

Editorial Commentaries

Editor's Introduction: Cabbages and Kings in the Classification of Seizures and the Epilepsies

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Laws are like sausages, it is better not to see them being made. Otto von Bismark

To the extent to which a new classification of seizures resembles a law or a sausage, it might be preferable to ignore how the classification is made. In the special articles that follow, we choose to take the opposite approach. These articles will expose to public scrutiny some of the deliberations and debate in this controversial area. Peter Wolf submitted the lead article. I asked Drs. Engel, Lüders, Avanzini, and Berg to provide responses. All articles were subject to peer-review and revision. These authors have debated their points of view for years. The thought underlying their positions has educational value, even in the absence of a full consensus.

The articles in this section occasionally refer to per-

sonalities or processes internal to the International League Against Epilepsy (ILAE), the owner of this Journal. I chose not to edit out such references, so the readers could see the sausage being made, but the primary purpose clearly is not criticism of persons or processes, but of ideas. Contrary to widespread opinion, the ILAE has not yet issued a suggested revised classification of seizures or syndromes. Discussion remains at the level of what such a classification should accomplish and comprise. As we proceed, we might keep in mind the advice of Albert Einstein that “*Things should be made as simple as possible—but no simpler.*” Few areas in epileptology will have such a great need for wise simplicity.

Of Cabbages and Kings: Some Considerations on Classifications, Diagnostic Schemes, Semiology, and Concepts

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*‘The time has come,’ the Walrus said, ‘To talk of many things: Of shoes and ships and sealing-wax, of cabbages and kings, And why the sea is boiling hot, and whether pigs have wings.’ Lewis Carroll, *Through the Looking-Glass**

Discussions about classification of seizures, epilepsy and epilepsy syndromes have appeared in journals (1–8), and at many national and international meetings. A task force of the ILAE is working on the complex issues of classification, and the ongoing debate shows the high interest of the epilepsy community. At some times, this discussion seems confusing. Why is that so? Classifications are related to definitions, and it may therefore be useful first to define the meaning of “classification.” This is not the same everywhere. Of three languages with a long tradition in scientific classifications, classification

in French, according to Robert, means “action de distribuer par classes, par catégories; résultat de cette action: classement, division. Science de la classification: systématique, taxonomie.” [Action of distributing by classes, by categories; result of this action: grouping, distribution. Science of classification: systematics, taxonomy]. Here, the usage of classification encompasses three distinct, well-defined meanings. In German, the second such language, Klassifikation has only one meaning and, unlike French, does not comprise the action of classifying (this would be called Klassifizierung or Klas-

sifizieren). To quote Meyers, a much-used dictionary, *Klassifikation* means (my translation) “a systematic distribution or arrangement of, amongst others, terms, objects and phenomena in classes (groups) [and subclasses (subgroups) etc.] that are each characterized by distinct criteria.” The English definition of “classification” is much less clear. According to the Oxford English Dictionary, classification signifies: (1.) The action of classifying or arranging in classes, according to common characteristics or affinities; assignment to the proper class; (2.) The result of classifying; a systematic distribution, allocation, or arrangement, in a class or classes; especially of things which form the subject matter of a science or of a methodical inquiry.

The English definition of “classification” therefore comprises several ambiguous meanings. Definition includes creation of a classification system, assignment of a concept to a classification system, and assignment of an individual item to the appropriate class of an existing classification system. Most of these meanings are mixed up in the present discussion of Epilepsy classification, which leads to jumbled discussions of “shoes, ships, sealing-wax, cabbages and kings.” We would perhaps benefit from a discussion using the more precise terms of French or German. Thus, what has been presented as a “semiological classification of epileptic seizures” by Lüders et al. (3,4) can in German not be called a *Klassifikation* at all (8), because it is not a taxonomic system. A different term is needed in German for such an arrangement (rather than “a classification”). However, English is the language in which this discussion must take place. Taxonomic, scientific classifications are not utilitarian. They are not written to be directly used by anybody, but to reflect the state of knowledge in a particular scientific field.

Johns Hughlings Jackson compared a botanist’s and a gardener’s classification of plants. The botanist, like all scientists, needs a taxonomy; the gardener something to use in daily work. Jackson returned to this comparison in no less than five of the articles included in his *Selected Writings* (9), published between 1873 and 1888. He detailed his views in a chapter entitled “On Classification and on Methods of Investigation” from 1874, in which he says (I, 191f): “There are two ways of investigating diseases, and two kinds of classification corresponding thereto, the empirical and the scientific. The former is to be illustrated by the way in which a gardener classifies plants, the latter by the way in which a botanist classifies them. The former is, strictly speaking, only an arrangement. The gardener arranges his plants as they are fit for food, for ornament, etc. One of his classifications of ornamental plants is into trees, shrubs, and flowers. His object is the direct application of knowledge to utilitarian purposes. It is, so to speak, practical. The other kind of classification (the classification properly so-called) is

rather for the better organization of existing knowledge, and for discovering the relations of new facts; its principles are methodical guides to further investigation. It is of great utilitarian value, but not directly.”

Unfortunately, the present epilepsy classification debate evidences very little of the terminological acumen displayed by Jackson. For example, Engel (10) pointed out clearly that Lüders et al. (3) had proposed not “a classification system, but rather a descriptive terminology of ictal events.” The latter statement could be argued; rather, it is a kind of diagnostic guide for the bedside, an “arrangement” in Jackson’s terms. But the argument then moves to a discussion of the “uses of a classification system for epilepsy,” mixing scientific with utilitarian purposes, “cabbages with kings.” Then a “pair of shoes” is added about the differentiation of limbic versus neocortical seizures, which has to do with the conceptualization of the seizure classification. The discussion then was topped with “sealing wax,” i.e., a discussion of neonatal seizures, an issue unrelated to seizure semiology, pathophysiology, anatomy or diagnosis. Mention of neonatal seizures belongs in the age-relations section of the syndrome classification. Another example is a recent paper in this journal (7) that compares “cabbages with kings,” or a botanist’s with a gardener’s classification, and finds that the latter one is more useful for the purposes of gardeners. This is obvious.

