Diabetic nephropathy (DN) is a major cause of ESRD, and the incidence of diabetes mellitus is rising rapidly. Pathologic classifications exist for several kidney diseases such as lupus nephritis, focal segmental glomerulosclerosis, and IgA nephropathy, yet there is no uniform classification for DN. Classification schemes lead to better communication between renal pathologists and clinicians, provide logistical structure for prognostic and interventional studies, and improve clinical management and efficiency. In 1959, Gellman et al. first reported an overview and clinical correlation of findings on renal biopsies from patients with DN. Before their study, the renal pathology in patients with diabetes mellitus was only described at autopsy. Gellman proposed an elaborate systematic evaluation examining glomeruli, tubules, arterioles, and the interstitium that was unsuitable for practical use. More recently, attempts were made to categorize patterns seen in DN after type 2 diabetes. Gambara et al. and Fioretto et al. made basic distinctions between typical and atypical DN as well as other glomerular diseases superimposed on DN. Although such schemes are useful for research biopsies, they also are not practical for clinical use.

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We decided to classify DN due to type 1 and type 2 diabetes together because there is substantial overlap with respect to histologic lesions and renal complications. Our aim was to develop a uniform classification system containing specific categories that discriminate lesions with various prognostic severities that would be easy to use. This proposal was launched by the Research Committee of the Renal Pathology Society in 2006 in San Diego and further discussed in Leiden in September 2008. Presented here is a consensus classification of DN developed by a group of international experts.

CLASSIFICATION OF DN

It is essential to evaluate renal tissue using appropriate standards for renal biopsy. These include hematoxylin and eosin, periodic acid–Schiff (PAS), Masson trichrome, and periodic acid methamine silver stains for light microscopy. Biopsies should contain at least 10 glomeruli, excluding incomplete glomeruli along the biopsy edge. Immunofluorescence requires the use of antibodies against IgA, IgG, IgM, C3, Clq, and kappa and lambda light chains to rule out other renal diseases. Electron microscopy (EM) must be performed; specific guidelines are discussed below. All of these methods are necessary for an accurate diagnosis of DN. DN should never be diagnosed without supportive clinical information, and a patient should carry a clinical diagnosis of diabetes mellitus to apply the classification. Furthermore, virtually any glomerular disease can accompany DN, postinfectious GN, and membranous glomerulopathy being the most common; thus, any coexisting disorders should also be described. Four classes of glomerular lesions in DN are presented in Table 1.

Classes of Glomerular Lesions

Class I: Glomerular Basement Membrane Thickening.

If the biopsy specimen shows no or only mild, nonspecific changes by light microscopy that do not meet the criteria of classes II through IV [in effect, in the absence of mesangial expansion, nodular increases in mesangial matrix (Kimmelstiel–Wilson lesions), and diffuse glomerulosclerosis of more than 50% of glomeruli] the biopsy is assigned to class I (Table 1 and Figure 1), in which by direct measurements with EM the glomerular basement membrane (GBM) on average is thicker than 430 nm in males 9 years and older and thicker than 395 nm in females. These cutoff levels are based on a deviation from normal GBM thickness plus 2 standard deviations as recently determined by Haas. For children younger than 9 years old, we refer to Table 1 in the paper by Haas. Upper limits for normal GBM thickness vary with the methods used to measure GBM width. For instance, using the orthogonal intercept method, upper limits of normal GBM thickness are 520 nm for adult men and 471 nm for women. In individual laboratories, the upper limits for normal GBM thickness have usually been established, and if other methods than direct GBM measurement are used, it is advised to use these locally established cutoff points.

Light microscopic changes in the GBM and epithelial foot process effacement by EM have no influence on the classification. Class I incorporates cases that have been called “normal or near normal DN” by Fioretto et al., but in our system, a certain degree of chronic and other reactive changes (e.g., changes of arterionephrosclerosis, ischemic type changes, or interstitial fibrosis) are accepted as part of this category. Diagnosing DN in cases without characteristic light microscopic glomerular lesions may be difficult, especially when a thicker GBM is also seen with aging or hypertension. The presence of arteriolar hyalinosis may be helpful in these cases, although it is not a prerequisite.

