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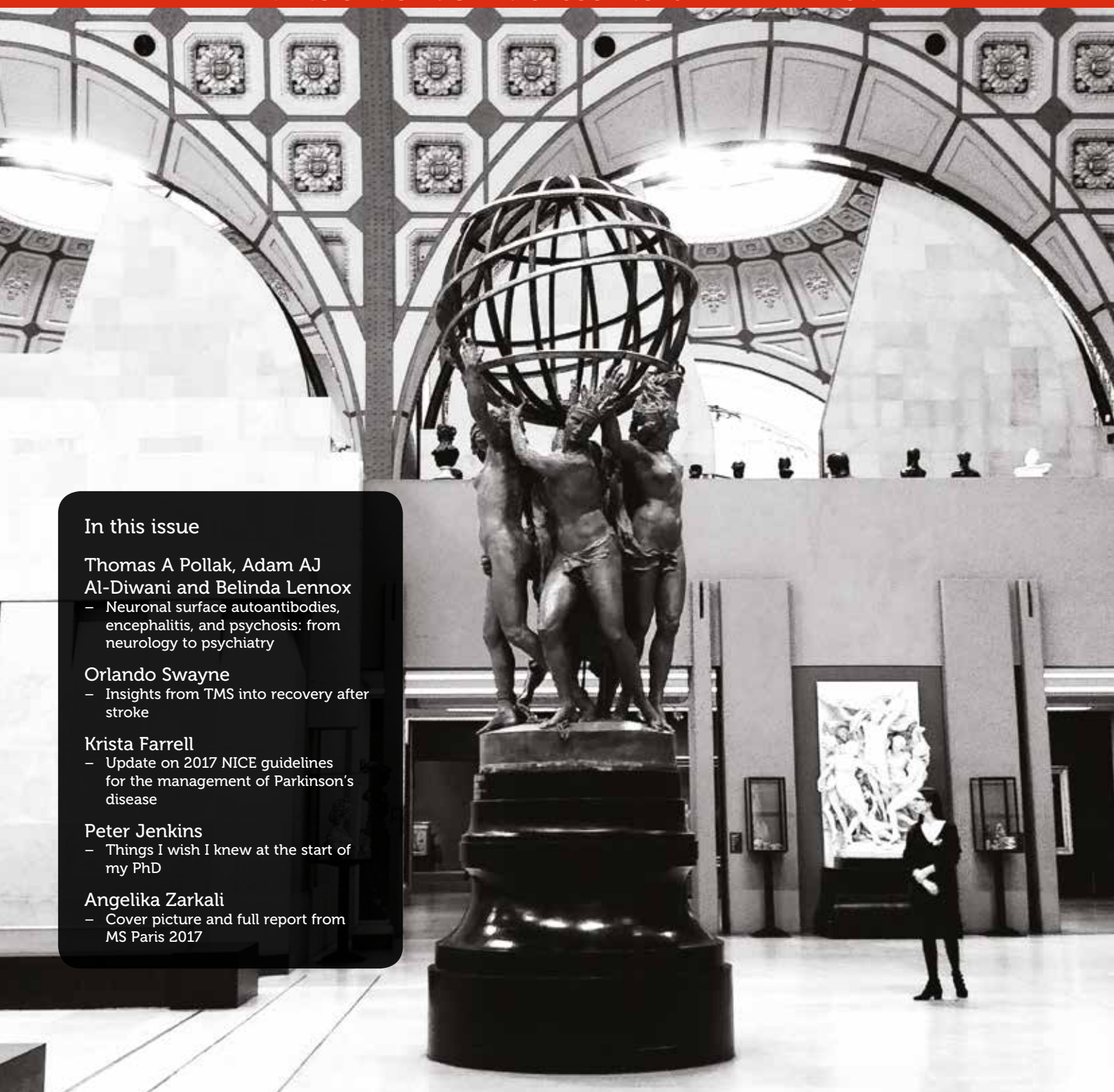
ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



In this issue

Chair:
Ms Samantha Colhoun
Queen Elizabeth Hospital, Birmingham

Chair:
Professor Carolyn Young
The Walton Centre, Liverpool

Modern Thinking in MS Management

long term management of patients

Hilton Birmingham Metropole

Friday 02 (eve) & Saturday 03 March 2018

This meeting is open to Consultants, Specialist Registrars and Nurses specialising in Multiple Sclerosis

Friday 02 March 2018		
19:00	**Registration**	
19:30 – 19:40	**Chairs' introductions**	Prof Carolyn Young, *The Walton Centre, Liverpool* Ms Samantha Colhoun, *University Hospitals Birmingham NHS Foundation Trust*
19:40 – 20:10	**What have we learnt to help us develop new therapies for progressive MS?**	Dr Jeremy Chataway, *University College London Hospitals* Dr Martha Bajwa Joseph, *Institute of Clinical Trials and Methodology, London*
20:10 – 21:10	**Dinner**	
21:10 – 21:40	**DEBATE: This house believes that platform drugs are no longer needed in MS care**	**FOR:** Dr Nikos Evangelou, *Nottingham University Hospitals NHS Trust* **AGAINST:** Dr Martin Duddy, *Royal Victoria Infirmary, Newcastle*
Saturday 03 March 2018		
08:45 – 09:00	**Chair's introduction**	Ms Samantha Colhoun, *University Hospitals Birmingham NHS Foundation Trust*
09:00 – 09:30	**The impact of MS on sexuality: What are the issues and how do we communicate them?**	Prof Carolyn Young, *The Walton Centre, Liverpool* Mr Marc Lucky, *Aintree University Hospital, Liverpool*
09:30 – 10:00	**Strategies for family planning in MS: an ongoing challenge**	Dr Peter Brex, *King's College Hospital NHS Foundation Trust, London*
10:00 – 10:30	**Supplements in MS: Are there any benefits from them?**	Ms Samantha Colhoun, *University Hospitals Birmingham NHS Foundation Trust*
10:30 – 11:00	**Coffee break**	
11:00 – 11:30	**Ageing with MS**	Prof Neil Robertson, *Cardiff University*
11:30 – 12:00	**Long term management of cognition in MS**	Dr Gordon Mazibrada, *University Hospitals Birmingham NHS Foundation Trust*
12:00 – 12:45	**Lunch**	
12:45 – 13:45	**Workshop session 1** *(Please choose 2 of the below sessions to attend)*	
	Assessing cognition (for the non-psychologist)	Prof Dawn Langdon, *Royal Holloway University of London*
	Helping patients understand their rights with disability law	Ms Helen Watson, *Aaron and Partners Solicitors, Chester*
	Management of complex symptoms – Spasticity and fatigue	Dr Rachel Farrell, *National Hospital for Neurology and Neurosurgery, London*
13:45 – 14:10	**Coffee break**	
14:10 – 15:10	**Workshop session 2** *(repeat of above workshops)*	
15:10 – 15:30	**Chair's summary, call to action and close**	Prof Carolyn Young, *The Walton Centre, Liverpool*

To register, visit: www.modernthinkinginms.com

For further details, please contact the meeting Secretariat. e-mail: registration@modernthinkinginms.com. Tel: 01932 254432

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Anne Donnelly, Co-Editor.

At the year-end, one might be tempted to shift into a slower gear, to ease through a life involving dark icy journeys to hospital or laboratory, in a sort of hibernation of the mind, but here is ACNR. This issue provides you with a good overview of what has been happening in UK and European neurology, and examining best practice in clinical neurology with a clear eye on the future.

The Autumn Lecture by Dr Gordon Plant at the ABN meeting in October (summarised by Dr Michael Foster) quoted Keats 'Season of mists and mellow fruitfulness," describing how a lifetime of hard work can bear fruits in the 'Autumn' with a fascinating description of 'Smartphone blindness.'

Claude Bernard, of Claude Bernard-Horner's syndrome (History of neurology article, Emeritus Professor JMS Pearce) seems also to prove this rule, publishing his work 'Introduction à la médecine expérimentale' in 1865 at the age of 52, in which he set out a philosophy of science which is still relevant today.

A review by Dr Thomas A Pollak et al provides us with an overview of the perplexing world of psychosis, encephalitis and neuronal surface antibodies.

Clearly these syndromes are at the forefront of our collective minds in 2017, with discussion from Dr M Zandi at the ABN and posters at the Royal College of Psychiatrists Faculty of Neuropsychiatry Annual Conference (George El-Nimr). Many questions remain unanswered and diagnostic dilemmas remain in these borderlands of autoimmune encephalitis and psychiatry.

More clarity was provided in the area of recent updates to the NICE guidelines for Parkinson's Disease, with a succinct overview by Dr Krista Farrell.

Dr Angelika Zarkali reported back from ECTRIMS 2017. It has been a landmark year, with the revision of the McDonald Criteria, evidence of benefit of disease modifying treatment in reducing both progression to secondary progressive MS and overall mortality rates. Clearly we are breaking through in many small ways, although trial data is modest.

For our junior trainees, Dr Pete Jenkins shares the benefit of his experience and valuable lessons learned. His article on how to prepare for a PhD would help you choose wisely and discussion about optimising your time in research is inspiring.

Dr Orlando Swayne's article provides an illuminating overview of transcranial magnetic stimulation (TMS). His article encompasses both advances in clinical neuroscience and rehabilitation (ACNR!) reflecting our scope.

Neurology in literature is also scrutinised by Dr A Larner, who looks at a Conrad character, and hypothesises about what the underlying diagnosis might have been based on unusual perseverative behaviour.

But what of Winter?
This icy morning brings to mind another poet, Robert Frost,
'The woods are lovely dark and deep, but I have promises to keep
And miles to go before I sleep,
And miles to go before I sleep'.

What better companion to carry you through this dark winter, to light the fires of inspiration and ignite debate than this November - January issue of ACNR?

Anne Donnelly, Co-Editor
Email. Rachael@acnr.co.uk

Thanks to all our peer reviewers this year
Christian Baumann; Sudarshini Ramanathan; Phillipa Pettingill; Tejal Mitchell; Nimeshan Geevasinga; Alan Pearce; Wallace Brownlee; Angelos Kolias; Mike Boggild; Shaun Watson; Eric Kelleher; Sian Alexander

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Prescribing information can be found on the following page

Dr Thomas A Pollak

is a Wellcome Trust Clinical Research Training Fellow in the Department of Psychosis Studies at King's College London. His research focuses on the neuroimmunological basis of psychiatric disease. He uses neuroimaging and neuroimmunological methods to characterise the significance of autoantibodies to neuronal surface antigens in early psychosis. Other research interests include glutamatergic abnormalities in psychosis and clinical neuropsychiatry. His clinical work is as a specialty trainee psychiatrist at South London and Maudsley NHS Foundation Trust.

Dr Adam AJ Al-Diwani

is a Wellcome Trust DPhil Training Fellow at the Department of Psychiatry, at the University of Oxford. He is a psychiatrist in training interested in the contribution of adaptive immunity to the biology of psychiatric illness. His DPhil centres around comparing autoimmune encephalitis with neuronal surface antibody-associated isolated psychiatric syndromes. In particular, he is interested in the immunising events associated with the generation of NMDAR antibodies. Additionally, he is collaborating with colleagues in the Wellcome Centre for Integrative Neuroimaging (WIN) to investigate possible fMRI and spectroscopic signatures associated with these illnesses.

Professor Belinda Lennox

is Associate Professor in the Department of Psychiatry, University of Oxford, and Honorary Consultant Psychiatrist in the Early Intervention in Psychosis service for Oxford Health NHS FT and in the Clinical Neuroimmunology group in Oxford University Hospitals NHS Trust. She runs a joint neurology/psychiatry clinic with Dr Camilla Buckley, Consultant Neurologist, for patients with autoimmune encephalitis.

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Neuronal surface autoantibodies, encephalitis, and psychosis: from neurology to psychiatry

Autoimmune encephalitis in the 2000s

It has been over a decade since the first description of an encephalitis presenting with psychosis, occurring in young women with ovarian teratoma.[1] This disorder, now known to be caused by autoantibodies which recognise the NR1 subunit of the N-methyl-D-aspartate (NMDA) receptor (NMDAR), has had a profound effect on the neurological landscape. NMDAR-antibody encephalitis has also had an effect on the cultural landscape, with Susannah Cahalan's bestselling account of her experience of the disorder, *Brain on Fire*, topping the *New York Times* bestseller list and being made into a Hollywood movie.

But why was the impact of this newly described disorder so great? After all, it was in the 1960s that Brierley, Corsellis and colleagues first penned their seminal descriptions of limbic encephalitis. All of the original case descriptions, like Cahalan herself, presented with psychiatric symptoms before going on to develop various neurological symptoms including seizures and cognitive dysfunction.[2]

Unlike these original cases, however, NMDAR-antibody encephalitis is highly responsive to immunotherapy. We now know that this is because NMDAR antibodies attach to the neuronal surface (unlike the classical 'onconeural' antibodies associated with paraneoplastic limbic encephalitis) and are therefore accessible *in vivo* to antibody-directed immunomodulatory therapies. This was not a novel paradigm as such, having been well established in myaesthenia gravis. However, this disorder was occurring within the central nervous system, thereby challenging the notion that antibodies or antibody-secreting cells could not cross the blood brain barrier and that the brain was an immune privileged site.

Further, as the number of reported cases began to increase, it became apparent that a minority of patients presented *solely* with psychiatric symptoms throughout the course of their illness.[3] What was novel was not the fact that CNS inflammation can cause an immunotherapy-responsive isolated psychiatric phenotype – indeed, neurologists have been treating psychosis due to SLE and other CNS inflammatory disorders for years, despite little understanding of the mechanisms underlying psychotic symptoms in these disorders. The real breakthrough lies in the fact that a relatively straightforward laboratory test has enabled the identification of an entirely new repertoire of neuronal autoantibodies that target relatively well-characterised membrane proteins involved in neurotransmission, offering a mechanistically plausible pathway from antigen to symptoms and indeed to psychopathology.[4] In 2017, many of these novel autoimmune encephalitides – associated with antibodies targeting the AMPA, glycine, GABA-A and –B receptors or other membrane proteins such as leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) – are now familiar to most UK neurologists. New antigenic targets – mostly extracellular, although occasionally intracellular/cytosolic – are being reported every few months (IgLON5, dipeptidyl-peptidase-like protein-6 [DPPX], and neurexin 3α encephalitis have all been described in the last few years)[5] (see Table 1). Unlike with syndromes associated with the classical onconeural antibodies, only a minority of patients have an associated tumour, such as an ovarian teratoma in NMDAR-antibody encephalitis; if a tumour is present, resection appears to expedite recovery.

The technology that has enabled this explosion of discovery of immunotherapy-responsive disease in an ever-growing number of patients is the development of cell-based assays (CBAs) for the detection of neuronal surface autoantibodies. CBAs are cell lines, transfected with a genetic construct containing the target antigen of interest. This leads to surface expression of the antigen, thereby avoiding exposure of pathogenically irrelevant intracellular epitopes and also maintaining the native conformation of the target protein. This is a crucial feature of this group of antibodies to which previous detection methods such as ELISAs and western blots are largely insensitive.

The impact on psychiatry

If the impact on neurology has been great, the impact on psychiatry has been no less profound. Of the original 100 cases of NMDAR encephalitis described by Dalmau and colleagues, 77% presented to psychiatric services, the majority with largely psychotic symptoms.[6] That proportion is perhaps smaller in the UK today, partly due to greater awareness amongst clinicians, but the fact remains that in its early stages, autoimmune encephalitis can be a *mimic* of first episode psychosis (FEP).