We should reserve the term “classification” in epileptology to taxonomic systems, i.e., Jackson’s “classifications properly so-called,” and call other things something different. Criticism (11) can be directed at the ILAE Task Force’s recently published proposal of a “diagnostic scheme for people with epileptic seizures and with epilepsy,” (12) but at least we did not call it a classification. The ILAE document (12) anticipates that a flexible and variable “approach to organization, categorization, and classification of seizure types will be devised for specific purposes.” Properly speaking, this is a feature of a diagnostic arrangement, but not of a classification. You can have, in one system, either taxonomy or flexibility, but not both. Since we obviously need both a classification and diagnostic guides in different circumstances, each should be developed. The classification should be the backbone of the diagnostic schemes or guidelines. A classification should be as detailed and precise as is possible. Those who use it for a utilitarian purpose then need to decide how much of the available detail they need for their particular purpose.

Is the current ILAE Classification of Epileptic Seizures (ICES) (13) suitable to serve as such a scientific backbone or do we need a new scheme? What really is wrong with the 1981 ICES? I believe that nothing fundamental is wrong concerning its taxonomic principles and system. Nevertheless, it is outdated. It also has a problem with the distinction of “simple” and “complex”

focal seizures, depending upon the concept of consciousness. It calls "focal" seizures "partial." Furthermore, it inappropriately includes information about the interictal EEG that belongs in the syndrome classification. If a classification is outdated and imperfect, the usual response is to update and revise it. It is hard to understand why that has not yet been done, especially since the authors of the ICES (the *crème de la crème* of international epileptology of the time) expected a revision (13). The originators of the Classification developed it from the then novel technology of ictal video recordings. They knew that they had only a subset of seizure types on video. They also were aware that the 1981 ICES was mostly a framework, a "skeleton" which needed to be "fleshed out, and the nuances elaborated" (13).

The novelty of the 1981 ICES was the approach to a seizure as an event unfolding over time, rather than a gestalt that is assessed after its completion. As a result, the classification was based upon the description of a sequence of signs and symptoms. It followed a semiological principle, by which every single sign and symptom is fully discerned and available for evaluation. At the time, we were fully aware of this change (14,15). When neurologists analyze seizures as they develop in time, we try to understand what brain phenomena are reflected in the development of the seizures. The more we understand, the more we will move from a mere semiological approach to a true semiology, i.e., an understanding of the significance of the signs and symptoms. This should be the ultimate scientific aim of our efforts at classifying seizures. The authors of the 1981 ICES were aware of this issue, but were constrained by the contemporary state of knowledge. They included some basic anatomical data in the "definition of terms" section of the ICES, and they designed the classification in a way that was open to such a development. This is perhaps the most important value of the old classification, and no newer proposal does the same.

Today, our anatomical understanding of the seizure phenomena has greatly improved, not the least due to the progress achieved by sophisticated presurgical investigations to detect the anatomic substrates of seizures. We could in fact now begin to develop the ICES into a true Semiological Seizure Classification. For such a classification, the preliminary seizure descriptions of the ICES can be used, but need to become more systematic, detailed and precise. Terminology must be supplemented with descriptions of newly included seizure types such as hypermotor seizures (3), which are widely accepted today. Each description would then be followed by an indication of its anatomic significance, modified by the precision and reliability of our present knowledge about that type of seizure. Thus, the description of Jacksonian seizures could be followed by "Jacksonian seizures re-

flect seizure activity in the contralateral motor strip, according to the motor homunculus."

Application of taxonomy can be problematic. For example, with tonic seizures, it may be difficult to distinguish focal from generalized seizures. In this case, the focal entry could read "Focal tonic seizures may remain strictly unilateral, involving a minor or major part of or the entire body half, but they may also extend bilaterally, more often in asymmetric than in symmetric fashion. In this case, differential diagnosis from generalized tonic seizures can be extremely difficult," supplemented by a corresponding entry in the section on generalized seizures. An anatomical clue does not necessarily disclose the localization of the seizure onset, but tells us only where there is seizure activity at the moment when the sign is observed: for example, "hypermotor seizures reflect seizure activity in the frontal lobes which, however, are often only secondarily involved."

The detailed classification of seizures with psychic symptoms of the ICES should be retained, and again supplemented with semiological information, such as for seizures with fear or anxiety: "Fear as a direct symptom of an epileptic seizure is sudden in onset, mostly brief, usually unprovoked, and without defined object. It is often accompanied by autonomic signs such as pupil dilatation, pallor, flushing, piloerection or palpitation. It must be differentiated from fear as a reaction to a seizure or an aura. Primary ictal fear is strongly suggestive of an epileptic focus in the amygdalar nucleus or nuclei, more likely on the right." The inclusion of new seizure types can only benefit from, and should in fact pass through a rigorous procedure similar to the 1989 ICES where the Commission on Classification and Terminology reviewed videotaped seizures before acknowledging any type.

