

Berg AT, Blackstone NW. **Of cabbages and kings: perspectives on classification from the field of systematics.** *Epilepsia* 2003 44:8-12.

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 pediatric 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, determination 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 adolescent 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 astatic 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 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."