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Antigen	Antigen description/epitope	Main encephalopathy syndrome; which possible psychiatric features?	Other associated neurological disorders
NMDAR (NR1 subunit)	Ligand gated ion channel subunit	Encephalopathy (usually extralimbic). Psychiatric features include anxiety, agitation, bizarre behaviour, catatonia, delusional or paranoid thoughts, and visual or auditory hallucinations. Also movement disorder, seizures, autonomic instability.[3,24,25]	Post-herpes simplex encephalitis relapse with chorea; idiopathic epilepsy; immunotherapy-responsive dementia.[26,27]
LGI1	VGKC- and AMPAR-associated secreted molecule	LE with or without faciobrachial dystonic seizures (FBDS). Psychiatric features include confusion, hallucinations, depression.[28]	Morvan's syndrome, NMT, epilepsy, REM sleep behaviour disorder[28]
CASPR2	VGKC-associated adhesion molecule	LE and Morvan's syndrome. Psychiatric features include confusion, hallucinations, agitation, delusions.[29]	NMT, epilepsy[28]
AMPAR	Ligand gated ion channel	LE. Psychiatric features include confusion, personality change, psychosis, apathy, agitation, confabulation. [30-32]	
$GABA_AR$	Ligand gated ion channel	LE with refractory seizures. Psychiatric features include confusion, affective changes (inc depression), hallucinations[33]	Varied presentations.[34]
$GABA_BR$	Ligand gated ion channel	LE with refractory status epilepticus. Psychiatric features include psychosis, agitation, catatonia.[30,35]	Opsoclonus-myoclonus; cerebellar ataxia; PERM[35,36]
D2R	Metabotropic receptor	'Basal ganglia encephalitis' with prominent movement disorder (dystonia, parkinsonism, chorea, tics). Psychiatric features include agitation, depression, psychosis, emotional lability.	SC, PANDAS[37]
DPPX	Auxiliary subunit of Kv4.2 potassium channels	LE with enteropathy. Psychiatric features include amnesia, delirium, psychosis, depression[38,39]	PERM[40]
MGluR5	Metabotropic receptor	'Ophelia syndrome': LE in association with Hodgkin lymphoma. One case of LE without lymphoma. Psychiatric features include depression, anxiety, delusions, visual and auditory hallucinations, anterograde amnesia.[41]	
IgLON5	Neural cell adhesion molecule of unclear function	Characteristic sleep disorder preceded or accompanied by bulbar symptoms, gait abnormalities, oculomotor problems and cognitive decline; a tauopathy, strongly associated with HLA-DRB1*10:01.[42,43]	
Neurexin 3α	Synaptic molecule involved in formation and maturation of synapses	Infectious prodrome followed by cognitive dysfunction, seizures, reduced consciousness, and orofacial dyskinesias; sometimes severe clinical course; mimic of NMDARE but with less prominent psychiatric symptoms.[44]	
ARHGAP26	A multidomain protein involved in regulation of endocytosis	Autoimmune cerebellar ataxia with dizziness and dysarthria; also memory dysfunction and depression.[45,46]	One patient reported with immunotherapy-responsive psychosis with suicidality, aggression, mutism.[47]
Synapsin	A synaptic vesicle-associated protein involved in regulation of neurotransmitter release.	69-year-old man with confusion, disorientation, seizures, and left hippocampal hyperintensities on MRI.[48]	Synapsin IgG also found in patients with neurological and psychiatric disorders (including psychosis, depression and bipolar disorder).[49]
AK5	An intracellular (cytosolic) nucleoside monophosphate kinase, expressed exclusively in the brain.	>50 yo; subacute pure anterograde amnesia, occurring in most cases after a prodromal phase of asthenia, anorexia, and depression. Hippocampal atrophy on MRI. Prominent anxiety, but seizures not reported.[50]	
GFAP	An intracellular (cytosolic) glial intermediate filament protein.	Corticosteroid-responsive meningoencephalitis or encephalitis, with or without myelitis. Presents with subacute onset of memory loss and confusion. Co-occurs with autoimmune endocrinopathy in one third, and with tumour in one third. Psychiatric symptoms reported in 29%.[51,52]	

adenylate kinase 5; ARHGAP26: Rho GTPase activating protein 26; ATD: amino terminal domain; BPAD: bipolar affective disorder; CBA: cell-based assay; ELISA: enzyme-linked immunosorbent assay; GFAP: glial fibrillary acidic protein; LE: limbic encephalitis; MDD: major depressive disorder; NMT: neuromyotonia; PERM: progressive encephalomyelitis with rigidity and myoclonus; RIA: radioimmunoassay; SC: Sydenham's chorea; PANDAS: paediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections. Table reproduced and updated with permission from Pollak et al. [4]

Similarities between NMDAR-antibody encephalitis and psychosis are not limited simply to delusions and hallucinations. Patients with psychotic disorders, even if antipsychotic-naïve, can present with catatonia, autonomic instability including hyperthermia, extrapyramidal signs including tremors and dyskinesias, hypersomnolence or acute insomnia, hyponatremia and even a delirium-like picture.[7]

In *Brain on Fire*, Cahalan is initially diagnosed with schizoaffective disorder by a psychiatrist, before she develops a frank encephalopathy and NMDAR-antibody encephalitis is diagnosed by her neurologist, Dr Najjar. Musing on her diagnostic journey, she asks a simple question: "*how many people currently are in psychiatric wards and nursing homes denied the relatively simple cure of steroids, plasma exchange, [or] more intense immunotherapy…?*". Cahalan was not alone in wondering whether encephalitis was just the tip of the autoimmune iceberg. By 2011, psychiatrists had begun to search for NMDAR and other neuronal surface autoantibodies in patients with so-called 'primary' psychotic disorders – those in which causation is thought to be complex or unknown. The first study to look for these antibodies in FEP found NMDAR and voltage-gated potassium channel complex antibodies in 7% of patients presenting to a community psychosis service in Cambridge. Importantly, one NMDAR autoantibody-positive patient was given plasmapheresis and made a full psychiatric recovery that was sustained at seven months follow-up.[8]

Reports of brain-reactive antibodies in psychosis are nothing new, dating back as far as the 1930s, but in looking for antibodies strongly suspected to be pathogenic by virtue of their role in the various newly-described autoimmune encephalitides, the argument for plausible antibody pathogenicity in psychotic disorders is strengthened. Most recently, Lennox and colleagues conducted the largest ever prospective study of neuronal surface autoantibodies (NMDAR, LGI1, CASPR2, GABA-AR) in first episode psychosis, involving 230 young people from 14 sites around the UK. We found that 8% of subjects had a neuronal surface autoantibody detectable in peripheral blood, and for NMDAR-antibodies the difference versus healthy control prevalence was statistically significant. Crucially, seropositive subjects were not distinguishable from seronegative subjects on the basis of clinical features alone.[9]

Other recent studies, using various assays and confirmatory testing methods, have identified potentially disease-relevant antibodies in patients with a variety of psychosis diagnoses, including chronic psychosis,[10] childhood-onset psychosis,[11] and postpartum psychosis.[12]

For psychiatrists, these developments are exciting and parallel similar discussions in neurology regarding the relevance of these antibodies in epilepsy, movement disorders and memory syndromes. They come at a time when psychiatry is increasingly looking towards neuro-immune interaction as a putative disease mechanism in psychotic and other severe mental illnesses. Genome-wide association studies suggest immune-related SNPs confer schizophrenia risk, raised inflammatory markers appear to characterise acute illness stages, and considerable epidemiological overlap with autoimmune disorders is attracting attention.[13] For decades, there has been little progress in the pharmacological treatment of psychosis, and we still largely rely on dopamine D2 receptor antagonism, which is the same mechanism of action as that of chlorpromazine, introduced in 1952. The possibility that even a subset of patients with psychosis may have an immunotherapy-responsive autoimmune basis to their disorder has therefore attracted considerable enthusiasm.

But is this enthusiasm premature? So far, there have been numerous case reports of good immunotherapy-responses in patients with psychosis, and the largest open-label case series to date demonstrated improvement in symptoms concomitant with reduction in antibody titre in each of 9 patients with acute psychosis and NMDAR antibodies who received immunotherapy.[14] But selection bias, placebo response to a dramatic, highly medicalised intervention, and regression to the mean cannot be ignored as potential factors here.

Current controversies

Biological psychiatry is replete with false dawns, and some authors are sceptical of the relevance of neuronal autoantibodies in psychotic disorders.[15] Critical debate tends to centre around two themes:

1) Serum neuronal surface autoantibodies are sometimes found in healthy people and in other, non-encephalitis diseases – therefore they can only have disease-relevance when there is a phenotype typical of classic descriptions of autoimmune encephalopathies.
2) Serum antibodies without associated detectable CSF antibodies are unlikely to represent an antibody-mediated brain disease.

There continues to be active discussion around these points which cannot be adequately summarised here, but the following comments point towards some relevant considerations:

1) Different CBAs appear to have different sensitivities and specificities. One theoretical factor contributing to this variation is that the fixation process may affect protein structure and permeabilisation may expose intracellular antigens allowing antibodies to bind that have a lower chance of pathogenic potential. One recent study in a first episode psychosis cohort demonstrated that live CBAs are more sensitive than fixed CBAs. Furthermore, single molecule imaging demonstrated to a high degree of likelihood that that even antibodies from weakly positive sera, far from being 'false positive', targeted the NMDAR.[16]
2) Whereas CSF antibodies, and evidence of intrathecal synthesis are frequently observed in typical NMDAR-antibody encephalitis, CSF positivity rates are much lower in other types, such as LGI1 or CASPR2-antibody encephalitis.[17] Further, in animal models it has been demonstrated that at relatively low titres the brain can act as an 'immunoprecipitator' of NMDAR antibodies (and by extension presumably other neuronal surface autoantibodies) meaning that unless the brain becomes saturated due to an excess of antibody, as may be the case when there is intrathecal synthesis and active, florid encephalitis, absence of detectable CSF antibody does not necessarily exclude a CNS-binding surface antibody.[18] Indeed, cases of seropositive but CSF-negative NMDAR encephalitis have been reported using a live CBA in the UK.[19]

Ultimately, despite these important scientific questions, as more patients are tested for these antibodies clinicians need a clearer evidence base regarding treatment decisions. A placebo-controlled double blinded randomised controlled trial, currently recruiting in the UK will help. The SINAPPS2 trial will randomise 80 patients with acute psychosis and neuronal surface autoantibodies to receive either active immunotherapy (IVIG and rituximab) or sham immunotherapy in addition to psychiatric treatment as usual [clinicaltrials.gov NCT03194815 / www.sinapps.org.uk].

Clinical best practice

Until the results of this RCT are known, which patients should be tested and what should neurologists make of a positive neuronal surface autoantibody test in a patient whose symptoms are largely, or indeed wholly, psychiatric in nature? Crucially, one would not wish to miss making a diagnosis of autoimmune encephalitis as soon as possible, and potentially allowing intervention before the disease progresses to a more florid neurological picture. 'Red flag' signs, then, are those which suggest a greater or lesser degree of encephalopathy:[7,20]

- Acute/subacute onset
- Autonomic instability
- Language disorder
- Impairment of consciousness
- Significant cognitive dysfunction
- Seizures
- Neuroleptic sensitivity

Patients with a positive serum autoantibody test should be investigated with EEG, MRI and CSF analysis and diagnosis of autoimmune encephalitis made with current guidelines in mind.[21] Where appropriate, the possibility of co-occurring tumour should be excluded. Ideally care should be shared between neurology and psychiatry; indeed throughout the UK, these disorders have heralded the development of innovative models co-working between neurology and psychiatry, both in inpatient and an outpatient settings.

In terms of psychiatric treatment, there is mounting evidence that patients with NMDAR-antibody encephalitis may respond poorly to antipsychotic treatment, with high rates of rhabdomyolysis and even development of a neuroleptic malignant syndrome (NMS)-type picture.[22,23] For this reason, benzodiazepines are preferred for initial management of behavioural disturbance and catatonia. If antipsychotics are required, sedating atypical antipsychotics such as olanzapine may be preferable.

With a considerable research effort now ongoing at an epidemiological, mechanistic, clinical and trial level, the identification of neuronal surface autoantibodies has re-energised biological psychiatry, suggesting new aetiological insights, and potentially offering new treatment avenues for a group of disorders affecting millions worldwide.

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Insights from TMS into recovery after stroke

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Transcranial Magnetic Stimulation (TMS) is a non-invasive technique whereby an electromagnetic coil held over the scalp is used to induce a brief electrical current in the cortex of the underlying brain. TMS may be used in a number of ways to gain *in vivo* insights into brain physiology and has provided a window into the cascade of physiological changes that occur following stroke. When stimulating the primary motor cortex in a healthy subject stimuli of an intensity above the motor threshold will give rise to a detectable evoked potential in a peripheral muscle. As the stimulus intensity is gradually increased the evoked potentials increase in amplitude up to a maximum, giving rise to a measurable recruitment curve. The motor threshold and the recruitment curve both provide measures of the excitability of the corticospinal tract. This incorporates the excitability of axons within the motor cortex, synaptic inputs onto pyramidal cells and the spinal alpha motor neuron pool. In paired pulse TMS a sub-threshold pulse is delivered a few milliseconds before a second suprathreshold pulse, both through the same coil. The first pulse conditions the response to the second, resulting in inhibition or facilitation depending upon the inter-stimulus interval and reflecting the activity in intracortical regulatory circuits. If two separate TMS coils are used then one may use a similar test-conditioning approach to explore inter-regional interactions, such as interhemispheric inhibition between the two primary motor cortices (Figure 1). Alternatively pulses may be delivered during a motor task, and the resulting effect on behaviour used to infer the stimulated region's role in task performance, for example during a simple reaction time or movement selection task. See Reis et al[1] for a summary of these techniques and their physiological basis.

Strokes that cause hemiparesis usually disrupt the corticospinal tract, and when testing the stroke hemisphere this may manifest as increased motor thresholds, flattened recruitment curves, or alternatively as the inability to elicit an evoked potential at all. An absent evoked potential in the acute post-stroke period is a poor prognostic indicator for motor recovery[2,3] and at that stage these markers of corticospinal excitability, when obtainable, correlate strongly with clinical measures of motor performance.[4] If these corticospinal excitability measures improve then they usually do so over the early weeks post-stroke, presumably reflecting spontaneous biological recovery around the infarct, and the physiological change is reflected in clinical improvement in this group. It has been a fairly consistent finding that the correlation between corticospinal excitability and clinical status declines with time, which may reflect reduced reliance on the original corticospinal projection once the network generating the motor output has reorganised. Some studies have shown hyper-excitability of the corticospinal tract from the non-stroke hemisphere during the acute phase in more severely affected patients, which is interpreted by some as a form of diaschisis.

Paired pulse measures have fairly reliably shown reduced inhibitory activity in the intracortical circuits after stroke. Such apparent disinhibition is hard to interpret in the stroke hemisphere, as these measures depend upon an unconditioned evoked potential of reasonable amplitude which may not be available or may require high stimulus intensities. However no such technical issue affects the intact hemisphere, and the absence or reduction of inhibition when tested in the contralesional primary motor cortex suggests a reduction in the tonic level of GABA-ergic inhibitory activity in intracortical circuits that extends far beyond the site of the stroke. In one study such intracortical disinhibition of the non-stroke hemisphere was seen in patients with cortical but not subcortical infarction,[5] suggesting that this phenomenon may relate to interruption of the transcallosal projection between the motor cortices. Few longitudinal studies of intracortical excitability have been performed but on the basis of the data available it seems that in the acute period disinhibition is seen regardless of clinical status, but that by three months it has resolved in those patients with a better clinical outcome, such that a clinical–physiological correlation emerges at around that time.[6] A recent meta-analysis of TMS studies has shown no overall abnormality of excitability in the intact hemisphere:[7] however if disinhibition were seen only in more severely affected patients then one may see clinical correlation without a group effect.

It is recognised that in healthy humans there is tonic inhibition of each hemisphere by its opposite, a situation that is likely to be important in the generation of unimanual versus bimanual movements. When this inter-hemispheric interaction is measured at rest with two TMS coils using a paired pulse conditioning approach there is robust inhibition. When tested in healthy subjects during a reaction time paradigm the baseline inhibition disappears or reverses as the onset of movement approaches. Murase and colleagues[8] found that such switching-off of interhemispheric inhibition was impaired in stroke patients, and that the extent of residual interhemispheric inhibition was greater in more severely affected patients. This result has been interpreted as suggesting that after stroke there is an imbalance of such interhemispheric interactions, with pathological inhibition of the recovering stroke hemisphere by the non-stroke hemisphere.

Interpretation of the physiological changes observed after stroke remains a matter of debate. TMS as a technique operates at the level of the whole system, drawing inferences from the effect of manipulations on the overall corticospinal output, but the pathological changes observed may be the result of dysfunction at one or more of several

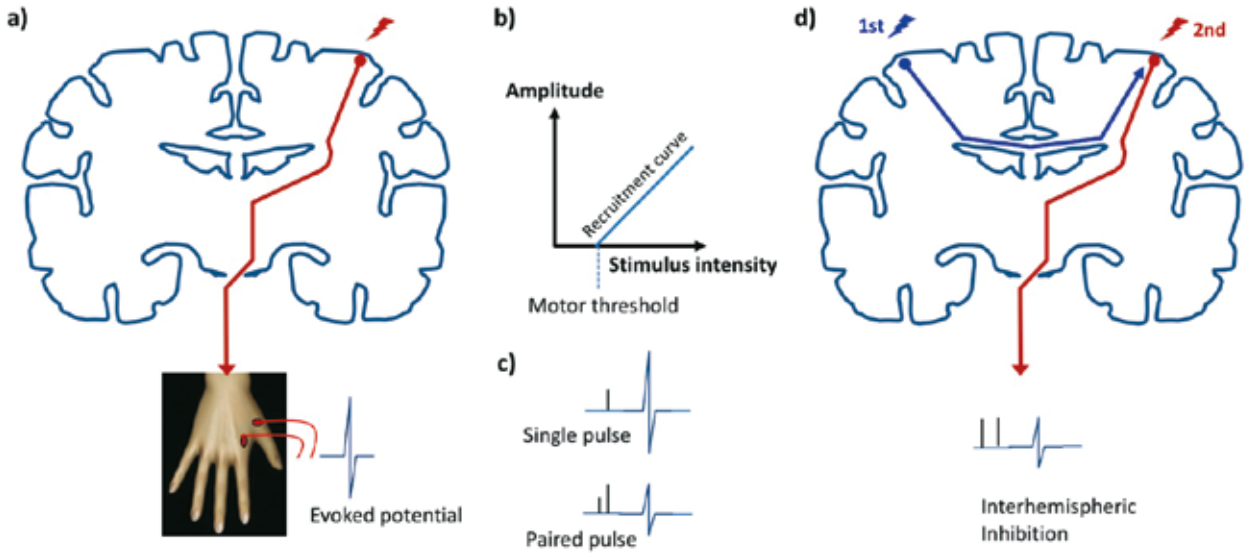

Figure 1. TMS measures of motor cortical physiology. a) Eliciting a Motor Evoked Potential (MEP) from the primary motor cortex, b) Measures of corticospinal tract excitability, c) Using paired pulse stimulation to measure Intracortical inhibition, d) Using two TMS coils to measure Interhemispheric Inhibition.

levels. These may include the effects of cytotoxic changes on local neurochemistry, altered inhibitory vs excitatory synaptic activity, or diaschisis due to disruption of inter-regional tracts. The TMS finding of widespread intracortical disinhibition is in keeping with MR Spectroscopy studies that show reduced cortical GABA content during this period after stroke.[9] A rapid reduction in GABA is also seen in healthy humans as a response to motor training or to experimental de-afferentation of one arm by ischaemic nerve block, which likewise causes intracortical disinhibition as assessed by TMS. In those contexts it is felt that such disinhibition creates a more favourable environment for synaptic plasticity to occur, and it is tempting to conclude that the same is occurring in the post-stroke period as a way of driving reorganisation of the motor output. It is also conceivable that disinhibition allows cortical regions that are disconnected from their usual corticospinal output projection to access instead the horizontal cortico-cortical connections that are prevalent in cortical layers 2 and 3, thereby reaching an alternative output projection. Such a phenomenon would allow for the shifts in cortical motor output maps that are well documented after stroke.[10] In one longitudinal study the correlation between disinhibition and clinical status was strong at three months but then became weaker in the chronic phase.[6] We interpreted this as suggesting that ongoing disinhibition becomes less important for motor function as the reorganised motor network becomes better established with time. Direct evidence for such a process is lacking however, and some would argue that disinhibition is an epiphenomenon rather than an adaptive response to injury. This alternative conclusion would be supported by the observation that reduced intracortical inhibition as measured by paired pulse TMS may be observed in other pathological states, including dystonia and Attention Deficit Hyperactivity Disorder.