Syndrome classification

Any revision of the syndrome classification would certainly require efforts similar to those formulating the 1985 Classification Proposal (16), in which every candidate syndrome at a three-day meeting was proposed by a presenter reviewing the literature, and then critically discussed. This would include new attempts at conceptualization, such as the recent proposal by Andermann and Berkovic (5). The kind of sifting a commission has to do when dealing with this part of the classification can be demonstrated by the differences between the "Guide bleu" of 1985 (17) and the Commission's document (16), both of which are based on the same meeting. This exercise needs to be done with the proposed syndrome diagnostic scheme (12).

The distinction made by the 1989 ILAE Classification of Syndromes (18) between localization-related and generalized epilepsies has been questioned. This distinction probably is only of temporary use. "Generalized" has

different meanings in the Seizure and the Syndrome Classification, and within each of them (19). The discussion of the regionality of both localization-related and “generalized” epilepsies (20) relates to this question, as well as more recent reflections upon the role of central nervous subsystems in “generalized” epilepsies (21). This is probably the direction in which the discussion will develop, eventually leading to an understanding that will supplant the need for a “generalized epilepsies and syndromes” category. Our current understanding of the pathophysiology and anatomy of “generalized” epilepsies is not yet adequate to replace this blurred concept by something more appropriate.

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Reply to “Of Cabbages and Kings: Some Considerations on Classifications, Diagnostic Schemes, Semiology, and Concepts”

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As Wolf notes (1), the efforts of the ILAE Task Force on Classification and Terminology to reevaluate, and revise, the 1981 International Classification of Epileptic Seizures (ICES) (2), and the 1989 International Classification of Epilepsies and Epileptic Syndromes (ICEES) (3), has engendered considerable interest and debate. The intentions of the Task Force were first presented in 1998 (4). A primary intention was to standardize purely descriptive ictal phenomenology based on suggestions of

Lüders (5). The Task Force endeavored to identify seizure types as diagnostic, rather than purely phenomenological entities, consisting of unique pathophysiological events with etiologic, therapeutic, and prognostic implications as a supplement to the diagnosis of epilepsy syndromes. The plan was to add eventually a classification of underlying substrates, including diseases associated with epilepsy, and a classification of impairment.

The Task Force has so far held three years of meetings

and intense discussions via a working interactive Internet site, <www.epilepsy.org/ctf>, a site open to the public. The result is a diagnostic scheme consisting of five axes, tentative lists of epileptic seizure types and epilepsy syndromes (6), and a glossary of ictal terminology (7). The ILAE accepted the basic concept of the diagnostic scheme at the last meeting of the General Assembly in Buenos Aires in May 2001. None of these proposals are yet complete, nor are any intended to constitute a classification as defined by Wolf (1). Lists of epileptic seizures and epilepsy syndromes remain works in progress. Considerable public debate is anticipated before agreements can be reached on a number of controversial areas. Controversies include clarification and description of the large group of Symptomatic Focal Seizures and the syndromes in which they occur, and acceptance of familial disorders with variable phenotypes such as the Idiopathic Juvenile Generalized Epilepsies (8), Generalized Epilepsy with Febrile Seizures Plus (GEFS+) (9), and Familial Focal Epilepsy with Variable Foci (10). The progress of the Task Force, however, has reached a point where it is reasonable to also begin to consider how to organize and categorize these lists of seizures and syndromes into classifications for various purposes. For this reason, Wolf's essay (1) is timely and most welcome.

ILAE acceptance of the Task Force proposals in May of 2001 created temporary confusion because of mistaken assumptions that these proposals represented a new classification. By now, everyone should realize that there is as yet no replacement for the 1981 ICES and 1989 ICEES, and that these are still the only official ILAE classifications of seizures and epilepsies. There is general agreement, however, that the new classifications yet to be developed will replace the terms "partial" and "localization-related" with "focal," will abandon the concept of "simple" and "complex" seizures based on impairment of consciousness, and will be unlikely to include a complete dichotomy between focal and generalized syndromes. As work begins in earnest on revising these classifications, two main issues arise, both of which are discussed by Wolf (1). The first, of course, is debate over what form these classifications should take. Should we create a scientific "botanist's" classification, or a practical "gardener's" classification? The other, at least equally important, issue is how should the Task Force go about making these crucial decisions. Should it be through closed workshops, or an open democratic process?

The Task Force has made the working assumption that sufficient information about pathophysiologic mechanisms and anatomic substrates of epileptic phenomena has accrued since the 1981 ICES and 1989 ICEES were created, to now permit development of a scientifically based taxonomic categorization upon which to build "botanist's" classifications for both seizures and syn-

dromes. This would certainly be the most academically satisfying approach. Whatever classifications are adopted, they must meet the practical needs of the "gardeners" who will be using them. There are many types of "gardeners," so a single taxonomic classification of seizures and of syndromes should be easily modified to meet the various purposes to which such classifications will be put, as outlined in the first report of the Task Force (4) (Table 1).

Problems have arisen with the current classifications because they cannot be easily adapted for multiple uses. For instance, Lüders (5) proposed a much more detailed classification of epileptic seizures because the 1981 ICES did not provide sufficient semiological localizing information for purposes of surgery, but Lüders' proposed classification is unnecessarily complicated for most general applications. On the other hand, the 1981 ICES and 1989 ICEES were too complicated for some epidemiological purposes, particularly in developing countries where diagnostic resources are limited, so that epidemiologists have tended to develop their own approaches to classification (11). Although the Task Force will initially strive to organize and categorize seizures and syndromes according to scientifically rigorous taxonomic formats, the intention then will be to reorganize these classifications into flexible and dynamic modular versions suitable for specific purposes, from teaching medical students to diverse areas of clinical and basic research.

