AD in the general population to date, now being also made available to the DS population. ◆

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Social Cognition Interventions in Neuro-Rehabilitation: An Overview

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Summary

- Social cognition difficulties include problems with understanding the mental perspectives and intentions of others (mentalising), emotion recognition, affective responses to social cues, affect regulation and social problem-solving and decision making.
- The assessment and rehabilitation of social cognition difficulties is a relatively embryonic and underdeveloped field in neuro-rehabilitation, despite the widespread prevalence of such difficulties across neurological conditions.
- The currently small range of interventions offered have diverged from initial social skills training approaches to include the specific training of component social cognitive abilities, approaches that use the body to aid in the comprehension of social information and approaches that use live interactions in social relationships as a core focus of the intervention.

Abstract

This article provides an overview of interventions developed and trialled in the embryonic field of social cognition neuro-rehabilitation. Interventions are categories under the headings of explicit skills training, embodied/relational interventions, and relational approaches.

The assessment and treatment of social neuropsychological impairments has received comparably less attention and development than other domains of cognition. These include difficulties in representing the intentions and perspectives of others (mentalising), recognising emotions, inferring nuanced social communications such as sarcasm and deceit, accessing social knowledge and emotion-based decision-making. Founded on distributed neuroanatomical substrates, impairments of these functions have been found to be present and enduring across major sub-groups of acquired brain injury (for review see [1]). The theoretical richness of the social neuroscience revolution has not been matched by translation of concepts and findings into rehabilitation practice. This article will review the embryonic field of social cognition rehabilitation, categorised into three intervention clusters: a) explicit skills training, b) embodied and affective interventions and c) relational approaches.

Explicit skills training

Social skills training for various clinical groups predates neuro-rehabilitation of social functioning. These were initially focused on teaching and role playing social and communicative behaviours without an underlying neuropsychological rationale, and examples of these approaches did feature in the neuro-rehabilitation literature over two decades ago.[2,3] More recently, both simple instructions and multi-media packages (using audio-visual interactive computer software stimuli) have been used to target specific social cognitive functions such as emotion recognition from face and/or voice, across a range of clinical groups, including psychosis[4] and acquired brain injury.[5-8] Other interventions have focused on multiple social receptive and behavioural functions, including emotion recognition and mentalising abilities.[9,10] Elsewhere, clinical and experimental studies have reported gains from training cognitive control operations adjunctive to mentalising and emotion recognition, such as focusing attention to certain parts of the face[11-12] and social problem-solving.[13]

These approaches are indirectly informed by theoretical frameworks that emphasise the intentional elements of social cognition functions,[14] such as mentalising and emotion recognition. Skills in accurately inferring/comprehending the perspectives of others (from visual, auditory and contextual aspects of communication) or identifying essential facial features (e.g., eyes, mouth) and matching with intact or relearned knowledge of differing emotional expressions. While some of the social cognitive abilities supported in this way have become more diverse over time, they may not have a significant impact on the spontaneous, intense and changing nature of real-world social interactions. In addition the studies above report mixed results in terms of intervention efficacy. However, some aspects of neuro-rehabilitation would clearly benefit from incorporating such approaches. An example would be vocational rehabilitation, where post-injury work performance involving formalised or scripted sets of narrowly defined social interactions with customers would be amenable to these social cognition rehabilitation packages.

Embodied & affective interventions

New theories and paradigms gaining prominence in social neuroscience, particularly following the discovery of neural mirroring systems, are accounts of embodied simulation, contagion and resonance.[15] These collectively emphasise the body-based affective/emotional and non-intentional dimensions of social cognition, such as the involuntary mimicry of facial musculature in response to the emotional expressions of others. In some scenarios, such as the experience of intense love for another, there is a deactivation of brain areas associated with intentional mentalising systems alongside an activation of these automatic, affective processes.

These theoretical emphases have begun to influence innovations in the rehabilitation of emotion recognition. Skye McDonald and colleagues in Australia[11] have evaluated a protocol where survivors of traumatic brain injury first approximate their facial expression to a task stimulus (e.g., an angry face) prior to identifying that emotion. Jacoba Spikman

and colleagues in the Netherlands recently reported details of their multi-modal 'T-ScEmo' intervention.[10] This includes emotion recognition training involving instructed facial mimicry, together with additional cues to associate the proprioceptive feeling of the survivor's facial expression with previous memories of similar sensations.

However these studies have reported mixed findings across participants and weak group effects. This may be related to sample characteristics, but also these approaches are necessarily making a process intentional (e.g., the experimenter instructing a survivor to mimic their face to a stimulus) that in natural occurrence, in healthy populations, is considered to happen involuntarily. The question is raised as to whether the same underlying process is being exploited in both healthy functioning and clinical rehabilitation.

Experimental studies of survivors' autonomic nervous system, bodily-mediated responses to both social cues (e.g., displays of distress) and during emotion-based decision making tasks have highlighted blunted responsivity (see [16] for review). Some authors have explored the hypothesis of a raised threshold for a triggered autonomic response conducive to adaptive social cognitive functioning, rather than a complete absence of such.[1] Evans, Bowman and Turnbull[17] have reported improvements on an emotion-based decision making task if clinical participants are directed to amplify their internal monitoring of bodily feelings (interoception) during task performance.

Relational approaches

The few approaches described thus far have focused on the individual survivor, conceptualising isolated social inputs and outputs, and their remediation/compensation. Fewer approaches still have actively used the relationships and presence of significant others themselves within social cognition rehabilitation. There is some evidence that this may be an important new direction for rehabilitation innovation, truly social cognitive interventions.

In mental health psychotherapy literature, an approach known as mentalization-based therapy (MBT[18]) has been developed in use with clinical groups who also demonstrate varied social cognition impairments, such as those with a Borderline Personality Disorder diagnosis. In MBT the therapeutic relationship with the clinician is used as the main vehicle to identify breaks in accurate mentalising, together with the characterising features of mentalising errors. MBT is practiced both as an individual and family therapy, and while yet to be formally evaluated within neuro-rehabilitation, offers significant face validity as a potential intervention.

Togher and colleagues[19] reported an RCT of the provision of communication partners to train survivor social communication skills through live interactions and a stable social relationship. Finally, Yeates and colleagues[20] report the use of a couples therapy intervention for survivors with both executive and social cognition impairments and their partners (who have been shown in previous research to emotionally withdraw and so provide fewer cues for survivors). Using case study quantitative evaluations of changes in measures of psychological distress and relationship functioning in survivors and partners, these findings tentatively support the 'raised threshold for autonomic responsivity' hypothesis mentioned above. In this case, both survivor bodily responses and the socio-emotional cuing of the partner is amplified to maximise affective empathic survivor responses and adaptive relationship functioning.

Conclusions

This is an area of rehabilitation in its very infancy, with a significantly limited evidence base. On the one hand, trials of social skills, emotion recognition and mentalising interventions have not used sufficiently ecologically-valid or meaningful outcomes. On the other hand, approaches informed by contemporary social neuroscience theories that aim to support a natural embodied process have reported mixed group findings or case study data, limited in its generalisability. However the range of approaches and conceptual frameworks being developed in this young field is notably diverse, at last in dialogue with current exciting developments in social neuroscience. These approaches, represented in the figure 1 below, signpost the range of possible directions for future innovation in social cognition rehabilitation. ◆

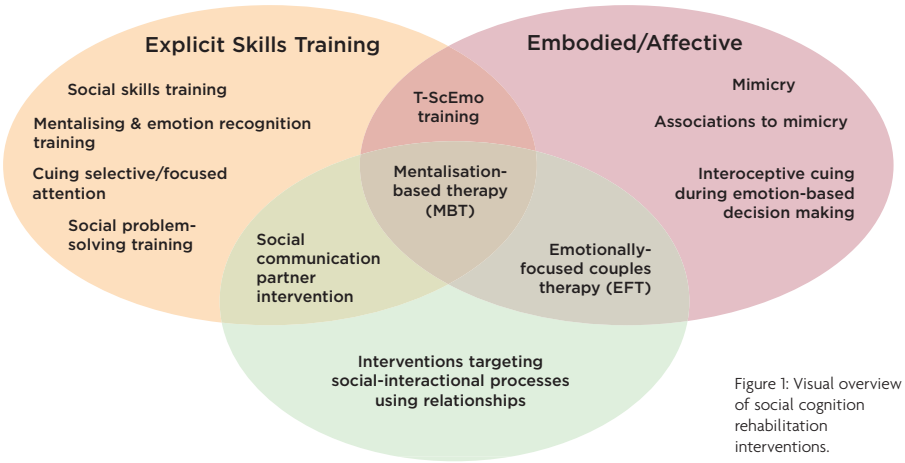

Figure 1: Visual overview of social cognition rehabilitation interventions.

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Introduction to the ACNR Stroke Series

In the last decade or so there have been radical changes in acute ischaemic stroke care, which have been at least partly driven by a need to provide access to early intravenous thrombolysis. Whilst this remains the only proven treatment, there are now many other promising approaches to achieving early reperfusion, including mechanical clot extraction and a variety of adjunctive methods, including renewed interest in neuroprotection by cooling. It seems highly likely that at least some of these treatments will be a part of our stroke units of the future. In this article, Phil White gives us a clear and concise overview of the key treatments tested recently or under evaluation, and shows that the rapid development of acute stroke care will continue to make it one of the most exciting aspects of acute neurology in the coming years.

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Clotbusting: Beyond Intravenous Thrombolysis for Ischaemic Stroke

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Professor White undertakes educational consultancy work for several device manufacturers, is co-PI for 2 RCTs of thrombectomy and holds grant funding from Covidien, Codman, Acandis and Microvention. Dr Bhatnagar – none to declare.

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Summary

- It is anticipated that more effective drug therapies (than tPA) will be available within five years.
- More use of advanced imaging techniques in hyperacute stroke within the NHS is a priority.
- IA Thrombectomy with modern technology looks promising but remains under clinical trial investigation.
- If endovascular approaches are proven then major stroke service reconfiguration would be required in a relatively short time frame.

Introduction

Over recent years, stroke has risen up the healthcare agenda in the UK. In terms of the need for neuroimaging, CT remains the mainstay but there is a strong need for more advanced brain imaging in many cases (such as CTA±CTP) and MRI availability is indicated 24/7 for a minority of patients (see Figure 1).[1] This review will briefly discuss emerging 'new' drugs, Neuroprotection (with EuroHYP-1 and IL-1RA), Plasmin, Ultrasound enhanced thrombolysis and endovascular treatment including the various recent and ongoing randomised clinical trials.

Approximately 50% of acute ischaemic strokes (AIS) are caused by large artery occlusion (LAO). IV rtPA (IVT) administered within 4.5 hours of onset of symptoms is the only unequivocally proven treatment.[2] Lees et al examined the relationship between stroke onset to start of treatment (OTT) with IV tPA treatment as assessed by day 90 modified Rankin score. The interaction was demonstrated to be statistically significant and the benefit from treatment decreased as OTT increased and no confirmed benefit was seen after 270 min[2] (see figure 2). The current UK target for IVT treatment for stroke is 10%, already exceeded as rate of 11.8% was reported in Sentinel Stroke National Audit Programme report – Royal College of Physicians December 2013. In the near future, it is likely that 20-25% of patients will be eligible for IVT.

New Drugs

Desmoteplase is a genetically engineered highly fibrin-specific thrombolytic agent, similar to a substance found in the saliva of a vampire bat Desmodus rotundus. In contrast to alteplase, it has higher fibrin selectivity. It has minimal neurotoxicity (cf. rtPA has been linked with neurotoxicity in pathologic conditions, especially cell injury induced by activation of excitatory amino acid receptors). A clinical trial programme, Desmoteplase in Acute Ischaemic Stroke (DIAS), has been investigating the safety and efficacy of desmoteplase.[3]

Three studies (Dose Escalation Study of Desmoteplase in Acute Ischaemic Stroke (DEDAS), Desmoteplase in Acute Ischaemic Stroke (DIAS), and Desmoteplase in Acute Ischaemic Stroke-2 (DIAS-2)) have been completed and two large randomised, double-blind, placebo-controlled, phase III trials are ongoing at >200 sites worldwide (DIAS-3 and 4) and another in Japan (DIAS-J). The objective of DIAS-3 and DIAS-4 is to determine whether patients (NIHSS (National Institute of Health Stroke Scale) 4-24, age 18-85 years) with major artery occlusions without extensive ischaemic brain damage can be safely and effectively treated up to nine-hours after onset with desmoteplase. These trials are using CTA or MRA to image arterial occlusion and also evidence of ischaemic oedema for patient selection.[4]

Argatroban is a short-acting direct thrombin inhibitor that selectively inhibits free and clot-associated thrombin. Combined with IV tPA, it has been shown to be safe in patients with moderate neurological deficits due to proximal intracranial arterial

