Heterogeneous Nature of Renal Lesions in Type II Diabetes

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ABSTRACT
The nature of renal damage in patients with type II diabetes remains unclear. This study was directed to evaluate pathologic changes in 52 patients affected by type II diabetes with overt clinical nephropathy by conventional and morphometric techniques. The duration of diabetes ranged from 6 to 384 months, urinary protein excretion ranged from 0.9 to 9.2 g/24 h, and serum creatinine ranged from 0.9 to 9 mg/dL. Specimens were examined semiquantitatively by light microscopy, immunofluorescence, and electron microscopy. Glomerular tuft cross-sectional area was measured by a versatile computer system. Pathologic examination revealed three distinct patterns arbitrarily defined as Classes 1, 2, and 3. Class I included 19 patients with typical changes of diabetic nephropathy characterized by a high score of glomerulosclerosis (mean score, 2.1), marked glomerular hypertrophy (23,632 μm²), and arteriolar hyalinosis (mean score, 2). There was a positive correlation between glomerulosclerosis and arteriolar hyalinosis scores (P < 0.05). Class 2 included 16 patients showing chronic and aspecific changes. As compared with Class 1 patients, these patients had less glomerulosclerosis (mean score, 1.3) and less arteriolar hyalinosis (mean score, 0.8) but more severe ischemic glomerular lesions (mean score, 1.4) and arteriosclerosis (mean score, 2). Class 3 included 17 patients showing glomerular disease superimposed on diabetic glomerulosclerosis. There were no differences in age, mean duration of diabetes, renal function, urinary protein excretion, and mean arterial pressure among the three classes of patients. This study indicates that renal lesions in patients with type II diabetes manifest in a quite heterogeneous fashion. Whether the three different patterns described may have different rates of progression to terminal renal failure or may have different responses to therapy needs to be further investigated.

Key Words: Glomerulosclerosis, morphometry, hypertrophy, arteriosclerosis, hyalinosis

Several studies have been performed in the last 20 yr to elucidate the nature of renal structural changes of diabetes and in particular the relationship between glomerular structural alteration and the evolution of the nephropathy to renal insufficiency (1–4). Most of these studies have been performed in type I insulin-dependent diabetes, a disease that is known to progress quite predictably to terminal renal failure in a relatively well-defined percentage of patients (1–3). By contrast, very few studies are available that define (1) the nature of glomerular lesions in type II non-insulin dependent diabetes of the elderly and (2) how they compare with those of type I. This is probably because patients with type II diabetes were until recently considered at relatively “low renal risk” on the basis of the observation that mortality for renal disease appeared more frequent in type I than in type II diabetes (5–9). Recently, however, the issue has been extensively reexamined.

A recent study has documented that proteinuria and prevalence of renal failure is comparable in type I and type II (10). However, glomerular volume increase, a finding of type I diabetes that predicts the development of overt nephropathy (11,12), does not occur in type II (13). Here, we sought to evaluate the nature of renal lesions in type II diabetes by combining conventional and morphometric techniques. In the same patients, renal function, urinary protein excretion, and systemic blood pressure were evaluated in relation to the duration of the disease.

Our results documented that type II diabetics may have three different patterns of glomerular changes, one of which is reminiscent of the classical form of diabetic glomerulosclerosis of type I diabetes and is also associated with glomerular hypertrophy. The other two types of lesions are more complex and are morphologically different from the above entity.
MATERIALS AND METHODS