GBM thickening is a characteristic early change in type 1 and type 2 DN and increases with duration of disease. GBM thickening is a consequence of extracellular matrix accumulation, with increased deposition of normal extracellular matrix components such as collagen types IV and VI, laminin, and fibronectin. Such accumulations result from increased production of these proteins, their decreased degradation, or a combination of the two. GBM thickening may already be present in type 1 dia-

Table 1. Glomerular classification of DN

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild or nonspecific LM changes and EM-proven GBM thickening</td>
<td>Biopsy does not meet any of the criteria mentioned below for class II, III, or IV GBM &gt; 395 nm in female and &gt;430 nm in male individuals 9 years of age and older*</td>
</tr>
<tr>
<td>IIa</td>
<td>Mild mesangial expansion</td>
<td>Biopsy does not meet criteria for class III or IV Mild mesangial expansion in &gt;25% of the observed mesangium</td>
</tr>
<tr>
<td>IIb</td>
<td>Severe mesangial expansion</td>
<td>Biopsy does not meet criteria for class III or IV Severe mesangial expansion in &gt;25% of the observed mesangium</td>
</tr>
<tr>
<td>III</td>
<td>Nodular sclerosis (Kimmelstiel–Wilson lesion)</td>
<td>Biopsy does not meet criteria for class IV At least one convincing Kimmelstiel–Wilson lesion</td>
</tr>
<tr>
<td>IV</td>
<td>Advanced diabetic glomerulosclerosis</td>
<td>Global glomerular sclerosis in &gt;50% of glomeruli Lesions from classes I through III</td>
</tr>
</tbody>
</table>

LM, light microscopy.

On the basis of direct measurement of GBM width by EM, these individual cutoff levels may be considered indicative when other GBM measurements are used.
betes patients who are normoalbuminuric.\textsuperscript{20,21} GBM thickening has even been described as a “prediabetic” lesion: In patients with proteinuria and isolated GBM thickening but without overt diabetes, 20\% were positive on a blood test for diabetes at the time of biopsy, whereas 44\% were diagnosed with diabetes at 6 months, and 70\% at 2 years after the biopsy was taken.\textsuperscript{24} Long-term glucose control and urinary albumin excretion (UAE) correlate strongly with basement membrane thickness.\textsuperscript{25}

In 1979, Jensen et al.\textsuperscript{26} were among the first to measure GBM thickness using the orthogonal intercept method. In brief, a grid with eight evenly spaced intersecting lines (four horizontal and four vertical) is placed over a photomicrograph, and GBM measurements are made at each point that a line on the grid intercepts an endothelial-GBM interface. Currently, some laboratories use computer-assisted measurements by which the mean width is calculated from approximately 50 measurements of the GBM at five different locations. The GBM width is then compared with GBM width from normal subjects, as determined previously by Steffes et al.\textsuperscript{27} and recently updated by Haas.\textsuperscript{16} Ideally, glutaraldehyde-fixed, plastic resin-embedded tissue should be used for EM, keeping in mind that other methods, particularly the reprocessing of paraffin tissue for EM, may cause artifactual GBM thinning as recently reported by Nasr et al.\textsuperscript{28} If computer-assisted measurements are not available, we recommend doing direct GBM measurements as recently modified by Haas.\textsuperscript{16}

Class II: Mesangial Expansion, Mild (IIa) or Severe (IIb).

Class II encompasses those patients classified with mild or severe mesangial expansion but not meeting inclusion criteria for class III or IV (Table 1 and Figure 1) and is analogous to the previously used term “diffuse diabetic glomerulosclerosis.” Mesangial expansion is defined as an increase in extracellular material in the mesangium such that the width of the interspace exceeds two mesangial cell nuclei in at least two glomerular lobules. The difference between mild and severe mesangial expansion is based on whether the expanded mesangial area is smaller or larger than the mean area of a capillary lumen. If severe mesangial expansion is seen in more than 25\% of the total mesangium observed throughout the biopsy, the biopsy is classified as IIb.
If this is not the case, but at least mild mesangial expansion is seen in more than 25% of the total mesangium, the biopsy is classified as IIa.