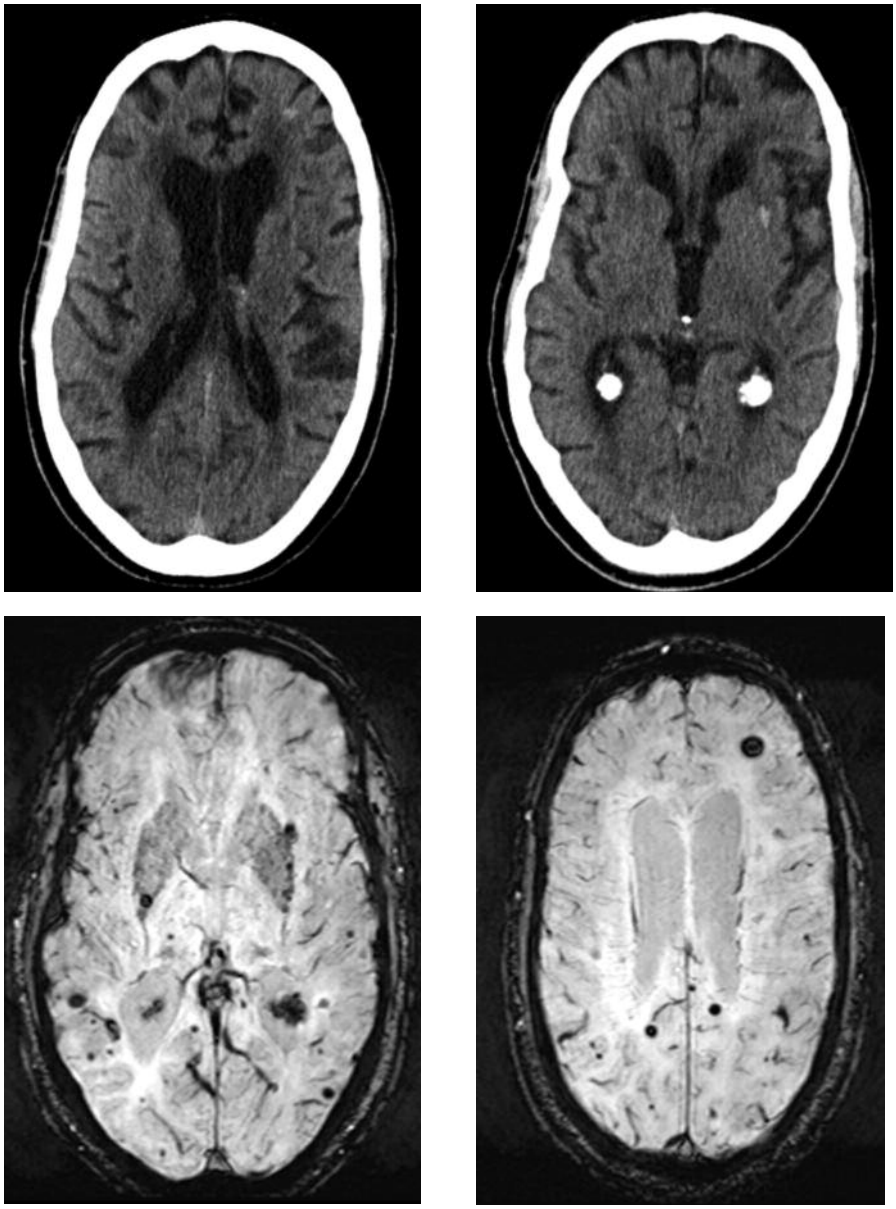

Figure 1: Clinical case highlighting advantages of MRI over CT: A 72-year-old male patient presented with acute onset right arm weakness and was considered for IV thrombolysis. CT (a, b) showed two small hyperdensities, which could represent small bleeds or cavernomas. Subsequent MRI (susceptibility weighted images c,d) revealed extensive cerebral microbleeds not seen on CT and probable amyloid angiopathy. The patient was not thrombolysed.

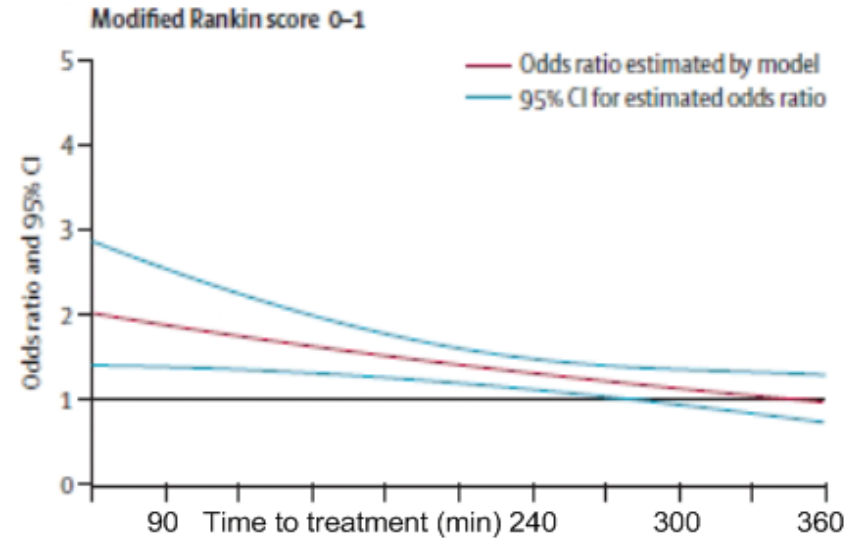

Figure 2: IV Thrombolysis treatment effect versus time (Modified Rankin Score (mRS) 0= No symptoms and mRS 1= No significant disability; able to carry out all usual activities, despite some symptoms).

occlusions and may produce more complete recanalisation than tPA alone.[5] A RCT of Argatroban With tPA for Acute Stroke (ARTSS-2) is an ongoing double blind phase IIb Multicentre Safety/Efficacy Study.[6] The purpose is to estimate the overall treatment benefit (improvement in disability) among stroke patients treated with tPA who are randomised to receive low-dose argatroban, high-dose argatroban or neither. The study started in October 2011 and the estimated study completion is December 2015.

Tenecteplase. A randomised trial of 75 patients who received alteplase (0.9mg per kilogram of body weight) or tenecteplase (0.1mg per kilogram or 0.25mg per kilogram) less than six hours after the onset of ischaemic stroke found tenecteplase to be superior to alteplase with respect to reperfusion and clinical improvement at 24 hours.[7] Longer term clinical benefit was also shown, particularly with the higher dose of tenecteplase. The higher dose of tenecteplase was better than the lower dose for all imaging and efficacy outcomes. Furthermore, there was no increase in the incidence of intracranial haemorrhage with tenectplase. However, a significant number of patients eligible for thrombolysis on the basis of standard clinical assessment and non-contrast CT were not included in this study because patient selection was based on CTP and CTA. Therefore, extrapolation of these results to all patients eligible for thrombolysis is not possible and although encouraging, will need confirmation through larger trials.

Neuroprotection

Neuroprotection aims to prevent salvageable neurones in the penumbral region of the infarct from dying.[8] A considerable number of treatments and agents have been unsuccessfully trialed in the past but hypothermia, ebselen (a glutathione-peroxidase mimic that is a free radical scavenger), statins, DP-b99 and IL-1RA are all under current investigation. We will concentrate on two that are under clinical trial in the UK.

European Stroke Research Network for Hypothermia (EuroHYP)-1

Inducing therapeutic hypothermia is used routinely in patients with cardiac arrest to limit neurologic deficit. It has shown significant efficacy in animal models of cerebral ischaemia. Various mechanisms proposed include preventing formation of free radicals, slowing cellular metabolism, reducing glutamate release and diminishing protein kinase C activity.[9]

EuroHyp-1 is an ongoing open, randomised, phase III, multicentre clinical trial in 20 different European countries testing the effect of inducing hypothermia in 1500 awake adult acute ischaemic stroke patients to determine whether systemic cooling to a target temperature of 34 to 35°C, started within six hours of symptom onset and maintained for 24 hours,

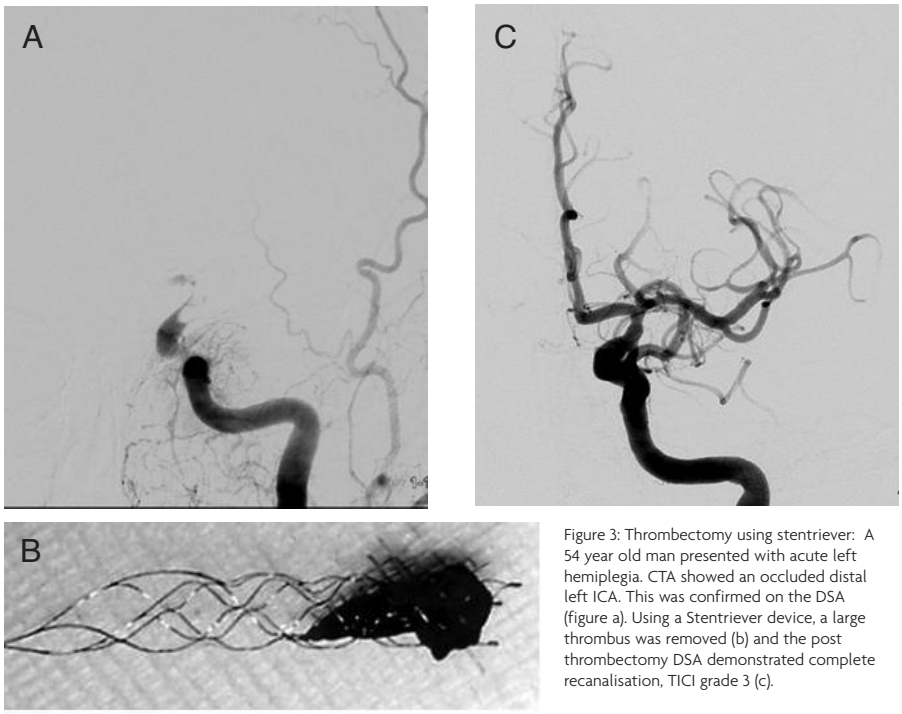

Figure 3: Thrombectomy using stentriever: A 54 year old man presented with acute left hemiplegia. CTA showed an occluded distal left ICA. This was confirmed on the DSA (figure a). Using a Stentriever device, a large thrombus was removed (b) and the post thrombectomy DSA demonstrated complete recanalisation, TICI grade 3 (c).

improves functional outcome at three months.[10] Cooling is performed with an intravenous infusion of 20ml/kg cold normal saline (@ 4°C) over 30-60 minutes followed by either surface or endovascular cooling to 34 to 35°C, maintained for 24 hours. Shivering will be prevented and treated with medication and all patients will receive the best medical treatment including intravenous thrombolysis, if indicated. A pragmatic trial is required as there are both safety concerns (mainly pneumonia risk increased with prolonged cooling and immobility) and tolerability concerns (prolonged shivering) with this therapeutic strategy as well as unproven efficacy.

IL-1RA

Interleukin-1 receptor antagonist (IL-1RA) is another putative neuroprotective agent that has shown promising effects in animal studies. It is a naturally occurring competitive antagonist to the IL-1 receptor and targets the neuronal injury (inflammation as well as excitotoxicity) following AIS. It has been shown to be effective after transient middle cerebral artery (MCA) occlusion in aged rats with comorbidities, suggesting it may be relevant in humans.[11] A meta-analysis of all pre-clinical ischaemia studies demonstrated that IL-1RA produced a 38% reduction in infarct volume in over seventeen studies. The efficacy improved with higher doses, central administration and early treatment.[12] IL1-RA has been tested in a phase II clinical stroke trial and shown to be safe and well tolerated. The clinical outcome improved compared to placebo at three months.[13] However, a phase III multicentre clinical trial is required to confirm its therapeutic benefits. This is in set up stage in the UK.

Plasmin

Plasmin is a direct-acting thrombolytic agent, which has to be administered via a catheter locally into the thrombus where it initiates thrombolysis but remains protected from α2-antiplasmin. Once within the circulation, α2-antiplasmin rapidly neutralises it preventing haemorrhage at distant sites of vascular injury, making it potentially safer than tPA.[14] Its' intravenous administration is safe but not effective as it gets neutralised in seconds.[15] Plasmin has been shown to be safe in patients with peripheral arterial or graft occlusion,[16] and efforts are now being directed towards stroke therapy. A dose-ranging study performed in a rabbit model of two-hour, thrombin-induced MCA occlusion showed that plasmin induced early recanalisation in all animals within 10 minutes after discontinuation of 3, 2, or 1mg infusions. Control saline infusion failed to induce recanalisation in all rabbits.[14] (1) A phase 1/2a clinical trial of Plasmin (Human) Administered Into the middle cerebral artery of Stroke Patients' is currently ongoing.[17] Plasmin is administered through a catheter into the thrombus within nine hours of stroke onset to determine the safety of escalating doses of Plasmin (Human) and to look at its clinical effectiveness. Approximately 40 patients have enrolled so far and the estimated completion is March 2014.

Ultrasound enhanced thrombolysis

tPA Thrombolysis can be potentiated using ultrasound, which delivers mechanical pressure waves to the clot and exposes more thrombus surface to the tPA. The international multicentre phase II CLOTBUST trial (n=126) showed that in patients with acute ischaemic stroke, the combination of tPA plus two hours of continuous transcranial Doppler (TCD) increased recanalisation rates, with better functional outcomes compared with tPA alone.[18] Administration of microbubbles may also enhance the effect of ultrasound on thrombolysis by reducing the threshold of the ultrasound waves needed to induce acoustic cavitation.

A multicentre international study, TUCSON determined the dose of new more stable lipid microspheres, which can be safely administered with tPA and TCD.[19] Another development is an ultrasound transducer incorporated within a catheter, which can also deliver the intra-arterial tPA. Known as the EKOS NeuroWave catheter, it uses 1.7–2.1 MHz pulsed-wave ultrasound with the emitting power of 400 mW, and is now being tested in randomised trials.[20]

Mechanical clot disruption/removal

Endovascular stroke treatment (EST) has been shown to have higher probability of recanalisation (approx. 80%) than intravenous tPA (approx. 46%).[21,22]

Recanalisation is most commonly assessed using the Thrombolysis in Cerebral Infarction classification (TICI). Grade 0 = no antegrade flow beyond point of arterial occlusion; grade 1 = contrast material passes beyond the area of obstruction but fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run; 2a = The contrast material passes beyond the obstruction and opacifies the arterial bed distal to the obstruction; however, the rate of entry of contrast into the vessel distal to the obstruction or its rate of clearance from the distal bed, or both, are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the previously occluded vessel (e.g., the opposite cerebral artery or the arterial bed proximal to the obstruction); less than two-thirds of the entire vascular territory is visualised; for example, in a patient with an M1 segment occlusion, the M1 may have normal flow but at least 1M2 segment remains occluded; grade 2b = same as TICI 2a, except flow is seen into two-thirds or more of the expected vascular tree but is slower than normal; for example, in a patient with an M1 segment occlusion, all M2 branches proximally are open with areas of small segmental distal occlusion or slow flow; grade 3 = Complete perfusion; antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction and clearance of contrast material from the involved bed is as rapid as that from an uninvolved other bed of the same vessel or the opposite cerebral artery (See Figure 4).

