Reclassification of Lupus Glomerulonephritis: Back to the Future

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The glomerular lesions that frequently accompany systemic lupus erythematosus (SLE) have been the subject of intense investigation by clinicians and pathologists for nearly a half-century (1). These efforts have generated numerous attempts to classify and categorize the pathological features of the glomerulonephritis of SLE (lupus nephritis, LN). The work of Kark,* Muehrcke, * Pirani, Schwartz, and the pathological features of the glomerulonephritis of SLE (lupus nephritis, LN). The work of Kark,* Muehrcke, * Pirani, Schwartz, and Pollak in Chicago (2,3) and of Baldwin, Lowenstein, Rothfield, Gallo, Silva, Gluck, Appel, McCluskey, and Pirani in New York (4,5,6) carried out from 1957 through 1977 provided a sound basis for the development of more formal classification schema that were to evolve from 1974 to the present time.

The terms minimal, mesangial, focal and segmental, diffuse, and membranous LN were eventually placed into a framework often referred to as the World Health Organization (WHO) classification of LN. The original WHO-style classification of LN was published in 1975 and again in 1978 (6,7). This classification was subsequently revised and published in 1982 as a result of a proposal from the Pathology Advisory Group of the International Study of Kidney Disease in Children developed during a meeting in Paris in April 1980 (participants were Rene Habib, Edmund Lewis, Jay Bernstein, Jacob Churg, Liliane Morel-Maroger, and Conrad Pirani.) (1,8). To the best of my knowledge, this 1982 classification scheme was the first one to receive formal adoption by the WHO. This 1982 classification of lupus nephritis should most properly be called the ISKDC/WHO classification. In 1995, a further modification of the 1982 ISKDC/WHO classification was published from WHO and the Collaborating Centre for the Histological Classification of Renal Diseases (Mount Sinai School of Medicine, New York) as a replacement for the 1982 classification (9). As clearly outlined by Lewis, Schwartz, and Korbet, both the 1982 ISKDC/WHO classifications and the revisions made in 1995 contained serious accumulated deficiencies that were generated by improved understanding of the pathogenesis of LN and by the availability of better data bearing on the long-term outcome with treatment of the various forms of LN categorized by the WHO classifications (10). They took particular exception to the classification of class III and class IV as a continuum, rather than to explicitly recognize distinct morphological differences within these categories, particularly with respect to prognosis and response to therapy. They called for a rigorous re-examination of the WHO classifications of LN. This challenge was met by a large (23 individuals) internationally representative group of distinguished renal pathologists and clinical nephrologists who met at Columbia University in May 2002 under the auspices of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS).

The culmination of their efforts to “modernize” the WHO classification of LN appears in this issue of the Journal of the American Society of Nephrology (11). The five-decade-long process of the classification of LN clearly tells us that even this new proposal should be considered a work-in-progress, and it will undoubtedly undergo further modification as new information regarding pathogenesis, specific mediation of glomerular injury, clinical-pathological correlations, and treatment effects emerge.

Nevertheless, the effort leading to the proposal for a new classification should remind us of the appropriate goals of any categorization schema. (1) To enhance the quality of communication between and among renal pathologists and clinical nephrologists regarding pathological findings in LN. Renal pathologists use their expertise and experience to translate static images (snapshots) into descriptive phrases; clinical nephrologists use these phrases to help develop a composite picture of disease in evolution (in individual patients). (2) To provide a logical structure for the categorization of groups of patients for epidemiologic, prognostic (outcome) or interventional studies (clinical trials). Such categorization would (hopefully) lead to better uniformity within and between studies and enhance the value in study design in terms of generalizability to the population as a whole. (3) To assist in the clinical management of individual patients with LN in terms of therapeutic decision-making and prognostication. To the extent that categories are mutually exclusive and predictive of the subsequent behavior of the disease (prognosis), identification of the nature of the glomerular lesions in LN could, at least theoretically, aid in the choice of therapeutic options available for the treatment of the patient. Although past and present classifications of LN are not primarily based on discrete knowledge regarding the underlying pathogenesis and media-tion of the individual categories, the existence of a framework should also enhance the ability to carry out meaningful studies aimed at elucidation of mechanisms underlying specific patterns of glomerular injury.