Expansion of cellular and matrix components in the mesangium is a hallmark of type 1 and type 2 DN.\textsuperscript{13,18} It can be detected in some patients within a few years after the onset of type 1 diabetes.\textsuperscript{20} When the mesangium expands, it restricts and distorts glomerular capillaries and diminishes the capillary filtration surface. In our classification, we do not distinguish between mesangial hypercellularity, matrix expansion, or “mesangiolysis”—any expansion of the mesangium that conforms to our definitions given above and in Table 1 belongs to class II.

Various indices have been proposed to describe the amount of mesangial expansion in DN. Mauer \textit{et al.} define mesangial expansion by mesangial fractional volume or volume density (Vv(mes/glom)), defined as the fraction or percentage of the cross-sectional area of the glomerular tuft made up by mesangium, expressed in the formula: Vv(mes/glom).\textsuperscript{18} Using this formula, many correlations have been made between mesangial expansion and clinical parameters of DN, particularly showing highly inverse correlations exist between Vv(mes/glom) and GFR.\textsuperscript{18,29,30} There is also a relationship between Vv(mes/glom) and UAE\textsuperscript{18,29} and blood pressure.\textsuperscript{31}

Another index to express mesangial expansion is the so-called “index of mesangial expansion” (IME) for DN.\textsuperscript{18} The IME is determined by a semiquantitative estimate of the width of mesangial zones in each glomerulus\textsuperscript{18}: grade 0 is normal, 1 is twice normal thickness, 2 is three times normal thickness, and so forth; half grades can also be assigned. The mean of the grades for each glomerulus for IME can thus be determined from a single biopsy. The IME closely correlates with the clinical parameters of DN, particu-
larly showing highly inverse correlations with at least one convincing Kimmelstiel–Wilson lesion is found and the biopsy specimen does not have more than 50% global glomerulosclerosis it is classified as class III (Table 1 and Figure 1). Kimmelstiel–Wilson lesions appear in type 1 and type 2 diabetes as focal, lobular, round to oval mesangial lesions with an acellular, hyaline/matrix core, rounded peripherally by sparse, crescent-shaped mesangial nuclei.\textsuperscript{32}

Paul Kimmelstiel and Clifford Wilson, a German and an Englishman who met at Harvard, first described nodular lesions in glomeruli from eight maturity-onset diabetes patients in 1936.\textsuperscript{33} According to Cameron,\textsuperscript{34} they barely noted the association with diabetes, and it was Arthur Allen who clarified the association in 105 patients with diabetes in 1941.\textsuperscript{35} Nodular sclerotic lesions may also occur in the absence of DN that are clinically related to hypertension, smoking, hypercholesterolemia, and extrarenal vascular disease.\textsuperscript{36}

It is claimed that in the initial stage of developing nodular sclerotic lesions in DN, two important processes take place: lytic changes in the mesangial area called mesangiolyis and detachment of endothelial cells from the GBM.\textsuperscript{37} Exactly how these two processes relate remains uncertain. Pauksakon \textit{et al.} detected fragmented red blood cells in Kimmelstiel–Wilson lesions, which supports the theory that microvascular injury contributes to the pathogenesis of these lesions. Dissociation of endothelial cells may disrupt the connections between the mesangial area and the GBM. This process precedes expansion of the Kimmelstiel–Wilson lesion.\textsuperscript{37} These lesions consist of an accumulation of mesangial matrix with collagen fibrils, small lipid particles, and cellular debris.\textsuperscript{39} A completely developed Kimmelstiel–Wilson lesion destroys the normal structure of glomerular tuft with a decrease in mesangial cells, especially in the central area.\textsuperscript{37} In 1992, a graphic method of analysis of the position of Kimmelstiel–Wilson lesions demonstrated the nodules were distributed in a horseshoe-shaped area corresponding to the peripheral or intralobular mesangium,\textsuperscript{40} excluding the possibility of hyperfiltration as being their main cause of development.

