



WHAT IS AN EPILEPTIC SEIZURE? UNIFYING DEFINITIONS IN CLINICAL PRACTICE AND ANIMAL RESEARCH TO DEVELOP NOVEL TREATMENTS

Raimondo D'Ambrosio, PhD¹
and John W. Miller, MD, PhD²

¹Associate Professor of Neurological Surgery, Neurology and UW Regional Epilepsy Center, University of Washington, Seattle, WA

²Professor of Neurology and Neurological Surgery, Director, UW Regional Epilepsy Center, University of Washington, Seattle, WA

After the great successes of the mid-20th century in the development of drug treatments for epilepsy, subsequent attempts to identify more efficacious therapies have led to incremental improvements but have not had an impact on the problem of medically intractable epilepsy. Indeed, one-third of epilepsy patients still continue to have uncontrolled seizures (1,2), and no method has been found to prevent the development of epilepsy in those at risk (3). Many investigators have proposed that further progress in creating new epilepsy treatments might be made using models with chronic recurrent spontaneous seizures (epilepsy), as opposed to acute evoked seizures. In addition, seizure semiologies and etiologies that approximate those of human epilepsy syndromes better than models currently used for drug discovery, are more likely to involve mechanisms of ictogenesis and epileptogenesis that are relevant to the corresponding human syndrome (4–8). Therefore, substantial efforts have recently been made to introduce into basic and translational research epilepsy models with realistic etiologies that more closely mimic human syndromes, such as stroke (9,10), head injury (11,12), early-life febrile seizures (13), and hypoxia–ischemia (14,15). These new models have a variety

of types of spontaneous seizures, including short nonconvulsive partial seizures. Because these seizures differ from the typical motor seizures currently employed in drug development, there could be controversy among investigators as to their significance and whether they are truly seizures. Although there is general agreement that epileptic seizures consists of occasional, sudden, hypersynchronous discharges of gray matter (16), the operational definitions of seizures and the endpoints used to assess treatment results still vary widely in clinical practice and experimental research. Thus, a clarification of the definitions of seizures is needed, because this determines the preclinical endpoints used to test novel therapies for seizure control and epilepsy prevention. This review will first discuss the differences among clinical and experimental definitions of seizures and the detrimental consequences of this disparity to the understanding of mechanisms of epilepsies and the development of better treatments. It will then propose an operational definition of seizures that apply equally well to both humans and animals. Adoption of these definitions could facilitate comparisons of data across laboratories and the translation of new therapies to the bedside.

Definitions of Seizures in Humans and Their Clinical Diagnosis

In clinical practice, the great majority of seizures are temporally discrete events with, stereotyped electrical and clinical occurrences, but there is no standard definition of the sundry behavioral, sensory, and perceptual manifestations of seizures. The identification of human epilepsy is not based on arbitrary criteria, such as specific motor phenomena (e.g., clonic or tonic–clonic activity), a minimum duration of seizures, or the presence of a postictal state, all used in some schemes to identify experimental seizures. There are telltale ictal behaviors, for which accompanying electrographic discharges cannot be observed or proven; however, there also may be subclinical seizures with electrographic changes on the EEG, without detectable behavioral accompaniment. Sometimes brief, stereotyped behavioral events, such as tics and certain other manifestations of movement disorders, can occur in humans but are not associated with electrographic changes, because they are not seizures. Even EEG, while it is more reliable than behavioral analysis, is not always sufficient by itself to prove epilepsy. A recent study determined that when video EEG monitoring data were analyzed by clinicians blinded to all other clinical data, they might arrive at different conclusions about whether seizures are epileptic in origin (17). Thus, the identification

Address correspondence to Raimondo D'Ambrosio, PhD, Associate Professor of Neurological Surgery, Neurology and UW Regional Epilepsy Center, University of Washington, Box 359915, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. E-mail: raid@u.washington.edu

Epilepsy Currents, Vol. 10, No. 3 (May/June) 2010 pp. 61–66
Wiley Periodicals, Inc.
© American Epilepsy Society

of human seizures is most secure when electrical and behavior changes occur together in a stereotyped fashion.

