



Epilepsy Surgery in 2019 : A Time to Change

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Epilepsy has been known to humankind since antiquity. The surgical treatment of epilepsy began in the early days of neurosurgery and has developed greatly. Many surgical procedures have stood the test of time. However, clinicians treating epilepsy patients are now witnessing a huge tide of change. In 2017, the classification system for seizure and epilepsy types was revised nearly 36 years after the previous scheme was released. The actual difference between these systems may not be large, but there have been many conceptual changes, and clinicians must bid farewell to old terminology. Paradigms in drug discovery are changing, and novel anti-seizure drugs have been introduced for clinical use. In particular, drugs that target genetic changes harbor greater therapeutic potential than previous screening-based compounds. The concept of focal epilepsy has been challenged, and now epilepsy is regarded as a network disorder. With this novel concept, stereotactic electroencephalography (SEEG) is becoming increasingly popular for the evaluation of dysfunctioning neuronal networks. Minimally invasive ablative therapies using SEEG electrodes and neuromodulatory therapies such as deep brain stimulation and vagus nerve stimulation are widely applied to remedy dysfunctional epilepsy networks. The use of responsive neurostimulation is currently off-label in children with intractable epilepsy.

Key Words : Epilepsy · Surgery · History.

INTRODUCTION

Humankind has long recognized epilepsy as a specific disease of the brain and tried to find remedies to treat it. Surgery for the epileptic brain, i.e., the removal of diseased or malformed cortex, began in the early stage of modern neurosurgery. Sir Victor Horsley, a brilliant pioneer of neurosurgery, performed operations on three patients with focal Jacksonian epilepsy in the 1880s²⁴. In the early 20th century, brain mapping was widely studied and applied to epilepsy surgery as intraoperative cortical stimulation and mapping⁴. Montreal

Neurological Institute (MNI) founded by Wilder Penfield became the center of these bold studies and practices. The invention of electroencephalography (EEG) by Hans Berger in 1924 greatly contributed to the understanding of epilepsy and heralded a new era of the objective diagnosis of epilepsy³². Through the decades that followed, EEG frequently combined with video recording of seizure semiology became part of standard presurgical evaluation²⁰. In the latter half of the 20th century, temporal lobe epilepsy (TLE) became the main subject of research on epilepsy⁴. The physiology and function of the amygdala and hippocampus were extensively studied,

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which culminated in Scoville and Milner's seminal paper on patients who received bilateral temporal lobectomies (including the famous patient, H.M.)²⁶. This study revealed that the hippocampus is mainly involved in the retention of new memories, and subsequent studies literally revolutionized modern neuroscience. The diagnosis of TLE was firmly established, especially with the advent of computed tomography (CT) and magnetic resonance imaging (MRI). The greater efficacy of epilepsy surgery for TLE over medical therapy was clearly demonstrated in a randomized controlled trial published in 2001³⁰. In the surgical group, 58% of the patients were seizure-free at one year, whereas only 8% of the patients in the medical group were free of seizures. During the late 20th century, high-resolution MRI became the mainstay of diagnosis for epilepsy. The addition of other imaging modalities using nuclear medicine tools and merging various data to define an epileptogenic zone became the routine of many epileptologists. Understanding brain cortical malformation, especially focal cortical dysplasia (FCD), has changed greatly, and surgical resection of lesions transformed into a more precise and safe procedure. The advent and approval of vagus nerve stimulation (VNS) in the 1990s opened a new avenue toward neuromodulation therapy in epilepsy³³. Responsive neurostimulation (RNS) has been introduced into clinical application since 2013 with promising results^{7,8}. Currently, the use of RNS is off-label in children with intractable epilepsy¹².

TIDES OF CHANGE

This is a brief history of epilepsy surgery since the late 19th centuries. In 2019, what we are facing in the field of epilepsy surgery is a rapid and fundamental change in what we once thought usual and standard. In 2017, the International League Against Epilepsy (ILAE) introduced a revised system of classification for seizure types and epilepsies^{5,23}. The differentiation of seizure types is the basic starting point for patient care and an initial diagnosis. Some seizure types are strongly associated with the diagnosis of specific epilepsy syndromes and treatment options. Many anti-seizure drugs (ASDs) are most efficacious for certain types of seizures. Some surgical procedures are also particularly effective for certain types of seizures, for example, callosotomy for drop attacks. Finally, the world-wide communication and sharing of common nomenclatures for