Considerable effort went into development of the 1981 ICES and 1989 ICEES, and they have been widely accepted and used; therefore, any changes must be carefully considered and justified. Wolf rightly emphasizes the need for a well-informed and deliberate process such as the three-day meeting in which candidate epileptic syndromes were presented and fully discussed by experts, resulting in the "Guide bleu" (12). Similar meetings of the current Task Force have taken place over the past four years, resulting not only in the lists of the seizures and syndromes in the recent proposal (6), but in detailed descriptions of most of these seizures and syndromes contained on the Task Force website <www.epilepsy.org/ctf>. The advent of the Internet has made it

TABLE 1. *Uses of a classification system for epilepsy*

Personal conceptualization
Teaching
Communication between physicians
Primary care physicians and other health workers
Neurologists and epileptologists
Presurgical evaluation
Clinical pharmacology trials
Epidemiological studies
Prognosis
Pathophysiological implications
Etiology

possible for the process of revising the current classifications to be much more democratic than it was fifteen or twenty years ago when deliberations were limited to “the experts” and conclusions presented to the ILAE membership as a *fait accompli*. Today, some discussions are still closed, others take place publicly at regional and international epilepsy congresses, while many others have used e-mail and our interactive website which permits anyone interested to participate. In addition, questionnaires were widely distributed in *Epilepsia* and on the website, to obtain feedback from our membership. Returns so far indicate that there is a high degree of interest in this process, and general support for most of the directions taken so far. Similar questionnaires will be used again as revisions of the 1981 ICES and 1989 ICEES are proposed.

The ILAE General Assembly has encouraged ongoing participation in development of the next classification system, by specifying that it be flexible and dynamic, rather than rigid and impossible to change without future General Assembly approval. Consequently, as soon as revised classification schemes are proposed, they will be subjected to the crucial test of application to all the various uses for which classifications are needed. As the classifications are used, inevitably there will be suggestions for improvement that can then be considered by the Task Force and, if appropriate, implemented. All who use the classifications will have ongoing opportunities to influence further alterations required to meet their own particular needs. Modifications of these classifications will also be made, as necessary, to account for the rapid advances in our understanding of the pathophysiologic mechanisms, anatomic substrates, and genetic bases of seizures and epilepsy. The work of the Task Force on

Classification and Terminology has been a slow and arduous process. We appreciate the active participation and patience of our membership as we begin the next stage of debate on classification itself.

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We read with interest the contribution of Prof. Peter Wolf (1). We certainly agree with his view that any new proposal for classification of epileptic syndromes should be based on clear principles, and that the first task of the ILAE Committee should be the definition of the principles they will use to design a new classification system of epileptic seizures and epileptic syndromes. Indeed, in

the recent report of the ILAE Task Force on Classification and Terminology, headed by Prof. Engel (2), a list of accepted epileptic seizures and epileptic syndromes is presented. However, there is no definition of what he means by accepted epileptic seizure or epileptic syndrome and it is also unclear what Committee or Task Force accepted these entities.

We also agree with Prof. Wolf that the discussion of seizure types is confusing. In the recent report of the ILAE Task Force (2), they indicate that new scientific advances now “permit creation of a list of seizure types that represent diagnostic entities, as opposed to phenomenological descriptions, based on known or presumed common anatomy and pathophysiology. Such diagnostic entities, like syndromes would have etiological, therapeutic and prognostic implications, and could be used to supplement syndromic diagnosis, or stand alone when syndromic diagnoses cannot be made.” In previous publications, we stressed the importance of clear differentiation between the classification of epileptic seizures and epileptic syndromes. We suggested that a clear distinction can be achieved by making a pure semiological (phenomenological) classification of the epileptic seizures (3–10) that contrasts clearly with a more pathophysiological classification of the epileptic syndromes based on the complete clinical and diagnostic picture. The semiological classification system has the advantage of placing the diagnostic emphasis on the epileptic syndrome. The semiological classification of seizures is similar to the systematic specification of a semiological neurological sign (for example, resting tremor), which is only one tool to define the underlying disease (for example, Parkinson’s Disease). There is no room for confusion between the classification of the symptomatology (neurological signs or semiological type of epileptic seizures) and the underlying disease or syndrome. Independent classification of semiological seizure types and epileptic syndromes permits also systematic studies of the occurrence of different semiological seizure types in the various epileptic syndromes and vice versa of the different epileptic syndromes that can be associated with any given semiological seizure type.

The 5-axis approach suggested by the Task Force adds unnecessary complexity and redundancy to the classification of the epilepsies. Axis 1 uses a “glossary” to replace the systematic semiological seizure classification that we have developed and tested in thousands of people with epilepsy in our and other centers. The proposed approach then adds a pathophysiological classification of seizures, whose terminology is very similar to the terminology used in the glossary. Additional complexity is added by a fourth syndromic axis. This redundancy and complexity of this scheme make it extremely unlikely that such a system will eventually be used by non-epileptologists. For example, in the glossary the ILAE Committee defines the terms myoclonic, atatic and atonic (11). In axis 2, Prof. Engel lists distinctive seizure types labeled as myoclonic seizures, atonic seizures, and myoclonic atonic seizures (2). Then on the syndromic level, Prof. Engel identifies an epilepsy syndrome with myoclonic-atatic seizures. (2) Would it not be preferable to adopt a system similar to the classification sys-

tems universally used in clinical neurology? At our institution, as at other epilepsy centers around the world, we successfully have used such an approach, to classify the patient with epilepsy by: 1. defining the seizures semiologically (equivalent to defining the neurological signs or symptoms a patient has); 2. determining the etiology of the epilepsy; and 3. identifying the location of the epileptogenic zone (equivalent to defining the location of the neurological lesion). This is then complemented by describing some essential clinical features (like mental retardation, etc.) and in selected cases by defining an “epileptic syndrome.” However, we believe that most of the currently described “epileptic syndromes” are redundant. These syndromes contain artificial data that are not useful beyond the clinical picture for making the diagnosis of epilepsy, or at the least are too complex. We need a critical review of all the epileptic syndromes, in order to crystallize those that are useful in everyday practice, to add meaningful information to the existing three-axis classification by semiological seizures, etiology, and location of the epileptogenic zone. We have started such a study and are testing the system by applying it retrospectively to thousands of patients seen at the Cleveland Clinic over the last twenty years.