The proposed new classification of LN builds upon the earlier versions, attempts to eliminate (or greatly reduce) am-
biguieties present in the 1982 and 1995 WHO versions, incorporates new knowledge regarding behavior of specific lesions, standardizes many definitions, and encourages uniformity and reproducibility of the reporting of pathologic findings. As pointed out by its authors, this new revision resembles those advanced in 1974 in many respects, thus the subtitle of this editorial, “Back to the Future,” may be especially apt.

The major changes present in the current proposed ISN/RPS revision, compared with categorizations found in the 1982 and 1995 WHO versions, are in the following areas. (1) It eliminates category I—normal glomeruli by light, immunofluorescence, and electron microscopy. This was largely a vestigial category, seldom used in clinical practice. (2) It clarifies the status of the category III lesions by sharply defining Focal as involvement of <50% of glomeruli in the biopsy sample, and it further characterizes the lesions as active (A), active/chronic-sclerotic (A/C), or chronic-sclerotic (C). Confusion in category III has been largely eliminated by this proposal. (3) The complexity of category IV lesions has been codified more precisely by defining Diffuse as involvement of >50% of glomeruli in the biopsy sample and by further characterization of the lesions as segmental (S) or global (G) and active (A), active/chronic-sclerotic (A/C), or chronic-sclerotic (C). This means that category IV LN can be characterized into six non-overlapping subcategories. (4) Category V has been simplified to include only those lesions that consist of a membranous pattern with or without superimposed mesangial lesions (similar to those seen in category II). The categories of Vc and Vd found in the 1982 ISKDC/WHO, but not in the 1995 WHO versions, have been eliminated. If lesions characteristic of category III or category IV LN are found in conjunction with a lesion of category V, they are to be reported separately. (5) Category VI (Advanced sclerosing LN) has been retained, but a stricter definition of at least 90% global sclerosis without residual activity is now required. This means that glomerular lesions showing 50 to 89% global glomerulosclerosis will be categorized within the predominant lesion category (III, IV, or V). This may pose a problem for renal lesions with moderately advanced global glomerulosclerosis in which the basic underlying pattern of glomerular injury is difficult to recognize.

On the basis of this new revision, it is believed that all or nearly all renal biopsies undertaken in patients with LN can be assigned to one of the 14 unique, non-overlapping categories used in this classification schema. Applying information available from current and past studies, it could be estimated that among lesions assigned to a category IV of LN (Diffuse segmental or Global LN), IV-G/A will have the most favorable prognosis with conventional therapy, IV-S/A/C will have a worse prognosis with conventional therapy, and IV-S or G plus V (Membranous LN) will have the least favorable prognosis with conventional therapy.

If this can be validated by prospectively designed studies, the new proposed classification will have made a major contribution and greatly enhance the utility of renal biopsy in the evaluation of LN.

The proposed classification schema is noteworthy for some of its detailed aspects. It is first and foremost a classification based on glomerular lesions evaluated by light and immunofluorescence microscopy. Electron microscopic findings were not included in the final classification because of the belief that access to such procedures could be limited and thus hamper the wide application of the new ISN/RPS classification. The focus on glomerular lesions does not mean that tubulointerstitial and vascular lesions are unimportant. Quite to the contrary; the authors have taken great pains to point out that non-glomerular lesions such as interstitial fibrosis, tubular atrophy, necrotizing extrarenal vasculitis, and thrombotic microangiopathy can have a critical influence on prognosis and response to therapy. Quite appropriately, the authors strongly recommend that such lesions, when present, be a part of the formal description of the pathological findings. It is interesting that no uniform schemata to semi-quantitate the activity and chronicity of the renal lesion of LN were recommended to be part of the report. Very likely this was due to the belief that such measures may lack reproducibility and thereby may not be reliable parameters to judge prognosis or potential responsiveness to therapy, over and above that embodied in the classification scheme as a whole.