Patients often are first diagnosed with epilepsy and first prescribed antiepileptic drugs (AEDs) based on a clinical history of abnormal behavior that has features stereotypic of seizures, even if there are no epileptiform findings on scalp EEG. In these cases, the physician judges from history or observation that treatment is justified without further corroboration from diagnostic testing. However, if a patient's events are not controlled by AEDs or if the clinical history is unclear, subsequent management often involves long-term video-EEG monitoring to capture examples of typical events; to demonstrate that they are indeed seizures rather than nonepileptic episodes, which may have psychiatric or physiological causes; and to characterize the patient's epilepsy syndrome. Thus, clinical diagnosis ultimately relies either on a clear clinical history, with a successful response to treatment, or on EEG.

The most common types of seizures in humans are the complex partial seizures (CPSs) that are defined as focal seizures with altered consciousness, and the next most common types are the generalized tonic-clonic seizures (GTCS) (18). In typical epilepsy surgery series that only include pharmacoresistant patients, CPSs are the predominant or exclusive seizure type (19). Clinical manifestations of partial seizures are diverse and depend on the brain regions of onset, the areas of spread, and the occurrence of secondary generalization (20). Semiology may range from intense clonic movements of part of the body to motionless unresponsiveness, lasting only a few seconds, to automatisms, which occasionally include socially embarrassing behavior, such as partial undressing, urination, or cursing (21,22). In fact, CPSs are most commonly disabling because of the associated disturbance of consciousness and not because of the presence or extent of motor manifestations. While a mean duration of approximately a minute has been reported for CPS events, durations from a few seconds to several minutes occur (21,23). A distinct postictal phase is reported in about 20% of CPSs (23). The predominance of CPSs in population surveys and in series of intractable epilepsy implies that adequate modeling of this seizure type should be a primary goal of modern, translational epilepsy research.

Localization-related epilepsy also manifests as simple partial seizures (defined as focal seizures without altered consciousness) or secondarily GTCS. The majority of simple partial seizures have nonmotor, subjective symptoms, including somatosensory, special sensory, autonomic, or affective components (24). Only 21% of simple partial seizures have electrographic changes on scalp EEG, and the duration of the events is quite variable, ranging from 2 seconds to about 6 minutes (24). GTCS may be preceded by variable manifestations of simple or CPSs. The motor manifestations of the GTCS itself, including the tonic and generalized clonic phases, have a mean

duration that averages about 1 minute but is rarely longer than 2 minutes (25).

The clinical manifestations of generalized epilepsy are often less diverse, consisting predominantly of absence, myoclonic, and GTCS. In the majority of events, absence seizures do not consist solely of motionless loss of responsiveness but also manifest some subtle automatisms, mild clonic components, or change in tone (26). Mental clarity returns immediately at the end of the seizure. While the majority of absence seizures last less than 10 seconds (26), longer ones do occur, as does absence status epilepticus (27).

In some cases of localization-related epilepsy with a clear clinical history, confirmatory evidence may include as little as well-documented interictal epileptiform spikes or sharp waves on the scalp EEG. In patients with epilepsy with associated EEG abnormalities, the distinction between interictal and ictal epileptiform discharges is somewhat arbitrary, because when continuous neuropsychological testing is performed, about 50% of patients show transient cognitive impairment during events that are generally regarded as subclinical or interictal (28). Preliminary evidence that suppression of interictal epileptiform discharges with AEDs may improve psychosocial function in some patients further demonstrates that these EEG abnormalities may be associated with effects on cognition (28).

The great diversity of ictal phenomena seen in localization-related and generalized epilepsy syndromes means that the operational definition of seizures in humans includes temporally discrete, repetitive episodes with stereotyped symptoms, and behavioral signs that have a broad range of semiologies and last from a few seconds to many minutes. To be relevant for translational research, experimental seizure definitions must adequately replicate this wide variety of human seizure types of different durations that are observed and treated in clinical practice.

Current Definitions of Experimental Seizures and Their Limitations

Currently, there is no universal approach to identifying and classifying seizures in animals, by electrophysiology or behavior. Definitions of experimental seizures are numerous and more restrictive than those used for humans. Most require that seizures are detected by ECoG and have a minimum duration, which varies widely among research labs and can be up to 30 seconds. Sometimes, seizures are expected to always be followed by postictal changes in behavior. Most commonly, experimenters require seizures to have specific clonic or tonic-clonic behavior. These arbitrary criteria diverge animal research from clinical practice, as they focus on specific types of motor seizures, while excluding other types that may better reproduce human CPSs.