However, improved recanalisation may not be associated with a better clinical outcome. Indeed,[3] neutral randomised controlled trials (RCTs) of endovascular stroke treatment; SYNTHESIS Expansion, IMS-III and MR RESCUE were recently published together in the *New England Journal of Medicine*.

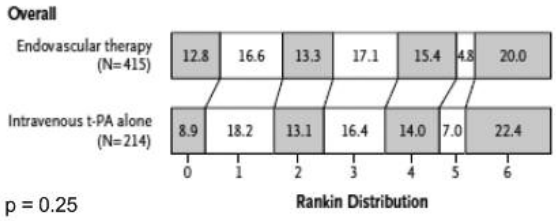

Figure 4: IMS-III overall Rankin distribution demonstrating no statistically significant difference in the functional outcomes between EVT and IV-tPA groups.

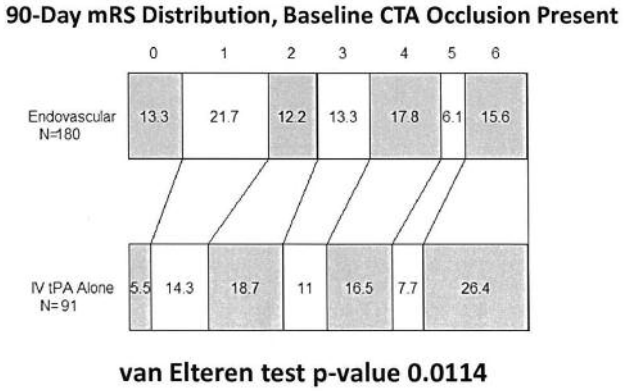

Figure 5: IMS-III patients with confirmed large artery occlusion on CTA prior to randomisation - 90-day mRS distribution.

SYNTHESIS expansion: This trial aimed to determine if the clinical efficacy of endovascular treatment (EST) was better than the current standard medical care. Between Feb 2008-April 2012, 362 patients were randomised. 181 were allocated IV tPA up to 4.5 hours from symptom onset and the other 181 allocated EST up to six hours from symptom onset. Primary outcome was survival free of any appreciable disability (modified Rankin score of 0 or 1) at three months. Designed to verify or refute a difference of 15% between the proportions of patients with a favourable outcome in the two treatment arms, this study failed to show the superiority of endovascular therapy as compared with intravenous t-PA.[23]

The study had multiple serious limitations including the fact that proven best medical therapy was withheld from half the participants (and it was delayed by 22 minutes on average in the IVT arm); any ischaemic stroke patients could be included, with no lower limit for NIHSS. Also, no vascular imaging such as CTA was performed to demonstrate LAO before randomisation. Only 165/181 patients allocated to EST group got EST and not all of those 165 had LAO. Most patients in the EST group only got loco-regional infusion of t-PA and fragmentation of the thrombus with a micro-guidewire (109). Only 56 patients (31%) then went on to have EST with a thrombectomy device and modern stent retrievers were used infrequently (13%). Crucially, EST was performed on average over an hour later than IV tPA therapy. Last, but not least, data on recanalisation rates and time to recanalisation were not presented nor was any formal Rankin shift analysis performed based on pre stroke baseline.

IMS-III: Interventional Management of Stroke (IMS) III trial was a phase III RCT that aimed to investigate if combined treatment with IV tPA followed by EST is more effective than IV tPA alone.[24] This is perhaps the key clinical question in hyperacute stroke treatment.

The primary outcome measure was a modified Rankin scale score of two or less at 90 days. 656 patients with NIHSS 8 or higher were randomised. 434 patients were randomised to EST after bridging (low-dose) IV t-PA and 222 patients to full dose IV t-PA. The trial showed no significant difference in the clinical outcomes between the two groups (see Figure 4) and was stopped early due to the crossing of a pre-specified futility rule.[24]

EST used was IA t-PA or any approved thrombectomy device. IA t-PA alone was used in 138 patients, Merci device in 95 patients, Penumbra in 54, EKOS in 22. Modern technology for thrombectomy, a Stentriever, was used as primary device in only five patients, and in a further eight as a bailout after MERCI/Penumbra/other had failed.

Again the trial has multiple major limitations. Only 282 (43%) patients had imaging confirmed large artery occlusion (LAO). Although IV rtPA was started at a mean of 121 minutes following stroke onset, EST was not started until a mean of 249 minutes (and mean procedural time was also prolonged at ~90 minutes)! Also, good reperfusion (TICI 2b or 3) was achieved in only 44% of patients with an M1 occlusion, and at a similar or lower rate for other sites of occlusion. This is far worse than in current technology trials.[25,26] This is significant as results of two trials published recently in the Lancet both found that stent retrievers are clinically superior to older thrombectomy devices.[25,26] Also, to date, we don't know that lower dose bridging IV tPA as used in IMS-III EST arm is as effective as full dose used in control arm (the on-going ENCHANTED trial should clarify this).

In the IMS-III patients who did have CTA confirmed LAO prior to randomisation, there was an 8.7% absolute difference in clinical good outcome for IVT and IAT compared with IVT alone even bearing in mind obsolete EST used in IMS-III, which was statistically significant, p=0.0114 on van Elteren test used for primary analysis (Figure 5). There were trends to better outcome with EST in severe strokes (NIHS scale>20), ICA/T occlusion sites, those treated with EST within 2h of stroke onset (compared with IVT alone) and EST within 90 minutes of IV tPA start.

MR RESCUE: The Mechanical Retrieval and Recanalisation of Stroke Clots Using Embolectomy (MR RESCUE) was a small phase II RCT. It aimed to identify patients with acute stroke who might benefit from thrombectomy using neuroimaging (CT or MR Perfusion) and to compare the effectiveness of thrombectomy (using the Merci Retriever or the Penumbra System) within eight hours of symptom onset to standard medical treatment.[27] In this trial, a favourable penumbral pattern was defined as a predicted infarct core of 90ml or less and a proportion of predicted infarct tissue of 70% or less (of affected territory). Between 2004-2011, in 22 sites, only 118 patients were randomised. The results were disappointing finding that a favourable penumbral pattern on neuroimaging did not identify patients who would benefit from EST and thrombectomy was not shown to be superior to standard medical care. However, the use of first generation thrombectomy devices was universal and there was a very prolonged time from stroke onset to EST (>6.5h) such that most patients couldn't receive tPA. Although the role of penumbral imaging remains unproven it is being incorporated into some current ongoing trials (eg. EXTEND-IA), which may clarify its role.

Although all three of these EST trials were neutral, none actually addressed the key clinical question, which is whether acute stroke patients (<4h post onset) with a proven relevant large artery occlusion (on vascular imaging) benefit from rapid THROMBECTOMY (not any EST) using established superior technology (stentrievers and/or large bore aspiration) added to IVT over IVT alone. An example of a current technology thrombectomy device, a 'Stentriever', is shown in Figure 3.

All patients in future trials should be proven to have large artery occlusion by CTA or MRA, as this is what mechanical thrombectomy can treat. Future trials should ensure that EST is performed as early as possible after IVT commences (≤90mins based on IMS-III data). Finally, future trials should use conscious sedation whenever possible rather than general anaesthesia, which in multiple studies has consistently been shown to be independently associated with poorer clinical outcome.[28,29] Separate trials are needed to study patients ineligible for IVT (a very heterogeneous group) and patients with posterior circulation LAO stroke, as here the patient profile and natural history are very different and recanalisation may be useful as late as 12 hours after stroke onset. There are many ongoing RCTs, including: a) publicly funded academic trials such as MR CLEAN in Netherlands, THRACE in France, PISTE in UK;

b) academic industry funded trials- REVSACAT in Spain, EXTEND IA in Australia, Alberta run THERAPY trial; c) company driven trials such as SWIFT PRIME (Covidien), and several more are in set up. Most of those named have begun recruitment and in MR CLEAN and THRACE it is far advanced.

Conclusion

There are grounds to anticipate that within five years we will have IV drug therapies for acute stroke that are both somewhat more effective than rtPA and where some benefit beyond 4.5h in readily identifiable subgroups of patients will have been demonstrated. This will represent incremental but important improvements in medical therapy for acute stroke. To identify (stratify) such patients will probably require much wider use of acute vascular imaging and/or MRI. The role of adjunctive ultrasound should be clarified. Thrombectomy trials that address the relevant clinical questions are ongoing. It is very possible that within five years modern thrombectomy may be proven to be of benefit when added to IVT for some groups of patients. It is very probable that the clinical benefit of early thrombectomy when thrombolytic drugs are contraindicated will also be demonstrated. Together these imaging and therapeutic advances are likely to drive major service reconfiguration in acute stroke services. ◆

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Godfrey Hounsfield and the Early Days of CT

Based with permission on a recent biography

Richard Waltham
Richard Waltham joined Godfrey Hounsfield's department as a research engineer three years after the first clinical CT scan. He worked on CT scanning at EMI from 1973 onwards.

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Richard Waltham is unpaid co-author of a biography of Godfrey Hounsfield. Profits from that biography go to the British Institute of Radiology, a charity which Godfrey Hounsfield left money to.

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Summary

- Godfrey Hounsfield in an example of how a person who failed at school can benefit from a second chance, in his case from the Royal Air Force.
- Until they saw the first scans few medical experts expected CT to have any useful impact. Godfrey said 'look we can get orders of magnitude more sensitivity', and they replied 'so what?'.
- Making such a breakthrough always needs determination and perseverance, which in Godfrey's case was supplemented by a remarkable degree of intuitive insight.
- Each new discovery brings with it the seeds of other, future, inventions. There are many discoveries, probably just around the corner, waiting for someone to bring them to life. Could this possibly be you?

On 1 October 1971, a machine built by an unassuming British engineer – Godfrey Hounsfield – took its first CT scan of a patient at Atkinson Morley Hospital (part of St. George's, London) under the supervision of Dr James Ambrose. They had pioneered an entirely new machine which became a household name, the CT scanner. It was a remarkable event. Godfrey had no previous experience of working in the medical field but was an engineer who had spent his working life, prior to X-ray scanners, developing computers and radar. His life provides an insight into the way in which inventions grow from initial conception and become reality through the sheer perseverance and determination of one remarkable individual. It is also a strong example of how a person who failed at school can benefit from a second chance.

Godfrey was born in 1919 and grew up on a small farm in Sutton-on-Trent. He left school at age 16 with no qualifications.[1] His school record card discusses his "intellectual retardation", and he did not study at a university. So his early years did little to suggest that he would pioneer such a great medical breakthrough or be awarded the Nobel Prize.

He volunteered for the Royal Air Force in October 1939, and his wartime years, during which he became a radar instructor, were a major turning point. His work on radar for the RAF gave him a very vivid example of a new technology which was hundreds of times better than the previous method, because navigating by dead-reckoning had large errors if the wind speed changed. Godfrey's subsequent projects can be seen as a constant search to find other fields which could be improved by large factors such as a hundred.

Initially he worked in RAF Maintenance Units which salvaged parts from crashed aircraft. It is not clear how he made the leap from that work to becoming an instructor in the new (and top-secret) topic of radar in 1943. He had experimented with electronics at home before the war, so perhaps some work on repairing aircraft radios drew attention to him. After he joined the radar team his work quickly drew attention from a very senior officer, Air Vice-Marshal John Cassidy. After the war John Cassidy helped Godfrey to get a grant to study at Faraday House college, which gave him a diploma.[2] The course was mostly on electric motor design, with little maths beyond school-level, so it contributed little to his work on CT except that it was useful when seeking a civilian job.

Hounsfield joining the RAF in 1939
(Photo courtesy of Andrew Hounsfield).

He joined the EMI company, where he worked on radar and computers until 1967. He led the design team for the EMIDEC 1100 computer which was successfully launched in 1957, mostly using skills which he had taught himself or learnt in the RAF. It was hundreds of times more reliable than earlier computers (such as Alan Turing's Pilot ACE) because it used an ingenious combination of transistors and magnetic torroids instead of valves.

In 1967 Godfrey's previous projects ceased to be of interest to EMI because of changes in company strategy. He was asked to suggest a new line of work involving pattern recognition, and he suggested what eventually became CT scanning. The company were unenthusiastic because they had no significant medical business, Godfrey had no medical knowledge, and his proposal was a

Godfrey Hounsfield and James Ambrose at RSNA 1972
(Photo courtesy of Mac Gollifer).

Godfrey and friends outside a Loire Valley chocolate factory in 1986
(Photo courtesy of Kathleen Dix).

high-risk leap beyond existing technology. So they sought external funding, and Godfrey managed to get a small amount of money from the Department of Health. His struggles for funding continued for the next four years, as he eked out the tiny amounts available from the DoH. The myth that his work was funded by The Beatles or from EMI's music profits is disproved by internal EMI documents.

He also had to struggle against adverse market research – visits to the radiology experts at the leading hospitals found that almost everyone (with notable exceptions James Ambrose, Louis Kreel, Evan Lennon and Frank Doyle) thought that his proposal was pointless. In 1970, most radiology experts thought that the future lay in higher spatial resolution versions of film radiography. They did not believe that Godfrey's proposal would show anything useful, perhaps because they did not anticipate that the vastly improved accuracy of density measurements would more than compensate for the fact that his first CT scanners could not resolve details of under 1.5mm. As Henry Ford once said "If I had asked people what they wanted, they would have said faster horses." Godfrey's recollection was "I kept on saying 'look we can get orders of magnitude more sensitivity', and they said 'so what?'. They couldn't understand that they would be seeing much more with my technique, as organs would be defined separately. It was very discouraging." Godfrey had correctly forecast that the absorption accuracy would be better than 0.5%, but nobody knew in advance that this would be valuable.

Everything changed after the first publication of the early CT scans in 1972. As soon as people saw those images they realised how valuable they were. Godfrey was inundated with orders for scanners and received a knighthood and dozens of academic awards. But it had been a long and difficult road to reach that point. His life would have been easier if he had chosen a project which optimised technology which his employer was interested in, rather than revolutionising a field which was new to him and to his company. He persevered because he knew that he was on the track of a hundred-fold improvement, and that vision drove him on.

