



## Issues in Clinical Epileptology: A View from the Bench. A Festschrift in Honor of Philip A. Schwartzkroin, PhD

From May 3–5, 2013, more than 40 former and present colleagues, students, and fellows of Philip Schwartzkroin, PhD, gathered at Pajaro Dunes Resort in Watsonville, CA, to commemorate Phil's retirement after a remarkable career in epilepsy research. We honored Phil as a researcher, mentor, teacher, and friend. Attendees represented a huge diversity of scientific interests and talents, emblematic of Phil's substantial and longstanding influence on the field. Phil's contributions—too numerous to elaborate here—have included methodological, conceptual, and translational advances that have enhanced the understanding of epilepsy on many levels, ultimately benefitting individuals affected by epilepsy.

After graduating from Harvard College in 1968, Phil enrolled as a graduate student in the PhD Program in Neurological Sciences at Stanford, completing his dissertation research in the laboratory of K. L. Chow in 1972. During his postdoctoral fellowship with Per Anderson in Oslo, Phil realized the potential of the hippocampal brain slice preparation for studying seizure mechanisms. He returned to Stanford with a slice chamber in hand; in collaboration with David Prince, the use of the hippocampal slice as a model to investigate epilepsy took off. The rest, as they say, is history.

In his faculty positions at the University of Washington (1978–2005), and then at the University of California–Davis, Phil continued to produce groundbreaking findings in epilepsy. Since 2005, Phil has held the Bronte Endowed Chair in Epilepsy Research at UC–Davis. Many of the PhD students, postdoctoral fellows, and clinician–research fellows who trained with Phil are still actively engaged in epilepsy research. Phil's scientific output of original articles, reviews, and books has been prodigious, including the highly regarded 3-volume *Encyclopedia of Basic Epilepsy Research* (2009). Highlights of Phil's career include the AES Research Award (1990), presidency of the American Epilepsy Society (1996, the first basic scientist to hold this position), NIH Javits Awards (1985–1992 and 1994–2000), designation as an Epilepsy Ambassador of the International League Against Epilepsy, and co-editorship (with Simon Shorvon) of *Epilepsia* (2005–2013).

Three half-day sessions focused on broad, fundamental questions in epilepsy, to be elaborated in an upcoming Festschrift volume edited by the conference's organizers, Helen Scharfman and Paul Buckmaster. Discussion topics spanned the historical spectrum and also delved into unresolved issues, ranging from basic questions (What is a seizure? What is an epileptic focus?) to "hot" and emerging topics in epilepsy

(What will be the role of rational therapies? How will the rapid discovery of genes predisposing to epilepsy and epileptogenesis affect basic understanding of mechanisms and clinical care?). The camaraderie among presenters and discussants, as well as the willingness of attendees to ask challenging questions, typified the Schwartzkroinian approach. An attempt to convey a sense of the discussions is presented here.

### What Is a Seizure?

Bob Fisher kicked off the conference with a discussion of this fundamental question, reviewing seizure and epilepsy definitions from Hughlings Jackson in 1870 up to the most recent definitions of the International League Against Epilepsy (1). The ILAE definition of an epileptic seizure as the transient occurrence of signs and symptoms due to abnormal or synchronous neuronal behavior in the brain, was discussed and critiqued. Use of clinical manifestations as the basis to define a seizure is fraught with diagnostic uncertainty, further confounded by the existence of seizure mimics and imitators. The EEG can sometimes help to identify a seizure, but the wide variety of nonictal transients and rhythmic activities can impede clarity. Furthermore, EEG changes may or may not accompany a clinical seizure. Multiple patterns of EEG activity can underlie a seizure, and the question arises as to why the brain has evolved so many different ictal patterns. Bob emphasized that a seizure evolves with time, and that invariant EEG discharges are likely to be nonictal, an observation of relevance when considering the variety of periodic EEG waveforms such as periodic lateralized epileptiform discharges (PLEDs). There are several reasons why a clinical–electrographic correlation is important, as this relationship guides treatment decisions, recommendations for a patient's vocational and recreational activities, and considerations of localization for potential surgery.