The use of arbitrary definitions of seizures in basic science may be rooted in research traditions that started with the study of evoked seizures. This endures because it facilitates the study of spontaneous seizures in several ways: 1) It permits distinguishing nonconvulsive seizures from normal behavior of the animal in the absence of ECoG or an experimentally set time of occurrence. 2) It simplifies the definitions of the transition from interictal to ictal events. 3) It allows exclusion of age-dependent short (<10 seconds) idiopathic seizures in experimental rodents that may occur equally in controls and manipulated animals. 4) It simplifies the identification of seizures when using visual inspection and automated seizure detection programs. The use of arbitrary seizure definitions may also reflect an incomplete appreciation by nonclinicians of the importance of partial seizures in humans. Misconceptions about CPSs are common, as illustrated by educational tapes that have been produced for the lay public and police to help prevent misidentification of nonconvulsive CPSs, as rude or aggressive behavior, intoxication, or an expression of a psychiatric condition (29–33). In addition, there may be a misconception that the most important seizure type to treat is GTCS, while the most common seizure type in the general population and, most importantly, in patients who are resistant to AEDs, is actually the CPS (18,19).

While it is typical clinical practice to determine a patient's epilepsy syndrome, which includes identifying the range of associated seizure types, full characterization of the epilepsy syndrome is rare in animal research. Rather, it is a common practice to try to identify and sort behavioral events within a preexisting classification system, such as the Racine scale, and thus, to neglect other types of seizures that may occur in the animal (34). In fact, typically, investigators studying acquired epilepsies wait for the development of clear behavioral seizures (i.e., clonic or tonic-clonic events meeting the criteria of Racine scale 3–5) and then use these as endpoints for testing therapies. There rarely is an attempt to assess the effects of the therapeutic intervention on spontaneous seizures that are associated with mild motor manifestations (Racine score 1–2 or not described by the Racine scale at all).

The Racine scale is widely used to define focal experimental seizures. This classification system was originally developed to describe electrically evoked motor events and was effective because the time of seizure occurrence was under the experimenter's control. The scale was originally conceived with five stages: 1) mouth and facial movements, 2) head nodding, 3) forelimb clonus, 4) rearing, and 5) rearing and falling. With modification, this scale has been useful for the behavioral analysis of spontaneous seizures paired to electrophysiological data. For example, Bragin and coworkers demonstrated spontaneous epileptiform ECoG activity coinciding with chronic behavioral events (staring, oral facial twitching, wet-dog shakes, clonic

forepaw movements, rearing, and loss of balance) resulting from unilateral kainate hippocampal injections (35).

However, the Racine scale can have significant limitations when it is used to study spontaneous seizures without simultaneous ECoG recording. Some types of chronic spontaneous seizures occurring after head injury in the rat are consistent with nonconvulsive human CPSs but are not represented by the Racine scale; thus, a new scale had to be developed to fully describe this syndrome (11,12,36). Seizures not rankable by the Racine scale were observed, in which the animal would first suddenly interrupt its normal exploratory or grooming behavior, briefly crawl on the bottom of the cage, and then stop with its head propped on its forelimbs, staying motionless for 1 to 10 seconds. After this stereotyped behavior, cortical discharges, and sometimes facial automatisms or dystonic posturing of a hindlimb, would appear. In addition, similar to what has been reported by Bragin et al. (35), seizures were observed that consisted of motion arrest by the animal, sometimes with facial automatisms. Since motion arrest is also part of normal behavioral repertoire of the animal, ECoG recordings were essential to distinguish these events from normal behavior (Figure 1). Thus, blinded analyses were performed to demonstrate that the episodes of motion arrest during epileptiform ECoG represented genuine seizures. Very similar, brief behavioral events have also been identified in humans, with simultaneous short electrocorticographic discharges recorded from surgically implanted subdural electrodes (Figure 2). Löscher and Brandt also found the Racine scale inadequate in a model of chronic epilepsy following status epilepticus. This scale could not describe some of the resulting partial seizures, which consisted of jerky backward movements of the head and coincident cortical epileptiform discharges, sometimes associated with short, clonic forelimb movement (37). Thus, the Racine scale cannot fully characterize epileptic syndromes in all animals, whether induced by classic or recent models. Not surprisingly, the Racine scale is also inadequate to describe many of the diverse behavioral manifestations of human CPSs.

