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Comment Letters

Comment on Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)

To the Editor:

Fisher et al. (1) state, "Little common agreement exists on the definition of the terms *seizure* and *epilepsy*," and they propose ILAE-endorsed definitions for these terms. Although their proposed definition of "seizure" is consistent with that which has been in use throughout the field for decades, their proposed definition of epilepsy is not. Fisher and colleagues (1) propose the following definition of epilepsy: "Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition." The definition of epilepsy in Fisher's Table 1 (1) requires the occurrence of at least one epileptic seizure but not that the seizure be unprovoked. Although it may be helpful to consider diverse conditions (febrile seizure, acute symptomatic seizure, single unprovoked seizure, and epilepsy) within the context of studying the seizure disorders, it is not helpful to consider all of these conditions as epilepsy. The more restrictive definition of epilepsy (recurrent unprovoked seizures), adopted by the ILAE Commission on Epidemiology and Prognosis (2), is related to therapeutic, management, and counseling approaches and supported by epidemiologic studies of seizure disorders. Furthermore, this definition has been largely adopted in clinical practice and was instrumental in developing practice guidelines (3).

The failure to clarify the concept of "enduring" is a problem with the proposed definition, and it is unclear how Fisher et al. (1) would define or make operational this term. Making operational "enduring alteration of the brain that increases the likelihood of future seizures (1)" would require a list of indicators of such an alteration. These, in turn, would have to be qualified and changed as knowledge increases. For clinical and scientific purposes, the operational criteria must be simple and robust. We suggest instead that the best way to know whether a person has an enduring alteration of the brain that increases the likelihood of future unprovoked seizures after a first seizure is the occurrence of a second unprovoked seizure.

This new definition would reclassify many situations previously excluded from the term *epilepsy* in recent studies. Examples include a single provoked seizure secondary to a neurologic insult (e.g., stroke), a single provoked or unprovoked seizure in someone with depression or migraine, and a febrile seizure in a child with cerebral palsy, with an epileptiform EEG, or with febrile seizure recurrence. The all-inclusive definition proposed by Fisher et al. (1) is consistent with use before the emergence of the epidemiologic studies of seizure disorders and epilepsy over the past 60-year period. The exclusion of these conditions from the diagnosis of epilepsy was based on large, carefully conducted clinical and population-based studies.

Most acute symptomatic seizures would be recategorized as epilepsy under the definition proposed by Fisher et al. (1). Acute symptomatic seizures have been defined as seizures in close temporal association with a transient CNS insult and presumed to be an acute manifestation of the insult. Although the risk of developing unprovoked seizure is higher in people with acute symptomatic seizures, in most, later seizures do not develop. Although the incidence of acute symptomatic seizure is similar to the incidence of epilepsy, the high early mortality and the protective effect of anticonvulsants on the development of acute symptomatic seizures dramatically distinguish this category of seizures from epilepsy.

By the proposed definition (1), many children with febrile seizures, the most common convulsive disorder, would be reclassified as having epilepsy. This would be true for children with developmental delay, neurologic abnormalities, epileptiform EEG abnormalities, complex febrile seizure, and recurrent febrile seizure. Regardless of the presence of such factors, in most children with febrile seizure, later unprovoked seizures do not develop (4,5). Restricting the diagnostic labeling of epilepsy to the few who truly have recurrent unprovoked seizures would seem prudent.

It is useful to study single unprovoked seizures within the context of epilepsy to better understand the underlying processes to increase the risk for the development of recurrent unprovoked seizures. Contrary to the proposed definition (1), the epidemiologic data on recurrence risks support separating single unprovoked seizure from recurrent unprovoked seizures (i.e., epilepsy). The recurrence risk is lower after a first unprovoked seizure (typically $<50\%$) than the recurrence risk after a second unprovoked seizure for both children and adults (6,7), suggesting that the recurrence of unprovoked seizure or lack thereof delineates different entities.