From April 1983 to November 1991, 52 patients (30 men and 22 women; age range, 49 to 83 yr) affected by non-insulin dependent diabetes were referred to the Division of Nephrology of Ospedali Riuniti of Bergamo because of clinical proteinuria. The duration of diabetes varied between 6 and 384 months; 41 of 52 patients had blood pressure higher than normal. Serum creatinine ranged from 0.9 to 9 mg%. Twenty-four-hour urinary protein excretion ranged from 0.9 to 9.2 g/24 h. All patients underwent a percutaneous renal biopsy. After renal biopsy, all patients were monitored in our outpatient clinic. Renal function parameters, urinary protein excretion, and arterial blood pressure were periodically measured; the duration of follow-up ranged from 1 to 49 months. Renal tissue obtained by needle biopsy was divided into three portions for light microscopy, immunofluorescence, and electron microscopy. For light microscopy, the specimen was fixed in Dubosque-Brazil solution, embedded in paraffin, and cut into 3-μm-thick sections. Sections were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), Jones silver methenamine, and Masson’s trichrome. For immunofluorescence, sections of snap-frozen tissue were cut 4 μm thick in a cryostat and then fixed in acetone for 5 min, air dried, and washed in phosphate-buffered saline. Sections were incubated for 45 min with antisera directed against human and immunoglobulin (Ig) G, IgM, IgA, C3, C1q, fibrinogen, and κ and λ light chains (Boheringer Biochemia, Mannheim, Germany) and were then extensively washed in phosphate-buffered saline. For electron microscopy studies, samples were fixed for 4 h at 4°C in 2.5% glutaraldehyde in 0.1 mol/L of cacodylate buffer at pH 7.4. After three washes in 0.1 mol/L of cacodylate, samples were postfixed in 1% osmium tetroxide for 1 h, dehydrated through ascending grades of alcohol, and embedded in epon resin. Sections were cut on a LKB-V ultramicrotome (Leika, Wetzler, Germany) and semithin sections were stained with toluidine blue and examined by light microscopy. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with a Zeiss 109 electron microscope (Carl Zeiss, Oberkochen, Germany). By light microscopy, pathologic examination and semiquantitative assessment of renal damage were performed in 24 sections stained with hematoxylin and eosin, Masson’s trichrome, PAS, and Jones silver methenamine. The number and the percentage of globally sclerotic glomeruli were determined. The following glomerular histologic findings were considered: sclerosis (nodular and diffuse), exudative lesions including fibrin caps and capsular drops, aneurysmal dilation of capillaries, thickening of capillary wall, intracapillary and extracapillary proliferation, thickening of Bowman’s cap-
lines of 90 glomerular tufts, randomly selected, in a cross-section stained with PAS, were traced and tuft cross-sectional areas were computed as described above.

All three patients used as controls had no history of renal disease, hypertension, or diabetes. Renal functional parameters were normal, and the urinalysis did not reveal proteinuria.

**Statistical Analysis**

A generalization of analysis of variance for categorical data was used to test the significance of differences in histopathologic findings among the three groups, taking into account the order of the scores in the response variable (Procedure CATMOD, version 6; SAS Institute Inc., Cary, NC). A one-way analysis of variance for continuous data was performed to analyze morphometric parameters after a log transformation (natural logarithm) of data: percentages of globally sclerotic glomeruli were analyzed without transformation of data. Multiple comparison was carried out by Fisher Protected Least Significant Differences Test and Scheffe $F$ test. The correlation between glomerulosclerosis and insudative lesions of the arterioles was analyzed by Spearman rho test. A Kruskal-Wallis test was used to compare the percentages of globally sclerotic glomeruli.

**RESULTS**

**Morphologic Findings**

Pathologic examination of renal biopsy specimens in the 52 patients included in this analysis revealed three different patterns of injury arbitrarily defined as Classes 1, 2, and 3, which were, respectively: classical diabetic-type lesion, aspecific and chronic glomerular and tubulointerstitial lesions, and different glomerular diseases superimposed on diabetic lesions.

**Class 1** consisted of 19 patients with findings typical of diabetic glomerulopathy [14], *i.e.*, marked glomerular hypertrophy associated with glomerulosclerosis both of diffuse and nodular type and diffuse arteriolar hyalinosis [14] (Figure 1). The spectrum and the extent of such changes are summarized in Tables 1 and 2. The total number of glomeruli examined was 297; the average number per biopsy was 16.7. Global glomerulosclerosis was observed in most patients and affected, on average, 24% of glomeruli. Glomerular aneurysms were not a prominent finding. Thickening of glomerular capillary wall and of Bowman's capsule was moderate. All specimens exhibited interstitial fibrosis and thickening of tubular basement membrane, whereas the degree of interstitial inflammation was mild. The arteriolar hyalinosis was rather pronounced and diffuse, whereas arteriosclerotic changes were not severe. A significant correlation was found between the scores of glomerulosclerosis and of hyalin lesions of arterioles ($P < 0.05$).

Immunofluorescence often revealed a weak linear deposition of IgG and of light chains along the glomerular basement membrane and occasionally along the tubular basement membrane. Coarse deposits of IgM and C3 were detected focally in the areas of sclerosis and hyalinosis. Electron microscopy examination displayed the typical changes of diabetic nephropathy characterized by a marked and diffuse thickening of glomerular basement membrane and by diffuse sclerotic lesions.