Godfrey thought in an unusual way which he described as "you've just got to use the absolute minimum of maths but have a tremendous lot of intuition".[3] This is easy to say, but very hard to get right. He used a lot of pictures and mental models, a lot of analogies, and he had a lot of curiosity about how everything in the world worked. This was uncomfortable for academics. How could this highly mathematical field be opened up by someone who was not an academic, not a mathematician, but a man who used the subversive art of intuition? Godfrey's answer would probably have been that he worked it out from first principles.

The prize money from Nobel and from the 1972 MacRobert award gave him financial independence, but he chose to continue working full time until his health failed at age 84. His work after CT included a room-temperature scanning tunnelling microscope which aimed to increase computer memory capacity by a factor of thousands. He designed software for artificial neural networks and to simulate genetic evolution. He assisted the team at Royal Brompton Hospital who were working on motion correction in MRI scans. One of Godfrey's computer programs took 2 hours to analyse each MRI data-set, and it is typical of the man that he set his alarm clock to wake himself up every 2 hours through the night so that he could make progress as quickly as possible.

Sir Godfrey Hounsfield rarely used his title, preferring to be called Godfrey. He liked working in small teams, but he was always slightly outside the formal structure - a man who set his own rules. Although some people of his seniority rarely talked to those beneath them, he would talk to anybody who was interested in his work, whether it was the cleaner, the panel-beater or the managing director. He was sociable: people who met him socially would see him as an amiable person who helped to wash up the coffee cups, and he'd prefer not to tell them of his past achievements. His focus was the future.

From his teenage years onwards he was interested in how things worked, and in how science and engineering could help to improve the world. He wanted to pass this enthusiasm on to the next generation. Although he dreaded public speaking, he agreed to speak to pupils at his former school. He wanted to tell them that "each new discovery brings with it the seeds of other, future, inventions. There are many discoveries, probably just around the corner, waiting for someone to bring them to life. Could this possibly be you?". What an inspirational message![4] ◆

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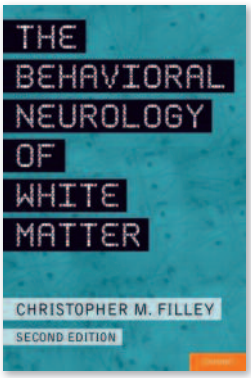
The Behavioral Neurology of White Matter (Second edition)

Filley's contention, elucidated in many previous journal articles and summarised in this book, is that disorders of white matter may be associated with a neurobehavioural syndrome with prominent cognitive impairments, sometimes amounting to dementia, which is in many ways akin to, and yet different, from subcortical dementia. The key features are cognitive slowing, executive dysfunction, impairment of sustained attention, impaired memory retrieval and visuospatial deficits. The relatively preserved functions are procedural memory and language (white matter integrity correlates with full-scale and performance, but not verbal, IQ), along with neuropsychiatric aspects (one might add the relative infrequency of epileptic seizures) and, unlike subcortical dementia, extrapyramidal function. The macroconnectivity of white matter is essential for information transfer across the brain, and contrasts with information processing microconnectivity within the grey matter; together they form complementary parts of the brain "connectome".

The brief first section examines the nature of white matter – myelin, saltatory impulse conduction, and the critical recent contributions of various neuroimaging modalities (MRS, MTI, DTI) in identifying white matter abnormalities (including in what was previously deemed "normal appearing white matter"). Examples of cognitive impairment in specific white matter disorders are cited in the second section; these encompass genetic, demyelinating, infectious, inflammatory, toxic, metabolic, vascular, traumatic, neoplastic and hydrocephalic disorders of both paediatric and adult provenance. The third section examines white matter in neurodegenerative diseases (including Alzheimer's disease, for which a "myelin hypothesis" has been developed), focal neurobehavioural syndromes (e.g. amnesia, aphasia), neuropsychiatric and neurological features. There is a final summation from the connectionist perspective of the behavioural neurology of white matter.

I must "fess up" and say that I never read the first edition of this book (published 2001), but I do not think the omission diminished my pleasure in reading this update. Filley has a fluent writing style which carries the reader easily along. While more might have been said about some conditions (e.g. cerebral amyloid angiopathy) and the quality of some MR images left something to be desired (many dating from neuroimaging atlases of the 1980s and 1990s), this is a stimulating read – well crafted, and thoroughly recommended for anyone with an interest in cognitive disorders, white matter disorders, or both. ◆



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Pages: 425

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Seizures and Epilepsy (Second Edition)

Epilepsy can be a challenge to the non-specialist. The classification of wide-ranging, apparently mysterious epilepsy syndromes threatens to baffle any clinician. Stepping in to the breach comes 'Seizures and Epilepsy'. The first edition was published some 25 years ago and this updated version covers epilepsy from basic physiology to recognition and management of complex syndromes.

The book is divided into Introduction, Phenomenology and Management, each of roughly the same length. The introduction covers changes in Epilepsy classification over the years and gives an update on research topics. The phenomenology section is based around the 2010 International League Against Epilepsy diagnostic criteria; the management section covers diagnostic approaches, pharmacological and non-pharmacological treatments.

This textbook is nothing if not comprehensive. The level of detail is astonishing especially as it is written by a single author. Single authorship has the advantage that the whole book hangs together seamlessly, whether on classification or treatment strategies. Despite this, areas of debate and uncertainty are acknowledged, with liberal referencing to provide support for specific points of classification or management.

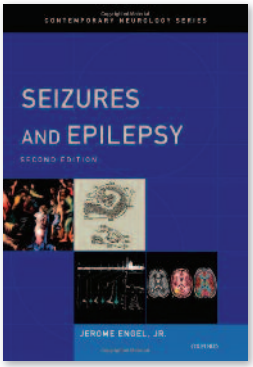
The introduction guides the reader engagingly through a history of epilepsy and its context in society before moving on to an extensive discussion of its evolving classification. This discussion is clearly written by a man who has been closely associated with developments in the understanding of epilepsy nosology; brevity is not its greatest virtue. The long list of definitions is, similarly, best considered as a reference resource than a read-through. The discussion on research by contrast is easily read, with the writing particularly well handled given the fast moving changes in this field. Dr Engel concentrates on advances in physiological understanding and highlights the uses and limitations of animal models.

The phenomenology section is presented with an eye for detail and a perspective that clinical classification provides the starting point for understanding seizure mechanisms. Descriptions of clinical syndromes are written with authority, demonstrating experience of a wide variety of child and adult seizures syndromes. In addition to psychiatric comorbidities and psychosocial adaptation, the more controversial areas of personality and mood changes are confronted.

Helpful tables in the chapter on general principles of treatment cover interactions between anti-seizure medications, side effects, and dosing schedules. I will be photocopying these for use in clinic! There are also useful discussions covering management in the elderly, pregnant women and people with comorbid medical, surgical and psychiatric conditions.

The beauty of this book is the balance between its clear overview of epilepsy and its mastery of detail on every topic. Each chapter finishes with a helpful summary, and conclusions which neatly tie together the chapter's main themes. Admittedly, the writing style is dense in places and a few bullet points might have helped break up the long pages of block text. Figures, where they appear, are often black and white line diagrams or graphs, of limited explanatory value. The quality of brain image reproduction could have been improved; in particular the many PET scans from the early 80s might have been updated to show colour and higher resolution.

This book is not for cover-to-cover reading, except for the very stout hearted. However, its detail and comprehensive coverage of the subject matter, and the author's passion for his subject definitely justify the effort. It is certainly an ideal reference manual for anyone dealing with the day to day practicalities of epilepsy. ◆



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Meningomyelitis, Cranial Neuropathy and Cerebral Vasculitis Secondary to Epstein Barr Virus and Varicella Zoster Virus Co-infection of the Central Nervous System

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- Myelitis
- Optic Neuritis

Abstract
Epstein Barr virus (EBV) and Varicella Zoster virus (VZV) co-infection of the central nervous system has not previously been reported. We describe a patient who presented with EBV meningitis complicated by bilateral optic neuritis and facial palsy who developed reactivation of VZV without skin manifestations. The VZV infection caused cerebral vasculitis with multiple cerebral infarcts and longitudinally extensive transverse myelitis leading to paraparesis. We postulate that VZV reactivation should be considered as a possible cause of neurological deterioration in patients with acute EBV infection so that prompt antiviral treatment can be initiated.

Case report
A 20-year-old previously well woman with a history of uncomplicated chicken pox as a child presented to another hospital's emergency department with a two-week history of sore throat and fevers not responding to oral amoxicillin and clavulanic acid. She was febrile, with enlarged tonsils and cervical lymphadenopathy. Epstein Barr virus (EBV) IgM was positive confirming a diagnosis of infectious mononucleosis. Throat culture was negative. She was discharged on day three on oral penicillin after brief treatment with intravenous antibiotics.

On day six, she re-presented with fevers and headache. She had meningism and photophobia but the remainder of the neurological examination was normal. There was no skin rash. A lumbar puncture (LP) yielded turbid cerebrospinal fluid (CSF) with elevated protein and mononuclear cell count (Table 1). She was commenced on intravenous ceftriaxone and penicillin. After seven days, CSF culture was negative and antibiotics were ceased.

On day 13, her visual acuity deteriorated to count fingers in the right eye and hand movements in the left eye. She had mydriasis of both pupils with a relative afferent pupillary defect in the left eye. There was a complete right sided lower motor neurone facial paresis. The remainder of her examination was normal. Repeat LP showed a greater lymphocytosis with further elevation of CSF protein (Table 1). The patient was transferred to our hospital.

The following day she developed acute urinary retention. Resting tachycardia was noted at 130 bpm with a postural blood pressure drop of 120/78 mmHg to 75/40 mmHg despite normal hydration status. Pyridostigmine was commenced up to 120mg tds with improvement in postural blood pressure. Hyponatraemia developed reaching a nadir of 116mmol/L with serum osmolality 257 mmol/kg, urinary sodium 79 mmol/L, urine osmolality 489 mmol/kg suggesting syndrome of inappropriate antidiuretic hormone (SIADH). This resolved with fluid restriction.

MRI brain with gadolinium (Figure 1A) demonstrated intense bilateral optic nerve sheath enhancement with lesser basal meningeal and internal auditory canal enhancement. She was treated with intravenous methylprednisolone 1g/day for three days followed by oral dexamethasone (2gms qid and weaned over several days). Extensive testing for other inflammatory and infective causes of optic neuritis was nega-

Table 1. CSF Results during admission

Day of Illness	6	13	21	36	51	71
Protein (g/L)	1.22	1.86	1.23	2.24	1.31	2.82
Glucose (mmol/L)	4.8	5.0	6.3	4.5	3.2	2.7
Erythrocytes (x106/L)	52	0	24	2072	40	0
Polymorphs (x106/L)	65	0	0	4	0	0
Mononuclear Cells (x106/L)	889	1070	110	32	4	5
EBV DNA	+		-	-	-	
VZV DNA	+ (16a)		+ (24 a)	+ (29 a)	+	-

Note: + = detected; - = not detected; a number of amplification cycles required to detect VZV DNA by PCR as a means of quantifying VZV DNA in CSF.

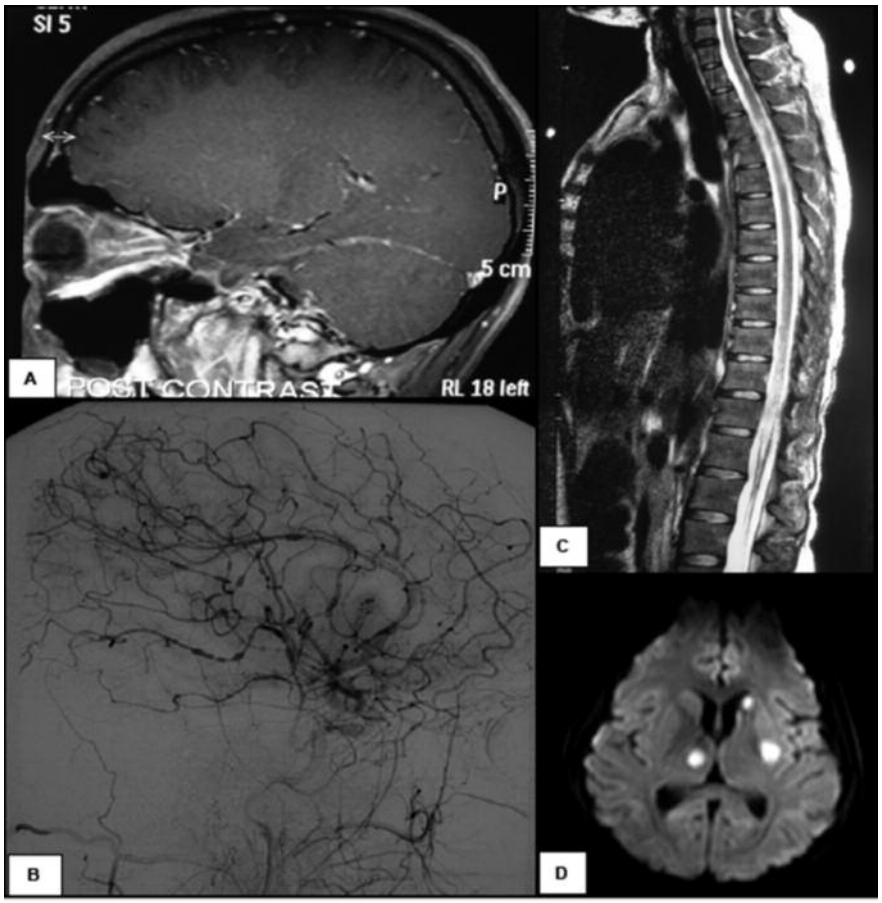

Figure 1. A. Sagittal T1 post-gadolinium MRI showing enhancement of optic nerve sheath. B. Right common carotid cerebral angiogram showing extensive beading and variation in calibre of cerebral arteries consistent with severe cerebral vasculitis. C. Sagittal T2 weighted spinal cord MRI with prolongation of T2 signal throughout the thoracolumbar cord. D. Diffusion weighted MRI from day 71 showing three acute infarcts.

tive. EBV polymerase chain reaction (PCR) of the initial CSF was positive, as was VZV PCR.