The concept of an imbalance between the two hemispheres and of excessive interhemispheric inhibition of the stroke hemisphere has gained a lot of traction and has provided the rationale for therapeutic approaches that aim to redress it. Non-invasive brain stimulation, either by repetitive TMS or transcranial direct current stimulation (tDCS), can induce measurable changes in cortical excitability that outlast the period of stimulation. Depending on the stimulation paradigm used one can induce either increases or reductions lasting minutes or in some cases hours. The most common approaches are either to apply excitatory stimulation to the stroke hemisphere or alternatively inhibitory stimulation to the non-stroke hemisphere (Figure 2), the aim being to enhance the response to conventional therapy by stimulating either before or during treatment. The concept of an overactive non-stroke hemisphere resonates with the widely reproduced functional imaging finding of increased movement-related brain activation on that side in more severely affected patients, which may normalise as clinical recovery progresses.[6] It is by no means clear however that this contralesional activity is the same phenomenon as that which generates pathological inhibition of the recovering hemisphere, or that it is necessarily maladaptive. There is evidence that at least some regions on the non-stroke side may support movement of the paretic side, such as the contralesional dorsal premotor cortex which displays increased functional connectivity to the primary motor cortex of the stroke in more affected patients and appears to support hand movement.[11,12] Furthermore a recent study suggested that reducing intact hemisphere excitability may in fact be detrimental to upper limb function in more impaired patients.[3]

As the role of contralesional brain regions in movement appears to differ depending upon factors such as clinical severity, extent of corticospinal tract disruption and possibly stroke location it would

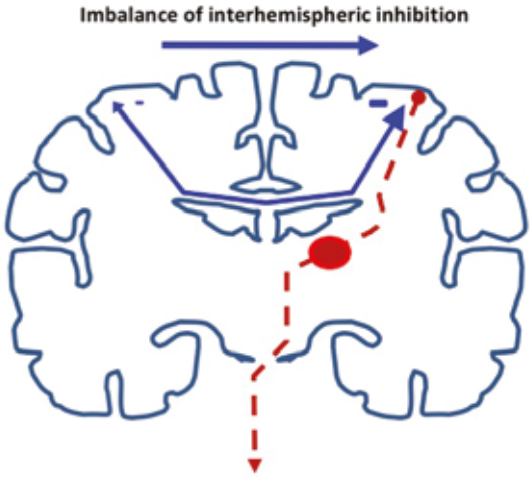

Figure 2. The interhemispheric rivalry model, whereby the intact hemisphere exerts a pathological degree of interhemispheric inhibition on the stroke hemisphere and hinders motor function in the paretic limb. This has given rise to the therapeutic strategies of either increasing excitability in the stroke hemisphere or reducing it in the intact hemisphere.

seem that reducing excitability on that side equally in all stroke patients may represent rather a blunt therapeutic approach. This is especially true of tDCS, whose effects incorporate most of the stimulated hemisphere. However, positive studies may be found in the literature for both repetitive TMS and tDCS when applied to either side of the brain (sometimes both), and although a comprehensive review of the outcomes is beyond the scope of this article the most promising approach appears to be inhibition of the non-stroke hemisphere by tDCS.[13] Non-invasive brain stimulation has not as yet entered routine clinical practice however, and there are a number of reasons why this may be, such as the large number of stimulation protocols available and uncertainty regarding the optimal time to apply stimulation. However, for the reasons discussed above it is important to consider the heterogeneity of the clinical syndrome when designing further trials. Opinions differ as to whether progress will be made using a 'one size fits all' design, the hope being that larger sample sizes will take care of heterogeneity, or alternatively whether targeting stimulation according to clinical and physiological factors would have a greater chance of success. This is likely to be worth getting right, as a large negative study would present an obstacle to further investigation in this field. It is likely to be the case that applying brain stimulation to the right patients could significantly enhance the outcome of post-stroke rehabilitation, with a clinically meaningful reduction in resulting impairment and disability.

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Claude Bernard

"Mais la méthode expérimentale a pour objet de transformer cette conception a priori fondée sur une intuition..., en une interprétation a posteriori établie sur l'étude expérimentale des phénomènes..." Claude Bernard: Introduction à l'étude de la médecine expérimentale.
["But the experimental method aims at transforming this a priori conception based on a vague intuition...into an a posteriori interpretation established on the experimental study of phenomena..."]

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The name Claude Bernard (1813-1878) is known across the world to medical students for the Claude Bernard-Horner's syndrome; but more important are his ground-breaking works in physiology, particularly homeostasis. Peter Wise provides an excellent, detailed account of his life and bibliography.[1]

Claude Bernard was one of the epoch-making giants of experimental medicine, who dominated the nineteenth century. His ideas, researches and scientific principles are enshrined in his *Cahier Rouge*[2] (compiled, 1850 -1860), his *Pensées – Notes Détachées*, and the now-famous *Introduction to the Study of Experimental Medicine*[3] that remain undiminished by time as inspiring works of reference for students of physiology and the natural sciences.

Claude Bernard (Figure 1) was born in 1813 in the village of Saint-Julien-en-Beaujolais. He attended the Jesuit school, and then the college at Lyon, which he soon left to become assistant at the Millet pharmacy in Lyon-Vaise. With a flare for the theatrical he wrote a comedy, and a play titled: 'Arthur de Bretagne' which in 1834 he presented to Saint-Marc Girardin a famous Parisian drama critic, who unimpressed, discouraged him from a career in theatre but urged him to study Medicine. He soon enrolled at the Faculty of Medicine of Paris, sharing lodgings with Charles Lasègue. He studied under François Magendie (1783-1855) in the Hotel Dieu. Magendie, impressed by Bernard's dissecting skills appointed him in 1841 as laboratory assistant.

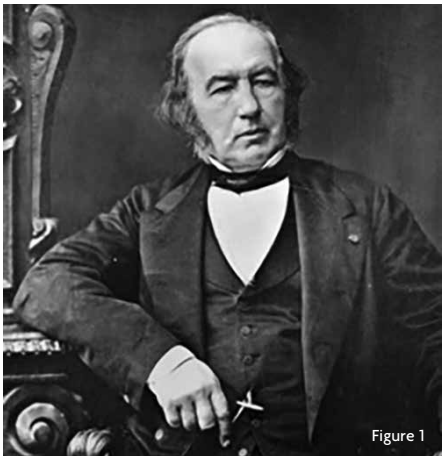
Figure 1

Figure 2

An 'arranged marriage' with the prosperous Marie Françoise Martin was engineered in 1845 by his mentors, Pierre Rayer and Théophile-Jules Pelouze to allow their protégé to develop his research potential under Magendie. Marie Françoise, an ardent anti-vivisectionist, chastised him for his animal experiments; their long marriage was unhappy and ended in separation in 1870. They had two daughters, and a son who died in infancy. After separation he formed a close friendship with Marie Raffalovich, a Jewish intellectual from Odessa, who later nursed him in his final illness.

Before receiving a galaxy of awards and distinctions,[1] in 1847 he was elected Magendie's deputy at the Collège de France, and in 1855, when Magendie died, Bernard was appointed to his Chair of Medicine at the Collège and succeeded to his Chair of Physiology at Sorbonne University. His crucial scientific principles flourished: an idea or observation led to a hypothesis, and then to either support or disprove it, he embarked on systematic experimentation making many scientific contributions, sketched below. His reputation spread and at Louis Napoleon's instigation he moved to the Muséum National d'Histoire Naturelle in 1868. He was later elected to the Academy of Sciences, the Academy of Medicine, and to the Imperial Senate — at the behest of the Emperor.

A memorial plaque in Paris (Figure 2) displays the site of Claude Bernard's laboratory from 1847 until his death in 1878. The Claude Bernard Lyon University commemorates his name. When he died he was accorded a public funeral – an honour never before bestowed by France on a man of science. He was interred in Le Père Lachaise Cemetery in Paris. A stone statue (Figure 3) graces the entrance to the Collège de France, replacing the original bronze barbarically destroyed by the Nazis.

Some scientific contributions

Glycogenesis

He began by studying pancreatic juices which he was able to show were vital in the process of digestion.[4] For this he was awarded the prize for experimental physiology from the French Academy of Sciences. He next studied the workings of the liver and showed that not only did it secrete bile but was, like the pancreas, an 'organ of internal secretions' (enzymes) that converted glycogen into glucose (glycogenolysis), and could store glucose in the form of glycogen (glycogenesis).[5]

To see whether the release of glucose from liver glycogen depended on a neural stimulus via the vagus, in a classical experiment in 1849 Bernard used a needle to stimulate the vagus in the floor of the fourth ventricle, and noted that the urinary and blood glucose increased. Bernard called this *piqûre* [puncture] *diabetes*. He later cut the spinal cord above the splanchnic sympathetic nerves; this blocked the *piqûre* phenomenon. He concluded that the sympathetic nerves directly released liver glucose. Subsequently, it was shown it was adrenaline released from sympathetic nerve endings that was the main cause of glucose discharge from the liver.

Sympathetic paralysis

Assisting Magendie he began his neurological researches.[6] His first in 1843, concerned the chorda tympani which when cut in the dog, was followed by a slow continuous secretion of saliva from the sub-maxillary gland. This secretion was called the 'paralytic' secretion.[7] From several experiments he established the existence both of vasodilator thermal and secretory, and the sympathetic vasoconstrictor nervous mechanisms.[8] He differentiated their functions:

> 'The sympathetic nerve is the constrictor of the blood vessels; the tympanicolingual nerve [chorda tympani] is their dilator'[3] (p.158)

In his several experiments he also established the concept of the physiological equilibrium of these two components of the autonomic nerves.[9]


Figure 3

Claude Bernard-Horner syndrome

In 1727, Pourfour de Petit (1664-1741) had described dilatation of the pupil (mydriasis) owing to stimulation of sympathetic nerves in a man whose neck had been injured by a gunshot wound. When he cut the sympathetic nerve on one side of the neck Petit showed the opposite phenomenon (miosis). In 1851 Claude Bernard repeated Petit's experiment; and gave a more precise description:

> "After the section of the cephalic branch of the great sympathetic, it is possible to observe a contraction of the pupil of the corresponding eye, accompanied by a narrowing of the palpebral opening, a retraction of the ocular globe, and an increase of the circulation, as well as of the temperature, in all parts of the corresponding face. If the upper extremity of the sectioned sympathetic is galvanized, all the phenomena observed after the removal of the influence of the great sympathetic changes at once, appearing an opposite presentation. The pupil enlarges, the palpebral opening augments, the eye protrude out the orbit. The former active circulation becomes weak, the conjunctiva, the nose, the ears previously red become pale. If the galvanism is stopped, all phenomena originally produced by the section of the sympathetic gradually reappear, disappearing again after a second galvanic stimulation."[9,10]

Edward Selleck Hare, House Surgeon to Stafford County General Infirmary, had described the physical signs in a letter to the Medical Gazette on 11 September 1838.[11] Weir Mitchell also gave an account five years before Horner, describing a 24 year old soldier with a gunshot wound of his neck:

> The pupil of the right eye is very small... slight but very distinct ptosis...The ball of the right eye looks smaller than that on the left...

Johann Friedrich Horner (1831-1886) was a Swiss ophthalmologist, who in 1869 observed similar signs and impaired facial sweating in a woman with a tumour invading the cervical sympathetic nerves.[12] These clinical signs are called the Claude Bernard-Horner syndrome.

Curare

Walter Raleigh discovered the paralysing effect of curare applied to poisoned arrow tips in Guyana in 1595. By experiments with curare Bernard initiated the modern distinction between neural and muscular paralysis.[13,14] In the curarised frog, he found that the muscle when directly stimulated retained its contractility; but when its nerve was stimulated no muscular contraction ensued. But, in the frog in which one leg was protected from the curare by a vascular ligature, the sensory nerves were not affected by curare.

> 'I finally reached this general proposition, that curare causes death by destroying all the motor nerves, without affecting the sensory nerves.'

This was the first demonstration of the selective action of curare on nerves. If the animal survived, the paralysing effects of curare would fully recover. This led to its use as a muscle relaxant. However, he failed to implicate the neuromuscular junction; Alfred Vulpian (1826-1887) showed that curare acted on the motor endplate that had been described by Kühne. These studies led Bernard to study asphyxia and anaesthetics. He also showed that spinal reflexes were initiated by excitation of sensory nerves without involving consciousness, but acted on motor nerves through the spinal cord. Vulpian confirmed this in experiments on decapitated salamanders and frogs.[13]

Milieu intérieur

Bernard's numerous experiments caused him to recognise a *Milieu intérieur*, a phrase that he coined to refer to the extra-cellular fluid environment, and its physiological capacity to buffer changes, to ensure protective stability for the tissues and organs of living organisms. He wrote:

> ...The blood constitutes an actual organic environment, an intermediary between the external environment and the (internal) living molecules, which cannot safely be brought into contact with their external environment...

He believed that all organs liberate into the tissue fluids special substances that maintain a physiological equilibrium of the "milieu intérieur." It established his concept of a stable balance of blood components, akin to his sympathetic- parasympathetic neural equilibrium. This notion opposed the old theory of "vitalism".[14] He said:

> "La fixité du milieu intérieur est la condition d'une vie libre et indépendante".[15]

This remains the underlying principle of homeostasis. Walter Bradford Cannon (1871-1945) coined the word homeostasis in 1926:[16] a self-regulating process by which biological systems tend to maintain stability while adjusting to conditions that are optimal for survival.

Scientific concepts in Experimental Medicine

Claude Bernard's historic role was to demonstrate the experimenter's need for a hypothesis to be either confirmed or refuted by the results of experiments.

Failing health after 1860 enforced time for leisure and reflection, out of which would come his masterpiece, *Introduction à la médecine expérimentale* (1865).[3] In this philosophical exposition he describes what makes a scientific theory good and what makes a scientist important: a true discoverer. Unlike many scientists, Claude Bernard, averse to flimsy conjecture, wrote about his own experiments and ideas.[2] He had developed and established the principles and practice of what is now accepted as the scientific method in medical research. In this fundamental approach he towered both over both his ancestors and contemporaries. Like Sherlock Holmes his method was of scrupulous observation and logical deduction. Amongst many memorable quotations his writings disclose:

- What makes a scientist important, he states, is how well he or she has penetrated into the unknown.
- Observable reality is our only authority.
- Experimental science is a constant interchange between theory and fact, induction and deduction. Induction, reasoning from the particular to the general, and deduction, or reasoning from the general to the particular, are never truly separate.
- The "philosophic spirit" is always active in its desire for truth. It stimulates a "kind of thirst for the unknown" which ennobles and enlivens science.

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'Neurological literature': Hyperkinetic motor perseverations

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Alexander Romanovich Luria (1902-1977) was one of the most celebrated neuropsychologists of the 20th century, noted perhaps particularly for his work on frontal lobe functions. Reading a volume dedicated to his legacy,[1] I was struck by a chapter describing the Executive Control Battery (ECB), developed by Luria's pupil Elkohonon Goldberg and based on Luria's studies.[2] Although not familiar to me as such, clearly the ECB has influenced other tests of executive function, such as the much briefer Frontal Assessment Battery (FAB)[3] (this has been used in some of the clinical work undertaken in Liverpool, either as the main focus of interest[4,5] or as comparator[6]).

ECB consists of four subtests, of which the first is the Graphical Sequences Test. This was designed to elicit perseverations, of which four types are described. The first of these, hyperkinetic perseveration, is described thus:

> Hyperkinetic perseveration ... is defined as an inability to stop a single elementary graphomotor component such as drawing a circle or straight line. ... Here the patient literally continues to draw a circle or straight line over and over.[7]

This account put me in mind of a possible literary example of this phenomenon, a character drawing repeated circles encountered in Joseph Conrad's 1907 novel *The Secret Agent*.[8] (Spoiler alert: if you have read this far and plan to read further, what follows discloses some of the key plot features of Conrad's novel.)

Adolphe Verloc, the titular "secret agent", lives in Soho with his wife, Winnie, her mother, and her brother, Stevie. The latter is "a terrible encumbrance", "delicate and, in a frail way, good-looking too, except for the vacant droop of his lower lip" (ref. 8, p. 7). Although he has apparently learned to read and write he is not able to sustain work, for example as an errand boy, although he "helped his sister with blind love and docility in her household duties" (9). Indeed his most frequent descriptor is docile or docility (47,126,136,182), but "In the face of anything which affected ... his morbid dread of pain, Stevie ended by turning vicious" (134). His future is a source of concern to his mother and sister. Evidently he has a limited verbal output, but feels deeply for the sufferings of poor people and animals. In addition:

> His spare time he occupied by drawing circles with compass and pencil on a piece of paper. He applied himself to that pastime with great industry, … (9)

At a meeting of Verloc's small circle of anarchists, they notice:

> … the innocent Stevie, seated very good and quiet at a deal table, drawing circles, circles, circles; innumerable circles, concentric, eccentric; a coruscating whirl of circles that by their tangled multitude of repeated curves, uniformity of form, and confusion of intersecting lines suggested a rendering of cosmic chaos, … (36)

Later, however, Stevie's behaviour changes:

> … when discovered in solitude [Stevie] would be scowling at the wall, with the sheet of paper and the pencil given him for drawing circles lying blank and idle on the kitchen table. (148)

This change is a marker of (or metaphor for?) Verloc's increasing influence over Stevie, culminating in his inducing (radicalising?) his brother-in-law to perpetrate a bombing in Greenwich Park, notionally on behalf of the anarchists. This goes wrong, the bomb explodes before being left, and Stevie is blown to pieces.