Duration-based definitions of epileptic seizures in animals, while practical, are also problematic, as they have no basis in human epilepsy. The fluid percussion injury model of posttraumatic epilepsy has recently been used to demonstrate the inadequacy of duration-based arbitrary definitions of epilepsy (36). Employing blinded analyses of behavioral and ECoG changes in the rat, it was shown that a common operational definition of a seizure from clinical practice (i.e., a stereotyped repetitive electrobehavioral event) could be fully satisfied for epileptiform ECoG events that are as short as 0.8 seconds, which was the shortest duration investigated. The most commonly observed behavioral change with this type of short seizure was a freeze-like motion arrest of the animal.

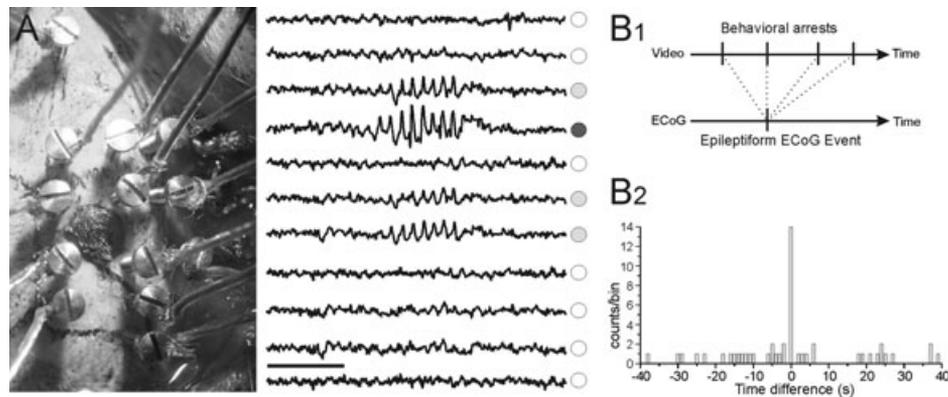


FIGURE 1. Evidence that behavioral analysis alone is not sufficient to fully appreciate some epilepsy syndromes. (A) Electrode implant (left side) in a rat following fluid percussion injury. Note the craniotomy through which the mechanical injury is delivered, and the surrounding epidural screw electrodes. Short focal spontaneous seizure (right side), lasting approximately 1.5 seconds, as detected by epidural ECoG chronically after head injury in the rat. Most of the short ECoG events coincide with motion arrest of the animal and are therefore, clinical seizures. Hollow circles indicate electrodes not involved with seizures, black circles indicate electrodes proximate to seizure onset, and gray circles indicate areas of seizure spread. Calibration bars indicate 1 second. (B) Unbiased evidence that short focal epileptiform ECoG discharges in the rat are ictal events is obtained by blinded examination of the behavior during ECoG monitoring. (B1) Schematic illustrating how the temporal sequence of behavioral arrests (video) and epileptiform electrographic events (ECoG) in video-ECoG data files were scored by an examiner blinded to the ECoG. (B2) Cross-correlogram of behavioral arrests versus seizures, reported as number of behavioral arrests versus the time before or after the seizures, represented at time 0. The time scale is in 1-second bins. The greatly elevated incidence of behavioral arrest during seizures (bin 0) demonstrates that while behavioral arrest may occur as part of normal rat behavior, it is also a form of ictal behavior. Thus, a simple behavioral analysis, without electrophysiological evaluation, cannot distinguish the two phenomena and is not sufficient to fully appreciate the epileptic syndrome of the animal. Figure adapted with permission, D'Ambrosio et al. (35).