The conventional division of a seizure into three phases—interictal, ictal, and postictal—can be helpful for diagnosis and mechanism, but these stages often have indistinct boundaries. With regard to seizure duration, for example, how long does an interictal discharge need to be for a clinical change to be observed? Recent documentation of behavioral changes during single interictal spikes underlies the complexity of distinguishing interictal from ictal events (2). Similarly, the postictal component of a seizure is not always clear cut on EEG (3). Since EEG is often ambiguous about whether a particular rhythm represents a seizure and because there is blurring of the interictal, ictal, and postictal phases for many seizure types, it is clear that we need a better understanding of what constitutes the pathophysiological and behavioral essence of the seizure. Further fundamental questions were discussed such as whether it is necessary for a seizure to always involve excessive



neuronal discharge or increased synchrony, whether a seizure can arise in areas of the brain other than cerebral cortex (e.g., subcortical regions such as the thalamus or basal ganglia), and whether certain behaviors are always required for the clinician to diagnose a seizure. As summarized in a recent commentary, “We probably have to live with a fuzzy definition” (4). Some clinical and electrographic seizures are unambiguous, others are very uncertain, and there is continuity between these two extremes.

Can some of these practical and conceptual questions be answered in the laboratory? Helen Scharfman plunged into this topic by considering recordings from animals. Recordings from hippocampus raise numerous potential confounds as to whether or not a particular pattern represents seizure activity. For example, the age of the animal is critical; younger animals have more sharp waveforms, as also seen in human EEG recordings (5). Sharp transients also vary by strain, gender, and recording site/cortical layer. Perhaps most importantly, the behavioral state of the animal is critical when analyzing EEG recordings. Helen showed examples of EEG tracings that clearly deviate from baseline activity and resemble paroxysmal ictal discharges, yet simply characterize the quiet, resting state of a normal animal after a period of active exploration. Therefore, false positive ictal-like activity should be a major caveat for epilepsy researchers using EEG recordings from animals. Ideally, recordings should be compared from both hippocampi as well as from extra-hippocampal sites. The challenge remains to distinguish normal from abnormal waveforms in behaving animals (6). This theme was further explored by David Prince, who discussed criteria for defining ictal activity in brain slices. His recent work involves two transgenic animal models, the C1q knockout (7) and  $\alpha\delta 1$ TH mice engineered with a mutation of thrombospondin (8). In both of these models, *in vitro* recordings showed cortical hyperexcitability at ages before the animals demonstrated seizures *in vivo*. David concluded that for *in vitro* activity to be classified as ictal, it needs to be elicited in an all-or-none manner by a threshold stimulus, have a minimal duration of 100 msec, and propagate across cortex. As summarized by Leena Knight, the essence of seizures likely involves evolving brain rhythms, sometimes synchronized or excessive, other times not; since definitions are in flux, the multiple potential confounds need to be considered carefully by experimenters.

### What Is an Epileptic Focus?

Another set of fundamental questions in epilepsy includes: What comprises a focus? What is the functional and importance of a focus, and can its removal “cure” seizures? Rather than consider a “focus” as a single, definable area of brain from which seizures originate, Pete Engel conceptualized a seizure as deriving from a distributed network of abnormal neuronal activity. He acknowledged that EEG spikes often localize to a specific area, with a larger adjacent region—an epileptogenic zone—being necessary and sufficient for seizure genesis. In that sense, a focus is not simply an abnormal area but a theoretical construct that cannot be measured. Much of epilepsy is progressive over time, complicating the definition of an isolated focus. Similarly, Pete stated that there is no recent evidence for the existence of an inhibitory surround, previ-

ously assumed be the region of cortex surrounding a focus that retards seizure spread. He stressed that even a generalized seizure begins “somewhere” in the brain, probably as a bilateral diffuse network rather than a single focus. In that regard, the difference between a focal and generalized seizure resides in the extent of the network abnormalities. Pete supported his contention that epilepsy is a distributed network by pointing out that sites of seizure generation are dynamic and that removal of a presumed focus may lead to subsequent seizure generation elsewhere. Further, some children with neocortical epilepsy have spikes everywhere but over their identified dysplastic lesion, and some people with mesial temporal sclerosis have their highest after discharge threshold in the presumed focus.

Are some interictal spikes “good” and others “bad”? Massimo Avoli’s presentation considered whether physiological changes observed in epilepsy can be homeostatic rather than pathological (9). For example, some neuronal changes may represent attempts of the brain to compensate for the pathophysiology rather than themselves being epileptogenic. Damir Janigro reviewed the role of the blood–brain barrier breakdown in epilepsy, emphasizing that blood–brain barrier disruption can itself lead to seizures but also that this breach can potentially be an advantage for antiepileptic drug delivery (10). Daryl Hochman added that in neocortical human epilepsy, afterdischarges can correlate with interictal spikes and seizure onset zones. Discussants reminded the group that in the early kindling literature, it was reported that no single lesion could reliably prevent kindling and that even removal of the amygdala could not avert amygdaloid kindling.