One week later, by day 21, there was minor improvement in the facial weakness and visual acuity, and bladder function returned. Repeat CSF examination showed a decrease in protein and cell count (Table 1). Repeat MRI revealed reduction in optic nerve enhancement. An acute infarct in the anterior aspect of the right thalamus was seen on diffusion weighted imaging.

On day 36 she became febrile to 38.7 degrees and had mild left lower limb weakness. Repeat CSF examination showed a further increase in protein, and reduction in cell count (Table 1). VZV PCR was positive but EBV PCR was negative. MRI demonstrated several subcentimetre acute infarcts within the right cerebellar hemisphere and the left external capsule. There was further meningeal enhancement with regions of nodularity, but optic nerve sheath enhancement had resolved. A formal cerebral angiogram (Figure 1B) revealed extensive beading and variation in calibre of the cerebral arteries particularly supratentorially, sparing the external carotid branches, indicating severe vasculitis. She was commenced on intravenous acyclovir 10mg/kg tds, intravenous methylprednisolone 1g daily for three days and intravenous immunoglobulin 20g daily for five days.

The next day, on day 37, she had a complete paraplegia with a complete motor and sensory level at T6 and there was a new right 6th nerve palsy. MRI spinal cord (Figure 1C) showed longitudinally extensive T2 signal within the entire thoracic cord with pachymeningeal enhancement but no enhancement of the cord. The first of five plasma exchange treatments was started and intravenous cyclophosphamide 1g was given.

On day 38, a bulbar palsy was noted with dysarthria, dysphagia, decreased palatal movement and decreased gag reflex. This improved over the following week with no change to treatment. On day 45, treatment was changed to prednisolone 30mg/day and oral valacyclovir 1g tds.

MRI on day 58 revealed several new foci of abnormal signal on diffusion weighted imaging within the left cerebellar hemisphere, the right precentral gyrus, the right thalamus and left caudate lobe. A SPECT scan was consistent with active cerebritis.

By day 71, the patient was able to read large print with her right eye. Her paraparesis had not improved. Repeat MRI spine was unchanged. She now developed sudden onset right arm weakness and expressive aphasia. MRI showed new acute infarcts in the left basal ganglia, right thalamus and left head of caudate nucleus (Figure 1D). Repeat CSF (Table 1) showed a further elevation of protein. VZV DNA was not detected. Flow cytometry of the CSF was normal. A brain biopsy of the right frontal lobe was performed which revealed no evidence of vasculitis, lymphocytic infiltrate or viral inclusions although there was some evidence of reactive T cells. EBV and VZV staining was negative.

After discussion with the patient and her family, treatment with antiviral agents and immunomodulatory therapy was discontinued and the patient was discharged home. At the time of discharge the neurological examination showed a dilated left pupil with a pale optic disc. Visual acuity was count fingers in the left eye and perception of light in the right eye. She had a right facial palsy, right arm weakness, expressive dysphasia and T6 paraparesis. At follow-up twelve months later there had been no further neurological events and although she had marked improvement in her right arm weakness and aphasia there had been no improvement in her visual acuity or paraparesis.

Discussion

The patient presented with typical features of infectious mononucleosis confirmed by positive EBV IgM antibodies. EBV infection may be complicated by meningitis, encephalitis, myelitis, optic neuritis and cranial nerve palsies, most commonly the facial nerve.[1] It can also be complicated by autonomic neuropathy and salt-wasting nephropathy.[2] Our patient had meningitis, bilateral optic neuritis, facial nerve palsy autonomic dysfunction and hyponatraemia. EBV infection of the CNS was confirmed with positive CSF PCR. Randomised controlled studies demonstrating efficacy of anti-viral treatment or corticosteroids in EBV infection of the CNS are lacking.[3,4] Corticosteroids in many case reports have good clinical effect. Treatment with corticosteroids in our patient initially resulted in clinical improvement of the optic neuritis, meningitis and facial palsy, a decrease in inflammation in the CSF and decreased enhancement on the MRI.

VZV PCR of the CSF was also positive initially, later becoming negative. VZV serology showed positive IgG and equivocal IgM confirming prior infection. There was no evidence of a rash during the current illness. Co-infection with VZV and EBV has been previously reported in a small number of immunocompetent and immunocompromised patients.[5] In these patients, the inflammatory response to the VZV was thought to trigger EBV reactivation. In our patient there was serological and clinical evidence of primary EBV infection and past VZV infection, thus the inflammatory response to EBV may have triggered reactivation of latent VZV.

Isolated cerebral vasculitis has not been reported with EBV infection. Systemic vasculitis with EBV infection may occur but usually in the context of immunosuppression.

VZV is more frequently causative of cerebral vasculitis and mixed large and small artery involvement is usual.[6] Multifocal vasculopathy mostly occurs in immunocompromised individuals although there have been several case reports of multifocal cerebral infarcts in immunocompetent patients with VZV vasculitis without skin involvement.[7,8] Consanguinity was present in the family, raising the possibility of a recessive immunodeficiency disorder. Immunoglobulins tested during the illness were normal. Lymphocyte subsets showed marked reduction in CD4 Helper cells and some reduction in pan CD3 positive T cells.

Treatment of VZV vasculitis is aimed at suppressing viral replication with acyclovir. Optimal treatment is not currently defined but in a recent case series of 23 patients, 66% improved or stabilised with acyclovir alone compared with 75% treated with acyclovir in combination with corticosteroids.[6] Due to the severity of the vasculitis in our patient, treatment with IVIg was added as was cyclophosphamide. In retrospect, the cyclophosphamide may have paradoxically exacerbated the vasculitis by allowing VZV to proliferate unchecked. The vasculitis appears to have remitted with cessation of both immunosuppressant medications and acyclovir. The amount of VZV DNA in the CSF (Table 1) was declining prior to treatment with acyclovir being instigated. VZV viral load in the CSF as detected by PCR has been correlated with the severity of neurologic disease.[9]

Myelopathy in our patient may be due to either EBV or VZV. Transverse myelitis is the least common neurological complication of EBV but occurs more frequently in younger individuals than adults.[1] Myelitis in VZV infection has been found to be due to parenchymal invasion by the virus and is more severe in immunocompromised individuals.[10] It may also be secondary to vasculitis.

Conclusion

In summary, we present a previously healthy young woman who presented with acute infectious mononucleosis complicated by meningitis, optic neuritis, facial nerve palsy and hyponatraemia. Reactivation of VZV caused cerebral vasculitis with extensive cerebral infarction, myelitis and poor neurologic outcome. This combination of complicated EBV infection with reactivation of VZV has not previously been reported. VZV infection should be considered as the cause of neurologic illness following EBV infection even in patients without a rash. This case questions whether antiviral treatment alone or in combination with cyclophosphamide should be used to treat the cerebral vasculitis which can complicate VZV CNS infection. ◆

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Accelerating the diagnostic odyssey of ataxia?

Reviewer: Dr Gemma Cummins, Van Geest Centre for Brain Repair, Cambridge University, UK.

Gene discovery is a crucial first step in the development of targeted therapeutics for many rare ataxia disorders, as it allows us to study the function of the protein or RNA mediating the disease process. Although some would lament that the rate of development of these new therapies has been disappointingly slow in comparison to the rate of gene discovery, these advancements have allowed thousands of patients a definitive diagnosis, enabling genetic counselling and better management. Next generation sequencing (NGS) is a new method of rapidly determining the nucleotide sequence of a genome at low cost and with impressive accuracy. It is hoped that it will further accelerate the speed at which patients with neurogenetic diseases are diagnosed, and ultimately stimulate further research into the neurobiology of these conditions

Németh et al. recently published an article in 'Brain' whereby they utilised this advanced technique to see if they could elucidate a molecular diagnosis for 50 patients in the UK with 'difficult to diagnose' ataxias. These patients had already had extensive negative biochemical tests, and had tested negative for Friedrich's ataxia, the common SCA genes and frequently several other genes initially screened for by their neurologists. They performed targeted capture on 58 genes already known to be associated with human ataxia, and an additional 59 genes considered to be good candidates from functional studies or animal data.

In total, they succeeded in diagnosing 9 out the 50 patients using NGS. In the cases where they made an eventual diagnosis, the delay was 3-35 years (mean 18.1 years) from disease onset. The best detection rate was in those with an adolescent onset and a family history (75%). The results of this pilot study demonstrate that NGS can improve diagnostic accuracy in cohorts of very challenging heterogenous patients. It is also cost effective: currently a single gene test using Sanger sequencing costs £700 as compared to a cost of £1000 to test for 50 genes with the Ataxia NGS panel. The authors discuss why even after NGS screening, some patients still did not have a molecular diagnosis. It is possible that some patients in this phenotypically diverse group may have had mitochondrial disorders (the mitochondrial genome is not included in the capture), neurodegenerative metabolic conditions or hereditary spastic paraparesis. It is also possible that some truly pathogenic mutations were classified as benign. Additionally, all sequencing technologies are limited in their ability to detect copy number variations such as large deletions or insertions. In future, it is likely that refined bioinformatics programmes, and whole genome sequencing methods will increase the detection rate further.

Németh AH, Kwasniewska AC, Lise S et al. Next generation sequencing (NGS) for molecular diagnosis of neurological disorders using ataxias as a model. Brain. 2013 Oct;136: 3106-18.

One More Time?

Reviewer: Lloyd Bradley, St Richard's Hospital, Chichester, UK.

The general consensus around timing of rehabilitation following an acquired brain injury is that the earlier things start, the better the outcome. Less explicitly expressed is the assumption that patients will reach a plateau at which point the aims of rehabilitation move from an active goal-orientated process to a passive care model.

The way that inpatient units are set up and funded means that inpatient rehabilitation is seen as a discrete and time limited process that comes to a very definite stop when a certain level of functioning has been reached, or when there are no longer goals to achieve. This paper from Germany suggests that for individuals who have sustained a traumatic brain injury, late inpatient interval rehabilitation many months

following original discharge from a health-care setting may be beneficial. Ninety four patients with either traumatic or vascular injuries were involved in a longitudinal cohort study of the efficacy of a rehabilitation programme in the chronic phase following severe brain injury.

This programme consisted of 300 minutes of multi-disciplinary therapy time a day directed towards specific goals. The patient group are defined as "severely brain injured" and yet the inclusion criteria seem a little vague (a Barthel Index of <20!). The referral process into the programme is also not made explicit and given the importance of patient selection for inpatient rehabilitation, perhaps this needed to be made more obvious.

Outcome measures were the Functional Independence Measure (FIM), Barthel Index (BI) and the Coma Recovery Scale (CRS). Over half of the patient group had tracheostomies in situ and 15% were at a level compatible with a vegetative state. The main "goal" achieved for the patient group was decannulation although only 37% of patients' admissions were rated as "successful" (most of these admissions achieving the goal of decannulation). There was little benefit seen for levels of awareness, communication and swallowing. Twelve patients admitted from nursing homes were able to be discharged back to their own homes after the intervention. It is interesting that the rate of change of the FIM was found to be greater (two points per month) in the late inpatient setting compared with the community (one point per month), but given the point change needed for a clinically relevant improvement is 27, this is obviously of doubtful relevance.

While there may be some merit in late interval inpatient rehabilitation, the 'community' setting to which these patients were discharged following their initial admission to rehabilitation is surely an important issue. If rehabilitation is seen as beginning and ending with inpatient units we may be missing an opportunity to facilitate greater gains after inpatient discharge by providing interventions and monitoring in the real world. Rehabilitation does not just happen in rehabilitation units.

Bender A, Bauch S, Grill E. Efficacy of a Post-Acute Interval Inpatient Neurorehabilitation Programme for Severe Brain Injury. Brain Injury. 2014;28(1):44-50.

Pregabalin vs Pramipexole for Restless Legs

Dr Gemma Cummins, Van Geest Centre for Brain Repair, Cambridge University, UK.

Restless legs syndrome can significantly impact on patients' quality of life and untreated it can lead to considerable fatigue and daytime somnolence. The mainstay of treatment for the condition currently is dopamine agonists, but they have the potential to cause iatrogenic worsening (augmentation) of RLS with long term treatment. Allen's team at the Johns Hopkins University recently published a double-blind RCT in the NEJM which suggests pregabalin, an alpha-2-delta ligand, may be a viable alternative treatment.

A total of 719 participants with moderate to severe RLS were assigned to receive daily either 300mg of pregabalin, 0.25mg of pramipexole, 0.5mg of pramipexole or a placebo tablet. After 12 weeks of treatment, patients taking pregabalin reported a significantly greater improvement in their symptoms compared with those taking placebo (71% versus 47%), and pregabalin led to improvements similar to those assigned to the higher dose of pramipexole. Furthermore, after 52 weeks of treatment, fewer patients on pregabalin experienced a worsening of their condition, as compared to those taking mirapexin (2% versus nearly 8%).

Regarding side effects, there were six cases of suicidal ideation in the group receiving pregabalin, and five in the group receiving pramipexole. This trial provides compelling evidence for the efficacy of pregabalin in treating this common and distressing condition. It also raises a number of other interesting issues regarding the pathogenesis of RLS. It implicates a role for non-dopaminergic drugs in the treatment of the disease, thus suggesting a role of non-dopaminergic pathways in the poorly understood aetiopathogenesis. It also indicates that drugs besides dopamine agonists can lead to augmentation (albeit to a lesser extent), which has been noted previously with the drug tramadol. The jury is still undecided as to whether augmentation is an effect of medications, a process intrinsic to RLS or related to patient characteristics.

Chokroverty S. Therapeutic Dilemma for Restless Legs Syndrome. N Engl J Med 2014; 370:667-.8

Comparison of pregabalin with pramipexole for restless legs syndrome. Allen RP, Chen C, Garcia-Borreguero D. N Engl J Med. 2014 Feb 13;370(7):621-31.

Sleep detoxifies the brain

Reviewer: Jemeen Sreedharan, Dept of Neurobiology/ Neurology, University of Massachusetts Medical School, Worcester, USA.