The practice of defining away experimental seizures that have subtle behavioral manifestations or short duration may, for multiple reasons, significantly hamper the development of better treatments. First, while screening potential antiepileptic therapies, new agents that may control human CPSs more ef-

fectively than existing AEDs might be missed. This, in turn, may result in the development of new, but redundant drugs that primarily target GTCS. Second, if a potential new antiepileptogenic therapy is tested in a model with both CPS and GTCS, but the treatment only prevents GTCSs, if the CPS which

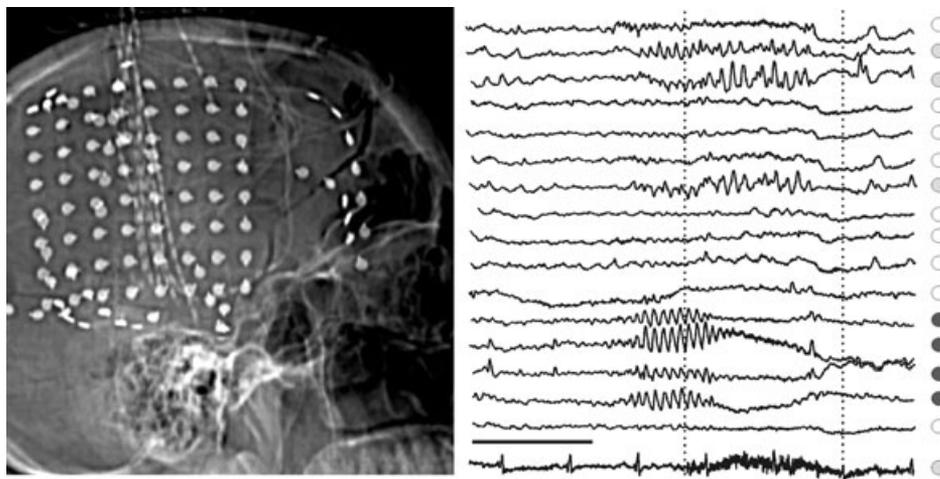


FIGURE 2. Similarity of short focal neocortical seizures in humans to those observed in the rat. Left panel) Lateral x-ray images of a patient's skull after electrode placement. C-right panel) Short seizures lasting approximately 2 seconds in the same patient, who presented with ictal sites in the motor cortex EMG revealed the occurrence of simultaneous ictal behavior, consisting of twitching of a pectoral muscle, during the short seizures. The skin electrode trace (lower trace) presents the evidence of muscle contraction during epileptiform ECoG events (vertical dotted lines). Thus, short seizures, similar to those observed in the rat (see Figure 1), also occur in humans. Hollow circles indicate electrodes not involved with seizure, black circles indicate electrodes proximal to seizure onset, and gray circles indicate areas of seizure spread. Calibration bars indicate 1 second. Figure adapted with permission, D'Ambrosio et al. (35).

remain are not recognized as seizures, this effect might be mistaken as antiepileptogenic, but the animals will still have epilepsy. Third, while investigating mechanisms of ictogenesis, a process that would prolong the duration of seizures beyond a set threshold will incorrectly appear to precipitate seizures, just as one that would shorten seizures below that threshold will falsely appear to prevent seizures. Thus, there would be confusion among mechanisms of seizure precipitation, maintenance, and termination—each important targets for therapy. Finally, some forms of experimental acquired epilepsy may present with a progressive increase in the duration and severity of seizures. In such models, the silent period between the epileptogenic event and the first seizure may actually merely be a period during which seizures go unrecognized, because an arbitrary criterion, such as a minimum duration, has been employed and excludes the earliest events (36).

Unifying Definitions of Seizures

The path to standardization of the operational definitions of epileptic seizures arises from the recognition that experimental animals can have seizures that replicate the variety of human CPSs and that the clinical definition of epilepsy will always be the reference point for research that has the ultimate purpose to prevent or control human epilepsy. Thus, operational definitions for experimental seizures should be based on the definitions used for humans and then expanded to include other seizure types that can be induced in animals but are species-specific, such as running seizures seen in audiogenic rodent epilepsy or the rearing and falling limbic seizures classified in the Racine scale. In addition, other research endpoints may be included that may not be seizures, per se, but nonetheless are useful in the investigation of mechanisms and treatments of epilepsy, such as activity that is interictal or transitions from interictal to ictal. The definitions of seizures used in research cannot be more restrictive than those used in humans.