various phenomena related to epilepsy is mandatory. The previous system of classification for seizure types and epilepsies was introduced by the ILAE in the 1980s^{34,35}. There have been few changes in this scheme for more than 30 years, although many argued the needs for reappraisal³. Scientific progress, new concepts about epilepsy, and even changing social interest in epilepsy urged the reappraisal of the classification scheme. One of the major changes in the 2017 revision is to replace the term 'partial seizure' with 'focal seizure'. Although the meaning (originating from only one hemisphere) is almost the same, 'focal' has a more anatomical connotation than the word 'partial'⁵. Likewise, the long-used terminology 'complex partial seizure' was substituted with 'focal impaired awareness seizure' for clarity for both medical personnel and laypeople. For the classification of epilepsy, multilevel diagnostic steps from seizure type to epilepsy type and further to epilepsy syndrome have been proposed. Etiological considerations at every step is emphasized and reflect the enormous amount of development in the etiological diagnosis of epilepsy, especially in structural and genetic causes. Changing long-held jargon is a hard task for many clinicians, and changing concepts is harder than just stating them. It is hoped that the revised classifications may enhance the understanding of epilepsy and encourage the anatomic and surgical imaginations of many surgeons.

Paradigms in drug discovery are changing and many novel ASDs have emerged for clinical use. The role of epilepsy surgery may change according to this trend. Since phenobarbital was introduced in 1912, many efforts have been made to develop effective ASDs against epilepsy. In the 1930s, through screening via an electroshock animal model, phenytoin was discovered as an effective ASD. Thereafter, many compounds were validated with screening tools. However, there was a period of stagnation between the early 1960s and mid-1970s, when only two major ASDs (valproate and carbamazepine) were adopted²¹. In 1975, U.S. National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) launched the Anticonvulsant Screening Program (ASP), a systematic screening program for potentially useful compounds. The ASP led to the discovery of many so-called third generation ASDs such as vigabatrin, lamotrigine, topiramate, and levetiracetam¹⁷. Behind this success, an important criticism has been made against the ASD development process²⁷. Even novel ASDs are largely ineffective in drug-resistant epilepsy patients who comprise 20–30% of all patients.

This means that current screening tools cannot sufficiently rule out less effective candidates or select compounds potentially effective in certain types of seizures. A unique example is levetiracetam. Levetiracetam initially failed to pass the screening tests using acute seizure animal models. However, levetiracetam showed robust suppression of seizure development in chronic epileptic animal models¹¹. In 2015, the ASP was reformulated as the Epilepsy Therapy Screening Program to incorporate drugs with antiepileptic properties¹⁷. To date, the process of ASD development has evolved from the use of serendipity to systematic screening. Recently, molecular genetic studies have found many novel targets of epilepsy against which specific drugs can be developed. Everolimus, an mTOR inhibitor, is used to control epilepsy in tuberous sclerosis complex (TSC)¹³. Interestingly, sequencing studies discovered that hemimegalencephaly is caused by somatic mutations of PI3K-AKT3-mTOR pathway¹⁴. FCD was also found to arise from somatic mutations of the TSC-mTOR pathways, raising the possibility of applying mTOR inhibitors to a wide range of epilepsy patients^{15,16}. Therefore, for patients with major malformations such as hemimegalencephaly that require extensive and challenging operations, epilepsy surgery may concede to tissue biopsies for sequencing studies and molecular targeted agents can be used for definite treatment.

For nearly a century, the core aim of epilepsy surgery has been the extirpation of diseased/malformed cortex. The identification of the brain areas responsible for seizure generation (epileptogenic zone) using every means and tool became the central tenet of neurology²². However, the concept of the epileptogenic zone was criticized as much as it was pursued. Above all, epileptogenic zone can be identified only after surgical removal, not prior to the operation which is more desirable. Defining the epileptogenic zone with all available resources cannot completely prevent surgical failure. Furthermore, some patients experience seizure recurrence years after surgery with an interval of seizure freedom. This phenomenon is not compatible with the concept of the epileptogenic zone. The common practice of prescribing ASDs to surgical patients for at least a few months after surgery seems to be a compromise between the concept and reality. Recently, accumulating evidence has indicated that focal epilepsy stems from multiple structures that comprise neuronal circuits²⁸. Multiple regions of abnormal circuits can act as independent nodes in a pathological network, underlying surgical failure if only a part of those regions are destroyed. In this view, epilepsy is a network disorder, and fo-