We agree with Prof. Wolf that the semiological seizure classification is a “gardener’s” practical classification system. The three-axis classification system defined above is also primarily a practical “gardener’s” classification that, however, can be used very effectively as a guide for treatment and prognosis. In most patients, epileptic seizures are only epiphenomena to another disease specified by the etiology in the three-axis classification outlined above. Creating special “epileptic syndromes” for these conditions is highly artificial. On the other hand, effective management of the epileptic seizures in these patients requires the definition of the etiology, the semiological seizure type, as also the location of the epileptogenic zone. These practical need justify such a three-axis classification system.

We appreciate Prof. Engel’s intention to have a general debate on the new development of the ILAE classification system. However, we would encourage the Task Force to again critically evaluate the procedure taking into consideration some of the following guidelines:

1. Try to define a classification system that is as simple as possible, avoiding any redundancy. A 5-axis classification is too complex for the use by general neurologists.
2. Define a classification system that is useful and applicable by epileptologists in technologically advanced Epilepsy Centers, and also by nonspecialists who have limited access to modern diagnostic technology. In the semiological seizure classification, this is achieved by defining a limited number

- of broad categories that can be easily applied by just taking the clinical history of the patient (for example by just specifying that a patient has motor seizures). On the other extreme, the semiological classification also allows detailed definition of the ictal semiology essential in advanced epilepsy surgery centers (for example, by classifying a motor seizure as a right hand clonic seizure → generalized tonic-clonic seizure).
3. Try to define a classification system that is close to the system used to classify other neurological disease. This approach would greatly facilitate its acceptance by general neurologists.
 4. Take a fresh look at all the epileptic syndromes, retaining only those that add useful information to the three-axis classification described above. We believe that only a very small proportion of patients with epilepsy have “epileptic syndromes” that require special definition and provide practically useful additional information.
 5. Do not mix glossaries and classification systems. Glossaries should be an addendum to a classification system, not an axis.
 6. As pointed out by Prof. Wolf, the Task Force on Classification and Terminology should define with precision the criteria they used to establish different categories in each axis, making sure that there is no overlap (redundancy) between the categories.
 7. We agree with Prof. Wolf that the ideal classification is the scientific “botanist” classification. However, it is difficult to understand why Prof. Wolf concludes in his comments that a practical “gardener’s” classification is *not* a classification (he uses this argument to dismiss the semiological seizure classification as a “guide for the bedside” or just an “arrangement”). We would encourage the Task Force on Classification and Terminology to actually look for a classification system that com-

plies with the points specified here, whether a practical or scientific classification, or is a mixture of each.

8. Do not publish preliminary data that can be interpreted as an approved classification system. Define a classification system that has been discussed in detail by all members of the Classification Committee, and apply it to a large patient population to test if indeed it is a practically useful system. Once this has been accomplished and the Task Force has had an opportunity to modify the proposed classification system after testing it “in the field,” it is time to publish the results.

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Of Cabbages and Kings: Perspectives on Classification from the Field of Systematics

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Wolf (1) raises a fundamental issue at the heart of current efforts to identify and classify syndromes and seizures in the field of epilepsy—the meaning of “classification” itself. Relative to the English, the German

meaning for “classification” is far more precise and imposes far more requirements on the process, particularly that it be systematic and use specified criteria. Unlike the original efforts, largely from the French school of pedi-

atric neurology, to identify specific forms (classes or syndromes) of epilepsy, recent efforts to expand the Classification of the Epilepsies have become somewhat mired down. Part of this failure may be due to a lack of any rigorous criteria for what constitutes a syndrome as well as a complete absence of a methodological approach for identifying syndromes, i.e., the absence of a true classification process and of a true classification.

Epilepsy does not represent the first naturally occurring “phenomenon” that scientists have tried to understand through classification. In this context, it may be instructive to study how biology has approached the classification of living organisms. Although it is perhaps inappropriate to draw rigid parallels between the classification of life and the classification of the epilepsies, studying the discipline of systematics developed within biology may help provide epilepsy with an initial model, useful concepts, and a vocabulary for discussing those concepts and developing an approach to classifying seizures and seizure disorders that is meaningful both scientifically (to the botanist) and clinically (to the gardener).

Philosophy of Realism: At the heart of the effort of classification is a fundamental notion elegantly summarized by a German scientist, Ax, “There is a real word that exists independently of our intellectual capacity to understand it.” (2) The goal of classifying is to find the natural order or breakdown of objects into natural classes in order to facilitate an understanding of the objects, the groups to which they belong, the relationships among the groups and to permit meaningful study of these naturally occurring phenomena. Applied to epilepsy, we would say that individual types of epilepsy exist independently of our ability to recognize or understand them. A “syndrome” ideally and given perfect knowledge should correspond to a natural class. Members of a natural class should share fundamental biological commonalities. Identification and understanding of these commonalities should provide insight into the mechanisms that result in the disorder and possibly insight into therapeutic approaches for treating or even preventing the disorder in the first place. We do not create these disorders, and our decision to call something a “syndrome” does not necessarily mean that it corresponds to a real, meaningful, biological entity. A very similar thesis was at the center of an argument made by Engel (3) in favor of abandoning the term “complex partial” for classifying seizures.