### What Can We Learn from Animal Models?

Animal models of seizures and epilepsy are the link between more reductionistic mechanism studies and human disease. Jong Rho led off the session by querying the best way to glean information from animal models in terms of drug discovery. How many models are sufficient? Can animal models truly mimic the human brain? Can we use informatics to obtain a good subset? He proposed a tripartite model whereby clinical features, cellular electrophysiology, and whole animal models form interacting points of investigation for developing antiseizure drugs and antiepileptogenic drugs. Using the example of infantile spasms, Aristeia Galanopoulou elaborated on the recent profusion of models for this devastating epileptic encephalopathy. Only a few years ago, there were no animal models of infantile spasms (11); now, at least six animal models of infantile spasms exist, each having advantages and disadvantages but each capable of addressing specific aspects of this disorder (12, 13). There is optimism that the various models might provide critical information about the age-dependence of spasms, the physiological basis of the unique interictal EEG pattern (hypsarrhythmia) that likely underlies the encephalopathy, and why infantile spasms are often responsive to treatment with adrenocorticotropic hormone (ACTH).

Scott Baraban discussed two exciting trends in the use of models to understand epilepsy: First, in the pilocarpine model, data indicates that transplantation of median ganglionic eminence progenitor cells can alleviate spontaneous recurrent seizures despite the occurrence of mossy fiber sprouting and



cell death (14). Second, zebrafish represent a model system with tremendous potential in epilepsy research. Zebrafish are complex vertebrates with transparent body surfaces, allowing analysis of complex neuronal activity and bursts of synchronized activity with visual ease (15). This model can be easily manipulated genetically, allows high throughput drug screening, and is being adapted to various epilepsy models, such as Dravet syndrome.

Jurgen Wenzel reviewed the relationship between structural lesions and epilepsy in a variety of genetic models. The *p35* gene is a neuron-specific activator of cyclin-dependent kinase 5, critical for neuronal migration and cortical lamination. Deletion of *p35* leads to cortical and hippocampal dysplastic developmental lesions and seizures, comprising a model of temporal lobe epilepsy (16, 17). In mice lacking the potassium channel  $K_v1.1$  alpha subunit (*Kcna1* gene deletion), another model of temporal lobe epilepsy, seizures precede the development of structural abnormalities and are therefore considered to be causative in this model (18). In the  $K_v2.1$  mutant, seizure threshold is decreased but there is no structural lesion. Therefore, there is a wide diversity of roles played by developmental and structural lesions in genetic models of epilepsy.

Behavioral and cognitive consequences of epilepsy in animal models were described by Carl Stafstrom, focusing on co-morbidities that can be examined experimentally with the goal of reducing these co-morbidities (19). An example with clinical translational relevance is depression. Depression is extremely common in patients with epilepsy, affecting up to 30% of individuals with epilepsy (20). The recent availability of animal models of depression opens avenues for exploring the neurobiological mechanisms of these overlapping disorders (21). For example, in the lithium-pilocarpine model of temporal lobe epilepsy, it has been proposed that activation of the interleukin-1 $\beta$  signaling pathway in the hippocampus leads to dysregulation of the hypothalamic-pituitary axis, upregulating serotonin receptors in brainstem regions such as the raphe nucleus. Disruption of raphe-hippocampal serotonergic transmission may then facilitate the development of depression (22).

### What Are Some of the Hot Areas of Epilepsy Research?

Leading off a session in which a variety of “hot research areas” and rational therapies were discussed, Jeff Noebels commented upon recent studies that have implicated interneuron dysfunction (so-called “interneuronopathies”) as a basis for some epileptic encephalopathies (23). At present, approximately 24 genes for epileptic encephalopathies have been identified, with a large variety of causative mechanisms including those that decrease neuronal activity, decrease excitability, and affect GABA synthesis, receptor binding or function (24). Emerging evidence suggests that the expression of genes regulating ion channels and synaptic function are strongly dependent on developmental stage. Just as acute seizures in the normal brain do not represent epilepsy, creating epilepsy in normal animals does not necessarily mimic natural epilepsy. The genetic background is critical in both situations. Steps required for a “cure” of genetically based epilepsy include finding the gene, mapping the associated neuronal circuits, discovering

how activity must be altered to stabilize neuronal synchrony, and then taking more precise aim at the target for treatment. Exome sequencing is ushering in a new era by which epilepsies will be classified by gene variance (25). Further advances in understanding the abnormal circuits in the epileptic brain are expected from novel techniques such as CLARITY, which can render an entire brain optically transparent for study of cellular and molecular details heretofore not possible (26).