Jackson's pathophysiological definition remains the foundation for identifying seizures in both humans and experimental animals (16). Repetitive events that are discrete in time and associated with stereotyped and coincident electrical and behavioral changes are seizures. This notion places no requirements for a minimum duration of the event, the presence of a postictal state, or the occurrence of clonic behavior. Events that are electrographically similar to seizures, but without detectable behavioral changes, could be subclinical seizures or interictal events—both could subtly affect cognition in patients and therefore, are of interest for the preclinical development of therapies. ECoG may be required to demonstrate nonmotor partial seizures in animals, since altered consciousness cannot be directly assessed. Seizures may be quite brief, as short as a second or two, as in humans. Special classification schemes,

such as the Racine scale, may be helpful to address specific experimental questions but are not useful as the foundation for defining what is a seizure.

Recent advances in data storage have made video-EEG/ECoG a practical tool for identifying and characterizing experimental seizures. Basic scientists can approximate the clinical practice of using both electrophysiology and behavior to first identify and characterize the epilepsy syndrome presented by the animal and then sometimes might choose ECoG or behavior to continue their work, based on which method is sufficient to detect all seizure types of the syndrome. Even with this approach, there may be situations in which there is honest disagreement among investigators. The way to remedy such controversies is to go back to basics by grounding experimental models in the context of the human epileptic condition and also by adapting clinical neurodiagnostic procedures to experimental laboratories.

Acknowledgment

Raimondo D'Ambrosio's work was in part supported by the National Institutes of Health (NS053928) and by CURE foundation.

References

1. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult Epilepsy. *Lancet* 2006;367:1087–1100.
2. French JA. Refractory epilepsy: Clinical overview. *Epilepsia* 2007;48(suppl 1):3–7.
3. Temkin N. Preventing and treating posttraumatic epilepsy: The human experience. *Epilepsia* 2009;50(suppl 2):10–13.
4. Meldrum B. Do preclinical seizure models preselect certain adverse effects of antiepileptic drugs? *Epilepsy Res* 2002;50:33–40.
5. White HS. Animal models of epileptogenesis. *Neurology* 2002;59(9 suppl 5):S7–S14.
6. White HS. Preclinical development of antiepileptic drugs: Past, present, and future directions. *Epilepsia* 2003;44(suppl 7):2–8.
7. Schmidt D, Rogawski M. New strategies for the identification of drugs to prevent the development or progression of epilepsy. *Epilepsy Res* 2002;50:71–78.
8. Sloviter RS. The neurobiology of temporal lobe epilepsy: Too much information, not enough knowledge. *Curr Rev Biol* 2005;328:143–153.
9. Kelly KM, Kharlamov A, Hentosz TM, Kharlamova EA, Williamson JM, Bertram EH, IIIrd, Kapur J, Armstrong DM. Photothrombotic brain infarction results in seizure activity in aging Fischer 344 and Sprague Dawley rats. *Epilepsy Res* 2001;47:189–203.
10. Kharlamov EA, Jukkola PI, Schmitt KL, Kelly KM. Electrophysiological characteristics of epileptic rats following photothrombotic brain infarction. *Epilepsy Res* 2003;56:185–203.
11. D'Ambrosio RD, Fairbanks JP, Fender JS, Born DE, Doyle DL, Miller JW. Post-traumatic epilepsy following fluid percussion injury in the rat. *Brain* 2004;127(Pt 2):304–314.
12. D'Ambrosio R, Fender JS, Fairbanks JP, Simon E, Born DE, Doyle D, Miller JW. Progression from frontal-parietal to mesial-temporal epilepsy after fluid percussion injury in the rat. *Brain* 2005;128(Pt 1):174–188.