The presence of at least one Kimmelstiel–Wilson lesion associates with longer duration of diabetes and less favorable clinical parameters.\textsuperscript{10,41} In a study of 36 patients with type 2 diabetes, patients with Kimmelstiel–Wilson lesions had more severe overall retinopathy and higher serum creatinine concentrations than those with mesangial lesions alone.\textsuperscript{18} In a study of 124 Chinese patients with type 2 diabetes, patients with at least one Kimmelstiel–Wilson lesion had relatively long duration of diabetes mellitus, a poor prognosis, and frequent evidence of diabetic retinopathy.\textsuperscript{41}

Kimmelstiel–Wilson lesions are often found in combination with mesangial expansion. The occurrence of Kimmelstiel–Wilson lesions is widely considered transitional from an early or moderately advanced stage to a progressively more advanced stage of disease.\textsuperscript{41,42} Therefore, in our classification, the occurrence of Kimmelstiel–Wilson lesions implies a separate class.

Class IV: Advanced Diabetic Glomerulosclerosis

Class IV implies advanced DN and designates those biopsies with more than 50% global glomerulosclerosis in which there is clinical or pathologic evidence that the sclerosis is attributable to DN (Table 1 and Figure 1). Glomerulosclerosis in DN is the end point of multifactorial mechanisms that lead to excessive accumulation of extracellular matrix proteins such as collagen types I, III, and IV and fibronectin in the mesangial space, which through stages of mesangial expansion and development of Kimmel-
stiel–Wilson lesions finally result in glomerulosclerosis. The clustering of sclerotic lesions in columns perpendicular to the kidney surface suggests that vascular factors relating to the interlobular arteries also contribute.

Designation of class IV lesions in our classification system is restricted to those cases in which there is evidence for DN. This evidence can come from other lesions in the biopsy as described for classes I through III. The occurrence of hyalinosis of the glomerular vascular pole or a capsular drop may also be taken as evidence for the presence of DN. Alternatively, if DN is the likely clinical diagnosis (e.g., by the presence of retinopathy) a biopsy with extensive glomerulosclerosis can also be classified as class IV. Glomerulosclerosis without evidence of DN should be mentioned as such in the conclusion of the pathology report but should not be assigned class IV.

**Tubulointerstitial Lesions, Vascular Lesions, and Nondiabetic Glomerular Lesions**

**Tubular Lesions.**

Concomitant tubular basement membrane thickening of nonatrophy tubules is apparent from the development of class II glomerular diabetic lesions and becomes more conspicuous in class III and IV, which is best seen in PAS or silver stains.

Interstitial fibrosis and tubular atrophy (IFTA) follow glomerular changes in type 1 DN that ultimately lead to ESRD. We score IFTA together as a disease progression. In Table 2, we score 0 if interstitial infiltrates are absent, 1 if they only occur around atrophic tubules, and 2 if the inflammatory infiltrate is also in other areas than around atrophic tubules.

### Vascular Lesions.

According to Stout et al., hyalinosis of the efferent arteriole is relatively specific for DN, but hyalinosis of the afferent arteriole occurs in numerous other settings. Chronic cyclosporine nephropathy is a typical example in which arteriolar hyalinosis occurs outside DN. Tracy et al. also report the presence of arteriolar hyalinosis in kidneys of young patients with coronary heart disease. Efferent arteriolar hyalinosis is an important lesion by which DN is distinguished from hypertensive nephropathy. However, most studies relate arteriolar hyalinosis to clinical parameters, not distinguishing between efferent and afferent arterioles, showing clear correlations with UAE and disease progression. In Table 2 we score 0 if no arteriolar hyalinosis is present, 1 if one arteriole with hyalinosis is present, and 2 if more than one arteriole is observed in the entire biopsy.

In addition to characteristic arteriolar hyalinosis, relatively nonspecific arteriosclerosis may be present in the biopsy specimen. Bohle and colleagues found increases in vascular disease associate with more severe glomerular disease. Osterby et al. use a so-called “matrix to media ratio” to investigate the role of arteriosclerosis and find this ratio is increased in patients with microalbuminuria, suggesting that arteriolar matrix accumulation occurs early in the course of DN. In Table 2 we score the most severely affected artery in the biopsy and assign a score of 0 if no intimal thickening is present, 1 if intimal thickening is less than the thickness of the media, and 2 if intimal thickening is more than the thickness of the media. Isolated or significant medial thickness may be associated with concurrent hypertension.