Classification of Life: The roots of the modern classification of life go back to Linneaus in the 18th century. His hierarchical approach to classifying forms of life—kingdom, phylum, class, order, family, genus, species—is what most of us learned about in an introductory biology course. In the United States, until the 1970s, determina-

tion of what constituted a species was based largely on expert opinion, a criterion with few criteria. During the 1970s and largely due to the “cladists,” the disciples of another German scientist, Willi Hennig, the field ultimately adopted a standard methodological approach for determining what constituted a group of organisms and the interrelations between these groups (4). These changes signaled a subsequent shift from the Linnean “category-based” approach to a focus on natural groups (5). The old and new approaches differed fundamentally in that the category-based approach implied biological equivalence between groups classified at the same level (e.g., mammals, a class of vertebrates, and crustaceans, a class of arthropods) where no such equivalence existed in nature. Phylogenetic systematics imposed no such arbitrary assumptions on the relationships between organisms or groups of organisms. Only the category of species remained as this did, by objective criteria (usually based on sexual reproduction), seem to represent a natural class.

Methods of Systematics: The methods of phylogenetic systematics involve three steps: (a) Identify homologous features in the organisms under study. (b) By comparison between the study group and related groups, determine which features are primitive (i.e., are common to all of the study organisms) versus which are derived (are shared by only some organisms and therefore indicate a common point at which that lineage branched from the others under consideration). (c) Construct a map (tree) of the relationships that reflects shared derived characteristics (the relative similarities and differences) of the different groups identified. The clusters of organisms found at terminal ends of each branch represent species. Prior to the era of molecular biological techniques, the preference and rule was to construct the most parsimonious map or tree in keeping with the notion that one should make as few supernumerary assumptions as possible. Molecular data may allow more complex modeling of the evolutionary process and may guide “tree-making” procedures. This allows for the testing of more intricate hypotheses that were previously relegated to the realm of speculation.

Relevance to Epilepsy: Classification in biology is a highly developed, rich intellectual discipline. As its German definition requires and heritage leads us to expect, there are underlying principles and rules that are followed. Both the explicit methods and the commitment to studying natural classes have considerable relevance to the endeavors to classify the epilepsies.

Currently there are no rules, guidelines, or standards for establishing whether a constellation of features constitutes a “syndrome.” In fact, there are no hard definitions or criteria for what exactly a “syndrome” is. Such

criteria are a prerequisite to developing methods for identifying syndromes. Even without a rigorous definition of a syndrome, however, one can still begin to discuss essential concepts and aspects of a scientific method needed for classifying forms of epilepsy.

Scientific accuracy versus clinical utility: Wolf takes the position that “taxonomic, scientific classifications are not utilitarian.” We agree that, in the end, a primary purpose of classifying epilepsy is clinical, to inform the evaluation, treatment, and management of patients and to provide some basis of expectation for prognosis. However, in the age of tremendous breakthroughs in molecular biology and our growing understanding of human genomics, there are increasing possibilities and unimagined potential for our improving understanding of human biology and disease to lead directly to better treatments and better means of prevention (6). Thus, we also all share the expectation that a better understanding of the biological bases of different forms of epilepsy should lead to better treatment, management, and, one can hope, outcomes. Consequently, a good utilitarian classification should represent the underlying biology of the epilepsies. Admittedly, our understanding of the underlying biology is highly imperfect and may not always have immediate clinical application. For these reasons, all of our understanding of the underlying mechanisms of the epilepsies (from the scientific botanist) may not be reflected in its entirety in a representation of the classification used at a given point in history for diagnosis, evaluation and treatment of some patients (for the utilitarian gardener). However, to take advantage of our biological understanding of the epilepsies, a clinical classification should, at some level, be based upon and reflect the available, relevant information about the underlying biology of the epilepsies and be adaptable as that information changes. The botanist can help the gardener.

Genotype versus phenotype: The gardener may help the botanist too. Accurate classification and therefore identification of biologically homogeneous groups permits advances in understanding cause. The advent of genomics and bioinformatics provide powerful tools for furthering our understanding of all forms of human disease including the epilepsies. These are only tools, however, and do not provide the understanding themselves. To realize their value, we need precise phenotypic characterization as well as careful analysis of associations between phenotypes and genotypes (once that information becomes available) performed in appropriately representative groups of patients. For this reason, requiring that classes of epilepsy correspond as closely as possible to naturally occurring phenomena is a *sine qua non* for understanding the bases—including genetic—of the epilepsies.

Methodological considerations: How studies are performed and analyzed is key to providing scientifically valid and useful information. Several issues need to be considered.

Representative versus truncated sampling: Many studies of syndromes come from highly selected groups of prevalent patients who were diagnosed at varying points in the past and who still seek care for epilepsy and other (perhaps related) neurological problems. This approach leads to a highly skewed sample of patients. One of the strongest forces on sample selection in this instance is prognosis. Patients who do well disappear after a while from the clinic (why should they keep coming back?). What are left are the most difficult or medication-dependant patients, a truncated sample. This renders it difficult if not impossible to conduct valid analyses of characteristics (both genotypes and phenotypes) as it can never be clear whether the characteristics identify the specific syndrome, determine its outcome, or may even, in some cases, be consequences of the outcome. For this reason, the work of identifying new syndromes should be focused in populations of recently diagnosed representative patients groups—before they can experience much attrition related to prognosis—and not on convenient but highly selected prevalence samples.