13. Dubé C, Richichi C, Bender RA, Chung G, Litt B, Baram TZ. Temporal lobe epilepsy after experimental prolonged febrile seizures: Prospective analysis. *Brain* 2006;129(Pt 4):911–922.
14. Williams PA, Dudek FE. A chronic histopathological and electrophysiological analysis of a rodent hypoxic-ischemic brain injury model and its use as a model of epilepsy. *Neuroscience* 2007;149:943–961.
15. Klein PM, Rakhade S, Jensen FE. Hippocampal depth recordings from long evans rats subjected to neonatal seizures reveal development of spontaneous limbic seizures. Proceedings of the American Epilepsy Society meeting. *Epilepsia* 2009;50(suppl11):385. Abstract.
16. Jackson JH. On the anatomical, physiological, and pathological investigations of epilepsies. *West Riding Lunatic Asylum Medical Reports* 1873;3:315–349.
17. Benbadis SR, LaFrance WC Jr, Papandonatos GD, Korabathina K, Lin K, Kraemer HC; NES Treatment Workshop. Interrater reliability of EEG-video monitoring. *Neurology* 2009;73:843–846.
18. Hauser WA. Seizure disorders: The changes with age. *Epilepsia* 1992;33(sup 4):S6–S14.
19. Henry TR, Drury I, Schuh LA, Ross DA. Increased secondary generalization of partial seizures after temporal lobectomy. *Neurology* 2000;55:1812–1817.
20. Penfield W, Jasper HH. *Epilepsy and the functional anatomy of the human brain*. Boston: Little, Brown, 1954.
21. Leppik IE. *Contemporary diagnosis and management of the patient with epilepsy. Chapter 2: The classification of seizures*. Newton, Pennsylvania: Handbooks In Health Care, 1997.
22. Swartz BE. Pseudo-absence seizures. A frontal lobe phenomenon. *J Epilepsy* 1992;5:80–93.
23. Theodore WH, Porter RJ, Penry JK. Complex partial seizures: Clinical characteristics and differential diagnosis. *Neurology* 1983;33:1115–1121.
24. Devinsky O, Kelley K, Porter RJ, Theodore WH. Clinical and electrographic features of simple partial seizures. *Neurology* 1988;38:1347–1352.
25. Theodore WH, Porter RJ, Albert P, Kelley K, Bromfield E, Devinsky O, Sato S. The secondarily generalised tonic-clonic seizure: A videotape analysis. *Neurology* 1994;44:1403–1407.
26. Penry JK, Porter RJ, Dreifuss RE. Simultaneous recording of absence seizures with video tape and electroencephalography. A study of 374 seizures in 48 patients. *Brain* 1975;98:427–440.
27. Lipman IJ, Isaacs ER, Suter CG. Petit mal status epilepticus. *Electroencephalogr Clin Neurophysiol* 1971;30:162.
28. Binnie CD. Cognitive impairment during epileptiform discharges: Is it ever justifiable to treat the EEG? *Lancet Neurology* 2003;2:725–730.
29. Epilepsy Foundation. Understanding complex partial seizures. VHS, Family Video Library, 1990.
30. Epilepsy Foundation. Seizure disorders and the school I (elementary). VHS, Family Video Library, 1991.
31. Epilepsy Foundation. Seizure disorders and the school II (secondary). VHS, Family Video Library, 1991.
32. Epilepsy Foundation and Police Executive Research Forum. Take another look: Police response to seizures and epilepsy. VHS, Family Video Library, 1992.
33. Epilepsy Foundation. How to recognize and classify seizures and epilepsy. VHS, Family Video Library, 2003.
34. Racine RJ. Modification of seizure activity by electrical stimulation. II. Motor seizure. *Electroencephalogr Clin Neurophysiol* 1972;32:281–294.
35. Bragin A, Engel J Jr., Wilson CL, Vizin E, Mathern GW. Electrophysiologic analysis of a chronic seizure model after unilateral hippocampal KA injection. *Epilepsia* 1999;40:1210–1221.
36. D'Ambrosio R, Hakimian S, Verley DR, Fender JS, Stewart T, Sheerin AH, Eastman CL, Ojemann JG, Miller JW. Functional definition of seizures provides new insights into posttraumatic epileptogenesis. *Brain* 2009;132:2805–2821.
37. Löscher W, Brandt C. High seizure frequency prior to antiepileptic treatment is a predictor of pharmacoresistant epilepsy in a rat model of temporal lobe epilepsy. *Epilepsia* 2009; Jun 26. [Epub ahead of print].

An alternative perspective by F. Edward Dudek and Edward H. Bertram, III will appear in the next issue of *Epilepsy Currents*.