Why do we sleep? It clearly has restorative properties in the broadest sense and it is thought to be important for memory consolidation. Forced sleep deprivation in animal models can kill. Another reason for sleep could be to prevent the build up of toxic moieties. Sleep deprived mice, for example, demonstrate a build up of amyloid beta, suggesting an intriguing link between Alzheimer's risk and sleep. A series of mouse studies from the Nedergard lab provide further evidence in support of this link.

Nedergard's lab showed last year that the mouse brain possesses something akin to a lymphatic system (Iliff 2012). Subarachnoid CSF enters the brain through channels around the outside of penetrating arteries. This paravascular space (the Virchow Robin space) is bounded on one side by the artery wall and on the other by astrocytic end feet (hence the phrase 'glymphatic' system). Aquaporin 4 water channels are concentrated at these end feet and are essential for fluid transfer. The passage of CSF appears to be one way: CSF flows from the subarachnoid compartment into the brain interstitium along para-arterial glymphatics, while brain interstitial fluid escapes along paravenular glymphatics into the ventricular system. They went on to show that amyloid beta protein is flushed out of the brain through the glymphatic system, the ventricles thus functioning as a latrine.

This year the same lab show that sleep profoundly increases the brain's toileting capacity. Xie et al infused fluorescent dyes into the CSF of mice and performed live imaging through cranial windows. They directly observed the movement of the dyes through the cortex of the brain while the animals were awake, asleep or under anaesthetic (these various states were confirmed using electrocorticography and EMG). Being asleep was associated with a dramatic increase in tracer movement through the cortex, because of a ~60% increase in the volume of the interstitial space. Although the mechanism of this increased capacitance is unclear (could it be due to neuronal and glial shrinkage?) Xie et al hypothesised that noradrenaline (NA), which is important for arousal, may be involved. Indeed, when they applied NA antagonists the interstitial volume increased.

This evidence suggests that sleep opens up brain extracellular spaces, allowing toxic substances that have accumulated in the brain to be efficiently flushed out into the ventricles. One broad implication of this is that sleep deprivation could increase one's risk of Alzheimer's disease. Indeed, Alzheimer's patients often have sleep disturbance, though how much of this is cause and how much the effect of neurodegeneration is not clear. For a detailed and incisive account of the 'hypnic hypothesis' of Alzheimer's disease essential bedtime reading comes in the form of a recent review by Clark and Warren (2013). Sweet dreams.

Iliff JJ, Wang M, Liao Y et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med. 2012 Aug 15;4(147):147.

Xie L, Kang H, Xu Q et al. Sleep drives metabolite clearance from the adult brain. Science. 2013 Oct 18; 342:373-7.

Clark CN, Warren JD. A hypnic hypothesis of Alzheimer's disease. Neurodegener Dis. 2013; 12:165-76.

ASPiH Annual Conference

Conference details: 19-21 November, 2013; Harrogate, UK. ***Report by:*** Lloyd Evans and Jason Chai, Medical Students Cardiff University.

The Association for Simulated Practice in Healthcare (ASPiH) held their annual conference on the 19th, 20th and 21st of November last year at the stunning Majestic Hotel in Harrogate. ASPiH is a new organisation formed in 2009, with the aim of sharing knowledge, skills, and expertise in the use of simulation. The theme of the conference this year was "Valuing Safe Professional Practice", a theme well suited to the current climate of the National Health Service.

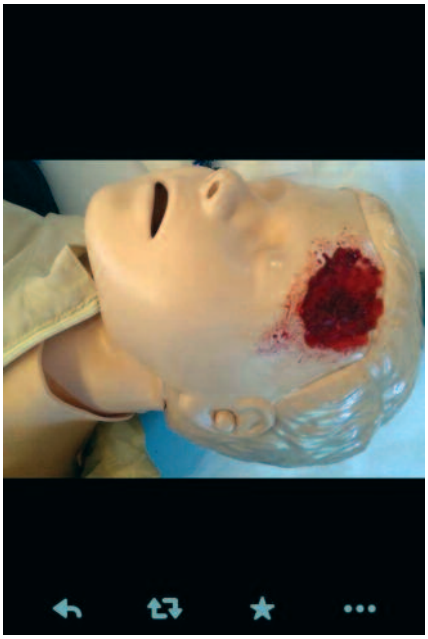
For the first time in ASPiH history, students were invited to present their innovative ideas on how healthcare could be improved with the use of simulation. With the support of the Department of Neurology, University Hospital of Wales, Cardiff, and the ASPiH Travel Bursary, we set out to learn and network with others from various professional backgrounds and to look out for current developments in simulation that may be suitable for application in the area of neurology and neurorehabilitation.

The main conference programme began with a keynote address by Professor Ieuan Ellis, Dean of the Leeds Metropolitan University, entitled "Real Health Challenges-simulated learning solutions". He challenged the audience to train healthcare professionals to provide good quality healthcare. He put forward ideas about the role of simulation in healthcare education, emphasising the need for innovative ideas that would engage students to encourage learning.

In fact, we learned later that it was Dr Howard S Burrows, a neurologist from the University of Southern California (USC), who pioneered the concept of simulation in healthcare 50 years ago. He used actors to simulate patients with various medical conditions to teach medical students. Although initially met with remarks such as "Hollywood invading USC", simulation has become an accepted part of modern medical education.

Following that, we (two final-year medical students) attended some of the workshops and presentations that ran in parallel throughout the two days.

One of note was "The use of vertebrate haptic feedback for cognitive behavioural change when moving and handling". A harness with sensors which monitored the position of the spine was worn by healthcare professionals to ensure that they maintained a "neutral spine" position when moving and handling patients, to prevent musculoskeletal back injuries. The harness would produce haptic feedback to the wearer to warn him/her when deviating from the "neutral



spine" position. The potential of the invention in neurorehabilitation was discussed especially for patients with spinal injuries relearning how to mobilise.

Another workshop was based on the theme of social media use within healthcare. With its ever expanding usage, social media has inevitably become an important factor in healthcare for both professionals and patients in the field of research, organisational and administrative work, and of course outright entertainment (good or bad). However, the workshop really got us thinking about how social media may have a role in the rehabilitation and treatment of patients. In neurology specifically, social media may be a tool for mildly dysphasic or dysarthric patients to communicate with other sufferers, without having to face the challenge of real-time face-to-face conversation.

It was also interesting to see exhibitions of relatively simple inventions that have or will contribute to simulation-based training. These included a gelatin-based model for pericardiocentesis which can be scanned with ultrasound, mannequins for laparoscopic surgery, and the use of animal tissue (pork belly) to resemble skin.

The first day ended with a keynote address by Dr Barry Issenburg, a leader in the field of simulation in healthcare, entitled "Achieving and Demonstrating Optimal Value from Simulation in Healthcare". He highlighted the factors that determine the effectiveness of simulated learning. Interestingly, although research has continually supported the use of simulation in medical education in the United States of America, when applied in a similar manner in Korean Universities the outcome was different as a result of cultural differences, staffing levels, and working conditions.

On the following day, students from various healthcare courses such as medicine and nursing presented their innovations in the hope of attracting interest and constructive feedback. We presented the concept of the "Compass Mentis©", a hand-held device which helps students simulate the necessary thought processes required to generate detailed and relevant differential diagnoses. Other student innovations include a mobile application to monitor ward activity, narrated videos for clinical examination, and patient stories using audiovisual clips to illustrate the patient perspective.

Later, Sir Stephen Moss spoke over lunch about the importance of maintaining quality in healthcare. He spoke about the importance of supporting frontline healthcare workers and valuing the "human impact" on patient care. His talk, which revealed the shortcomings described in the Francis report served as a reminder of the tragic consequences of complacency.

In the afternoon, we participated in a workshop entitled "Prioritising the Acute Medical Take using simulation". Participants including doctors, nurses and medical students were challenged with prioritising a list of patients with acute medical and surgical conditions. The different reasons for prioritising became apparent in the discussion and facilitation during the workshop. Prioritisation which integrates and acknowledges human factors and medical aspects may be relevant to the planning of rehabilitation programs which

often involve complexity and collaboration between doctors, physiotherapists, nursing staff, and the patients themselves.

The event concluded with closing remarks and prize giving to the winners of the workshop, oral and poster presentations.

All in all, the conference brought together healthcare professionals involved in simulation to share their ideas and work together towards improving patient care. The atmosphere was one of "a can-do-but-rehearse-it-first spirit" unstifled by hierarchy and fueled with the enthusiasm of creative minds. The limitless possibilities of simulation in healthcare for the assimilation of medical knowledge and its application in real clinical practice was an eye-opener.

A conference about simulation in medicine is not the stuff of coffee-table discussion, and funded study leave is in short supply but we would recommend this conference for the opportunities it provides to develop new ideas and to see how useful simulation can be in training. Would we go again? Yes. ◆

Acknowledgements: We would like to thank Dr. Tom Hughes for his advice and support in writing this report. Our attendance in this conference would not have been possible without the support of the ASPiH Travel Bursary and the Department of Neurology, University Hospital Wales.

ABN Autumn Meeting

Conference details: 24th October, 2013; RCP, London, UK. ***Report by:*** Basil Ridha, Consultant Neurologist, Royal Sussex County Hospital, Brighton.

The one day ABN Autumn Meeting was held at the Royal College of Physicians (RCP) in London. It was preceded by a one day joint meeting between the Association of British Neurologists (ABN) and the RCP tackling acute neurological conditions for the jobbing general physician. The one day ABN meeting managed to squeeze in cutting edge reviews of diseases spanning the whole nervous system from higher cortical function all the way to muscle disease. Professor David Burn from Newcastle University gave a comprehensive review of clinical features, risk factors, diagnostic biomarkers, pathogenesis and treatment options of cognitive impairment in Parkinson's disease. Interestingly, although 40% of Parkinson's disease patients have mild cognitive impairment at presentation, about 25% of Parkinson's disease patients never develop dementia. Dr Tom Foltynie from the National Hospital for Neurology and Neurosurgery then discussed the challenging topic of managing difficult Parkinson's disease patients. He gave helpful tips for the management of refractory tremor, fluctuations, dyskinesias, gait freezing and non-motor symptoms. His talk included videos with striking improvement of tremor and dyskinesias following deep brain stimulation, which has become significantly safer with the advent of MRI guided surgery.

Dr Simon Rinaldi from Oxford University followed with a comprehensive review of Guillain Barre Syndrome, including clinical features, accuracy and optimal timing of diagnostic procedures, and evidence based treatments. It was interesting to learn about the role of antibodies towards ganglioside complexes rather than single gangliosides in isolation in the pathogenesis of the disease. Professor Sarah Tabrizi from the National Hospital then gave a superb overview of cutting edge longitudinal research mapping the natural history of Huntington's disease. This has been vital for the development of robust biomarkers of disease progression when testing potential disease modifying drugs in Huntington's disease. Professor Rosalie Ferner from Guy's Hospital gave an excellent overview of the diversity of clinical features of neurofibromatosis types 1 and 2 spanning the central and peripheral nervous system and non-neurological features. This was followed by Dr Kevin Talbot from Oxford University giving an insightful overview of the latest genetics of motor neuron disease with a focus on the recently discovered C9orf72 mutation and its diverse phenotypic presentations.

After a tasty lunch, the first afternoon session kicked off with Dr Benedict Michael from Liverpool University giving a stimulating talk about the value of measuring pro- and anti- inflammatory cytokines in the CSF in order to predict clinical outcome following HSV encephalitis. Afterwards, Professor Neil Scolding from Bristol University outlined the expanding landscape of currently available and emerging disease modifying therapies in multiple sclerosis, each with its distinct advantages, risks and costs. This was nicely followed by Dr Robin Franklin from Cambridge University giving an intriguing talk about the role of cellular pathways, particularly RxRγ in the activation of progenitor cells and remyelination to aid recovery following an acute demyelinationg episode.

During the final afternoon session, Professor John Duncan from the National Hospital for Neurology and Neurosurgery gave an excellent overview of the multidisciplinary evaluation process epilepsy patients go through for the consideration of epilepsy surgery. This involves integration of findings from cutting edge neuroimaging and neurophysiological techniques in order to maximize chances of seizure freedom, whilst minimizing the risk of neurological deficits as a result of surgery. The last stop of the day's tour of the nervous system was with muscle disease. Professor Michael Hanna from the National Hospital for Neurology and Neurosurgery gave a comprehensive clinical and pathological overview of inclusion body myositis highlighting the diversity of abnormal protein aggregation, which may aid in identifying potential treatment targets for this inflammatory and degenerative disease. ◆

Improving Outcome in CNS Tumours

Conference details: 27 September-1 October, 2013; Amsterdam, The Netherlands. ***Report by:*** Dr Sunil Upadhyay and Dr Sanjay Dixit, Consultant Clinical Oncologists at Castle Hill Hospital, Hull.

ECCO-ESMO is the premier conference held in Europe which is attended by clinicians involved in the management of cancer from all over the world. Building on the previous successes, this year it was organised by ECCO in partnership with ESTRO, ESMO, ESSO, EACR, EONS and SIOPE, a true multidisciplinary gathering. As expected, large numbers of professionals gathered recently in Amsterdam, one of the most beautiful and charming cities in Europe, from every discipline of oncology to share their ideas, present ground-breaking results from ongoing research and discuss the best way forward to implement practice-changing evidence on a single platform to conquer the dreadful disease: brain tumours. More than 18,000 delegates attended and over 3300 abstracts were presented. The theme of 2013 conference was genomics and the multidisciplinary approach. High quality debates, multiple educational lectures and symposia on topical subjects turned out to be some of the most popular events. It was understandable that the data presented were heavily loaded in favour of tumours like breast, lung, colorectal and urological cancers. However, other primary tumour sites like nervous system, malignant melanoma and gynaecological cancers were also well represented.

Malignant glioma, one of the common central nervous system (CNS) primary tumours, has a very aggressive behaviour and limited success leading to poor outcomes with currently available treatment modalities for the majority of unfortunate sufferers. Most of the glioblastoma patients eventually experience relapse. Management of these individuals is complicated by the fact that re-treatment with high dose radiotherapy can risk radiation induced critical damage to the normal brain tissue. Options for further chemotherapy may also be limited due to the development of drug resistance. Therefore, use of currently available chemotherapy agents have been of limited value resulting in poor quality of life and a fatal outcome sooner rather than later.

