

Exclusivity versus the Hierarchy, or Fear and Loathing of the Undefined



In the quest to find order amidst chaos, philosophers and scientists have spent lifetimes analyzing, disputing, manipulating, and interpreting ideas, and have been subject to torture and even death, such as the perceived nobility or morality of the cause. Classification of childhood arthritis is not in that league, but, perhaps surprisingly, it has stirred the imagination of many pediatric rheumatologists, and provoked the emergence of modified or alternative ways of describing the clinical heterogeneity of this group of diseases. For decades we have survived, if not benefited by, the differences between the American College of Rheumatology (ACR)¹ and European League Against Rheumatism (EULAR)² classifications of chronic arthritis in childhood. As problematic as the differences between the classifications themselves was their misapplication and the carelessness with which they were used in describing patients in clinical and other studies.

In an international effort to overcome the limitations of the earlier classifications, and to engender international consensus and agreement on classification, the International League of Associations for Rheumatology (ILAR) proposed³ and revised⁴ criteria for what was termed juvenile idiopathic arthritis (JIA). The ILAR criteria are based on inclusion and exclusion criteria and seek to define groups of patients with a high degree of internal homogeneity and without overlap among the 6 specific categories: oligoarthritis (persistent or extended), rheumatoid factor (RF) positive polyarthritis, polyarthritis RF negative, systemic arthritis, psoriatic arthritis, and enthesitis related arthritis. As a result, a category, “undefined arthritis,” is also included for patients who fulfill criteria for no category or for more than one category. And therein lies a problem: fear and loathing of the undefined. In order to minimize what was perceived to be an excessive number of patients allocated to the “undefined arthritis” category, Fantini⁵ and Manners, *et al*⁶ have suggested similar hierarchical approaches to classification.

In this issue of *The Journal*, Manners and her colleagues report a study of 50 children with oligoarthritis, more than half of whom were felt not to fulfill criteria for any defined category of the ILAR classification, and were therefore categorized as “undefined arthritis.” In their analysis of the reason for this result, the authors concluded that the major problem in applying the ILAR criteria was the inadequacy of information about the family history. The authors presumed that the lack of knowledge of the presence or absence of a family history of psoriasis or of an HLA-B27 associated disease, for example, was in itself grounds for allocation to the “undefined arthritis” category. If, to use examples from the Manners article, the child was adopted, or the father’s identity was unknown, or the parents simply did not know whether there was a family history of psoriasis or HLA-B27 associated disease, such lack of information precluded categorization of the patient into a category for which the inclusion and exclusion criteria were fulfilled. It was not, I think, the intention of the ILAR classification to accommodate the *lack* of information in such a way. Circumstances such as these accounted for 18 of the 28 unclassifiable children. Excepting these patients, there remained only 10 who would be “undefined.” In a disease in which we recognize great clinical heterogeneity, but lack specific diagnostic laboratory tests, this may be an acceptable, even a desirable proportion. Rather than considering this group of patients to be problematic, they might be considered to be a source of clues for the improvement of the classification (as Manners and her colleagues have recognized), and for further insights into the disease. The authors’ unique interpretation of the data points out, however, that greater clarity is required and that modification of the soon to be published second revision of the ILAR criteria should indicate that only known information need be considered in the exclusion criteria. Manners, *et al* have also identified the difficulty imposed by the presence of psoriasis or a family

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history of this disorder. This will be recognized in a new revision of the ILAR criteria.

Manners, *et al* have devised a classification system by which 49 of the 50 patients with oligoarthritis in their study could be categorized, leaving only one who was unclassifiable, because the patient met criteria for 2 separate categories. This accomplishment suggests that the categories as defined in the classification they propose are less homogeneous than those proposed in the ILAR classification. Patients with other types of arthritis were not studied in this report, and it is uncertain how the proposed classification system would perform when applied to the classification of actual patients with other arthritides; this should be evaluated.

Manners' study is a welcome addition to the discourse about classification of arthritis in childhood, and provides support for modification of the ILAR criteria, an ongoing process. Although the suggested hierarchical approach is interesting, it should not be considered to be a modification of the ILAR criteria since it contravenes the fundamental basis of the ILAR criteria: the use of both inclusion and exclusion criteria to describe homogeneous groups of patients with no overlap among categories. The exclusions constitute an integral part of the ILAR criteria to help ensure that the categories are as homogeneous as possible. For example, in the hierarchical classification suggested by Manners, *et al*, patients who are finally categorized as having oligoarthritis RF negative have been "screened" by several exclusion criteria (presence of HLA-B27, presence of more than 5 affected joints, presence of psoriasis or dactylitis and nail changes, presence of rheumatoid factor, and presence of features of systemic arthritis). It is likely that this is a homogeneous group, similar to the oligoarthritis of the ILAR criteria. However, patients classified as having other categories of JIA would have fewer, and in the case of systemic arthritis, none of the exclusionary criteria applied. This approach does not provide the assurance of clinical homogeneity or of mutual exclusivity. In the proposed classification system, family history is not considered. This offers the advantage of simplicity, but may also limit the homogeneity of patient groups.

Clinical criteria cannot be expected to provide a conclusive solution to the problems of classification, and their resolution requires that new and innovative approaches to the immunologic, biochemical, and genetic description of patients will be required. In one such study⁷ of HLA associ-

ations with JIA subgroups as defined by the ILAR criteria, each category had different patterns of HLA associations, suggesting, the authors concluded, that the ILAR classification system does define genetically distinct groups of patients.

Clinicians and scientists will continue to struggle to understand the interrelationships among and distinctions between the juvenile idiopathic arthritides. Ideas will be analyzed, manipulated, and interpreted in the search for validity. Manners and her colleagues have proposed a new classification "...only for stimulating discussion among clinicians." Doubtless it will do that. However, the approach used in the ILAR classification appears to offer the current best, but hopefully not the last best hope of facilitating the communication needed to achieve better understanding of the arthritides of childhood. One day, the causes of these diseases will be found, and the need for a classification of juvenile *idiopathic* arthritis will disappear. In this way the classification should sow the seeds of its own obsolescence.

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