A major problem with the proposed definition (1), particularly for those with single seizure and with febrile seizure, is that labeling patients with only a single seizure as having epilepsy, when many will never experience another seizure, will cause unnecessary use of anticonvulsant drugs, increase stigma, and result in social and

occupational limitation. This does not serve the needs of these patients and is inconsistent with epidemiologic data.

The inclusion of associated conditions in the proposed definition (1) raises concerns on several levels. Although general agreement may exist that "for some people with epilepsy, behavioral disturbances such as interictal and postictal cognitive problems, can be part of the epileptic condition (1)," the definition as written seems to require these disturbances for the condition to be epilepsy. Thus a person with multiple unprovoked seizures and a likelihood of more would not have epilepsy by the definition of Fisher et al. unless one of these associated conditions also was present. This aspect of the proposal creates a new unnamed category that may be quite large—people who clearly have recurrent unprovoked seizures, but lack documentation of associated conditions. Even if the proposed behavioral component is accepted as an essential ingredient in the definition of epilepsy, it is unclear how this would be made operational.

Other consequences ensue from this definition. The incidence of "epilepsy" will increase at least threefold, and the increase in prevalence will be greater, particularly in developing countries, which may provide political leverage. Undesired consequences of use of this definition will be the invalidation of prognostic studies, including those of mortality, long-term prognosis for seizure remission, and response to initial therapy.

Contrary to the proposal of Fisher et al. (1), widespread acceptance of and agreement over the definitions of seizures and epilepsy are in general use in the field. We fail to see the advantages of the proposed definitions to the individual patient, to epilepsy as a condition, or to the study of epilepsy and the convulsive disorders. Maintaining a common language has been acknowledged in several ILAE Commission and Task Force reports as a prerequisite to communication and comparability of research from different groups. In addition, the medical, social, and emotional implications of epilepsy and seizures speak in favor of a separation between acute symptomatic seizures, febrile seizures, and unprovoked seizures and, for those with unprovoked seizures, between single and repeated episodes. To this end, the current definitions have been most successful. They are based on a process similar to the evidence-based approaches used for evaluating therapies and therapeutic policies. They may be subject to revision as new information comes to light, but this process should be respected. It does not appear that proposed definitions advance the field in any way.

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REFERENCES

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: Definition proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470–2.
2. Commission on Classification and Terminology of the International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 1993;34:592–6.
3. Hirtz D, Berg A, Bettis D, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice Committee of the Child Neurology Society. Practice parameter: treatment of the child with a first unprovoked seizure: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2003;60:166–75.
4. Annegers JF, Hauser WA, Elveback LR, et al. The risk of epilepsy following febrile convulsions. *Neurology* 1979;29:297–303.
5. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who experience febrile seizures. *N Engl J Med* 1978;61:720–7.
6. Shinnar S, Berg AT, O'Dell C, et al. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. *Ann Neurol* 2000;48:140–7.
7. Hauser WA, Anderson VE, Loewenson RB, et al. Seizure recurrence after a first unprovoked seizure. *N Engl J Med* 1982;307:522–8.

On the Definition of Epileptic Seizures and Epilepsy

To the Editor:

We have some comments on a recently published article on the definition of epileptic seizures and epilepsy (1):

1. As the authors say, those definitions are important for medical professionals. However, their article has just two references, which seem insufficient both to support their views and to allow others to assess the scientific basis of their assertions.