The "idiot character as gullible bomber" is picked up on in Patrick McDonagh's cultural history of idiocy (ref. 9, especially at pp. 310-8), which examines the "symbolic work of idiocy in this discourse" (23). McDonagh suggests that Stevie's "mystical circles replace language" (317) and that "the novel's conflicting ideological positions lie ... in the eternal chaos of Stevie's circles" (318). The novel itself was based on an 1894 incident, similar in many respects, including the assertion that the bomber was an "idiot".

Is any medical explanation of Stevie forthcoming? From within the text itself, we have this opinion from Comrade Alexander Ossipon, "- nicknamed The Doctor, ex-medical student without a degree", who lectures to working-men's associations on the "socialistic aspects of hygiene" (ref. 8, p. 37), i.e. eugenics (ref. 9, p. 315). Observing Stevie drawing his circles in the kitchen, Ossipon opines that he is "typical of this form of degeneracy", and that "It's enough to glance at the lobes of the ears. If you read Lombroso - " (ref. 8, p. 37). Another anarchist, Karl Yundt, then promptly rubbishes the views of Lombroso.

With the benefit of hindsight, we might perhaps suggest that Stevie has some form of learning disability (without fits; ref. 8, p. 8), although if he has acquired the ability to read and write and draw with compasses this may be mild. Another possibility is that repeated head trauma may have contributed to his difficulties, since it is reported that his father called him a "slobbering idjut" and his disciplinary measures included physical blows when he was impatient with his son (8,140,192). Learning disability or mild traumatic brain injury might produce evidence of executive dysfunction, as indicated by hyperkinetic motor perseveration.

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Update on 2017 NICE guidelines for the management of Parkinson's disease (PD)

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The 2006 NICE guidelines have been updated this year, and as per the 2006 document, the guideline advises on the care of people with Parkinson's but does contain a number of changes and new sections including the management of Impulse Control Disorders and patient nutrition, and also provides more detailed advice on the palliative care of PD patients.

Summary of Recommendations

PD diagnostics
Clinicians are not to use SPECT, PET, MRI and MR volumetry in the diagnosis of Parkinson's disease. These modalities remain at the disposal of those undertaking PD clinical trials. Levodopa challenges, amorphorhine challenges, and smell tests are also not to be used.

Neuroprotection
Physicians are not to prescribe vitamin E, Coenzyme Q10, dopamine agonists and MAO-B inhibitors as neuroprotective agents.

Motor Symptoms

First line Treatment
Clinicians are advised to offer levodopa as first line therapy to those patients whose motor symptoms impact their quality of life. MAO-B inhibitors, DA agonists and levodopa can be considered for patients whose quality of life is not impacted by PD. Ergot derived dopamine agonists are not to be offered first line.

Patient communication
Information should be given in oral and written form to patients and their carers.

The possibility of impulse control disorders, psychotic symptoms, excessive sleepiness and sudden onset of sleep with dopamine agonists should be discussed, and documented as having been communicated to the patient.

Motor complications
Clinicians are advised to initiate a non-ergot dopamine agonist as adjunctive therapy. Ergot derived therapies should only be considered in patients who are inadequately controlled on the former.

Amantadine can be considered in patients with dyskinesia who are inadequately managed on existing therapy.

Impulse control disorders (ICDs)
Clinicians are advised that DA agonist therapy, a history of impulsive behaviour, alcohol consumption and smoking present a higher risk of developing an ICD which can arise at any disease stage. Patients must be told about the different ICDs, who to contact if an ICD develops and that if an ICD does arise, that their DA treatment will be reviewed and may be altered. This discussion should take place at each review and particularly when any modifications to therapy are made.

Written and oral information on ICD s must be given to patients and documented.

Management of ICDs
If a patient develops an ICD, its impact on patient life, possible treatment, including reducing or stopping dopaminergic therapy should be discussed. Dopamine agonists should be slowly reduced first monitoring for improvement in the ICD and any symptoms of dopamine agonist withdrawal. Specialist CBT is also recommended if reduction in dopamine therapy is ineffective.

Non motor symptoms

Sleep
Modafinil is only recommended for the treatment of excessive daytime sleepiness once reversible causes have been identified and treated.

RBD
Clonazepam or melatonin can be considered for the treatment of RBD.

Nocturnal Akinesia
Either levodopa or oral dopamine agonists can be considered for the treatment of nocturnal akinesia. If these are not effective, physicians should consider rotigotine.

Orthostatic Hypotension
Review of causes of hypotension such as antihypertensives, dopaminergics, anticholinergics and antidepressants is advised. Where treatment is required clinicians should use midodrine. If midodrine is contraindicated or not tolerated fludrocortisone can be started.

Depression
Clinicians are now referred to the separate NICE guidance on management of depression in chronic physical health problems.

Hallucinations
The first line management of hallucinations in PD is a reduction in medication. Quetiapine is now recommended for use in patients without cognitive impairment and clozapine is recommended if standard therapy is ineffective. Olanzapine should not be offered.

PDD
Cholinesterase inhibitors should be offered to patients with mild to moderate PDD and can be considered in those with more severe disease. Memantine should only be considered if cholinesterase inhibitors are contraindicated.

Drooling
Pharmacological intervention can only be considered if non pharmacological approaches such as SALT are unavailable or unhelpful. Glycopyrronium can then be considered and if ineffective, patients can be referred for Botulinum toxin type A. Other anticholinergics (such as atropine drops) are only recommended if there is minimal risk of cognitive side effects.

Physiotherapy and OT
The 2017 guideline suggests that physiotherapy be offered to patients with PD who are experiencing balance or motor function problems, and OT offered to those who are having difficulties with ADLs.

Nutrition
This is a new section and physicians are advised to refer patients to a dietitian for specialist advice. Patients are advised to take their meal with the highest protein content towards the end of the day but a total reduction in protein intake should be avoided. Vitamin D supplementation is now recommended, whereas creatine supplements are not to be offered.

Surgical management of PD
The content on specific target for DBS has now been removed and clinicians are now advised to consider surgery only in cases where best medical therapy has failed.

Palliative Care
This advice has been expanded and clinicians are to offer patients and their carers oral and written information on disease progression, adverse effects in advanced PD, advanced care planning, options for future management, as well as information on all the available services for their care.

Conclusion
The NICE guideline on PD offers evidence based guidance on the management of patients with PD, provides clear guidelines and standards for the management of the disease and will allow for the organisation and delivery of optimal care to patients throughout the UK.

Highlights from the National Epilepsy Nurse Meeting, sponsored and organised by Veriton Pharma (sponsorship details on page 19)

CHALLENGING THE STATUS QUO

28-29 June 2017, St Johns Hotel, Solihull, West Midlands

Chairman: Dr Rohit Shankar

The Epilepsy Specialist Nurse (ESN) plays a critical role in the management of epilepsy, including in children and young adults. This well-attended national ESN meeting considered the development of the ESN role to meet changing demands in today's NHS, as well as the treatment of status epilepticus and complex prescribing in epilepsy. With lively interactive workshops, the meeting also provided the opportunity to share best practice, particularly in the emergency community management of epilepsy.

Pitfalls of current practical prescribing in epilepsy

Error is part and parcel of the clinician's life. Outlining the pitfalls of current practical prescribing in epilepsy, meeting chairman Dr Rohit Shankar (Consultant in Adult Development Neuropsychiatry, Truro) stressed that while errors cannot be eliminated, every conscious effort must be made to reduce them.

A recent GMC Report[1] suggested that as many as one in 20 prescriptions written by GPs contain an error, and around one in every 550 prescriptions a serious error. Epilepsy involves complex prescribing in people who may have other chronic mental, neurodevelopmental or physical co-morbidity, yet the long-term consequences are often given little consideration. In particular, prescribing of 'rescue medication' requires understanding of a multifaceted system where family and carers from diverse settings administer drugs to vulnerable individuals.[2]

To ensure consistency, checks and balances are vital to take account of the clinician, patient and environmental factors which, individually and together, can impact on prescribing risk and errors. Treating the patient with epilepsy can affect family dynamics, and the clinician must be aware of this. In assessing risks and benefits there must therefore be a partnership between the clinician and the patient/family, rather than a top-down approach.

When buccal (oromucosal) midazolam is prescribed as rescue medication, there is no obvious direct mechanism to reassure the specialist that the drug is used safely and correctly. People (including carers) vary, as does the level of training they receive. Making everyone aware of safety is vital. A holistic plan with appropriate ongoing training will ensure the competence of everyone involved and self-empowerment is key. As Dr Shankar says, safety is everyone's business. We can't just manage the epilepsy. We must look at it holistically.

> "Safety is everyone's business. We can't just manage the epilepsy. We must look at it holistically."
> **Dr Rohit Shankar**

Guidelines for treatment of status epilepticus

Discussing the latest guidelines for treatment of status epilepticus, Professor Matthew Walker (Department of Clinical Experimental Epilepsy, UCL Institute of Neurology, London) noted that the definition of status epilepticus was previously accepted as seizures lasting 30 minutes and longer. Treatment should begin sooner however, and early, aggressive treatment of seizures lasting longer than 5 minutes is vital to avoid long-term consequences and improve prognosis.[3] This has resulted in a reappraisal of the definition of status epilepticus.

Status epilepticus is not uncommon. Incidence is between 10 and 60 per 100,000 person years,[4] with the higher incidences occurring in poorer populations. Over half of patients with status epilepticus have no prior history of epilepsy, and it is often triggered by an acute illness. In children, without a prior diagnosis of epilepsy, the major cause is infections accompanied by fever. In adults, without a prior diagnosis of epilepsy, the main causes include stroke (particularly in the elderly), hypoxia, metabolic disorders and alcohol intoxication or withdrawal (the most common cause in young adults).[4,5] In people with a diagnosis of epilepsy, status epilepticus is often precipitated by antiepileptic drug withdrawal.

Pseudostatus is common and can be misdiagnosed as status

epilepticus, particularly in A&E. Yet non-convulsive status epilepticus is underdiagnosed in A&E because the symptoms and signs are often subtle (e.g. clouding of consciousness, confusion).

Intramuscular midazolam for injection was superior to intravenous lorazepam in a study of status epilepticus treated by paramedics,[6] probably because venous access can be an issue and intramuscular dosing is more easily administered. Midazolam is easy to administer, has a rapid distribution half-life (6 minutes) and a rapid elimination half-life (2-4 hours), meaning buccal midazolam is preferred for community use.

In the only recent guideline for the treatment of status epilepticus (from the American Epilepsy Society) benzodiazepines are the initial therapy of choice.[7] For hospital and paramedic administration, intramuscular midazolam for injection or intravenous lorazepam or diazepam is recommended.[7] In the community, NICE (UK) recommends this should be buccal midazolam.[8]

Status epilepticus not responsive to intravenous diazepam or lorazepam should be treated with intravenous phenytoin, valproate or levetiracetam in adequate doses. If the person remains in status epilepticus, then neuronal death and physiological compromise may be occurring and anaesthesia is required in ITU.

> "Buccal midazolam is the preferred treatment for community use."
> **Professor Matthew Walker**

Promoting the case for the Epilepsy Specialist Nurse

According to a report by Epilepsy Action, at least 60% of people with epilepsy (nearly 280,000 in the UK) will require ongoing access to an adult, paediatric or learning disability ESN.[9] Michelle Knight (Epilepsy Specialist Nurse, Dorset Epilepsy Service) highlighted the value of the ESN in delivering a high standard of care, avoiding admissions, reducing dropout rates, freeing up consultant time, liaising with other services, and providing community services, advice and education, and a point of contact and consistency. (See Figure 1)

As one of two Dorset Epilepsy Service ESNs, Michelle has seen her role change over time to meet the demands of a growing case load. With a population of 765,700 (a high percentage aged over 65) Dorset has 8000 cases of 'active epilepsy' in a large and diverse rural area where public transport is limited. Meeting the brief of covering Dorset's three main hospitals, with six-monthly reviews in clinic, proved challenging. Home visits and rescue medication training were time consuming, administrative delays were frequent and the percentage of DNAs high.

To tackle these issues the MyCareCentric Epilepsy programme is currently being piloted by Poole Hospital and the Dorset Epilepsy Service. This collates patients' healthcare data, captures lifestyle patterns via a wearable device and uses a smartphone app to provide clinicians with real-time information. Other initiatives include monthly clinics held at local GP surgeries and using home telemetry, both well received by patients.

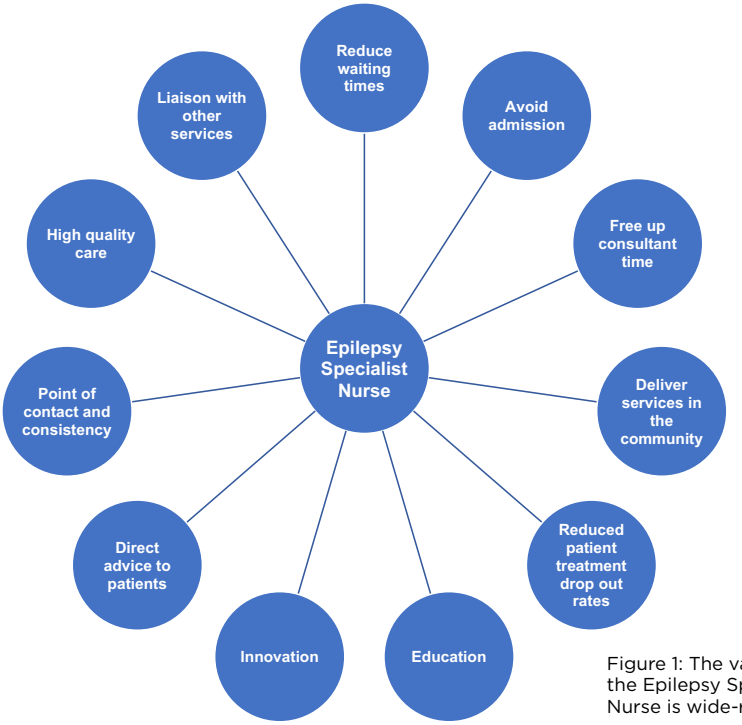

Figure 1: The value of the Epilepsy Specialist Nurse is wide-ranging

Providing ongoing training to first responders and paramedics has also proved beneficial in reducing hospital admissions. Regular training has been set up for healthcare professionals across Dorset, with excellent take up. Study days for GPs have also been successful, as well as basic epilepsy awareness days held around Dorset for patients' friends and family. These include specific rescue medication training.

Michelle's take home message is that communication is vital – share ideas with others and talk to other professionals. She also urges thinking outside the box. Look at your patient group to see what works and what doesn't. Above all, don't be afraid to challenge the norm.

> "Don't be afraid to challenge the norm!" **Michelle Knight**

Summary

In closing the meeting, Dr Shankar stressed that creating innovative programmes like those discussed seems straightforward, particularly with ever-advancing technology. However, the fundamental issue is cost along with many ethical questions in deciding who should get what. The value of epilepsy specialist nurses is clear, as is the case for rescue medication in the community.

Epistatus® 10 mg Oromucosal Solution Midazolam was granted UK Marketing Authorisation in April 2017 for use in the treatment of prolonged, acute convulsive seizures in children and adolescents aged 10 to less than 18 years, who have been diagnosed with epilepsy. Ready-to-use Epistatus pre-filled syringes are now available to prescribe.

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EDM-1035-2017
Date of preparation: October 2017
Prescribing information can be found on page 18

Oxford Specialist Handbooks in Neurology – Stroke Medicine – Second Edition

When asked by your boss, 'Would you like to review a book? You'll get a free copy,' how could you refuse? And so, I had my first experience of reading a textbook cover to cover. 596 pages later, I had learnt a few things – how to say 'no' in the future … and quite a lot about Stroke Medicine too!

This textbook is written by Hugh Markus – Professor of Stroke Medicine, Anthony Pereira – Consultant Neurologist and Geoffrey Cloud – Consultant Stroke Physician, representing the three key areas of expertise in Stroke – academic neuroscience, clinical neuroscience and internal medicine. It is aimed at Stroke Trainees and Stroke Consultants (from Neurology and General Medicine backgrounds). As a Geriatrics registrar, I work regularly in Stroke and unsurprisingly found the book to be very instructive. For those without a specialist interest in Stroke, however, the authors portray Stroke, its prevalence, its diagnosis and the management of its long term sequelae, in the context of the NHS as a whole.

Authors: Hugh Markus, Anthony Pereira and Geoffrey Cloud
Published by: Oxford University Press
Price: £39.99
Pages: 144
ISBN: 0199218773

Reviewed by: Daniel Burke, Specialist Trainee in Geriatric Medicine, University Hospital Aintree, Liverpool.

The textbook is full of useful facts, easy to read and good illustrations (such as those intended to show patients in relation to risk factors). Depending on how much you need to know, the authors provide ample information but also cover the basics in easy to follow language. Those looking to know it all can read on; those who need to know the basics can access what they need. The authors break down some very complex topics – neuroanatomy and 'stroke syndromes' – into manageable chunks, providing good revision material for exams and a good reference point for a difficult topic.

As well as describing the pathology and pharmacological treatment of stroke, the textbook covers history-taking and examination skills. This highlights the importance of a thorough history to make the diagnosis, and to identify risk factors and anticipate future problems. Clear definitions of clinical findings are given, along with the methods for recognising them. The section on the cranial nerves is especially strong in this regard.

There are real-life examples of acute stroke images, alongside some MR Physics and explanations of what specific MR sequences signify. I feel this has given me more confidence to ask the right questions when working with radiologists, especially 'out of hours': may we have gradient echo, please? I will also know when to drop in the transcranial Doppler option; that machine is in the corner of the stroke unit, but I've never seen it turned on. On a more basic level, the authors also explain the rationale for traditional tests in the acute setting, for example ECG for old Myocardial Infarction, Left Ventricular Hypertrophy or Atrial Fibrillation or Chest X-Ray for Pneumonia or Congestive Cardiac Failure. These may be critical data but if the tests are done without thought, the findings may not be given their due weight. Where relevant, as in the use of ASPECTS to assess CT, the authors provide links to websites where you can practise.