Ben Strowbridge and colleagues are developing fascinating new techniques to study spatial learning and memory in intact animals. Intracellular recordings from dentate gyrus neurons during short-term memory tasks in awake, behaving mice have demonstrated that the animals encode specific temporal sequences involving specific circuits (27). To determine whether animals use only visual cues when they learn a spatial task or also require nonvisual sensory input, Ben employed a virtual reality task, and found that visual cues were indeed sufficient (28). Application of these behavioral techniques to animals with epilepsy will expand understanding of the mechanisms by which seizures alter a wide range of cognitive functions (29).

The importance of ion channel regulation in neuronal excitability, a topic of direct relevance to epilepsy, was emphasized by Jim Trimmer. A-type voltage-gated potassium channels, which regulate action potential propagation and neurotransmitter release, are altered after pilocarpine-induced status epilepticus in layer- and subunit-specific ways, contributing to the hyperexcitable circuit dysfunction following these seizures (30). Jim also discussed antibody-based methods to validate ion channels as targets for drug discovery (31). Rob Berman explored why seizures might be so common in neurodevelopmental disorders, such as such neurofibromatosis, autism, and Rett syndrome (32, 33). Emerging evidence favors various sorts of synaptic dysfunction in these disorders, with the ever-growing list of gene mutations (e.g., neuroligin, Shank3, TSC1/2, PTEN, CDKL5) providing multiple routes to neuronal hyperexcitability and seizures, possibly with therapeutic opportunities arising from their discovery (34). Lastly, Elsa Rossignol considered the potential for personalized medicine in epilepsy, first requiring the identification of cell-type specific dysfunctions and then creatively designing therapies based on mechanism (35, 36). These targets might include histone deacetylase inhibitors, mTOR antagonists, verapamil, and so on. She underlined the importance of next generation sequencing for determining epilepsy etiologies and developmental biological and optogenetic techniques for implementation of cell based epilepsy therapies.

### How Can Epileptogenesis Be Studied/Modified?

Deciphering the process by which the brain becomes epileptic (epileptogenesis) and discovering ways to intervene in this process remain among the most critical areas of epilepsy research (37, 38). In particular, understanding epileptogenesis in the developing brain will facilitate prevention of both epilepsy and its co-morbidities in the young population. Nico Moshé recalled that Hippocrates was the first to comment that children are more susceptible to seizures than are older individuals. Nico discussed factors in the developing brain that could lead to such increased seizure susceptibility, including incomplete



myelination, altered subunit composition of ion channels, and immature balance of synaptic excitation and inhibition (39, 40). He stressed that not every seizure will lead to brain damage or epilepsy and that seizure-related brain damage is age- and region-specific (41).

In a masterful overview of the pilocarpine model of chronic epilepsy, Paul Buckmaster addressed the question of whether synaptic reorganization is necessary or sufficient for the development of temporal lobe epilepsy. Using rapamycin to suppress mTOR and block mossy fiber sprouting, Paul showed that spontaneous seizures occurred nonetheless, leading to the conclusion that mossy fiber sprouting is not essential for chronic epilepsy, at least in the pilocarpine model (42).

While the effects of sex hormones on neuronal excitability have long been recognized (43), their role in the modulation of epilepsy has been underappreciated. Catherine Woolley noted that brain synthesis of neurosteroids can markedly alter neuronal excitability on a sex-related basis (44). Specifically, in female rats, estradiol decreases inhibitory postsynaptic currents by promoting endocannabinoid signaling via metabotropic glutamate receptor (mGluR) coupling; curiously, this effect is not seen in males. It is obvious that the effects of hormones on neuronal excitability need much deeper attention.

Mike Haglund presented data on the use of light-scattering techniques to evaluate blood volume changes in humans during neurosurgical procedures and in primates undergoing epilepsy (45). This fascinating technique allows precise localization of an epileptic focus based on concurrent EEG and optical imaging techniques, and also suggests the existence of an inhibitory region surrounding the excitatory focus.