Differentiation: A syndrome or class of epilepsy should identify a group of patients who are more alike to each other in some fundamental way than they are to other otherwise similar patients. What constitutes “fundamental” of course depends ultimately on a rigorous definition of what constitutes a “syndrome.”

To differentiate between classes of epilepsy requires studying patients who have been differentiated from other classes but who are not further differentiated among themselves. One must then characterize and analyze the diversity within this group (important characteristics) to identify the classes into which different patients fall.

For example, the cryptogenic localization-related epilepsies (CLRE) do not constitute a homogeneous group. It would be inappropriate to try to establish a specific syndrome within this general group by demonstrating that a subgroup was fundamentally different from patients with idiopathic generalized epilepsy (IGE). This is not interesting. All of those in the CLRE group already share characteristics that make them fundamentally different from those with IGE. This does not help to establish subgroups within the broader classification of CLRE. The differentiation must be made within the group with CLRE.

As another example, recent work has suggested that, within the IGE syndromes, there is a cluster of adoles-

cent onset syndromes that may represent a single syndrome with variable phenotypic expression (7). This is an interesting and testable hypothesis. To examine this further, it will be necessary to show that these adolescent onset groups share a derived gene mutation or environmental interaction that is not present in other forms of IGE. Unless other forms of IGE are studied and contrasted to the adolescent forms of IGE, it remains unclear whether the adolescent IGE syndromes are as different from each other as they are from other forms of IGE (Figure 1a) or are truly a cluster unto themselves within the overall grouping of IGE syndromes (Figure 1b).

Lumpers versus splitters: Related to differentiation is the debate about lumping together what may or may not be similar forms of epilepsy or splitting a part groups that may represent minor variations of the same form of epilepsy. Ideally any method for classifying the epilepsies should require identification and measurement of all potentially relevant characteristics (be they phenotypic characteristics, gene mutations, etc.) and appropriate analyses to determine which characteristics truly define and differentiate between “syndromes.” Implicitly, one must be prepared to split before one can lump. Thus we must always be on guard against unwittingly lumping because we are unaware of certain characteristics on which we should have split.

Statistical methods: More than the naturalistic descriptive approach will be needed to identify and differentiate new syndromes. Within molecular biology,

several statistical approaches have been developed largely based on clustering and discriminate algorithms and customized to address the specific needs of taxonomic analysis (8). These programs tend to be tailored to the analysis of nucleotide sequences or amino acids and are based on the assumption that evolutionary mechanisms largely, if not entirely, explain all variation among organisms. This would most likely be an inappropriate assumption for epilepsy.

More general clustering and discriminate techniques are routinely used in the social sciences. There is no reason that they could not be used in epilepsy. In fact, an excellent example of just such an effort is provided by Kaminski et al. (9) who used correspondence analysis (a discriminate technique (10)) to distinguish myoclonic atstatic epilepsy from Lennox-Gastaut syndrome.

Limitations of the analogy: Phylogenetic systematics developed to address specific needs within biology and not within epilepsy. Many limitations will surely become evident if we attempt to apply phylogenetic systematics directly to epilepsy. For example, a plant cannot become an animal. By contrast, one form of epilepsy can “evolve” to another (e.g., a localization-related epilepsy to Lennox-Gastaut syndrome) (11). Of note, Loiseau and colleagues explored some of the advantages and difficulties of applying some of the initial statistical methods used in phylogenetic analysis to the problem of classifying the epilepsies (12). A careful study of how biologists have tackled the classification of life as well as

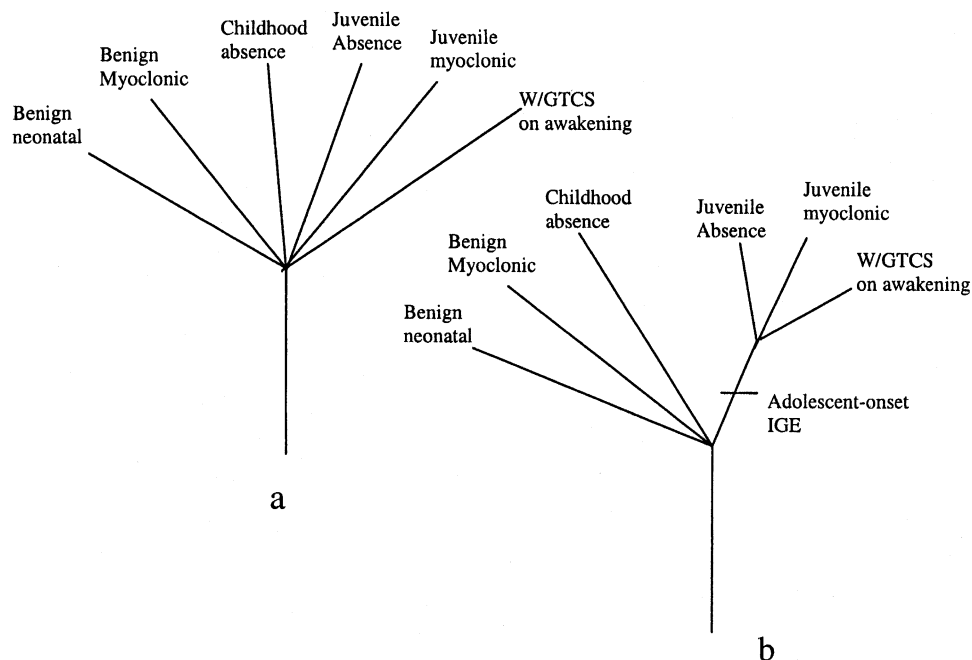


FIG. 1. (a) The various idiopathic generalized syndromes are equally different from each other; (b) The adolescent-onset idiopathic generalized syndromes share one or more derived characteristics that make them more similar to each other than they are to syndromes outside their cluster.

examination of points for which their methods are not directly transferable to epilepsy—thereby forcing us to articulate the differences and perhaps to think about the specific needs in epilepsy—would do much to advance the efforts to classify the epilepsies.