I often deal with intracranial bleeds and always refer to the neurosurgeons. Cases are discussed, and either managed conservatively or transferred for urgent neurosurgical intervention. I am therefore comfortable to undertake conservative management, but largely unaware of procedures and outcomes in the neurosurgical group. The chapter 'Cerebral Haemorrhage' clearly explains all the options from medical management such as Nimodipine in Subarachnoid Haemorrhage, to endovascular and surgical intervention in intraparenchymal bleeds. This has given me some perspective of what's available 'out there'.

The textbook cites a multitude of trials and other studies relating to different areas of treatment. Where formal evidence is lacking the authors lend their authority to pragmatic approaches, offering reassurance to front-line clinicians uncertain as to when to anticoagulate for atrial fibrillation following acute stroke, when to perform carotid endarterectomy following transient ischemic attack and so on.

As a doctor on a stroke unit, my input can often seem minimal as, following the diagnosis and initiation of treatment, the input is mainly from physiotherapists, occupational therapists, speech and language therapists, dieticians and nursing staff. The chapter "Recovery and Rehabilitation" recognises the crucial importance of each player in the clinical team.

The authors have a holistic approach to management of stroke, from thrombolysis and thrombectomy to managing post-stroke depression. They do cover the critical moments in the life of an on-call 'med reg' (and the patient) such as seizures or severe hypertension in the acute stroke. However, clearly laid out lists of pros and cons of thrombolysis would have been useful along with flow charts on how to manage specific acute problems. That being said, perhaps that very specific guidance of this kind has to be sought from locally determined protocols.

Overall, this textbook is a great source of information, for trainees and established clinicians working in the Stroke field – whether as Geriatricians, Acute Medicine specialists or Neurologists. If only I could be sure of recalling the key information at the key moment, success would be guaranteed. In any case, I am comforted by having an easy point of reference for all my queries on Stroke.

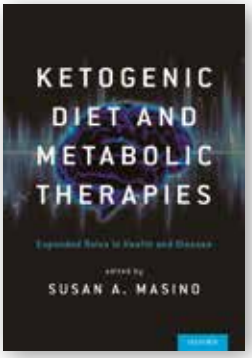
Ketogenic diet and metabolic therapies: expanding roles in health and disease

'Ketogenic diet and metabolic therapies: expanding roles in health and disease' by Masino, presents a comprehensive review of this quickly developing area of nutrition and metabolism.

The authors, world experts in their research fields, begin with the robust base for the diet's use in the management of refractory epilepsy before branching out into novel applications of the diet; including cancer, autism spectrum disorders, aging and spinal cord and traumatic brain injury. The book goes beyond similar texts in the area, discussing areas of increasing popularity within public, clinical and research communities.

The author also proficiently combines dietary evidence with basic science, discussing mechanisms underlying the antiepileptogenic benefits and pathophysiologies other than epilepsy; concluding with the role of ketogenic diets as metabolic alternatives in health, fitness and disease.

Sceptics should expect nothing less than the title describes. Those wanting to dip their toes into ketones - wondering what it is all about, and those looking to branch out into the potentially vast new applications of the diet, should expect a worthwhile, enthusiastic read!



Edited by: Susan Masino (Ed) • **Published by:** Oxford University Press • **Price:** £87.00 • **ISBN:** 0190497998 • **Pages:** 424pages
Reviewed by: Kirsty Martin-McGill, Research Dietitian, The Walton Centre NHS Foundation Trust, Liverpool, UK.

Cognitive Behavior Therapy for Insomnia in Those with Depression – A Guide for Clinicians

This book explores the relationship of sleep with depression and the treatment of insomnia by means of cognitive behavioural therapy (CBT-I). Although aimed at clinicians, the volume's clear language potentially makes it an interesting read for non-professionals too.

The book highlights the significance of insomnia in depression and the importance of its assessment and management, using cognitive behavioural therapy. There are 10 chapters that systematically and progressively explain the assessment and stepwise treatment of CBT-I. Worksheets and pro formas are provided separately, in 11 appendices, to help the reader understand the concepts and the processes of the treatment.

In the initial chapters, the authors explain the neurobiological basis of sleep. They shed light on the biological and psychological factors that render a person vulnerable to insomnia, and may perpetuate the problem. What might have been rather dense is, in fact, very clear and concise!

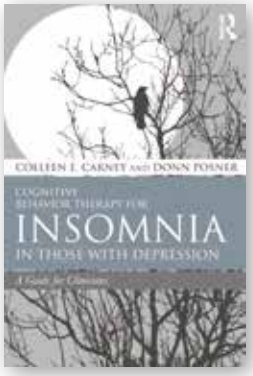
A comparison of pharmacological treatments and CBT-I is made later in the book. Though brief, it is sufficient to allow clear distinctions as to the merits and drawbacks of each approach.

The various methods of delivering CBT-I have also been listed, as well as contra-indications for the use of CBT-I. These should help clinicians to identify the right candidates for the treatment in question.

The authors highlight some common barriers and constraints in the therapeutic process that a therapist or client may face, and suggest strategies to counter these. An effective method utilised to illustrate this and other concepts is to frame them as conversations, taking place between therapist and client. They also provide a case study to show the practical application of CBT-I, which is especially useful.

Throughout, an evidence-based approach is employed, with references provided, allowing for further reading to be easily identified, if so wished.

The book is short, and makes for light reading. Those for whom sleep psychotherapy features within their professional repertoire may be few, among ACNR readers. However, ACNR readers who encounter low mood and poor sleep in their practice must be very many. Any of the latter interested in helping their patients, without resorting to pills, might benefit from a look at Carney and Posner's book.



Authors: Colleen E Carney and Donn Posner
Published by: Routledge
Price: £90
ISBN: 978-0-415-73838-5
Pages: 206

Reviewed by: Dr Salman Kazim Siddiqui, Specialist Trainee in Old Age and General Adult Psychiatry, Health Education England, North West, UK.

Neurological Advocacy Service is two years' old

Advocacy Centre North's advocacy service for people with neurological conditions in Newcastle and Gateshead has completed its second year. Thanks to funding from the Big Lottery Fund we have been delivering this pioneering service, which is the first and only specialist advocacy service in the country for people with neurological conditions, including stroke, acquired brain injury, Parkinson's, Multiple Sclerosis, muscular dystrophy, Motor Neurone Disease and autism.

Advocacy Centre North
Shoulder to shoulder with you

The service is provided using both paid and volunteer advocates who receive specialist training delivered in partnership with Northern Neurological Alliance. Their specialist knowledge of this client group and their needs significantly enhances the service. The trained advocates have offered Independent Advocacy on a wide range of issues ensuring people with neurological conditions have access to the services that they need and that they communicate their wishes in often challenging circumstances.

During the first year we set up the service in a way that ensures it meets the needs of people with neurological conditions and the service:

- Provided 2358 hours of direct advocacy support to 69 people
- Recruited and trained 12 new volunteer Advocates

100% of clients who returned questionnaires said their advocate was "excellent".

During the second year we are proud to say that the service:

- Provided 3835 hours of direct advocacy support to 111 people
- Recruited, trained and supervised 44 volunteer advocates
- Supported people with 20 different neurological conditions, some with multiple conditions and some with no diagnosis as yet.

Our Neurological Advocacy Service is being externally evaluated by Barefoot Research and Evaluation. An interim report covering the first 18 months of the service has been published. It includes case studies, statistics and recommendations.

The report says: "After 18 months, the project has become well established with two highly specialised neurological advocates and a developing team of trained volunteers. The service is working with a diverse caseload with a number of complex cases referred in from a range of sources, including self and family. They are developing as a centre of expertise in Newcastle and Gateshead for neurological advocacy services. The client need is showing some early differences to other advocacy services, such as higher number of cases per referral and an increased complexity to those cases. These differences will be monitored as the project and evaluation progresses."

To download a copy of the evaluation go to http://www.cvsnewcastle.org.uk/advocacy-centre-north/community-services or contact us for a paper copy.

Advocacy Centre North is part of Newcastle Council for Voluntary Service. Information about Advocacy Centre North and how to refer to this and our other services is available at: www.advocacycentrenorth.org.uk

BIG LOTTERY FUND
LOTTERY FUNDED

Newcastle Council for Voluntary Service

Things I wish I knew at the start of my PhD

Peter Jenkins, BMBCh MA,
has just completed a PhD at the Cognitive and Clinical Neuroimaging Laboratory, Imperial College London and has returned to clinical training at St George's Hospital, London.

Stepping out of clinical work to undertake a PhD can be a daunting challenge. At this stage of their career, few clinicians have sufficient experience of research to know what to expect, how to maximise the opportunity and to recognise, let alone avoid, the potential pitfalls that present themselves during a research degree. In mitigating this inexperience, I think it is crucial to choose all of the elements of your project – the project content, your supervisor and the research environment – very carefully.

These are very personal choices but it is worth bearing a few salient points in mind. PhD projects vary enormously in their detail and it can be overwhelming when trying to decide what to do. A few simple questions can help to narrow these choices down. Firstly, would you like to explore the basic science, possibly using molecular or genetic techniques; or would you rather do a more translational project, such as a clinical trial? This decision may be swayed by previous experience; if you learnt a technique during your undergraduate degree you may feel more comfortable continuing along the same path. Secondly, is there an area you are particularly interested in? Undertaking research in a particular specialty will automatically guide your future career in that direction, although this is by no means a strict rule with plenty of people taking a different path after research. Finally, projects can differ in the degree to which they have been pre-organised. Some are fully planned and 'ready to go', whilst others have no pre-determined structure and are hence more explorative. Pre-planned projects have several benefits; their scope and deliverability are evident from the outset, some of the practical organisation may be in place already and it is likely that the underlying hypothesis has been deliberated carefully and deemed timely and relevant. However, this prescriptive nature may not appeal to those wanting greater autonomy over the direction of their research and some can find it restrictive.

Supervisor and environment selection are also important. Again, these are a matter of individual choice but I would suggest a few factors to consider. First, think carefully about the type of supervisor you want. Do you want a supervisor who is very involved and monitors everything you are doing on a weekly, or even daily, basis? This is good in terms of support but may prove too constricting for some. You should explore these questions: ask previous PhD students about their experiences as well as interviewing members of the existing research group and the supervisor themselves – after all, it is in no-one's best interest to have a poor relationship between student and supervisor! Secondly, ensure that your supervisor in particular and the group in general are productive. This can be checked easily through literature searches for the group's recent publications as well as discussion with previous PhD students to ensure that they completed their degree. Finally, don't ignore the rest of the research group. Helpful post docs are worth their weight in gold and will often be the person or persons to whom you will direct most of your day-to-day questions.

Having selected your project and supervisor and with funding in place, the enjoyable part begins! However, be prepared for considerable change: for me, leaving the wards and regimented clinical work to enter the research world was a slight shock to the system. Having spent years as a slave to a pager, rosters and rigid clinical duties, sudden autonomy and freedom may feel very strange. But, be warned, a different kind of discipline is essential. Do not get carried away with your new-found independence and freedom from rigid timetables because three years in the research world flies by. Most PhD students will describe their final year as a hectic rush to the finish post and the more you can achieve early on the better. First, set targets with clear time constraints. This will assist you in remaining on track to complete everything you want before the end of your research project. Secondly, the best single piece of advice I received was to write a review paper in my first year. This is helpful in several ways; not only does it guarantee that you understand the literature for your project but, if done well, it will also provide an early publication (a huge morale boost) as well as being used to form the basis of your PhD introduction. Year one may seem very early to be considering starting to write your thesis but I assure you that at the end of year three, you will be very pleased to have this ready-made introduction to your final thesis.

As the PhD progresses it can become disheartening if things are not progressing as quickly as you'd hoped. Ethical and local approval processes can take a year to cement in place – emphasising the benefit of a project that has already been approved and is ready to start. If bureaucracy is moving slowly, make the most of this 'down-time': explore other data from your group that can be analysed in order to get your publications up and running, ensure the skills you will need once the project starts are up to speed (e.g. brush up on your statistics or learn any new essential practical techniques), and finish that review paper over which you continue to procrastinate! Regular meetings with your supervisor and disciplined target-setting are also valuable during this time to keep you on track to complete. Most importantly, try not to get demoralised – delays are almost inevitable and, invariably, things do not all fall into place until the final year.

If you ask most PhD students when they were busiest, most will report the final year is a mad rush of data analysis, paper publication and thesis writing and early preparation of your thesis introduction as well as proactive and opportunistic analysis of other data can alleviate the stresses of the 'last-minute rush'. Ideally, you should finish your thesis prior to returning to clinical work. This does not always

happen but writing a thesis while holding down a full-time clinical job is a difficult task and you will be thankful if the bulk is written before you step back on the wards. Publications, posters and presentations will inevitably linger on after the PhD. Be prepared for this and see it as a positive feature rather than an irritation; apart from anything else it will keep you in touch with the research world.

These are personal thoughts and other PhD graduates will undoubtedly have different experiences. Personally, I found my research time immensely rewarding and would encourage anyone interested to explore the opportunity. There will always be unforeseen obstacles, but by being organised and writing early you will be better equipped to deal with these hurdles as they arise.

Table of useful resources:

Topic	Useful websites/resources	Description
Literature appraisal	www.ucl.ac.uk/ich/support-services/library/training-material/critical-appraisal	There are many websites, books and journal articles discussing this topic, which is undoubtedly a key PhD skill. I have provided a simple introductory article that has links to more extensive reviews on this topic.
Thesis writing	LaTeX – (www.latex-project.org)	Some people swear by using LaTeX for writing a thesis. It is a typesetting program that involves a steep learning curve, but once mastered affords more flexibility than the more common word processing programmes.
Statistics	R – (www.r-project.org)	R is an open source statistics and graphics programme. There is a great online community answering questions about how to use it including www.r-bloggers.com. If you prefer textbooks Discovering Statistics Using R by Andy Field is a good option. It can also be used to make excellent plots.
Referencing	Reference managing software (numerous options including EndNote, Bibdesk, Mendeley)	Managing and referencing the huge number of papers that you will read is vital. There are numerous reference managers around and I have listed a few. Bibdesk in particular can be linked to LaTeX and is open source. They all provide a similar service but whichever one you choose, make sure you spend some time learning how to maximise its functions as this will save you a great deal of time.
Illustrations and figures	Adobe Illustrator	Adobe Illustrator is not free but is fantastic for creating amazing figures and illustrations. There are numerous online tutorials, including from Adobe themselves https://helpx.adobe.com/uk/illustrator/tutorials.html

To list your event in this diary email Rachael@acnr.co.uk by 6th January, 2018

NOVEMBER

Specialist Multiple Sclerosis Masterclass – MS Academy
22-24 November, 2017; Sheffield, UK
info@neurologyacademy.org
T. 0845 338 1726 – Module 2: 15 June 2018

Palliative Care MasterClass
27 November, 2017; Manchester, UK
www.neurologyacademy.org

DECEMBER

Encephalitis Conference 2017
4 December, 2017; London, UK
E. conferences@encephalitis.info

2018 – JANUARY

Non-Motor Symptoms Roadshow – Parkinson's Academy
Thursday 18 January, 2018; Halifax Hall, Sheffield, UK
http://parkinsonsacademy.co/courses/nms-roadshow/

16th Annual King's Neuromuscular Symposium
26th January 2018; London, UK
E. knmsymp@gmail.com or ow.ly/OL0C30fF24S to register.

FEBRUARY

Society for Research in Rehabilitation Winter Meeting and 40th Anniversary
6 February 2018, The Watershed, Harbourside, Bristol BS1 5TX
E. patricia.dziunka@srr.org.uk
www.srr.org.uk

10th World Congress for NeuroRehabilitation – WCNR2018
7-10 February 2018; Mumbai, India
E: traceymole@wfnr.co.uk
www.wcnr2018.com

2018 ILAE British Chapter Clinical Epilepsy Course for Junior Doctors
15 February, 2018; Queen Square, London, UK
https://ilae-2018course-clinical-epilepsy-junior-doctor.eventbrite.co.uk
E. members@ilaebritish.org.uk

JUNE

Parkinson's Advanced MasterClass – Parkinson's Academy
12-14 June, 2018; Halifax Hall, Sheffield
http://parkinsonsacademy.co/courses/advanced-masterclass-course/

MS Non-specialist MasterClass – MS Academy
26-28 June, 2018; Halifax Hall, Sheffield, UK
http://multiplesclerosisacademy.org/courses/general-ms-masterclass/

SEPTEMBER

Parkinson's Foundation MasterClass – Parkinson's Academy
4&5 September, 2018; Halifax Hall, Sheffield, UK
http://parkinsonsacademy.co/courses/foundation-masterclass-course/

NOVEMBER

MS Specialist MasterClass – MS Academy
21-23 November, 2018; Halifax Hall, Sheffield, UK
http://multiplesclerosisacademy.org/courses/specialist-ms-masterclass/

2019 – APRIL

Festival of Neuroscience
14-17 April, 2019; Dublin, Ireland
https://www.bna.org.uk

JUNE

World Parkinson Congress
4-7 June, 2019; Kyoto, Japan – www.wpc2019.org

Association of British Neurologists autumn meeting 2017

Conference details: October 12, 2017, London, UK. ***Report by:*** Michael Foster, Core Medical Trainee, Royal Brompton. ***Conflict of interest statement:*** None declared.

The Association of British Neurologists autumn meeting was held on 12 October, barely a stone's throw from the National Hospital for Neurology and Neurosurgery. The meeting was well-attended by upwards of 200 delegates, and opened by the ABN president Mary Reilly.