cal epilepsy is not focal, as we thought. Even when a highly epileptogenic lesion, such as hypothalamic hamartoma, exists, the neocortical region can be an independent source of seizures²⁵. That many patients with epilepsy have comorbid neuropsychiatric disorders supports the existence of brain network abnormalities in epilepsy²⁸. Epileptic patients have a 43% higher risk of depression than normal population⁶. Obsessive-compulsive disorder is also highly associated with chronic epilepsy, notably TLE¹⁰. Much of the evidence for the network hypothesis was obtained from studies using depth electrodes and SEEG. The network hypothesis again in turn strongly supports the use of SEEG for the presurgical evaluation of epilepsy patients. If seizures originate from a widespread network including deep subcortical structures, mapping with SEEG is superior to an invasive study using subdural grids. Pioneered by Jean Talairach and Jean Bancaud in the 1950s, SEEG has gained worldwide popularity²⁰. SEEG is less invasive and safer than subdural grids, which have higher complication profiles²⁹. SEEG is more suited for the evaluation of deep-seated areas, multilobar/bilateral exploration, and the mapping of functional networks¹⁸. The SEEG procedure can be automated to frameless robot-assisted positioning of electrodes¹⁹. If a malfunctioning network is to blame in epilepsy, it is possible to destroy or isolate epileptogenic nodes in the network to quench a seizure rather than to shatter the entire network. SEEG electrodes installed for diagnosis can be co-opted for therapeutic intervention using radiofrequency thermocoagulation or laser interstitial thermal therapy^{1,2}. The emerging neuromodulatory therapies for epilepsy such as deep brain stimulation (DBS), VNS, and RNS, owe much of their efficacy to the network-like nature of epilepsy in the generation and propagation of seizures, although much has to be discovered about their exact mechanism^{9,31}.

CONCLUSION

Epilepsy surgery has developed for more than one hundred years. In 2019, we are facing great changes in the paradigms of epilepsy diagnosis, medical treatment, and surgery. The emerging concept of epilepsy as a network disorder is the core of these many changes. What we should remember is that too many patients with intractable epilepsy remain. We need greater consideration of past footprints and discarded pathways to discover novel therapies for this fatiguing disease.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

