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Title: New Perspectives in Epilepsy Neuropathology

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Editorial for the 2018 annual review on epilepsy

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As epilepsy surgery programmes commenced in the 1950s, many eminent neuropathologists embraced the opportunity to study the varied lesions identified in relation to electroencephalography, neuroimaging, psychometry as well as outcome following removal of what was termed the 'alien' brain tissue [1-3]. Beyond their insightful and meticulous histological descriptions, they began to address the questions of what caused these lesions, how they gave rise to epilepsy (the processes of 'epileptogensis') and how they related to other co-morbidities or mortality associated with epilepsy. Now in 2018 we have built on these foundations and, through the evidence amassed from decades of experience, there is greater confidence that resective surgery is a current treatment of choice in selected patients with refractory focal epilepsies. Furthermore, the main lesion types are largely comparable between epilepsy centres, the commonest pathologies being temporal lobe epilepsy with hippocampal sclerosis (HS), low-grade epilepsy-associated tumours (LEAT) and focal cortical dysplasias (FCD) [4]. The pivotal role for the neuropathologist in the modern era of epilepsy surgical programmes has become ever more apparent, confirming that indeed 'pathology matters' [5]. Histological interpretation still remains the gold-standard for

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the classification and sub-classification of many entities, provides prognostic information and moreover human tissue resources play a central role in biobanking for research programmes, enabling breakthrough discoveries.

However, as Clive Bruton commented '*histological diagnosis in epilepsy is not an exact science*' [2] and the limitations of an H&E and microscope used in isolation is now a greater reality that we need to face. This 2018 *Annual Review in Neuropathology and Applied Neurobiology* brings together some of the quantum leaps made in recent years in our understanding of epilepsy, enabled through tissue-based research. These include novel molecular findings, correlations with advanced neuroimaging studies, the involvement of neuroinflammatory, neurodevelopmental and neurodegenerative processes and underlying disease mechanisms enlightened by innovatively designed experimental models. The importance of updating histology classification systems, for example the focal cortical dysplasias and tumours, in light of these new discoveries is highlighted as well as the imperative need for greater multidisciplinary investigations to push forward the frontiers on SUDEP research and prevention. The over-arching objectives in epilepsy research remain to improve and harmonise diagnostic approaches across clinical disciplines to maintain best practice and to identify biomarkers and novel treatment targets ultimately to prevent morbidity and mortality associated with seizures.

In the last decades, neuroinflammatory mechanisms have come to the forefront as key contributors to the hyper-excitability underlying seizures. Through pivotal interactions between astroglia, microglia and neurones, this expanding field offers exciting new avenues for intervention, prevention and treatment of refractory focal epilepsy with anti-inflammatory pharmaco-modulation. In the article by **Erwin van Vliet and colleagues,** a comprehensive review is presented of the current evidence from human and experimental data for pro-inflammatory cytokines as both disease biomarkers as well as treatment targets with a particular focus on the Interleukin-1 receptor/Toll-like receptor signalling pathway [6].

One of the main hindrances in human tissue-based research in epilepsy is the advanced stage of the disease by the time surgery is carried out. **Albert Becker** provides a timely review of the range of experimental models currently employed, from kindling, traumatic brain injury to neurodevelopmental models, which can address this temporal gap. The discovery of candidate molecular signalling cascades and modulated neurotransmitters systems orchestrating pro-epileptogenic processes during the very earliest and latent phases before unremitting seizures have developed, offer exciting and promising horizons for the

development of interventional anti-epileptogenesis (in addition to anti-seizure) treatments in the future [7].

Hippocampal sclerosis still remains one of the commonest lesions [4] and evidence for associated more widespread and progressive pathology may be responsible for memory impairment and cognitive decline that can accompany temporal lobe epilepsy. With a multi-disciplinary authorship **Tai and colleagues** explore the possible causes of such decline, if this fits a neurodegenerative model and evidence for a central role of tau. This review draws together the intriguing links between network hyperexcitability and tau [8], brain injury in epilepsy and the enhanced epileptiform activity noted in Alzheimer's disease [9]. Furthermore the power of modern MRI approaches to monitor progressive changes and disease involvement of extra-temporal networks and subcortical regions is overviewed [10].

Two reviews in this series focus on FCD, the commonest malformation in epilepsy surgical practice [4]. Since the first descriptions of FCD by the neuropathologists Bruton and Corsellis in 1971 [3], the tantalising similarities (as well as differences) from the cortical lesions of tuberous sclerosis have been puzzled over. This mystery has only very recently been solved through deep sequencing molecular studies. In their timely review, **Marsan and Baulac** focus on the novel identification of different activating, and often somatic mutations, in mTOR pathway genes in FCD. The review also explores how different mutations and their timing during development could influence the range of malformation observed and their exciting potential as both biomarkers and targets for novel drug treatments (reference link pending).

As Clive Bruton astutely stated, neuropathology interpretation in epilepsy is *'almost certainly measured best by peer group analysis in formal diagnostic committees' [2]*. This has been exemplified in the last six years by the International League Against Epilepsy (ILAE) diagnostic methods commission. 'Task forces' of clinicians, radiologists, neuroscientists and neuropathologists have drawn up practical consensus classification systems, including for the FCDs [11]. **Najm, Sarnat and Blumcke** now review that although this has been widely adopted internationally and successfully implemented across clinical and research disciplines, there remains an ongoing need for its updating in the light of new clinical and molecular advances in our understanding of FCD biology (reference link pending).

The LEATs largely escaped revision in the 2016 WHO classification of CNS tumours. In the review by **Stone et al**., they overview the new entities described and discuss the advances in the molecular biology of the glioneuronal tumour group. They present a vision that genomic and expression data may in time enable a simpler classification system of this tumour group to emerge that cannot be achieved using histology alone. Furthermore, the impact of tumour-related epilepsy beyond the LEAT group is reviewed and the common mechanisms involved, including peri-tumoural impairment in glutamate homeostasis, glial coupling and blood brain barrier function [12].

Finally, despite all the advances made in epilepsy surgical neuropathology, the rate of sudden and unexpected death in epilepsy (SUDEP) remains unchanged as does our understanding of the precise mechanisms. Many neuropathologists will encounter several cases of SUDEP a year and in a review co-authored by a team of health professionals regularly dealing with these deaths, a proposal for a better co-ordinated multidisciplinary approach to these post-mortems is argued in order to facilitate research and understanding in this area [13].

Contribution: This author is the only contributor to this editorial.

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