### Other Glomerular Lesions

In 1994, Stout et al. defined “insudative lesions” as consisting of intramural accumulations of presumably imbibed plasma proteins and lipids within renal arterioles, glomerular capillaries, Bowman’s capsule, or proximal convoluted tubules. Insudative lesions in Bowman’s capsule are called capsular drop lesions, and in afferent and efferent arterioles they are called hyalinized afferent and efferent arterioles. In glomerular capillaries they are called fibrin cap lesions, although this term is considered obsolete and moreover is a misnomer because the lesion does not contain fibrin; we prefer the term hyalinosis for these lesions.
Capsular drops are mainly located between the parietal epithelium and Bowman’s capsule of the glomerulus. Capsular drops are prevalent in advanced DN and associate with disease progression. The common belief, reviewed by Alsaad et al., is that capsular drops are specific but not entirely pathognomonic of DN. Stout et al. report a prevalence of capsular drops in 5.3% of biopsies without diabetes. However, finding a capsular drop in a biopsy can help distinguish DN from other causes of glomerulosclerosis.

By light microscopy, glomerular hyalinosis describes the same staining characteristics as the capsular drop lesion but it occupies the capillary lumen instead of being attached to Bowman’s capsule. This lesion is not a specific finding in DN, because similar lesions are recognized in focal glomerulosclerosis, arterionephrosclerosis, and lupus nephritis. Finally, there is increasing recognition of abnormalities in the glomerulotubular junctions with focal adhesions called “tip lesions” and atrophic tubules with no observable glomerular opening (so-called “atubular glomeruli”). These lesions are typically found in more advanced stages of nephropathy associated with overt proteinuria.

Interobserver Reproducibility
To assess the reproducibility of our consensus classification, a pilot study was performed in which five pathologists independently classified 25 renal biopsies with DN using PAS stains only into class I, II, III, or IV. Two pathologists scored all biopsies independently. Results of the raw data are given in Table 3. The reproducibility of the glomerular class score was evaluated using an intraclass correlation coefficient. Analyses were carried out using SPSS software (version 16, SPSS, Inc., Chicago, IL). There was disagreement in seven cases: twice on a difference between class I and II, twice on a difference between class II and III, and three times on a difference between class IIa and IIb. Overall, the results seem satisfactory, resulting in an intraclass correlation coefficient of 0.84.

Table 3. Assessment of interobserver agreement for scoring of DN classes I through IV

<table>
<thead>
<tr>
<th>Biopsy Number</th>
<th>Observer 1</th>
<th>Observer 2</th>
<th>Observer 3</th>
<th>Observer 4</th>
<th>Observer 5</th>
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</table>

Y, yes; N, no; interclass coefficient = 0.84.

Flow Chart and Scoring Form
A flow chart was devised to help distinguish the four classes of DN (Figure 2). Supplemental Figure 1 shows the scoring form we recommend for classifying glomeruli in DN and for scoring of extraglomerular lesions or other features.

CONCLUSIONS
We developed a classification scheme for DN consisting of four progressive classes supported by international consensus. The classification is based on glomerular lesions, with a separate evaluation for interstitial and vascular lesions. We chose a classification scheme based on glomerular lesions because these are relatively easy to recognize with good interobserver agreement as shown by our pilot data and because glomerular lesions best reflect the natural course of progressive DN. Of course, glomerular and interstitial lesions contribute to the decline in renal function in DN and may be independent factors in the progression of DN; however, many studies also show that severity of chronic interstitial and glomerular lesions closely associate.

Although in some clinical practices there is a policy to only perform a renal biopsy to exclude causes of renal disease characterized by proteinuria other than DN, there is increasing demand to classify the severity of disease in those patients with pure DN. Our classification system for histopathologic lesions in DN can be used for patients with type 1 and type 2 diabetes, because it is now generally recognized that substantial overlap exists between these two types with respect to histologic lesions and renal complications. Various studies also report different proportions of nondiabetic nephropathies in patients with diabetes and proteinuria. The classification system proposed here is only for DN, but it can also serve to classify DN when it is complicated by another superimposed disease.
Little is known about the pathogenesis of lesions developing in DN, but it is suggested that if we could unravel the various pathways ultimately leading to glomerulosclerosis in DN, this could open up new possibilities for intervention to prevent or forestall nephropathy. Most likely, intra- and extraglomerular cells are involved in the progressive accumulation of extracellular matrix proteins in DN. We suggest that progression evolves from GBM thickening to mesangial expansion, Kimmelstiel–Wilson lesions, and global glomerulosclerosis, respectively, which is reflected in the four classes of our classification system. Using our system to evaluate protocol biopsies of patients with DN may further unravel the complex pathways of DN.