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References

1. Catenox H, Bourdillon P, Guénot M, Isnard J : The combination of stereo-EEG and radiofrequency ablation. **Epilepsy Res** **142** : 117-120, 2018
2. Cobourn K, Fayed I, Keating RF, Oluigbo CO : Early outcomes of stereo-electroencephalography followed by MR-guided laser interstitial thermal therapy: a paradigm for minimally invasive epilepsy surgery. **Neurosurg Focus** **45** : E8, 2018
3. Engel J Jr : Classifications of the International League Against Epilepsy: time for reappraisal. **Epilepsia** **39** : 1014-1017, 1998
4. Feindel W, Leblanc R, de Almeida AN : Epilepsy surgery: historical highlights 1909-2009. **Epilepsia** **50 Suppl 3** : 131-151, 2009
5. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. : Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for classification and terminology. **Epilepsia** **58** : 522-530, 2017
6. Fuller-Thomson E, Brennenstuhl S : The association between depression and epilepsy in a nationally representative sample. **Epilepsia** **50** : 1051-1058, 2009
7. Geller EB : Responsive neurostimulation: review of clinical trials and insights into focal epilepsy. **Epilepsy Behav** **88S** : 11-20, 2018
8. Geller EB, Skarpaas TL, Gross RE, Goodman RR, Barkley GL, Bazil CW, et al. : Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. **Epilepsia** **58** : 994-1004, 2017
9. Hachem LD, Wong SM, Ibrahim GM : The vagus afferent network: emerging role in translational connectomics. **Neurosurg Focus** **45** : E2, 2018
10. Kaplan PW : Obsessive-compulsive disorder in chronic epilepsy. **Epilepsy Behav** **22** : 428-432, 2011
11. Klitgaard H, Verdu P : Levetiracetam: the first SV2A ligand for the treatment of epilepsy. **Expert Opin Drug Discov** **2** : 1537-1545, 2007
12. Kokoszka MA, Panov F, La Vega-Talbott M, McGoldrick PE, Wolf SM, Ghatan S : Treatment of medically refractory seizures with responsive neurostimulation: 2 pediatric cases. **J Neurosurg Pediatr** **21** : 421-427, 2018
13. Krueger DA, Wilfong AA, Holland-Bouley K, Anderson AE, Agricola K, Tudor C, et al. : Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. **Ann Neurol** **74** : 679-687, 2013
14. Lee JH, Huynh M, Silhavy JL, Kim S, Dixon-Salazar T, Heiberg A, et al. : De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly. **Nat Genet** **44** : 941-945, 2012
15. Lim JS, Gopalappa R, Kim SH, Ramakrishna S, Lee M, Kim WI, et al. : Somatic mutations in TSC1 and TSC2 cause focal cortical dysplasia. **Am J Hum Genet** **100** : 454-472, 2017
16. Lim JS, Kim WI, Kang HC, Kim SH, Park AH, Park EK, et al. : Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy. **Nat Med** **21** : 395-400, 2015
17. Loscher W : animal models of seizures and epilepsy: past, present, and future role for the discovery of antiseizure drugs. **Neurochem Res** **42** : 1873-1888, 2017
18. Minotti L, Montavont A, Scholly J, Tyvaert L, Taussig D : Indications and limits of stereoelectroencephalography (SEEG). **Neurophysiol Clin** **48** : 15-24, 2018
19. Ollivier I, Behr C, Cebula H, Timofeev A, Benmekhbi M, Valenti MP, et al. : Efficacy and safety in frameless robot-assisted stereo-electroencephalography (SEEG) for drug-resistant epilepsy. **Neurochirurgie** **63** : 286-290, 2017
20. Reif PS, Strzelczyk A, Rosenow F : The history of invasive EEG evaluation in epilepsy patients. **Seizure** **41** : 191-195, 2016
21. Rho JM, White HS : Brief history of anti-seizure drug development. **Epilepsia Open** **3(Suppl Suppl 2)** : 114-119, 2018
22. Rosenow F, Lüders H : Presurgical evaluation of epilepsy. **Brain** **124(Pt 9)** : 1683-1700, 2001
23. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. : ILAE classification of the epilepsies: position paper of the ILAE Commission for classification and terminology. **Epilepsia** **58** : 512-521, 2017
24. Schijns OE, Hoogland G, Kubben PL, Koehler PJ : The start and development of epilepsy surgery in Europe: a historical review. **Neurosurg Rev** **38** : 447-461, 2015
25. Scholly J, Staack AM, Kahane P, Scavarda D, Regis J, Hirsch E, et al. : Hypothalamic hamartoma: epileptogenesis beyond the lesion? **Epilepsia** **58 Suppl 2** : 32-40, 2017
26. Scoville WB, Milner B : Loss of recent memory after bilateral hippocampal lesions. **J Neurol Neurosurg Psychiatry** **20** : 11-21, 1957
27. Shorvon S, Schmidt D : The right and the wrong with epilepsy and her science. **Epilepsia Open** **1** : 76-85, 2016
28. Spencer DD, Gerrard JL, Zaveri HP : The roles of surgery and technology in understanding focal epilepsy and its comorbidities. **Lancet Neurol** **17** : 373-382, 2018
29. Taussig D, Chipaux M, Fohlen M, Dorison N, Bekaert O, Ferrand-Sorbets S, et al. : Invasive evaluation in children (SEEG vs subdural grids). **Sei-**

- zure, 2018 [Epub ahead of print]
30. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group : A randomized, controlled trial of surgery for temporal-lobe epilepsy. **N Engl J Med** **345** : 311-318, 2001
 31. Yu T, Wang X, Li Y, Zhang G, Worrell G, Chauvel P, et al. : High-frequency stimulation of anterior nucleus of thalamus desynchronizes epileptic network in humans. **Brain** **141** : 2631-2643, 2018
 32. Zifkin BG, Avanzini G : Clinical neurophysiology with special reference to the electroencephalogram. **Epilepsia** **50 Suppl 3** : 30-38, 2009
 33. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. **Neurology** **45** : 224-230, 1995
 34. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. **Epilepsia** **30** : 389-399, 1989
 35. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. **Epilepsia** **22** : 489-501, 1981