The first session took on an almost accidental theme of neurology absorbing areas of traditionally psychiatric practice. Michael Zandi gave an update on autoimmune encephalitis; he described the unreliability of some autoantibodies, and therefore the renewed importance of the clinical diagnosis. This was highlighted with voltage-gated potassium channel complex antibody: they may be artificially elevated in, for example, snake handlers, with regular exposure to dendrotoxin; testing for LGI1 and CASPR2 would be more reliable. He also outlined the identification of some new autoantibodies, including anti-IgLON5, dipeptidyl-peptidase 6 and neurexin 3 . Finally, he explored the question of whether some first-episode psychosis was actually autoimmune encephalitis, and described the initial stages of an ongoing trial aimed to assess this.

Orla Hardiman proceeded to discuss the future of motor neuron disease (MND), with insights gained from the use of an MND register in Ireland. She described how little progress had been made on developing disease-modifying agents, but underscored how the multiple disease mechanisms underlying MND would be unlikely to uniformly respond to a single agent. She went on to explain how use of the register had identified a higher incidence of psychiatric and developmental conditions in families of patients with MND, including bipolar disorder, autism, suicide and schizophrenia; indeed, amyotrophic lateral sclerosis and schizophrenia had been shown to share some susceptibility genes. The neurological absorption of psychiatry continued!

Nicholas Fox gave an update on dementia, a condition still shared between psychiatry and neurology. Considering the increased uptake of private, home-delivered genetic testing, he offered a reminder of the important susceptibility genes: specifically, ApoE- 4. The search for biomarkers continues, with debate surrounding the relevance of amyloid accumulation before clinical presentation – perhaps Alzheimer's disease can be diagnosed before Alzheimer's dementia; clinical trials are ongoing.

Session 2 began with Anton Emmanuel discussing neurogastroenterology, perhaps another specialty set to succumb to the neurological advance. He described his work in patients with spinal cord injury, and how treatment for bowel function and continence needs to be individualised. It was interesting to learn about the interaction of gut health and psychological stress: the ability of mice to tolerate stress was diminished by elimination of the gut biome, and a restrictive diet increased anxiety and worsened confusion.

Exciting developments in acute stroke care were subsequently presented by Iris Grunwald. She described the development of a mobile stroke unit, including a CT scanner, which is now in use in East Anglia. By effective use of telemedicine and teleradiology, it has facilitated early stroke treatment in 60% of patients referred, versus 4% of those who had to come to hospital. The hope is that this will allow efficient triage to appropriate centres (including need for thrombectomy) and consequently improve outcomes.

The Autumn Lecture was delivered by Gordon Plant, following an enthusiastic citation from Hadi Manji. It was romantically titled 'The Season of Mists and Mellow Fruitfulness of John Keats,' and opened with a reflection on the literary association of autumn with advancing age. As suggested by the title, his preferred metaphor was Keats', where autumn was the time to reap the bounty of previous seasons, which he described both personally and professionally. His recent identification of the phenomenon of smartphone blindness (often misdiagnosed as a transient ischaemic attack) confirmed autumn was indeed a fruitful season.

Session 3 opened with a brief update on the Shape of Training, and was followed by David Bennett discussing neuropathic pain. He used some inherited pain disorders, such as inherited erythromelalgia, to highlight the role of the Nav1.7 ion channel in pain, and in particular speculating whether other as-yet-unidentified mutations in the channel could act as risk factors for neuropathic pain. A recent systematic review had confirmed current management is well-supported by the evidence, but patients often did not reach therapeutic doses.

A fascinating insight into veterinary neurology from Holger Volk of the Royal Veterinary College followed. His presentation focused mainly on seizures and epilepsy, and contrasting the reaction of online audiences to videos of either pets (sympathy) or humans (ridicule) having seizures. He highlighted the continuing use in animals of certain anti-epileptic drugs now unfashionable in human medicine (for example phenobarbital) and how owner preference results in a large number of affected animals going untreated. LGI1 and CASPR2 made a cameo appearance, and Dr Volk closed with a warning on selecting pets for their paedomorphic traits, noting a preponderance of hydrocephalus secondary to dysfunctional skull anatomy.

Alasdair Coles opened the final session with an update on new therapies in multiple sclerosis (MS). Noting the high number of biologics coming to market, he highlighted that the goal of therapy was now improvement in function, rather than slowing of progression. The challenges now surrounded what effect these new therapies have on secondary progression, and ensuring greater access to these therapies. Professor Coles finished by demonstrating how the costs of MS drugs (including non-biologics) had risen steeply in comparison to non-MS drugs, and how none of the trials in support of biologics occurred outside of pharmaceutical companies.

Jon Sussman provided a refresher on myasthenia gravis, reporting improvements in prognosis with earlier immunosuppression. He advocated the use of prednisolone, and encouraged faster rates of dose increases. He also described new data on thymectomy: patients receiving thymectomy were able to maintain remission on lower doses of prednisolone, with a commensurate increase in strength. More patients following thymectomy were able to stop steroids altogether. Dr Sussman recommended use of thymectomy in new generalised myasthenia and in seropositive ocular disease.

The final talk was delivered by Fiona Godlee, editor of the BMJ, titled 'Fewer Tests, Choosing Wisely'. Noting improvements in life expectancy alongside increases in health spending (although much progress was due to public health measures), she contrasted the similarly-increasing levels of over-diagnosis. Features of the phenomenon include an increase in incidence of a diagnosis with stable mortality (as seen with pulmonary embolism); risk factors being called diseases (such as pre-diabetes); and a shift in diagnostic definitions without greater benefit. Commenting on dementia, she explained that the expectation that treating pre-dementia will improve outcomes (described by Dr Godlee as a 'leap of faith') was not yet supported by the evidence. These extra diagnoses could be a burden for patients with no obvious gain. Building on Alasdair Cole's comments, she closed by lamenting the lack of raw data for many of the interventions we use, and argued that drug companies should not be allowed to test their own products.

This closed what had been a day of interesting, engaging and provocative talks, with descriptions of detailed neuroscience and their application to clinical practice.

The ABN next meets in Birmingham for their Annual Meeting on 9-11 May 2018.

Royal College of Physicians

Association of British Neurologists

Conference:

From Holmes to House – 500 years of the diagnostic neurologist

20 March 2018, London

Join us as we follow the history of neurology and take a look at the influence that new technology and interventions hold within this rapidly evolving specialty.

Programme highlights:

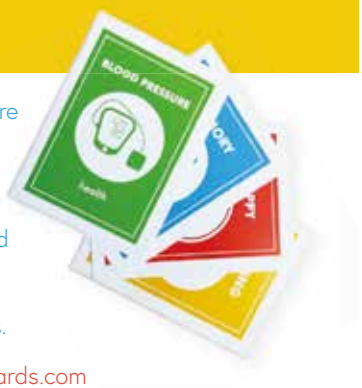
- updates on neuroimmunology – how these affect patient care
- updates in neurogenetics – how these affect patient care
- updates in neuroimaging
- the risks of overdiagnosis in neurology
- clinical reasoning in neurology.

CPD 5 credits

> See the full programme and book your place at:

rcplondon.ac.uk/Holmes-to-House

Stroke Touchpoint Cards



Choose cards to structure discussions, normalise issues and focus on the topics that matter.

Facilitate person-centred conversations between stroke survivors and healthcare professionals.

www.stroketouchpointcards.com

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UWE Bristol – University of the West of England

Hosted by Dr Praveen Kumar

Key Note Speakers

Symposium: Musculoskeletal Strand

- Prof Nicola Walsh, *Professor of Knowledge Mobilisation & Musculoskeletal Health, University of the West of England*
- Prof Candy McCabe, *Florence Nightingale Foundation Chair in Clinical Nursing Practice Research & Royal United Hospitals NHS Foundation Trust, Bath, University of the West of England*

Symposium: Neuro Rehabilitation Strand

- Prof Roshan das Nair, *Professor of Clinical Psychology & Neuro-psychology, University of Nottingham*
- Prof Carolyn Young, *Consultant Neurologist , The Walton Ct, Liverpool*

Bipin Bhakta Memorial Lecture: 'Upper Limbs Matter - Biomechanics for Rehabilitation'

- Emeritus Professor Garth Johnson, *Biomedical Engineer, founder member of the SRR, Newcastle University*

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This event no. 115072 has been approved by the Federation of the Royal Colleges of Physicians of the United Kingdom for 5 category 1 (external) CPD credit(s).

BNPA British Neuropsychiatry Association

The BNPA AGM
1ST – 2ND March 2018
Kings Place, York Way, London

The themes of the meeting will include:

- sleep disruption in neuropsychiatric disorders
- stress and the brain
- social cognition

Registration: www.bnpa.org.uk

For all other questions or enquiries including exhibitors and sponsors contact Jackie Ashmenall
Telephone: +44 (0)20 8579 0543
Email: hello@bnpa.org.uk

MS Paris 2017, the joint ECTRIMS/ACTRIMS Meeting

Conference Details: October 25-28, 2017, Paris, France. ***Report by:*** Angelika Zarkali, Neurology Registrar, East Kent University Hospitals Foundation Trust ABN Trainee Committee Secretary. ***Conflict of interest statement:*** None declared.

The 7th joint ECTRIMS/ ACTRIMS conference, held this year in Palais de Congress in Paris, closed its doors after four days of exciting clinical and research advancements. With more than 10,000 delegates and 3978 abstracts, this was the largest conference in Multiple Sclerosis so far.

The programme was full, starting on Wednesday 25th of October with a day aimed at Registrars and junior Consultants including 18 teaching courses on clinically salient topics across the whole of the MS spectrum, as well as two "Nurses sessions", emphasising the important of MS Specialty Nursing both for clinical outcomes and research advancements.

The main conference started the following day with an unexpected cabaret performance, followed by a lecture by Dr Hans Lassman, University of Vienna, that succinctly explained the advances made in clarifying the pathophysiology of this inflammatory disorder, the insights into the phenotype of brain infiltration by T and B lymphocytes, the clinical implications of these findings and further questions for research.

Over the next three days, during the 25 parallel sessions, more than 2000 posters and multiple sponsored symposia, we heard about clinical and scientific advances in adult and paediatric MS, as well as other demyelinating conditions such as Neuromyelitis Optica spectrum disorders. The most important findings presented at this year's ECTRIMS/ACTRIMS meeting, that will imminently affect clinical practice are:

1. The 2017 Revision of the McDonald Criteria were presented by Jeffrey Cohen, Cleveland Clinic in one of the most well-attended sessions, followed by an in-depth presentation of the implications of the new criteria for clinicians by Jeremy Chataway, National Hospital for Neurology and Neurosurgery. The main changes in the criteria are:

- In patient with typical Clinical Isolated Syndrome and fulfilment of the Dissemination in space criteria, the presence of Oligoclonal bands (OCBs) can now make the diagnosis of MS
- Cortical lesions are included in the Dissemination in time criteria
- Primary progressive MS criteria have remained the same but also now include cortical lesions
- No distinction is made between symptomatic and non-symptomatic lesions.

2. Advancements in the treatment of Progressive MS: "We can treat progressive disease although results have been modest so far"; this was an encouraging theme throughout the meeting, with many presentations highlighting the emergence of new, effective treatment options for a previously untreatable condition.

Remarkable attendance rate at the Conference Hall

Musée D' Orsay at Night during the Conference Networking Event.

- **Ocrelizumab (ORATORIO study):** Humanised monoclonal anti CD20 antibody. This was the first positive phase 3 clinical trial in Primary Progressive MS showing that Ocrelizumab is reducing disability progression in SPMS. An open label extension trial was recently completed showing that ocrelizumab effect is sustained with ongoing treatment. The benefit of DMTs in older patients ay be reduced, particularly in progressive MS.
- **Siponimod (EXPAND trial):** Selective modulator of Sphingosine 1 Phosphate receptor. Significantly delayed disability progression by 26% in six months in patients with Secondary Progressive MS. Siponimod also reduced MRI disease activity and brain volume loss at 12 and 24 months.
- **Ibudilast (SPRINT- MS trial):** Phosphodiesterase and macrophage inhibitory factor inhibitor. Initial data showed that ibudilast slowed the progression of brain atrophy in progressive MS (both primary and secondary).
- **Natalizumab improving upper limb function in SPMS:** Although not improved EDSS or lower limb function, natalizumab led to improvement in upper limb function (9 hole peg test) in SPMS patients.
- **Future Pipeline:** Progressive MS is an active research area with many ongoing trials including MS STAT2, SPI2, MS SMART as well as new molecules such as Laquinimod, Mastinib (tyrosine kinase inhibitor), Ibudilast and Idebenone.

3. New treatment options for Relapsing Remitting MS:

- **Ozanimod (RADIANCE trial):** Highly selective Sphingosine 1 Phosphate receptor agonist. In a Multicentre, randomised, double blind trial examining ozanimod versus interferon in patients with active disease, ozanimod was found to have a 38% reduction in annual relapse rate over three years compared to interferon.

community therapists network

Mental Fitness: a practical approach to supporting Mental Health

14th December 2017, Blackburn

Why is it some people manage to lift themselves out of a depressed mood without too much support whereas others really struggle? This half day workshop will address this and other issues and offer some practical thoughts on managing a person's mental health, especially after a traumatic life event.

Lead by Mental Health First Aid Trainer, Chris Morgan and Neil Bindemann, Exec Director of the Primary Care Neurology Society, this workshop will look at mental fitness, how it can offer a very practical approach to supporting peoples' mental health and potentially offer a more prevention-based strategy. For more details of the morning and for further details including previous workshop feedback plus to book your place go to www.communitytherapy.org.uk and click on the workshop link. Places are available at £75.

Learning How to Use the TOM

27th February 2018, Manchester

This popular workshop, lead by Prof Pam Enderby, gives participants all the essential knowledge to enable them to use the Therapy Outcome Measure in their clinical practice, with confidence. Delegates will go away with a greater understand of why the TOM is being used extensively across the health service. You will also learn how best to collect and measure outcomes data on clients receiving therapy/treatments. The day includes both theoretical and practical components, with ample opportunity to practice with the TOM and rate various patients, with guidance from Prof Pam Enderby. To book your place at the special price of £135 (normally £175) please go to www.communitytherapy.org.uk. Use the code ACNR135 in the promotional code box when booking.

Mental Capacity Assessment - Getting it right!

2nd March 2018, London

Lead by two leading experts in the field, Mark Jayes, a speech and language therapist since 2003, with specialist knowledge of Mental Capacity Assessment and Mathieu Culverhouse, Associate at Irwin Mitchell with expertise in Mental Capacity Law, this practical workshop will help you get to grips with assessment of mental capacity, including an overview of common communication disorders and how these can impact on mental capacity. To learn more, including the feedback from delegates who attended the last workshop and to secure a place at the special price of £95 go to www.communitytherapy.org.uk and use the code ACNR95 in the promotional code box when booking.

To register your interest in attending the next TOMs workshop please email info@communitytherapy.org.uk

In addition, secondary endpoints were met, including reduction in the number of T2 lesions and reduction in total brain volume loss and grey matter volume loss at two years. Although there were some cardiac effects, these were relatively mild.

- **Opicinumab (SYNERGY trial):**
  Anti lingo 1 monoclonal antibody.
  SYNERGY assessed the efficacy of opicinumab in patients with relapsing MS as an add on therapy to interferons. The post-hoc analysis of SYNERGY data presented in the conference, indicated an increased effect of opicinumab versus placebo (when used at the same time as interferon) in patients with shorter disease duration and lower rates of Magnetisation transfer ratio (MTR) in MRI suggestive of lower myelin content.
  Biogen announced the initiation of a phase 2 double blinded control study (AFFINITY) to further study the effect of opicinumab in these patients.
- **Ocrelizumab improving visual function in relapsing MS (OPERA studies):**
  Ocrelizumab was associated with a significant improvement in visual outcomes at 12 weeks in RRMS patients compared to interferons.

4. Need for early treatment to prevent progression:
JWL Brown from University of Cambridge in a plenary session, as well as A. Fabiatos from Melbourne, winner of a poster award, both presented data from MSBase, on the risk of secondary progression and the effect of Disease Modifying Therapies.

Improving disability trajectory was associated with a decreased risk of SPMS whilst greater level of disability, trajectory and age was associated with a higher risk.

Patients on all included treatments (injectables, figoolimod, natalizumab and alemtuzumab) showed reduced risk of conversion to SPMS compared with untreated patients.

The risk reduction was higher in most effective therapies (natalizumab/alemtuzumab) than injectables (HR: 0.65).

Treatment within five years of the first relapse was associated with significant delay in the time to progression compared to later treatments. Longer duration of therapy was associated with decreased risk of SPMS.

These results highlighted the importance of early diagnosis and early DMT.

Finally, DMT has an impact on mortality: An international population based study presented as a poster by E. Kingwell showed that exposure to interferons was associated with reduced all-cause mortality rates in patients with MS.

Overall, the 7th ECTRIMS/ACTRIMS meeting this year highlighted the extraordinary advancements in this field of Neurology both in terms of mechanistic insights and therapeutics. Most importantly, it brought together clinicians from across the globe in a beautiful venue, promoting further discussion and collaborations.

The 8th ECTRIMS meeting will be held in Berlin, Germany on the 10th-12th October 2018 with hopefully even more exciting discoveries!

Top 5 highlights from ECTRIMS/ACTRIMS 2017

1. The 2017 Revision of McDonald Criteria: Lumbar punctures are back in diagnosis of MS
2. Progressive MS is treatable: current options Ocrelizumab and Siponimod, many more currently evaluated
3. Early disease modifying treatment in relapsing MS delays secondary progression
4. Ozanimod is superior to interferon in reducing relapses in RRMS
5. Opicinumab can be an effective add-on to interferon in RRMS; further evaluation in the AFFINITY trial starting soon

Neurology Academy showcases improved care and service development

The Neurology Academy has launched its new website showcasing the variety of educational courses on offer to healthcare professionals and how graduates are changing the face of patient care. With an established reputation for building advanced clinical expertise, the Academy now boasts MasterClass courses in Parkinson's, multiple sclerosis, dementia, and palliative care. New training will soon be available in migraine and headache, stroke, epilepsy, and mental health.