2. The authors state that seizures can originate in the cerebral cortex, in thalamocortical interactive systems, or in the brainstem. As clinicians, we wonder which parts of the brainstem could be accepted as a source of seizures, and we would appreciate some relevant citations. We also would like to know whether seizures can arise in the cerebellum, as has been claimed (2–4). For us, it would be important to know the official position of the International League Against Epilepsy (ILAE) on these matters.
3. We agree with the idea of sustaining the diagnosis of epilepsy after the first epileptic seizure, just as we consider that a patient has a cerebrovascular disease after his first stroke. What is difficult for us to interpret is the sentence "multiple epileptic seizures due to multiple different causes in the same patient would not be considered to be epilepsy." In some examples in the literature, a patient is considered to have two types of epilepsy (5).
4. Another sentence from the article deserves a comment: "a single epileptic seizure due to an enduring epileptic abnormality would indicate epilepsy, and a single epileptic seizure in a normal brain would not." We can imagine an example: a teenager without any remarkable past event has a first generalized tonic–clonic seizure on awakening. In this case, we could suspect the presence of an idiopathic generalized epilepsy. However, if no family history of epilepsy exists and both the magnetic resonance image and the first electroencephalogram are normal, how could we demonstrate the "enduring epileptogenic abnormality"? If we could not, should we retain the ILAE term "unprovoked" isolated seizure to classify such cases and keep them apart from epilepsy and acute symptomatic seizures (6)?
5. Stigma, exclusion, restrictions, overprotection, and isolation were all common in patients with tuberculosis some decades ago, but not now. In our opinion, these elements are not inherent to any disease and should not become part of the definition of tuberculosis or epilepsy.
6. Finally, we do not understand why an official paper of the ILAE must be assessed by anonymous referees to be published in the official journal of the ILAE. What would have happened if they had advised not to publish the manuscript? The potential submission of the paper to another journal would appear strange indeed. Perhaps a better idea would be to present the important papers of the ILAE in preliminary form to an audience of epileptologists in some international meeting. This open discussion of the paper might have enriched it and might clarify its repercussions on the diagnosis and classification of epileptic seizures and syndromes.

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REFERENCES

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470–2.
2. Harvey AS, Jayakar P, Duchowny M, et al. Hemifacial seizures and cerebellar ganglioglioma: an epilepsy syndrome of infancy with seizures of cerebellar origin. *Ann Neurol* 1996;40:91–8.
3. Chae JH, Kim SK, Wang KC, et al. Hemifacial seizure of cerebellar ganglioglioma origin: seizure control by tumor resection. *Epilepsia* 2001;42:1204–7.
4. Mesiwala AH, Kuratani JD, Avellino AM, et al. Focal motor seizures with secondary generalization arising in the cerebellum: case report and review of the literature. *J Neurosurg* 2002;97:190–6.
5. Koutroumanidis M, Hennessy MJ, Elwes RDC, et al. Coexistence of temporal lobe and idiopathic generalized epilepsies. *Neurology* 1999;53:490–5.
6. ILAE Commission Report. The epidemiology of the epilepsies: future directions. *Epilepsia* 1997;38:614–8.

Epileptic Seizures and Epilepsy

To the Editor:

The article by Fisher et al. (1) introduces a modified consensus on the definition of epilepsy. The new definition appears more appropriate from an epileptologists' perspective other than few shortcomings: The term *enduring alteration in the brain* is qualitative rather than quantitative. How do we define or measure this enduring alteration? Although enduring alteration in the brain can be appreciated in the presence of epileptiform discharges and certain structural abnormalities, in other situations, this cannot be determined. By this definition, how do we classify a patient immediately after a temporal lobectomy for mesial temporal sclerosis who does not have epileptiform discharges? It would be nice to have guidelines to determine when a patient with a previous diagnosis of epilepsy is no longer considered to have epilepsy and that the enduring alteration in the brain has been fixed. This would do a great service to many patients who have been seizure free for a considerable time. The implications not only will affect their psychological well-being but also will contribute positively to their social and vocational interests.

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REFERENCE

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470–2.

Response: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)

To the Editor:

We appreciate the comments of our fifteen colleagues who commented on the "definitions" article (1–3). Before responding to the substance, we first would like to assert that the definition of epilepsy expressed eis open to revision, but it was carefully considered. The process of forming the definition spanned three years of an ILAE subcommittee, and the definitions passed through three levels of nonanonymous review (subcommittee, Commission on Diagnostic Methods, ILAE Executive Committee), and then anonymous review in *Epilepsia*, done with a guest editor to maintain anonymity, since the first author also is an *Epilepsia* editor. In response to the point of Dr. Gomez-Alonso and associates (3), publication of an article in a peer-reviewed journal, such as *Epilepsia*, is not and should not be automatic, simply because it represents a consensus of an official ILAE body.