An important question for every histologic classification system is whether it is predictive of clinical outcome. As in other proposals for classifying renal disease (e.g., for lupus nephritis and focal segmental glomerulosclerosis), we chose not to assess clinical outcome as part of this proposal. We feel validation should be done in separate prospective studies, preferably including protocol biopsies of patients with type 1 and type 2 diabetes and clearly defined clinical end points.

DISCLOSURES
None.

REFERENCES

Figure 2. Flow chart for classifying DN.

Supplemental information for this article is available online at http://www.jasn.org/
EXPERTS CREATE CLASSIFICATION SYSTEM FOR LEADING CAUSE OF KIDNEY FAILURE

Categorization Should Improve Patient Care

Washington, DC (February 17, 2010) — An international group of medical experts has crafted a much-needed classification system for diabetic nephropathy, the leading cause of total kidney failure, according to a study appearing in an upcoming issue of the Journal of the American Society Nephrology (JASN). The effort should improve communication among health professionals, help researchers design better clinical studies, and guide patient care.

Current estimates suggest that 285 million people worldwide will live with diabetes in 2010 and that the incidence of diabetes will continue to rise. As a result, the incidence of diabetic nephropathy, or kidney damage that arises as a complication of diabetes, will likely increase as well.

Diabetic nephropathy is a complex condition with varying degrees of severity and varying effects on the kidneys. While researchers do not fully understand the mechanisms involved in the development and progression of diabetic nephropathy, they know that too much blood sugar in diabetic patients can damage the clusters of tiny blood vessels in the kidneys that help remove waste from the body. Eventually, the kidney structures begin to leak and kidney failure ensues.

Unlike other kidney conditions, diabetic nephropathy has no standard classification system. Recently, however, a unique cooperative effort among groups of experts from 16 universities spread over seven countries in three continents developed a uniform international classification system that reflects the current understanding of the various forms of diabetic nephropathy. Jan Anthonie Bruijn, MD, PhD (Leiden University Medical Center, the Netherlands), who led the effort, hopes that the classification system will standardize definitions of different classes of diabetic nephropathy and encourage uniform and reproducible reporting of cases among different medical centers.

The new classification system categorizes diabetic nephropathy by varying degrees of severity that will be easy to discern in the clinic. The experts divided the condition into
four progressive classes, with the first class being the mildest and the fourth class being the most severe. The system may help guide clinicians as they treat affected patients. In addition, it could aid researchers as they continue to search for the mechanisms involved in the development and progression of diabetic nephropathy.

The classification effort was commissioned by the Research Committee of the nonprofit Renal Pathology Society. Study co-authors include Thijs Cohen-Tervaert, MD, Antien Mooyaart, PhD, Emile de Heer, PhD, Ingeborg Bajema, MD, PhD (Leiden University Medical Center, the Netherlands); Kerstin Amann, MD (University of Erlangen-Nuernberg, in Erlangen, Germany); Arthur Cohen, MD, Mark Haas, MD, PhD (Cedars-Sinai Medical Center); H. Terence Cook, MD (Hammersmith Hospital, in London, UK); Cinthia Drachenberg, MD (University of Maryland, Baltimore); Franco Ferrario, MD (San Carlo Borromeo Hospital, in Italy); Agnes Fogo, MD (Vanderbilt University Medical Center); Kensuke Joh, MD (Sendai-Shaho Hospital, in Sendai-city, Japan) Laure Noël, MD (Hôpital Necker, Université René Descartes, in Paris, France); Jai Radhakrishnan, MD (Columbia University); and Surya Seshan, MD (Weill Cornell Medical College).

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