Some caveats should be expressed regarding the proposed classification. It has not (as yet) been accepted by the WHO as a replacement for the 1982 or 1995 WHO classifications. This is a small point, as the widespread adoption of the new classification proposed by the ISN/RPS will rest largely on whether it is user-friendly and clinically applicable rather than on its endorsement by a third party. Like all classifications that have preceded it, this classification suffers from the static (snapshot) nature of the starting material. SLE is notorious for its unpredictable behavior and for the possibility of transformations (migration from one category to another) during exacerbations. Such transformations may require repeated renal biopsies to determine category migration, since clinicopathologic correlations are not very precise. Thus, many patients with LN will evolve thru several categories, spontaneously or under the influence of therapy. This fact complicates the utility of categorization of findings in individual renal biopsies for the prediction of long-term outcome. This fact is not a specific criticism of the present classification, but is rather one directed at a generic weakness of all classifications of LN.

At the present time, we do not know how reproducible and reliable the proposed classification will be in comparison to earlier classifications when applied to “real-world” situations. The elimination (or reduction) of ambiguity (particularly regarding categories III and IV in the 1982 and 1995 WHO versions) and the development of non-overlapping categories or subcategories of LN that characterizes the present proposal would be expected to improve reproducibility. However, prospective studies comparing the 1982, 1995, and 2003 revisions are required to evaluate this point further.

Clinical nephrologists should welcome the new ISN/RPS classification of LN. If widely adopted by renal pathologists, it should make reports of renal biopsy evaluation easier to interpret. However, the descriptions are likely to be longer and more detailed. Hopefully, a uniform method of reporting the findings will emerge that places the primary ISN/RPS classification (I to VI or combinations thereof) first, the description of the active and chronic glomerular lesions second, and the attendant tubulointerstitial and vascular lesions third. I also believe that a description of the nature, locale, and extent of deposition of immunoglobulins, complement components, and fibrin (ogen)
along with a description of the nature, locale, and extent of electron-dense deposits would be a helpful addition to the description of the renal biopsy, which complements the determination of LN category.

The emergence of new proposals for classifying the renal pathology of LN also raises an old question that has never, at least in my opinion, been directly addressed in a truly scientific manner. Specifically, in an era where modern treatment of LN (steroids and cytotoxic agents) is associated with high levels of initial responsiveness (partial or complete remission) and a narrowed gap between individual categories of LN with respect to long-term prognosis, what is the marginal value of renal biopsy (with classification of the lesions found) over and above clinical evaluation (age, sex, race, duration of disease, blood pressure, extrarenal manifestations) and the application of simple, non-invasive laboratory tests (serum creatinine, urinalysis, urine protein excretion, hemoglobin concentration, complement component levels, auto-antibody serology) in estimating prognosis and guiding therapy? Earlier studies, using the 1982 classification scheme, have shown that predictive models based largely on clinical parameters alone were not materially improved upon by the information added by renal biopsy and categorization (13,14). I suppose that one of the promises, as yet unfulfilled, of the new ISN/RPS classification of LN is that it will provide information of clear and unequivocal benefit, over and above that provided by the simple clinical measures described above. Greater precision and reliability of prognosis in LN based on morphology will give to the clinical nephrologist information that can be of value in making crucial decisions regarding treatment of individual patients with LN. I have no doubt about, and can also recollect numerous anecdotes testifying to, the critical value of renal biopsy in patients believed to have LN. Renal biopsy has helped to guide therapy, to make general judgments regarding likely outcomes of treatment, and even at times led to management strategies not anticipated before renal biopsy, including the avoidance of dangerous treatment regimens. One can only hope that the new ISN/RPS classification will lead to a leap forward in establishing the true role of renal biopsy in the management of LN. Based on the improved clarity of the language used, it will almost certainly enhance communication between and among renal pathologists and clinical nephrologists. In and of itself, this is an important outcome, as one of the chief obstacles to true progress in this field has been the lack of a uniformly applied and generally accepted vehicle for interchange of information.

Finally, some speculation about the future of morphological classification of LN may be in order. As data begin to emerge on the utility of gene expression arrays (genomics) and high throughput protein expression analysis (proteomics) to classify and predict outcome and survival in neoplastic diseases, it would seem logical to apply these techniques to renal biopsy material (15,16). Protein mass profiles obtained from as few as 100 cells, when analyzed by computerized class-prediction tools (15), could offer a whole new paradigm for classification of LN, theoretically closer in concept to fundamental pathogenetic and mediator pathways than analyses of morphology. Technical obstacles do not seem to be insurmountable, as already shown by work on non-small cell lung cancer (16). Here too, a link to the “Back to the Future” theme of this editorial can be glimpsed.

References