Webster's dictionary defines the word "definition" as "a statement expressing the essential nature of something" (4). Some definitions are "mechanistic" and others "operational." We favored the former, but are sympathetic to the desire of some to use operational definitions for specific purposes, because the two are not mutually exclusive. Some studies may choose to continue to use the "two spontaneous seizures" definition for ease of application. A mechanistic definition does not require intrinsically that it be easily applied; rather, the key is that it captures the essence. What then is the essential nature of epilepsy? In 1888, Gowers declared that "epilepsy is applied to a disease in which there are convulsions of a certain type, or sudden impairment of consciousness, but in which the convulsions are not directly due to active organic brain disease. . ." (5). No requirement for two seizures was expressed. As pointed out by Beghi et al. (1), the "two seizure" requirement came later. How clear is this commonly recognized definition? The older definition typically is taken to require two "unprovoked" seizures, but the meaning of "unprovoked" is elusive. Does provocation include sleep deprivation, stress, hormonal cycles, and many other immeasurable factors? All seizures are provoked by some internal or external stimulus, whether or not we recognize the provocation. We submit that the existing definition is flawed and ambiguous, although in a familiar way that brings comfort to some epidemiologists.

The subcommittee and reviewers believe that the essence of epilepsy is an exhibited seizure, in conjunction with an enduring predisposition to generate further epileptic seizures. For example, most practitioners would choose to treat an individual with an astrocytoma with anti-seizure medications after a single seizure. As such, it seems inaccurate to call this treatment for an acute symptomatic seizure, since the acute seizure already has happened. In fact, the treatment is to reduce the relatively high likelihood of a future seizure. We assert that this circumstance refers to a condition that should be called epilepsy. Conversely, circumstances can be imagined with two seizures, widely separated in time and due to different causes, not correctly labeled as epilepsy. The inclusion of associated conditions was discussed extensively in the committee. Whether such conditions are so universal as to be an intrinsic part of the definition can continue to be debated.

Our definition should not affect the approach to a first seizure. In fact, physicians usually try to ascertain whether there is an enduring epileptogenic abnormality before making a diagnosis. The conditions mentioned by Beghi et al. (1), such as recurrent febrile seizures or a seizure within a week of a stroke, do not meet our definition of epilepsy. The subcommittee did not feel justified, at current levels of knowledge, in putting numerical criteria on the "enduring predisposition," but if we had, it would have been calibrated to a level (e.g., more than a 50% lifetime risk) that would have rendered the prevalence of epilepsy not so different from those that exist today. We agree with Dr. Ahmed (3) that clarification of the meaning of enduring predisposition," including expert input from epidemiologists, would be welcome.

In conclusion, the easiest definition is not always the best. In American baseball, rule changes, which have happened about twelve times since the days when Gowers was alive (6), have driven baseball statisticians to despair, but most of the changes have made for a better game. We are sorry that Beghi et al. (1) believe that the new definitions, "do not advance the field in any way"; however, the stimulus to discuss, debate, refine and revise such definitions may in fact advance our understanding and the clarity of our thinking.

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REFERENCES

1. Beghi E, Berg A, Carpio A, et al. Comment on Epileptic seizuers and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy. Epilepsia. 2005;46:1698–1699.
2. Gomez-Alonso J, Andrade C, Koukoulis A. On the Definition of Epileptic seizures and Epilepsy. Epilepsy 2005;46:1699–1700.
3. Ahmed S. Epileptic Seizures and Epilepsy. Epilepsia 2005;46:1700–1701.
4. http://www.m-w.com/cgi-bin/dictionary.
5. Gowers WR, A manual of diseases of the nervous system. Birmingham, AL: Gryphon Editions, 1983:(original 1888)1078.
6. Schwarz A. The history of rule changes. ESPN Baseball. Available at: http://espn.go.com/mlb/columns/schwarz˙alan/1503763.html