As the practice of medicine should be based on science, scientific purposes in classification should be (now and in the future) consistent with utilitarian purposes. Botanists and gardeners may share common goals. The field of epilepsy needs a scientifically rigorous, systematic approach to help us understand the natural order that surely exists in the diverse set of disorders that we call “the epilepsies.”

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Of Cabbages and Kings: Do We Really Need a Systematic Classification of Epilepsies?

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Pappataci! che mai sento! “Pappataci”! What’s this I hear?

*La ringrazio. Son contento. I thank you and I am happy
Ma di grazia Pappataci But, for mercy’s sake,
Che vuol poi significar? What’s the meaning of “pappataci”?*

L’Italiana in Algeri (G. Rossini)

I hesitated before entering the arena of the classification debate, but decided to take the risk. The following views are personal, and not officially those of the ILAE President or Board.

I shall consider the classifications of epileptic seizures and epileptic syndromes separately. It seems to be generally agreed that our present knowledge allows us to draw up a seizure taxonomy reflecting our “understanding of the significance of signs and symptoms” (1), based on the 1981 ICES and taking into consideration Hans Lüders’s proposal (2). However, I do not agree with

Peter Wolf’s statement that the 1981 ICES (3) faithfully reflects seizures “unfolding over time.” It may be true for some types of seizure, such as Jacksonian and tonic-clonic seizures, whose typical time course is implicit in the definition, but it is not true for others. In particular, the sequence of events characterizing some partial seizures are not easily incorporated into the 1981 ICES (3) definitions, and Hans Lüders’s classification (2,4) provides some helpful concepts for overcoming its limitations. The situation is more complicated when it comes to classifying epileptic syndromes or the epilepsies, as I prefer to call them. Past efforts to classify the epilepsies along the spectra of idiopathic-cryptogenic-symptomatic or partial-generalized categories (5) have advanced our clinical conceptualization. However, ongoing clinical observation and neurobiological studies mandate a revision of our taxonomy (6).

One key question is how the use of the larger idiopathic category helps the clinician or advances our understanding. When I have diagnosed a patient as having childhood absence epilepsy, or a GEFS-plus syndrome, or any other type of epilepsy that is accepted as being idiopathic, what do I gain from putting my diagnosis in the box of the idiopathic syndromes? Idiopathic syndromes share several (but not all) common traits, but would it not be an advantage to be as specific as possible? General categories might be useful for certain purposes, for example, pharmacological trials, in which the authors might wish to give the percentages of the entrants with idiopathic, cryptogenic, or symptomatic epilepsy. Nevertheless, this aggregation of patients contains a trap; some papers give the strong impression that large categories mix “cabbages and kings.” How much more advantageous it would be for the reader to know how many and which patients were classified as having JME, how many as having BECT, and so on!

Similar considerations apply to the utility of the partial (focal)-generalized categorization. We can argue for days about BECT or West syndrome being a partial (focal) or generalized epilepsy, but would either conclusion affect in any way our attitude toward a single patient or a group of patients? On the other hand, forcing every diagnosis into a category may lead to decisions that are simply based on theoretical assumptions. Temporal lobe epilepsy is associated with mesial temporal sclerosis, but current evidence does not prove that it depends on MTS, as would be implied if this diagnosis were put in the category of symptomatic epilepsies. Here again, whether or not an association is considered causative (thus determining a classification in the symptomatic or in the cryptogenic category, respectively) would not influence the clinical attitude and scientific approach to this disorder.

In his thoughtful paper (1), Peter Wolf stresses the concept that a classification reflects the state of our knowledge in a given field, and metaphorically highlights the difference between botanists’ taxonomies and the lists made by the gardeners for utilitarian purposes. From this point of view, I doubt that the principles underlying the previous classification reflect our state of knowledge of “nature and nurture” in epilepsy. Genetic studies (7) are revealing previously unknown types of epilepsies, which sound to us like the *pappataci* did to Mustafa bey in Rossini’s opera, but they have so far failed to identify the genetic basis of the most common, putatively genetic, idiopathic epilepsies. On the other hand, the pathogenetic mechanisms underlying symp-

tomatic epilepsies seem to be much less clear than we thought, as studies on epilepsies associated with hippocampal sclerosis, cortical dysplasias, or genetically determined structural and biochemical defects are increasingly revealing to us.

It is my opinion that we are losing the ground that the previous “botanists” taxonomy of epilepsy was based upon, without a safety net of a new conceptual framework.

What are we then to do? If we cannot be botanists, let’s be gardeners and cultivate the plants we have learned to identify and take care of, even if we do not yet know whether they belong to the thallophyte family or not. To step out of the metaphor, I think that all possible efforts should concentrate on: (a) revising the classification of seizures for which the present pathophysiological information is sufficient, in order to build the necessary conceptual framework; (b) reaching a consensus on a list of epilepsies (8) (or epilepsy types, or epileptic syndromes) for which natural history, constellation of signs and symptoms, prognosis, methods of evaluation and therapy are clear; and (c) creating denominations that clearly designate the distinctive characteristics of the individual syndromes while avoiding the eponyms that tends to deter “nonepileptologists” (but also epileptologists) from adopting the proposed denominations. How such an effort will lead to a systematic classification, cannot yet be elucidated. Personally, I do not think that continuing discussion and debate will upset too many epileptologists.

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