It is now apparent that malignant glioma is a heterogeneous entity. Therefore, there has been considerable interest in finding a new approach, particularly molecular profiling, detection of potential biological drivers and the use of biological agents in its management. Survival prediction of the outcome with chemotherapy depends on molecular characteristics such as deletion of chromosomes 1p and 19q, mutations of *IDH1/2* and methylation of repair enzyme MGMT. The significance of the mutation of *IDH* genes in gliomas is growing and the future of their place in the development and management of anaplastic glioma is becoming clearer. The *IDH1* gene encodes cytoplasmic, while *IDH2* encodes mitochondrial enzyme isocitrate dehydrogenase. The *IDH1* mutation is more common (40%) compared to *IDH2* in gliomas. Both these mutations are associated with 1p and 19q co-deletion. The presence of these mutations carries a better prognosis in all grades of glioma but its predictive value remains unknown. Accumulated D-2-HG can be detected by MR- spectroscopy and could be utilised as a diagnostic marker. Inhibitors of mutated *IDH1* and *IDH2* have shown reversal of various epigenetic hyper-methylation changes. Therefore, they could be useful therapeutic targets.

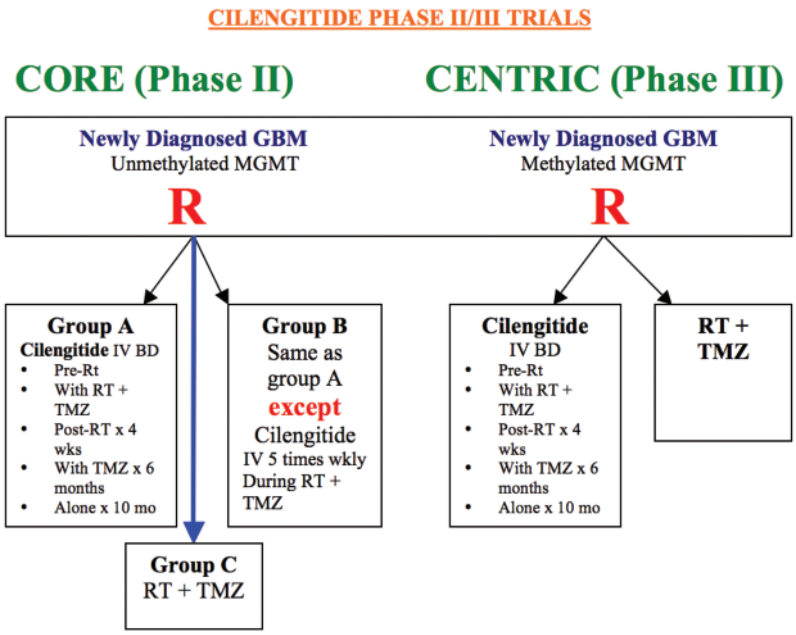
In addition, the CD95 signalling pathway has also been recently identified to be an important signalling pathway in tumour progression. In a multicentre, phase II trial, 84 recurrent glioblastoma patients were randomised to receive re-irradiation alone or re-irradiation plus weekly intravenous dose (400 mg) of APG101, a CD95/CD95L inhibitor fusion protein similar to an antibody known as APG101. The data presented by Prof Wolfgang Wick showed that 21% of the patients in the combination arm compared to only 4% in the re-irradiation alone arm were alive at six months. The 2 years survival was 22% for the combination compared to only 7% for control arm. It was encouraging to see that the risk of death was reduced by 40% in the experimental treatment group but it did not reach statistical significance. This is the first controlled trial of re-irradiation in glioblastoma. Although the size of the APG101 protein molecule is potentially too large to cross the protective blood-brain barrier, radiotherapy is considered to open up this barrier to target the tumour. Tumours expressing the CD95L protein carry poor prognosis and responded better to the APG101 combination treatment in this study. However, further research is needed to understand the exact mode of action and development of drug resistance, along with its use in CD95/CD95L over-expressing tumours as well as in combination with other agents like temzolomide. **Abstract 3304**

The MGMT gene is an important promoter of an important resistance factor against alkylating agents. With methylation there is an inactivation whilst with unmethylation there is an activation of this gene. Temozolomide has improved the survival in patients with newly diagnosed glioblastoma modestly and very marginally if the tumour MGMT was not methylated. Bevacizumab in combination with irinotecan (BEV-IRI) is approved and frequently used in the USA for the management of relapsed glioblastoma. The clinical activity of this doublet led the clinicians to wonder whether similar benefits could be achieved by inhibiting tumour angiogenesis with bevacizumab in newly diagnosed glioblastoma, a deadly disease with limited treatment options. The results of ***GLARIUS***, a phase II (n=182), randomised (2:1) trial comparing bevacizumab, irinotecan and radiotherapy with standard radiotherapy and temozolomide in MGMT-non-methylated newly diagnosed glioblastoma was reported to show remarkable improvement in the median progression-free survival (PFS) of 9.7 months with BEV-IRI compared with 6 months with the standard treatment (HR=0.3, p=<.0001). Similarly, a significant advantage was observed in overall survival in the BEV-IRI arm (16.6 vs. 14.8 months) compared to the standard arm. These preliminary results are promising and provide additional evidence to support the activity of irinotecan in this dreadful disease. **Abstract 3300**

Continuation of Bevacizumab (bev) beyond progression is another area of interest among the investigators following success observed in colorectal and ovarian cancers. ***Avaglio*** is the first randomised, double blind, placebo controlled, phase III study to evaluate the efficacy and safety of the addition of bev to standard temozolomide plus radiotherapy for newly diagnosed glioblastoma. The study met the co-primary end point of median PFS of 10.6 vs 6.2 months (HR=0.64; p <0.0001) in favour of the bev group. Clinical deterioration-free survival was also increased from 3.9 months to 6.4 months and time to deterioration, irrespective of the type of progression, increased from 5.6 months to 8.5 months. The Karnofsky-performance status (KPS) above 70 was maintained for a median duration of 6 months in the placebo arm compared to 9 months in the bev arm. Off steroids were 45% vs. 61% patients and adverse events observed in 51% vs. 66.8% in placebo and bev arm, respectively. Arterial thrombo-embolism increased in the bev arm (1.3% with placebo and 5% in the bev arm), but there was no difference in venous thrombo-embolism (8% with placebo and 7.6% with bev). Subsequent chemotherapy was delivered in 64% of patients in placebo and in 57% of patients in the bev arm. There was no difference in the pattern of progression. **Abstract 3301A**

The current standard of care for glioblastoma consists of concurrent radiotherapy-chemotherapy with temozolomide followed by 6 more cycles of maintenance temozolomide. Unfortunately, the median PFS and overall-survival (OS) remain extremely poor. Significant improvement remains the unmet need in this extremely angiogenic malignancy. For the management of glioblastoma, integrin inhibition is probably one of the most important goals because it targets both pathological tumour vasculature as well as the direct tumour cells. Over 3500 newly diagnosed patients with glioblastoma were screened for MGMT methylation and in the ***Centric*** trial, patients with posi-

tive methylation (n=540) were randomised to be treated with standard radiotherapy and temozolomide with (n=272) or without (273) cilengitide, which is a selective αvβ3 and αvβ5 integrin inhibitor and interferes with cell attachment and migration. Cilengitide 2000mg intravenous twice weekly was administered and continued for up to 18 months of progression. It is important to note that there was no placebo therapy in the control arm which would have been unethical for patients to have been unnecessarily visiting the clinics for placebo infusion. The median survival was 26.3 months in cilengitide and 28 month in the placebo arms. Although median PFS was longer at 10.6 months in the cilengitide arm compared to 7.9 months in the placebo, the difference was statistically not significant. Centric trial updates did not identify any subgroup which could have benefited from cilengitide either. Similarly, no major safety concerns were identified. Despite a negative outcome in this trial, integrin remains an attractive target. **Abstract 3302** (see figure).



Whilst in the Centric trial, cilengitide was used in methylated GBM; **CORE** an ongoing phase II trial, used cilengitide in unmethylated tumours with the addition of two different dosage schedules (an additional intensive dose) of cilengitide infusion. In this multicentre, randomised, open-label study, compared to the control arm, there was no significant benefit between the three groups of patients. **Abstract LBA 40**

These results illustrate the challenging behaviour of primary brain cancer. The challenge is monumental but progress in scientific research and new discovery is relentless leading to rapid expansion of our knowledge. We have already achieved new milestones for many other tumours and hope to celebrate the discovery of effective therapy for CNS tumours soon. ESMO 2013 clearly was a mega success. The organisers and speakers deserve admiration to be able to attract such a large audience and present many new ground breaking research data on a wide variety of tumours. The feather in their cap was the inclusion of many sessions focused specifically for oncology nurses and other support professionals. The presentations are available in the form of a webcast on the ESMO site though there is a small charge but the readers would find them extremely valuable, particularly those who could not attend this wonderful meeting. ◆

Abbreviations: European Cancer Organisation (ECCO), European Society of Medical Oncology (ESMO), European Society for Radiotherapy and Oncology (ESTRO), European Society of Surgical Oncology (ESSO), European Association of Cancer Research (EACR), European Oncology Nursing Society (EONS) and the European Society of Paediatric Oncology (SIOPE)

British Society of Rehabilitation Medicine: Rehabilitation Technologies

Conference details: 12-13th December 2013. Royal College of Physicians London. ***Report by:*** Dr John Burn, Consultant Rehabilitation & Brain Injury, Poole Hospital.

The Royal Hospital for Neurodisability at Putney has an active rehabilitation technology department and presented evidence at the start of the day on the management of patients with severe brain injury. This included a recent study that examined the effect on swallowing of alternative sitting positions. Such patients swallowed more safely when in a tilt in space position and the whole seat is rotated backwards (maintaining 90degrees between the seat and the back), when compared to a conventional upright position.

There is a drive to reduce the cognitive load of both augmented communication (AAC) equipment and environmental control equipment (ECE) that enable severely disabled users to control everyday electronic appliances. This can be achieved by 'intelligent' devices that learn from previous use and context, and from using familiar visual images rather than icons. Commercial technical advances are driving this and equipment such as Head Up Displays ('Google Glasses') may soon make AAC users indistinguishable from their able bodied peers. The same is happening with ECE in the form of home automation and the multiple functions of the ubiquitous iPad. The newest version with IOS 7 includes a switch facility whereby the camera picks up head movement and could enable the user to select an option from a sequential display of alternative peripheral switches. Touching the screen is quicker but apparently the more recent iPad has a capacitive rather than a resistive screen which is less responsive to ataxic actuation. We were then introduced to the potential of robotics. UK research and experience is focused on the use of upper limb devices as an adjunct to stroke rehabilitation. Other devices may be of practical help and we were shown the concept of an assisting drone operating both in the house and in the neighbourhood.

Taken together these two days, supported by posters of superior quality, had a profound impact on the clinical practice of all who attended. It bodes well for the move by the BSRM to an annual scientific meeting with the next one planned to be held at Bristol on 13-15 October 2014. ◆

See www.acnr.co.uk for a report on ***Prolonged Disorders of Consciousness*** by Dr John Burn

Definitions

Vegetative State
A state of wakefulness without awareness in which there is preserved capacity for spontaneous or stimulus-induced arousal, evidenced by sleep-wake cycles and a range of reflexive and spontaneous behaviours. It is characterised by complete absence of behavioural evidence for self- or environmental awareness.

Minimally Conscious State
A state of severely altered consciousness in which minimal, but clearly discernable, behavioural evidence of self- or environmental awareness is demonstrated. It is characterised by inconsistent but reproducible responses, above the level of spontaneous or reflexive behaviour, which indicates some interaction with their surroundings.

To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th April, 2014

March

1st Liverpool MS Study Weekend
15-16 March, 2014: Liverpool
www.liverpoolmscourse.org.uk
E. lucie@medivents.co.uk

Deep Brain Stimulation Masterclass Roadshows
20 March, 2014 – Evening; Oxford, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

3rd International Symposium on Basal Ganglia Speech Disorders and Deep Brain Stimulation
24-25 March, 2014; London, UK
Dr Elina Tripoliti, E. e.tripoliti@ucl.ac.uk
www.ucl.ac.uk/ion/articles/events/basal

International Brain Injury Symposium: 'How to navigate through the rehabilitation pathway' (Day 1)
'Changes and challenges in Disorders of Consciousness' (Day 2)
27-28 March, 2014; London, UK
E. institute@rhn.org.uk
www.rhn.org.uk/bisymposium

Modern thinking in MS Management (for Physicians)
28-29 March 2014; London, UK
Laura Pegg. T. 01932 450326
www.modernthinkinginms.com

April

Deep Brain Stimulation Masterclass Roadshows
3 April, 2014 – Evening; Bristol, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

8th World Congress of Neurorehabilitation (WCNR 2014)
8-12 April, 2014; Istanbul, Turkey
For more information see www.wcnr2014.org, or
E. traceymole@wfnr.co.uk

Deep Brain Stimulation Masterclass Roadshows
24 April,2014 – Evening; Sheffield, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

May

Deep Brain Stimulation Masterclass Roadshows
8 May, 2014 – Evening; Manchester, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

ABN Annual Meeting
7-9 May, 2014; Cardiff, UK
E. info@theabn.org
Telephone: 020 7405 4060

4th Essential Stroke Imaging Course
10 May, 2014; Liverpool, UK
Contact Kath Tyler,
T. 07799 723 925
Email:essentialcourses@hotmail.com

Magstim Neuroscience Conference 2014
10-11 May, 2014; Oxford, UK
T. Angharad Lewis, 01994 240798
www.magstim.com/
magstim-neuroscience-conference-2014

14th Annual Pain Therapeutics Conference
19-20 May, 2014; London, UK
See www.pain-therapeutics.co.uk or contact
Fateja Begum on +44 (0)20 7827 6184,
E. fbegam@smi-online.co.uk

Primary Care & Public Health 2014
21-22 May 2014; Birmingham, UK
T. 0151 709 8979,
E. info@sterlingevents.co.uk

June

Parkinson's Classic Masterclass 25c
Module 1 - 3-5 June, 2014; Bristol, UK
For further information contact
info@redpublish.co.uk

Deep Brain Stimulation Masterclass Roadshows
30 June, 2014 - evening; North London
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

July

ISMRM Workshop on: Function MRI: Emerging Techniques & New Interpretations
July, 2014; Charleston, SC, USA
www.ISMRM.org
T. +1 510 841 1899

Deep Brain Stimulation Masterclass Roadshows
1 July, 2014 - 1.30 /5.30pm; South London, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

September

Parkinson's Registrar's Masterclass 26s
17-18 September, 2014; Location TBC
http://www.redpublish.co.uk/courses/
E. info@redpublish.co.uk

Deep Brain Stimulation Masterclass Roadshows
TBC Sept/Oct, 2014 – Evening; Newcastle, UK
www.redpublish.co.uk/courses/other-courses/
For further information contact
info@redpublish.co.uk

ABN Autumn Meeting
30 September-1 November, 2014; Stratford, UK
E. info@theabn.org
T. 020 7405 4060

October

Ketogenic Dietary Therapies International Symposium
7-10 October 2014: Liverpool UK
E. liverpool2014@matthewsfriends.org
www.matthewsfriends.org

November

Parkinson's Classic Masterclass 25c
Module 2-27 November, 2014; Location TBC
For further information contact
info@redpublish.co.uk

Association of British Neurologists Annual Meeting

Cardiff 7-9th May, 2014

Croeso i Gaerdydd! Welcome to Cardiff!