Whatever your role, these individually tailored courses are a unique opportunity to build confidence by learning from leaders in the field. Education takes place in small groups with a relaxed atmosphere and a practical focus that goes well beyond the evidence base.

Delegates attending residential courses receive individual mentor support while completing a project in an area of interest. Through their projects, graduates have implemented changes that are making a valuable impact on service development and a real difference to patient care. You can explore previous graduate projects and upcoming courses on the Neurology Academy's new website: www.neurologyacademy.org

Neurology Academy

PREVIEW: Digital Healthcare: Cutting Edge Innovation

Conference details: February 8, 2018, London, UK.

At Digital Healthcare: Cutting Edge Innovation an outstanding agenda of speakers will update delegates on the very latest developments happening within the NHS as it strives to modernise in the digital era. We will hear about the latest recommendations that are shaping policy and the subsequent support that is being made available to make advancements. The conference will serve as an opportunity to be updated on some of the latest issues surrounding data protection and security, whilst reiterating the importance of information sharing to achieve interoperability and greater integration. We will learn how technology is now being utilised more effectively in public health and how it is providing patients the chance to self-manage their conditions better. The conference will also showcase innovative products, some for the present day, some more for the future, to reveal the true power of technology.

Festival of Neuroscience

Conference details: April 10-13, 2017, Birmingham, UK. ***Report by:*** Tarek Gaber and Zafar Mehmood, Taylor Neurological Rehabilitation Unit, Leigh Infirmary, Lancashire. ***Conflict of interest statement:*** None declared.

One of the main strengths of the Festival of Neuroscience is the British Neuroscience Association's generosity towards their sister societies and sponsors. Having over fifty symposia, workshops and special events hosted by a diverse array of professional societies such as the Biochemical Society, British Society of Neuroendocrinology, Association of British Neurologists amongst others, allow the delegate to explore both core and obscure domains of neuroscience from completely different perspectives. Eventually a more rounded three dimensional insight is crystallised about subjects ranging from computational neuroscience to management of common disorders in a clinical setting.

With a 378 page book of abstracts, this review can only attempt to touch on a few of the main themes that had the highest profile and the reviewers found particularly interesting as clinicians.

1- Glutamate:

The overwhelming majority of the pharmacological agents used in neurology and psychiatry exert their mode of action by enhancing or blocking one of the main neurotransmitters such as GABA, Dopamine, Serotonin and Acetylcholine. Glutamate and GABA are the main excitatory and inhibitory neurotransmitters respectively but whilst GABA agonists are integral part of neuropharmacology, only a handful of drugs can claim efficacy by influencing Glutamate (mainly through blockade).

Basic scientists have a favourable view of Glutamate as the main hero of synaptic plasticity and subsequently the most established and investigated concept of neural modulation: Long Term Potentiation LTP (as the Canadian Psychologist Donald Hebb put it 50 years ago: If they fire together, they wire together). Graham Collingridge of the university of Bristol gave a detailed history of LTP and how it could be affected in his Plenary lecture; whilst many speakers showcased the recent advances in manipulating LTP mechanism to enhance and sometimes delete memories (M. Fanselow of UCLA, Z. Padamsey of Oxford University).

Speakers discussing Glutamate from a clinical perspective have a less favourable view, as its role in many pathological processes is well established. Neurodegeneration and epilepsy (M. Cunningham of the University of Newcastle) are two of the pathologies that were heavily covered. LTP is also believed to be the primary cellular mechanism priming addiction and chronic pain.

All neuroscientists seem to agree that a crude attempt to antagonise Glutamate action is bound to fail. Glutamate is used in more than 90% of synapses and even when it is not the dominant neurotransmitter (such as in the case of the basal ganglia with 70% Dopamine and 30% GABA synapses), Glutamate plays a major role regulating the action of these dominant neurotransmitters. A very impressive body of work is created now analysing how Glutamate pathways and cell signalling differ in the normal physiological states and how it turns into a potent cytotoxic killer in pathological processes. Targeting specific cell signalling molecules seems to be the rational way to influence specific disease processes whilst maintaining Glutamate's important action in maintaining a normal synaptic function.

2- Microglia

When Santiago Cajal coined the name Glia (glue in Greek) he was reflecting the view that Glial cells are basically fillers. The focus on the neurone as the primary place where interesting things happen seems to be unjustified after hearing the advances in understanding microglial function and how it goes wrong in disease processes. Two symposia were dedicated to microglia. Only a few number of speakers were interested in the classic role of microglia as a part of the CNS immune system; the focus now is to understand the role microglia play in neuroplasticity, as each cell surveys more than 150 000 neurones in its patch, pruning and attacking the frail and inactive neurones and synapses as it goes. The more plastic a brain area is, the more abundant microglia are (brain stem has the lowest population of microglia as it is one of the least plastic areas).

Microglial proliferation is a classic feature of many pathologies; H. Perry of the University of Southampton believed that they play a key role in the pathogenesis of many degenerative diseases where their proliferation, aberrant morphology and spinal loss are key features. Focusing on the immune response with microglia at its heart seems to be a promising approach to further understand neurodegeneration. A UK based lab has a poster replicating last year's Nature report by a Japanese group successfully producing microglia from human Induced Pluripotent Stem cells. A clearer understanding of the role of microglia is bound to happen thanks to this development.

Talking about stem cells, Andrea Brand of the University of Cambridge presented her work in trying to manipulate the dormant brain stem cells in fruit flies and is hoping that further understanding of the mechanisms controlling the transformation of the stem cells to different neural cell types may have important implications for humans.

3- Genetics and epigenetics

The mapping of the human genome in the turn of the millennium ushered the birth of a new domain for genetic studies, Genome Wide Association Studies (GWAS). This powerful tool is now widely used to establish the genetic co-relation of many diverse medical conditions. Three symposia showcased the recent trends in genetics and epigenetics research with language disorders, epilepsy and developmental disorders discussed. GWAS among other methods showed how complex and diverse the genetic changes can be. The iconic FOXP2 gene seems to be only a small part of the story of language development, however it remains the most studied and understood gene related to speech disorders. S. Vernes of the Max Planck Institute gave an excellent up to date review of the current understanding of that gene.

Epigenetics was the buzz word in many presentations and posters with a focus on how in utero or early life stress is strongly linked to adult pathology via epigenetic mechanisms. However, well established genetic links continued to dominate the research landscape with a single gene such as APOE 2 and its link to Alzheimer's Disease having a whole symposium discussing the molecular abnormalities and the potential targets for therapy.

We feel that at these times of unprecedented pressure in clinical practice, it is more important than ever to take a step back and try to catch up with the fundamentals of neuroscience and have an insight into how the landscape and paradigms of neuroscience and subsequently clinical practice are changing.

The next Festival of neuroscience will be held in Dublin in 2019.

North Staffordshire Sixth International Neuropsychiatry Conference on Huntington's Disease: New Horizons

Conference details: June 27, 2017, Stoke-on-Trent, UK. ***Report by:*** Dr George El-Nimr, Consultant Neuropsychiatrist and Honorary Clinical Lecturer.
Conflict of interest statement: None declared.

With over 100 delegates, the conference attracted a global audience of experts and practitioners, sharing insights and updates on relevant clinical, medico-legal and research issues relating to Huntington's disease (HD).

Following the Trust welcome, the conference delegates heard from two family members who spoke powerfully and insightfully on the experience of living with HD. Alice Rivières, French writer, gave an inspiring talk entitled "Becoming extra-ordinary, a journey through Huntingtonland". Ms Rivières proposed that "if Huntington's disease is a world waiting to be discovered, she – Huntington's – is indeed female", as in the French language, the words "land" and "disease" are feminine – and needs her own language, her own mythology and her own founding texts. In order to help her in her exciting mission, Ms Rivières created Dingdingdong, an institute for the coproduction of knowledge about HD, comprising a team of artists and researchers from social sciences. Ms Rivières articulately set the theme of the conference in exploring the new Huntington's planet.

Dina D'Sousa, who is a member of the European Huntington Association, and Asun Martinez, President of the International Huntington Association, were able to highlight how two international bodies can have one common goal. Their talk addressed how support groups and voluntary organisations have an instrumental role in supporting families and facilitating advanced research. Their noble effort to work with HD sufferers and carers, as well as supporting ongoing research, is certainly quite inspiring to those working with other similar disorders.

Dr George El-Nimr, (pictured right) Consultant Neuropsychiatrist and event organiser, gave a talk on how our patients actually perceive the world. It is not uncommon for our patients to be judged by others in a negative light. Clinicians working with people with HD are often troubled, having to fight on behalf of their patients to explain to the outside world how the condition can colour the behaviour and personality. Unfortunately, characteristics such as stubbornness, self-centredness and laziness are attributed to individuals rather than to the behaviour of the illness. Understanding how our patients do actually experience their inner world and see the world around them can help us considerably in understanding why they behave in a certain way. For example, our patients' difficulties in reading certain facial emotional expressions, controlling their own impulses, multi-tasking or working out possible consequences of behaviours and events can explain a number of behaviours that are viewed unfavourably by others. Similarly, problems with social cognition and impaired Theory of Mind can also explain various aspects of the behaviours and assist in formulating a management plan for such difficulties. The talk also addressed why some of our patients may appear extremely reluctant to engage in certain activities, especially new ones, and how caregivers can benefit from understanding the background of such difficulties.

Dr David Crauford, Senior Lecturer from the University of Manchester, discussed challenging behaviour associated with HD and how this can be adequately managed. Dr Crauford highlighted how, historically, clinicians and researchers have tended to focus mainly on the motor aspects of HD, but the cognitive and behavioural changes often have a much greater impact on quality of life for patients and carers. Mood changes, irritability, perseveration (repetitive thinking / behaviour) and loss of motivation (apathy) are the most common and troublesome behavioural changes, and are seen in other neuropsychiatric disorders as well as HD. Anxiety and irritability can in turn lead to impulsive aggression, while perseveration can also result in difficult and challenging behaviours. Anosognosia (lack of awareness of symptoms or deficits) is common in patients with HD and is presumed to be a consequence of the cognitive changes affecting frontal lobe/executive function, but often causes further difficulties for diagnosis and management. Many of these behavioural manifestations of HD respond well to symptomatic treatment, and this talk focused on strategies for managing challenging behaviour in HD.

The conference delegates were privileged to hear from Professor Josef Priller from Germany, who spoke about current thinking in relation to symptomatic treatment. The presentation outlined recent advances in the treatment of HD, with a particular focus on neuropsychiatric symptoms of HD. He also provided examples of the translation of basic science results into HD clinical trials.

The conference also hosted a number of interactive workshops that were well received and enhanced the educational value of the event. The workshop, entitled "Young people on board", was organised by the Huntington's Disease Youth Organisation. Ms

Catherine Martin explored the difference open communication can make. The workshop looked specifically at the impact and changes in young people.

Bill Crowder of the Huntington's Disease Association delivered a thought-provoking workshop on end of life issues. Mr Crowder explored some of the care challenges, including planning for the future, symptom management and spiritual needs, and discussed issues that go beyond the hands-on care which is equally important for the individual and family alike. How the Huntington's Disease Association can help people living with HD and support them and professionals in providing the most appropriate care and support was also discussed.

A rather popular workshop on "How far have we come?" constituted an important part of the day. Dr Akshay Nair, a psychiatrist and Clinical Training Fellow, along with Lauren Byrne, a research assistant, offered a research update on the topic. Workshop facilitators highlighted the fact that a wide range of research is ongoing, including clinical trials, the development of novel biomarkers and using cognitive neuroscience to better understand the symptoms of HD. The workshop provided an overview of some of the recent research highlights, concentrating on ongoing clinical trials, brain imaging research and new blood tests for HD. Some exciting upcoming research studies were also discussed.

Conference attendees were also interested to hear from Gemma Eason of Irwin Mitchell Solicitors, who spoke about the legal framework and managing the affairs of someone with HD within this. She highlighted that this is an area where the correct approach really depends on the level of capacity of the individual concerned. Lasting Powers of Attorney, Deputyships and Trusts were covered. Ms Eason was also able to provide guidance on the best approach to address such issues and how to access legal advice.

Daniela Rae, Research Fellow of the University of Aberdeen, gave a stimulating talk on "Optimising the standards of care". Ms Rae emphasised that health and social care delivery faces significant challenges, particularly in complex, chronic and multi-morbidity conditions. There are increasing health / social care demands and financial pressures on funding and resources. There is a drive towards delivering patient-centred care closer to home.

Professor Hugh Rickards of Birmingham University then addressed the issues of research and clinical care in HD and whether they are friends or foes. Quite articulately, Professor Rickards pointed out that what people with illnesses of all kinds really want to know can be boiled down to two essential questions: "What's going to happen in the future?" and "What can anyone do to change that?". Research has actually led to the discovery of a gene which has made the diagnosis much more sensitive and specific. Professor Rickards also highlighted the potential dangers that come with research. One must make sure that research facilities do not feel like "research fodder" for those participants and there is also the danger that we think more about rating scales than about people. Just because something is measurable doesn't mean it's important. Research can take up clinical time that might have been better spent. Finally, research communities can sometimes hang on to cherished ideas long after their sell-by dates and we need to guard against that. As long as we take care, research and clinical care can and should be great, mutually respectful friends, Professor Rickards emphasised.

The conference concluded with a panel discussion entitled "Ask the expert; challenging symptoms and legal dilemmas". This interactive session addressed difficult questions that patients, clinicians and researchers may face in the current climate.

The event attracted excellent feedback and demonstrated the great appetite for similar educational events that will satisfy the educational needs of clinicians and researchers, as well as keeping patients and families well informed.

British Society of Neuroradiologists: Trainee Day and Annual Meeting

Conference details: September 14-16, 2017, Cambridge, UK. ***Report by:*** Dr Andrew Nanapragasam, Academic Clinical Fellow in Radiology and Founder of the educational website and social medial platform "Radiology Nation." Twitter: @nanapragasam ***Conflict of interest statement:*** None declared.

The British Society of Neuroradiologists' (BSNR) annual meeting is the premier meeting for UK neuroradiologists. In recent years, the scientific meeting has been supplemented by a "trainee day". The 2017 trainee day & conference were held from the 14th to the 16th of September at Queen's College, University of Cambridge. The trainee day can be attended either in conjunction with, or independent from, the annual conference.

The 2017 trainee day,organised by Dr Tilak Das (consultant neuroradiologist based at Addenbrooke's Hospital), featured a series of highly adept speakers. Prof Jonathan Gillard challenged the accepted thinking on stroke pathophysiology, Dr Ian Craven gave an engaging lecture on making the transition to Consultant life, and Mr Thomas Santarius used 3D glasses to demonstrate brain anatomy and neurosurgical techniques. Following the morning of lectures, six workshops were held in the afternoon. These sessions gave trainees the opportunity to benefit from quality, interactive teaching on a variety of neurological conditions.

Priced at only £50, the trainee day is incredible value for money, especially considering that the fee included attendance at an evening garden party and dinner!

The BSNR meeting itself was just as memorable as the trainee day. The meeting was a two day bonanza of scientific research on a variety of diagnostic and interventional topics, interspersed with lectures from invited speakers. Professor David Menon, Consultant Anaesthetist at Addenbrooke's, delivered a convincing case for thinking of traumatic brain injury as a chronic rather than an acute disease. Conference attendees were also treated to a lecture from Mr Henry Marsh, Consultant Neurosurgeon and bestselling author of *Do No Harm*, who gave an honest account of his life's work, and addressed the difficulty of owning up to one's shortcomings. Day two began with Dr Stavros Stivaros, Consultant Neuroradiologist from Royal Manchester Children's Hospital, who delivered a compelling lecture on the in vogue issue of artificial intelligence in radiology. The final invited speaker, Professor Paul Fletcher, Consultant Psychiatrist from the University of Cambridge, had the audience captivated with an incredible presentation on perceptual biases. The meeting was brought to a close with a fiendishly difficult, but highly educational, neuroimaging quiz courtesy of Dr Daniel Scoffings, Consultant Neuroradiologist from Addenbrooke's Hospital.

In summary, the 2017 British Society of Neuroradiologists annual conference & trainee day were fantastically organised, informative, and enjoyable. Attendance at this meeting is highly recommended for anyone with an interest in neuroradiology, regardless of whether you are a Radiologist, a Neurosurgeon, or a Neurologist!

Learning points from the British Society of Neuroradiologists' trainee day and annual conference:

- Provision of a 24/7 mechanical thrombectomy service is an important initiative for the optimal treatment of stroke patients
- Artificial intelligence is likely to be integrated into clinical practice in the near future, but it does not pose an existential threat to diagnostic or interventional neuroradiologists
- Henry Marsh's example of self-reflective practice provides a lesson for us all.

Royal College of Psychiatrists: Faculty of Neuropsychiatry Annual Conference

Conference details: September 14-15, 2017, Stoke-on-Trent, UK. ***Report by:*** Dr George El-Nimr, Consultant Neuropsychiatrist and Academic Secretary to the Faculty of Neuropsychiatry. ***Conflict of interest statement:*** None declared.

With a host of distinguished international speakers, adopting various session formats, the Faculty's conference covered important clinical and research topics that have contributed to its continued success over recent years. As in previous years, the event was heavily subscribed, having earned its place in the diary of many colleagues.

Towards the end of the two-day conference, it was refreshing to witness such a lively debate around how far services should investigate patients with mild cognitive impairment. The conference also presented an inspiring exploration of what the humanities can teach today's clinicians when it comes to contemporary understanding of the mind.

The conference delegates also heard about the impact of neuropsychiatric disorders on carers and families and how this can potentially be an enriching and fulfilling experience rather than a devastating one.

In addition to keynote talks, the conference offered a host of interactive seminars covering various clinical, legal and research topics. These sessions have addressed a wide range of educational needs in a format that has always proven to be highly valued by colleagues from around the UK and other countries. The international and transcultural perspective of the conference has certainly added further educational value to the event.