### What Is the Role of Synaptic Plasticity?

The final session dealt with the topic of synaptic plasticity and how neuronal circuits are reorganized in epilepsy. Synaptic plasticity is usually defined as relatively short-term changes in efficacy. Longer-term structural plasticity is also important for development and lesion recovery as well as epileptogenesis, as emphasized by Dennis Turner. He warned that certain antiepileptic drugs may suppress the plasticity needed for recovery, and that some neuronal sprouting is likely to be compensatory.

Continuing the theme of synaptic plasticity, Bob Wong discussed the common neurodevelopmental disorder, fragile X syndrome, which is due to absence of fragile X mental retardation protein (FMRP). Individuals with FXS have mental retardation as well as an increased incidence of seizures (46). In a normal animal, FMRP inhibits the synthesis of several dendritic proteins by limiting mRNA translation. In fragile X knockout mice (*Fmr1*), lack of FMRP allows enhanced dendritic protein synthesis, causing an increase in long-term depression (LTD), a form of synaptic plasticity that underlies learning and memory. In *Fmr1* knockout mice, increased activation of group I mGluR (especially mGluR5) leads to enhanced LTD and cognitive impairment, popularly known as the mGluR theory of mental retardation (47). Bob's lab has identified a novel depolarization-activated, voltage-gated inward current,  $I_{mGluR(V)}$ , that becomes prolonged in *Fmr1* knockout mice and can lead to epileptic bursting in CA3 neurons, providing a possible explanation for the increased seizure predisposition in this syndrome (48, 49).

The ion carrier of  $I_{mGluR(V)}$  might be calcium-mediated transient receptor potential canonical (TRPC) channels (50).

Finally, the control of protein synthesis by the eukaryotic initiation factor 4E-binding protein (4E-BP2), a repressor of mRNA translation, was discussed by Jean-Claude Lacaille. Removal of translational repression in mice by deleting 4E-BP2 upregulated synthesis of glutamate subunits GluA1 and GluA2 and enhanced AMPA-mediated synaptic transmission (51). In these 4E-BP2 knockout mice, the threshold for the late phase of long-term potentiation (LTP) is lowered, and the LTP is no longer mTOR-dependent. Therefore, this mutation alters a specific type of long-term synaptic plasticity and can result in altered learning and memory as well as an autism-like phenotype (52).

### Final Comments

The lively discussion engendered at this conference is difficult to express on paper. Hopefully, this brief summary captures some of the essence of the discussion, but it does not attempt to review comprehensively any of the topics discussed. A few references are provided for further reading. The information provides a starting point for thinking about some of the fundamental questions in epilepsy and how these can be addressed experimentally with potential benefit to humans. That theme epitomizes the career of Dr. Phil Schwartzkroin. Phil's influence on the field of epilepsy is hard to overestimate. The excitement among epilepsy veterans as well as those new to the field was tangible at this meeting. Attendees were confident that Phil's spirit of rigorous inquiry will continue for many more generations.

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by Carl E. Stafstrom, MD, PhD

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Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	x				
2. Consulting fee or honorarium	x				
3. Support for travel to meetings for the study or other purposes	x				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	x				
5. Payment for writing or reviewing the manuscript	x				
6. Provision of writing assistance, medicines, equipment, or administrative support.	x				
7. Other	x				

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.

**Section #3 Relevant financial activities outside the submitted work.**

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institutio*	Name of Entity	Comments**
1. Board membership		0	0	Charlie Foundation	
2. Consultancy		yes	0	Questcor	Consulting on infantile spasms
3. Employment	x				
4. Expert testimony	x				
5. Grants/grants pending	x				
6. Payment for lectures including service on speakers bureaus	x				
7. Payment for manuscript preparation.	x				
8. Patents (planned, pending or issued)		no	yes	Wisconsin Alumni Research Fund	Patent for research on antiepileptic effects of 2-deoxyglucose
9. Royalties		yes		1. UpToDate 2. CRC Press	1. On-line chapter on epilepsy mechanisms 2. Book: Epilepsy: Mechanisms, Models, Translational Perspectives
10. Payment for development of educational presentations	x				
11. Stock/stock options	x				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	x				
13. Other (err on the side of full disclosure)	x				

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4 Other relationships**

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

  x   No other relationships/conditions/circumstances that present a potential conflict of interest.

     Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.  
Epilepsy Currents Editorial Board