The 2014 Annual ABN meeting is being held in the magnificent Millennium Centre and if the wonderful architecture is not enough to entice you, we have a rich mix of education and research sessions not to be missed.

There are teaching sessions that we think you will find useful and interesting on 'Neurology and general medicine', Genetics, Multiple Sclerosis and peripheral neuropathies. There are video sessions on epilepsy and sleep disorders and an interactive session on movement disorders. Once again we are running updates, this year on neuro-oncology, muscle disease and depression in neurology.

We are delighted to welcome Prof Marty Samuels from Harvard who will be telling us 'How neurologists think: what my errors taught me'. Prof Matthew Kiernan will be talking on 'MND – a clinical deconstruction'. We look forward to Prof Michael Hutchinson's lecture as the ABN Medalist.

In response to the dramatic changes in the NHS we are running a session on Clinical Commissioning and the Shape of Training. These are interesting times indeed.

We have some of the traditionally very highly rated sessions – the clinical case competition (ACNR sponsored) and the CPC – this year with Graham Lennox in the hot seat – and neuro-ophthalmology.

There are a few innovations too. This year we have a session that has been opened up to the Special Interest Groups and Affiliated Societies. They are being given the space to run mainly clinical and case based sessions which will allow them to network with fellow subspecialists but also to try to entice colleagues and trainees to join them. Movement disorders, cognitive neurology, rehabilitation, traumatic brain injury, peripheral nerve, myology, myasthenia, and neuro-ophthalmology will all be represented. Take your pick.

This year the programme will be available as an App and we will be experimenting with tweeting and texting of questions...well, at the chair's discretion.

On the Tuesday before the main meeting, we have a roadshow designed to encourage medical students and foundation doctors interested in neurology and a training day for neurology registrars. We are running our second 'Need to Know Neurology' course for GPs – which you might want to encourage GPs in your area to attend.

On Tuesday evening we have a session on 'How to get ahead in Research' – including sessions on how to give a successful presentation, how to write a paper and how to get a grant...Looks like a great meeting. Definitely not to be missed.

'Rydym yn edrych ymlaen at eich gweld (we look forward to seeing you)...

Geraint Fuller
President,
Association of British Neurologists

The full programme can be found online at www.theabn.org, under meetings and events.

Forget what you think you might know about the youngest Capital city in Europe. Yes, there is an abundance of history: Cardiff Castle and the St Fagans National History Museum are great day trips, particularly for the kids. But dump the daffodils, drop the dragons and lose the leeks; we hope to provide you with a flavour of this hip and interesting city.

The Millennium Centre and the Bay

We are delighted that the conference venue is the state of the art Wales Millennium Centre (WMC) in Cardiff Bay. The controversial exterior was designed to mirror the industrial heritage of the South Wales valleys with slate and copper plating. This produced a large brown building that some have compared to a slug. Visitors will discover a landmark building with a stunning modern interior.

Cardiff Bay is Europe's largest waterfront development. It may be the shops and restaurants of Mermaid Quay that first catch the eye, but iconic buildings include the snowy white Norwegian church, the red-brick Pierhead building and the stylish Senedd buildings. The Senedd, the seat of the National Assembly of Wales will be our neighbour in May. The building's complete transparency is an apparent metaphor for good government. The waterfront location also ensures that the building is coated in seagull poop; this is not seen as a metaphor for good government. Entry is free, including the chance to observe the Senedd in session, and guided tours are available if pre-booked.

The bay development was made possible by the creation of the £220 million barrage which creates a sheltered fresh-water bay. We recommend a brisk walk across the barrage, with its bridges and sluice gates, to Penarth where the Custom House provides a superb eating opportunity. The bay is famously the site from which Captain Scott departed on the Terra Nova for his doomed exploration of the South Pole in 1910. Delegates who are not dissuaded by this ominous portent can take a boat trip to the enigmatic island of Flat Holm or join Cardiff Sea Safaris for an exhilarating powerboat ride. For other water sports we can highly recommend the International White Water centre or the International Pool, both found in the nearby Sports Village. Whether you're a serious canoeist, fancy a go at surfing, enjoy water slides or just like the idea of being thrown down a tumultuous river course in a flimsy inflatable, this location has something for you.

Eating and drinking in the Bay

Mermaid Quay houses the predictable middle and high-end chain restaurants that are ubiquitous on the UK high street. However, for something different why not try Signor Valentino's – the menu adds a distinctly Welsh accent to traditional Italian fare. There are also two good brasseries (Bayside & Woods) in the Bay as well as British and Irish Lions' captain, Sam Warburton's favourite Indian restaurant – the Juboraj. ffresh is the restaurant located within the WMC which offers high class dining prepared with local ingredients. They offer a good value, pre-theatre menu if you find time to book up for a WMC performance.

Underneath Jolyons boutique hotel (opposite WMC) discover 'bar cwtch' (cwtch is an untranslatable Welsh word; it is simultaneously a safe and warm hug as well as a snug). In addition to wood stone oven pizzas and tapas, this tiny bar can accommodate those in search of a subterranean cocktail.

Cardiff Bay – home of Doctor Who

The bay is now home to Roath Lock – BBC Wales' new 'drama village.' Doctor Who, Torchwood, Casualty, Upstairs Downstairs and the Welsh language soap 'Pobol y Cwm' are the major productions here. As well visiting the impressive Doctor Who experience, fans could while away an hour or so on the Doctor Who walking tour or on a guided bus tour of the city. There is nothing wrong with wallowing in fifty years of memorabilia or cosying-up to a Dalek, if this is your want, however the rest of Cardiff is just a five-minute bus or train ride away.

Into the City

Enthusiastic visitors may enjoy a trip in to the city centre proper. As an alternative to traditional public transport, a waterbus provides regular links from Cardiff Bay to Bute Park, along the river Taff. From the botanic idyll of Bute Park, a short stroll will take you to Cardiff Castle, the Millennium Stadium or the bustling retail core of Cardiff. Nestled between the popular St. Mary Street and Queen Street is the recently developed St David's centre, an undercover shopping opportunity. However, the discerning delegate may prefer to amble through the historic arcades that extend left and right from St. Mary's Street. Discover Spillers (the oldest record store in the world), Wally's Delicatessen with its Viennese-style coffee house, the overwhelming Troutmark books or the hip outfitters, Barkers.

Alongside a host of city centre pubs of variable quality there are a few gems. Buffalo Bar offers bar food, cocktails and live music, while Gwdihw offers coffee, free wifi and board games by day and has a well stocked bar at night. For live music, Clwb Ifor Bach is a bone fide institution. The fun is spread across three floors in this ever-popular culture-magnet, which has the dual purpose of being a lightning rod for new music and perpetuating the Welsh language. For good food try the Potted Pig, Casanova's or the Thai House.

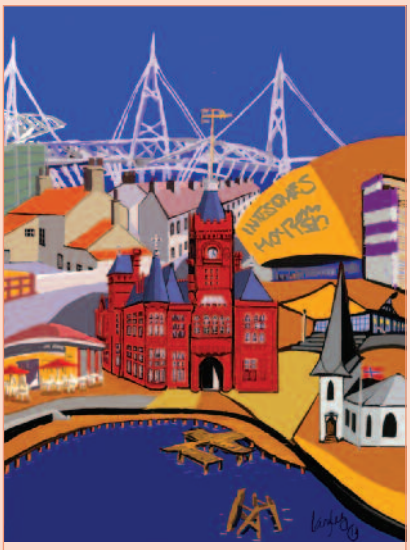
The nearby suburb of Pontcanna is home to many members of Cardiff's art and media scene and offers some trendy alternatives to the city centre. Bully's is a family run French restaurant with 'some exotic twists'. A gourmet Indian restaurant experience can be enjoyed at the Purple Poppadom and the Chapter Arts Centre offers cheap and cheerful eats as well as exhibitions and the latest in world cinema.

And afterwards..

And if you'd like to extend your trip and explore further west after the conference try the nation's favourite beach at Rhossili Bay on the Gower peninsula or experience rural Pembrokshire and take in a game of rugby. The Cardiff Blues are due to play away to the Scarlets in Llanelli during the weekend following the conference; a fierce derby and the last match of the regular season to boot.

I hope you find the Cardiffians a friendly bunch: if we can help with your trip at all – just drop us a line. Rhys-Thomas@doctors.org.uk or emma.tallantyre@nhs.net

Croeso y Caerdydd
Rhys Thomas & Emma Tallantyre



"Cardiff Bay and the Grange"
A montage of Cardiff Bay and Grangetown. Artist: Christopher Langley. Featuring Grange Cottage, The Norwegian Church, The Senedd Building and The Millenium Centre, this was the centrepiece of the Abstract Wales Exhibition in May 2013.

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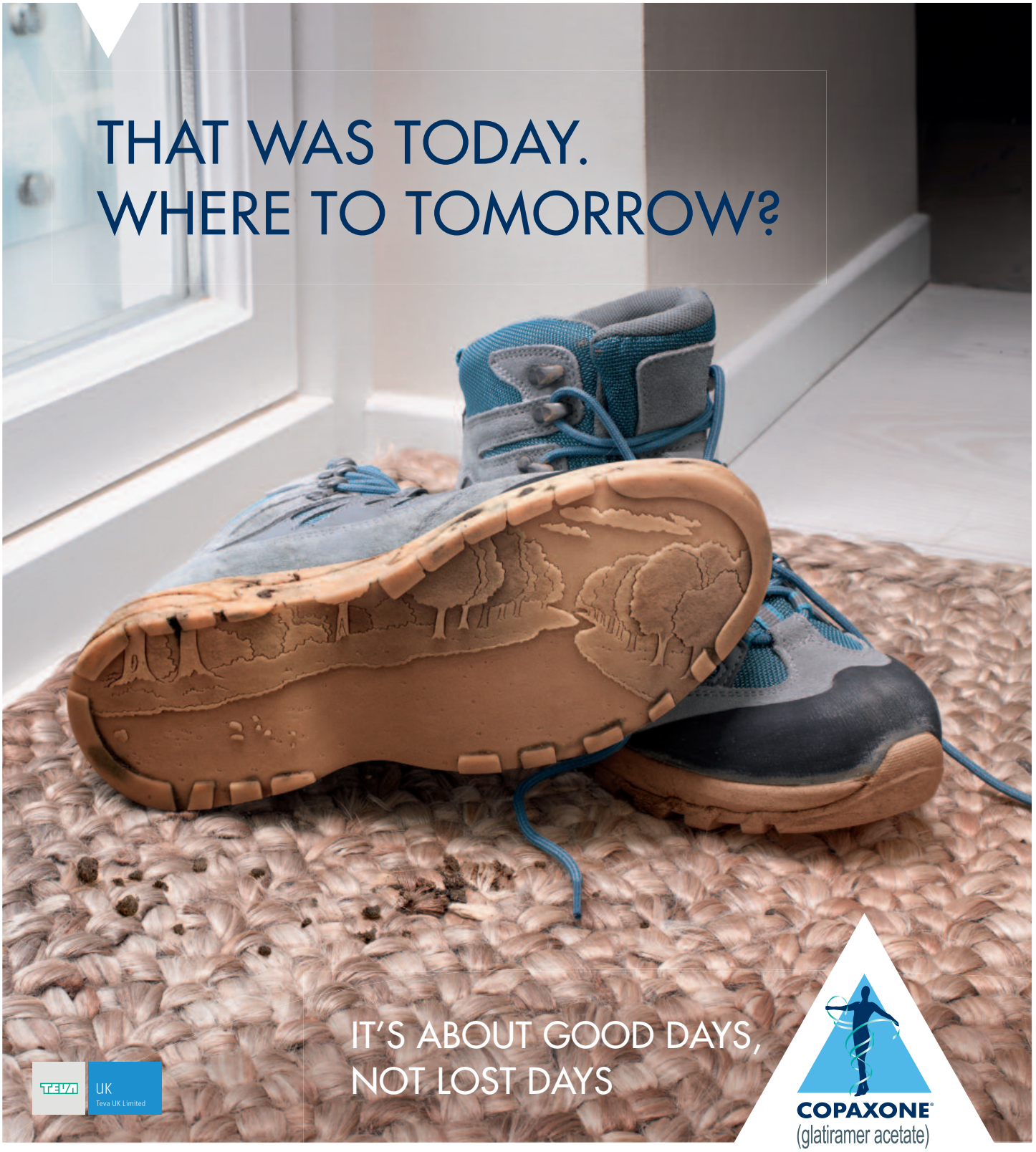

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Date of preparation: October 2013 **Job code:** UK/CPX/13/0008I

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