Following introductions from Professor Eileen Joyce, Faculty Chair, the conference opened with an update from Professor Wendy Burn, our newly appointed President of the Royal College of Psychiatrists. Professor Burn talked about neuropsychiatry within the College and the College's plans in relation to training in neurosciences.

Chaired by Dr George El-Nimr, Academic Secretary, the first plenary addressed issues around image, imagery and the imagination. First, Adam Zeman, Professor of Cognitive and Behavioural Neurology at the University of Exeter gave a detailed account on phantasia and discussed the neurology of visual imagery. Professor Zeman gave a fascinating account on how the "mind's eye" can be impaired in certain individuals. Professor Giacomo Rizzolatti then discussed the contribution of his group in discovering the mirror mechanism and its social and clinical implications. He described the functions of the mirror mechanism located in the parieto-frontal network of monkeys and humans and how this mechanism enables one to understand others in an immediate, phenomenological way without recourse to cognitive inferential processing. He also discussed the role of the mirror mechanism in understanding basic Darwinian emotions, focusing on disgust, fear and joy. His talk was followed by another interesting talk from Professor Velakoulis who gave a presentation on the neuropsychiatry of younger onset neurodegenerative disorders.

In the context of the following plenary session, mild traumatic brain injury and post-concussion syndrome were addressed from the neurological perspective and bio-markers by Professor David Sharp. The neuropsychological aspect, chronicity and treatment were then addressed by Dr King, Consultant Clinical Neuropsychologist. His presentation reviewed the neuropsychology of mild head injury and post-concussion symptoms, in both the early stages after injury and when problems are chronic. His talk also addressed the factors which contribute to persisting symptoms and the evidence base for psychological interventions for post-concussion symptoms. Neuropsychiatric perspective and medico-legal dilemmas were subsequently discussed by Dr Robin Jacobson who highlighted the non-specificity of the post-concussional syndrome along with the predominant model suggesting early physiogenesis and perpetuation of symptoms on a predominantly psychological basis. The medico-legal aspects of mild traumatic brain injury was also reviewed, including the assessment of the duration of post-traumatic amnesia and the use of effort tests in neuropsychological examination.

The afternoon of the first day of the conference featured a number of seminars that were very well received by the conference delegates. These included discussing the auto-antibodies in psychosis, smart technology and epilepsy management, updates on the neurobiology of obsessive compulsive disorder and the role of expert witness in acquired brain injury claims.

The last plenary of the day was an exciting session that addressed epilepsy and the mind. It talked about how the humanities can inform our contemporary practice. Professor Steve Brown talked about music, epilepsy and the brain. Professor Brown highlighted how the subject of human language and communication encompasses a spectrum from verbal language, music, dance, movement and gesture, as well as the visual arts. He explained how music contributes to internalised thought and external social interactions, as do other art and language forms. It was interesting to hear how scientific approaches have emphasised the crucial importance of music and music related skills in general cognitive development. Conference delegates had the opportunity to learn how music can also induce particular mood states which in turn may modify behaviour and cognitive functions. The example of musicogenic epilepsy was discussed, highlighting how music is one of a large number of sensory experiences that may evoke seizures in predisposed individuals. Studies of such specific seizure evocation help inform not only the mechanisms of epilepsy but also the neural pathways and interactions that play a part in music. It was also fascinating to hear how music has also been postulated as an anti-epileptic tool, although it is not entirely clear how this relates to specific pieces of music. The potential influence of music on intelligence was also highlighted. Similarly, the potential positive impact of exposure to music and music education on basic cognitive and emotional development has an impressive evidence base.

Dr Maria Vaccarella, Lecturer in Medical Humanities at the University of Bristol, then talked to the conference attendees about epilepsy in contemporary fiction and its relevance to clinicians. Literary authors have long used epilepsy as a characterisation or plot device, but usually in a stereotypical way. More recent epilepsy narratives, instead, provide compelling insight into the stigma and difficulties associated with this condition. In her talk, Dr Vaccarella highlighted a selection of such narratives to demonstrate how literary texts can help us better understand patients' views on controversial issues, such as poor compliance with anti-epileptic medications. Examples from her own research on literary presentations of epilepsy surgery were discussed along with their application in a

clinical context.

On the final day, the programme launched in poetic vein, with Mr Peter Maeck's moving presentation entitled "Remembrance of Things Present – Making Peace with Dementia". This presentation combined Mr Maeck's poetry, prose and photographs to celebrate his father's brave, good humoured struggle with Alzheimer's disease. The presentation highlighted how initial feelings of depression yield ultimately to a realisation that dementia's grip is loosened by the power of poetry, pictures, music and love, which can break down cognitive boundaries by freezing time initially then melting it, enabling a coming-together in a lyrical middle realm between what has gone before and what is yet to be. This session stimulated significant audience engagement through the Q and A session.

Offering a global perspective, a plenary session on cardiovascular disease and brain ageing highlighted specific transcultural lessons. Professor Ingmar Skoog first explored the role of vascular factors in neuropsychiatric conditions. This was followed by another impressive presentation by Professor Krishnamoorthy. This presentation covered a novel integrative model of care that blends psychological approaches with complementary and alternative medicine in India. The talk specifically addressed how behavioural and psychological dysfunction can be managed in a specific clinical setting.

In addition to poster presentations that were entered into a trainees' competition, the conference also hosted a session dedicated to oral presentations delivered by trainees and again, culminating in a prize-giving at the end of the conference. There were a number of high quality research presentations, including potential neural correlates in imaging studies in relation to functional weakness, the psychiatric phenotype of anti-NMDA receptor encephalitis, quantitative EEG findings as a potential prognostic biomarker in anti-NMDA encephalitis and chemokines in depression in health and in inflammatory illness.

Similarly, a selection of seminars were well attended by conference delegates. These included ECT in neuropsychiatric disorders, new and future drugs in sleep medicine, neuropsychiatry on the shop floor: discussing difficult clinical cases and neurological assessment and investigations: what do psychiatrists need to know?

Before announcing the best presentation and prize giving, the conference concluded with a lively debate chaired by Dr Peter Byrne. The debate had the title of "This house believes that the investigation of patients with Mild Cognitive Impairment is clinically unhelpful and economically unjustified". The controversy of this topic was highlighted right from the beginning when votes were taken. Many of the attendees were unable to express strong views either way. The two positions were presented by Dr Jeremy Isaacs, who proposed the motion, and Dr Jonathan Schott, who argued against it. The debate was helpful in informing clinicians' views on the threshold and the details of assessments for which patients with Mild Cognitive Impairment should be considered.

The Faculty's business meeting took place on day two of the conference, when the membership was updated on the work of the Faculty and ideas for next year's conference were invited.

It was agreed that next year's conference will also be held at the Royal College of Psychiatrists in London on the 13th and 14th September 2018.

PREVIEW: UK Stroke Forum set to help experts conquer stroke

Booking is now open for the 2017 UK Stroke Forum, which is hosted by the Stroke Association. The event will bring together over 1,400 stroke care professionals from across the stroke care pathway in Liverpool from 28-30 November.

Held at the ACC Liverpool, the UK Stroke Forum is the largest multidisciplinary stroke conference in the UK. The event provides opportunities for stroke professionals and researchers to come together so they can learn from each other, share ideas and ultimately improve standards of care for stroke survivors.

The three day conference will include an update from Professor Sir Bruce Keogh, NHS Medical Director, and a one-day dedicated training stream designed specifically for primary care. This stream will provide guidance on prevention, diagnosis and management of stroke in primary care, with workshops focusing on cognitive difficulties after stroke.

Dr Katie Gallacher (pictured), RCGP Representative for the UK Stroke Forum, said: "Every stroke survivor deserves the chance to make their best possible recovery. The consequences of stroke can be devastating for patients and their families, and primary healthcare professionals have a crucial role in helping stroke survivors rebuild their lives. The UK Stroke Forum is an essential event for healthcare professionals to find out the latest clinical guidelines for stroke, and help shape the future of the stroke care pathway.

"The event will combine 20 main conference sessions, each focused on a different aspect of stroke care, with expert speakers and researchers giving talks on the latest research updates and service improvements. Delegates can also visit exhibition stands, take part in practical workshops and debate sessions, and listen to stroke survivors sharing their experiences. I'd urge people interested in attending to register as soon as possible."

For more information and to register for the 2017 UK Stroke Forum, visit www.ukstrokeforum.org, email ukstrokeforum@stroke.org.uk or call 0845 521 2505.

Applied EEG Neuroscience specialists BrainTrainUK launches new QEEG service

Advanced QEEG Brain Mapping (AQBM) is now available for the first time in Europe. Using Sterman-Kaiser Imaging Labs software, AQBM is a significant advance on existing QEEGs. AQBM captures more data and provides unprecedented levels of information, analysis and interpretation. Analysis includes:

- Peak Frequency
- Sensory integration
- Visual perception & memory integration
- Motor, body, emotive ability
- Social & executive perception
- Cortico-limbic integration
- Verified neuromarkers for pyschological pathologies

Managing Director Stuart Black says, "The analysis of corticolimbic integration makes AQBM unique. The tool assesses the balance of instinct and reason driving interpretation and behaviour. Neuromarkers identify correlations between EEG patterns and traits by Brodmann Area." AQBM enable increased understanding of brain functions for therapy and inform EEG Biofeedback protocols.

Available in BrainTrainUK's clinic locations in London, Surrey, Bucks, Herts and Yorkshire. For more information call 0207 118 0887 or email enquiries@braintrainuk.com

Epistatus® 10mg oromucosal solution Midazolam now available to prescribe

Veriton Pharma Ltd (formerly Special Products Ltd) has announced that Epistatus® 10mg Oromucosal Solution, Midazolam, is now available to prescribe. The NHS price for a single 10mg in 1mL prefilled syringe is £45.76.

Epistatus® is licensed for use in the treatment of prolonged, acute convulsive seizures in children and adolescents aged 10 to less than 18 years, who have been diagnosed with epilepsy[1]. Buccal midazolam is recommended by NICE[2] for the management of prolonged acute convulsive seizures, and is preferred by most patients and carers compared to the administration of rectal diazepam[3,4].

Epistatus is presented "ready-to-use" in a novel, pre-filled, single-dose syringe, to provide carers with the confidence that they are administering the correct dose[1,5]. The pre-filled syringe is contained within a specially-designed, secure and tamper-evident protective packaging.

Dr Rohit Shankar FRCPsych, Consultant in Adult Developmental Neuropsychiatry – CFT and Hon. Associate Clinical Professor – Exeter Medical School commented, "The importance of having an alternate licensed preparation for use in the treatment of prolonged, acute convulsive seizures, especially in a different mode of delivery is an asset to both clinicians and patients."

In response to market research and insights, Veriton Pharma has invested heavily in the development of this new bespoke syringe, which is designed to allow simple administration of the dose into the buccal cavity[5].

For further information on Epistatus 10mg oromucosal midazolam pre-filled syringes, please visit www.epistatus.co.uk

References:
1. Epistatus 10mg oromucosal solution. Summary of Product Characteristics.
2. National Institute for Health and Care Excellence (2012). The epilepsies: the diagnosis and management of epilepsies in adults and children in primary care. NICE clinical guideline CG 137.
3. Nakken K and Lossius M. Buccal midazolam or rectal diazepam for treatment of residential adult patients with serial seizures or status epilepticus. Acta Neurol Scand: (2011); 124:99-103.
4. acute prolonged convulsive seizures in children. European Journal of Paediatric Neurology (2010); doi10.1016/j.ejpn.2010.05.009.
5. Data on file – Excerpts from Epistatus Patent Application.

Commercial agreement allows people with MS in England immediate access to cladribine tablets (Mavenclad®)

NICE also recommends use of Merck's multiple sclerosis therapy cladribine tablets (Mavenclad®) for highly active disease in adults

NHS England has approved a commercial agreement that allows NHS patients in England immediate access to the new multiple sclerosis (MS) treatment, cladribine tablets (Mavenclad®). NHS England and Merck, the manufacturer of cladribine tablets, have partnered on the commercial access agreement.

The agreement follows the recent positive recommendation from the National Institute for Health and Care Excellence (NICE). NICE issued a Final Appraisal Determination (FAD) that recommends cladribine tablets as an option for treating highly active MS in adults. Use of cladribine tablets is recommended only if a person has rapidly evolving severe relapsing–remitting multiple sclerosis, that is, at least two relapses in the previous year and at least one T1 gadolinium-enhancing lesion at baseline MRI or relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as one relapse in the previous year and MRI evidence of disease activity.

This is the first MS disease-modifying therapy that has gone straight to a positive final recommendation in the NICE appraisal process. In the FAD, NICE concluded that cladribine tablets are less costly than other treatments and require less frequent dosing and monitoring requirements. The recommendation in the FAD forms the basis of NICE's final guidance (Technology Appraisal Guidance, TAG), anticipated in early 2018, and once this is published the NHS must provide funding within 90 days.

Cladribine tablets are taken for a maximum of 10 days in the first year and a maximum of 10 days in the second year, with no additional treatment needed in years three and four. Patients can take cladribine tablets at home from the first dose as treatment does not require hospital administration.4 Monitoring is limited to the first two years only, meaning that cladribine tablets have the lowest administration and monitoring burden of all available high efficacy disease modifying therapies.

Cladribine tablets received marketing authorisation from the European Commission in August 2017 based on an extensive 12-year clinical trial programme.

Applied EEG Neuroscience specialists BrainTrainUK launches new QEEG service

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Specialist Neurological Rehabilitation Service in Lincoln rated Outstanding by the CQC

A neurological rehabilitation centre in Lincolnshire has been rated 'Outstanding' by the Care Quality Commission (CQC), placing it in the top 1% of healthcare services in the UK.

The Laurels, which opened in 2014 and is run by Christchurch Group, provides specialist community-based transitional rehabilitation in north-east Lincoln. It supports adults with neurological conditions resulting from injury, illness or disease. The service offers accommodation for 12 residents and is a Headway Approved Provider.

Inspectors praised the service for its calm and caring atmosphere, its strong, values-led leadership and the creative and individualised approach to support displayed by the registered manager and staff, which provided clear therapeutic benefits for residents. The CQC also highlighted how residents were actively involved in the preparation and on-going review of their personal care plan and supported to make decisions about how they wanted to be supported.

Richard McKenzie, Christchurch Group Chief Operations Officer, added:

"I am delighted that the Laurels has been awarded 'Outstanding' status. We are proud to deliver life-changing, evidence-based outcomes for adults with neurological conditions. To have a service recognised as being in the top 1% of regulated healthcare services in the UK is an incredible achievement."

VERITON PHARMA LTD New company name for Special Products Ltd

Veriton Pharma Ltd has been announced as the new company name for Special Products Ltd.

This name change has occurred both to incorporate the company's past heritage with its future ambitions to make trusted medicines available for everyday living.

The Chief Commercial Officer commented: "With the launch of Epistatus® 10mg in 1mL Oromucosal Solution Midazolam (as maleate), on the 8th of September 2017, and our extensive range of existing unlicensed medicines, we would like to assure our customers and partners that the excellent service and quality they have come to expect from us as a company will continue and all contacts at the company will remain the same."

With its legacy of technical expertise, which began in a world-renowned children's hospital over 20 years ago, Veriton Pharma sources and supplies licensed medicines for CNS and over 75 high-quality, UK batch manufactured unlicensed medicines in the fields of epilepsy, neurology and rare paediatric conditions that licensed products cannot meet.

Headquartered in Weybridge, UK, Veriton Pharma, is a privately owned, speciality pharmaceutical company which also has regional offices in the Middle East and Australia.

European research study aims to improve treatment for traumatic brain injury

ICON plc, a global provider of drug development solutions and services to the pharmaceutical, biotechnology and medical device industries, has contributed to a complex pan-European traumatic brain injury (TBI) research study involving over 4,500 patients in 65 sites in 20 European countries.

ICON provided site management and source data verification (SDV) services to the study, which was supported by the EU and led by Professor Andrew Maas from the University Hospital Antwerp (Belgium) and Professor David Menon from the University of Cambridge (UK). ICON's Dr Valérie Legrand, VP Project Management and a recognised expert in CNS, also provided clinical expertise as a member of the project's Management Committee.

The Lancet Neurology Commission on TBI was launched at the European Parliament on 7th November 2017 and set out clinical and research priorities and recommendations to address the varied challenges in TBI.

The Commission on TBI identifies 12 key recommendations and policies to improve the prevention, quality of care and clinical research in TBI. It seeks to identify strategies to better characterise TBI, increase prognostic accuracy, and adopt a more precision-medicine approach to treatments. The Commission also promotes the use of new tools for clinical evidence generation and implementation, so that research outputs can be more rapidly integrated into clinical care. Moreover, it highlights the importance of international collaboration of funding agencies and researchers to provide a global response to reduce the individual and societal burden of TBI.

Read Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research free online at http://bit.ly/2jbGfst

Walk With Path

Walk With Path is a health-tech start-up focused on improving mobility and reducing the risk of falls across a broad population, including the elderly and those with chronic diseases. The company launched its first product, Path Finder, in June 2017. Since then, there has been positive feedback from people with Parkinson's disease.

Path Finder is designed to alleviate 'freezing of gait' in Parkinson's disease, by providing visual cues that act as external triggers.

The company also recently started studies with UCL, looking at how the next product, Path Feel, can aid people in improving balance. Path Feel is an insole designed to improve balance. It provides a vibrational feedback to the soles of the feet, to assist those with neuropathies and general balance issues, feel more balanced and confident.

Future falls prevention workshops will be hosted in central London next year. For more information email Neil@innervate.co.uk

Path Finder – visual cues to overcome 'freezing' episodes in Parkinson's

Path Feel – an insole to improve balance

Ask your patients if having children is part of their plan

UK/UKCPX/16/0031a
Date of Preparation: February 2017

TEVA UK
Teva UK Limited