**Class 2** consisted of 16 patients. The histologic pattern was characterized by the presence of chronic and rather nonspecific changes affecting the entire structure of the kidney (Figure 2). The total number of glomeruli was 259; the average number per biopsy was 16.2. The percentage of globally sclerotic glomeruli was 42%, which was significantly higher than that in Class 1 diabetics ($P < 0.05$). The nonsclerotic glomeruli did not appear enlarged and showed rather mild changes (mean score of sclerosis, 1.3; mean score of exudative lesions, 0.8, mean score of aneurysms, 0). By contrast, the score of ischemic changes was significantly higher than that observed in Class 1.
TABLE 1. Renal histopathology by conventional analysisa

<table>
<thead>
<tr>
<th>Class</th>
<th>GSC%</th>
<th>SC</th>
<th>ISCHL</th>
<th>GBMT</th>
<th>EX</th>
<th>BCT</th>
<th>AN</th>
<th>IP</th>
<th>EXP</th>
<th>DEP</th>
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<td>0.2c</td>
<td>1.1</td>
<td>1.2</td>
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<td>0</td>
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<tr>
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<td>42d</td>
<td>1.3</td>
<td>1.4</td>
<td>0.9</td>
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<td>1.1</td>
<td>0.3</td>
<td>1</td>
<td>0.1</td>
<td>1.5</td>
<td>0.6</td>
<td>0</td>
</tr>
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</table>

a Abbreviations are as follows: GSC%, percentage of globally sclerotic glomeruli; SC, glomerular sclerosis; ISCHL, ischemic glomerular lesions; GBMT, glomerular basement membrane thickening; EX, exudative lesions; BCT, Bowman's capsule thickening; AN, aneurysms; IP, intracapillary proliferation; EXP, extracapillary proliferation; DEP, intraglomerular deposits. Except for GSC%, results are expressed as mean score.

b $P < 0.05$ versus Class 2.

c $P < 0.001$ versus Class 2.

d $P < 0.05$ versus Class 2.

TABLE 2. Renal histopathology by conventional analysisa

<table>
<thead>
<tr>
<th>Class</th>
<th>IE</th>
<th>II</th>
<th>IFB</th>
<th>TBMT</th>
<th>TDL</th>
<th>TNL</th>
<th>C</th>
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<td>1.2</td>
<td>0.8</td>
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<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>1.2</td>
<td>1.4</td>
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<td>0.1</td>
<td>1</td>
<td>1.3</td>
<td>0.7</td>
<td>0.9</td>
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</table>

a Abbreviations are as follows: IE, interstitial edema; II, interstitial inflammation; IFB, interstitial fibrosis; TBMT, tubular basement membrane thickening; TDL, tubular degenerative lesions; TNL, tubular necrotic lesions; C, casts; AH, arteriolar hyalinosis; AS, arteriosclerosis; ALS, arteriosclerosis. Results are expressed as mean score.

b $P < 0.001$ versus Class 2.

1 ($P < 0.05$). Glomerular lesions were associated with moderate thickening of Bowman's capsule and with a rather severe interstitial fibrosis and tubular atrophy. The score of arteriolar hyalinosis was lower than that in Class 1, but the difference did not reach a statistical significance ($P = 0.1$). By contrast, the score of arteriosclerosis was significantly higher (2 versus 0.9) than that in Class 1 ($P < 0.001$). Immunofluorescence was negative in most cases or showed occasional focal and segmental glomerular deposits of C3 and IgM. Electron microscopy revealed some changes consistent with the diagnosis of diabetic nephropathy. However, sclerotic lesions were rather mild and definitely less than in patients with Class 1. The thickening of glomerular basement membrane was moderate.

Class 3 consisted of 17 patients. The histologic pattern was characterized by changes consistent with the diagnosis of diabetic glomerulosclerosis on which other types of lesions unrelated to diabetes were superimposed (Figure 3). The total number of glomeruli examined was 213; the average number per biopsy was 12.5. As shown in Table 1, the pattern of histologic lesions was rather similar to that observed in Class 1; however, changes were less severe and diffuse than in Class 1. At variance with Classes 1 and 2, in this group of patients, immunofluorescence and electron microscopy features played a relevant role in determining the final diagnosis. Diabetic glomerulosclerosis in Class 3 patients was associated with the following types of lesions: diffuse intracapillary proliferative glomerulonephritis, consistent with the diagnosis of acute glomerulonephritis (six cases); membranous glomerulopathy (two cases); minimal change glomerulopathy (two cases); IgA nephropathy (two cases); focal, extracapillary glomerulonephritis (two cases); extracapillary and necrotizing glomerulonephritis (two cases); and amyloidosis (one case).
Morphometric Analysis

Results of morphometric analysis are reported in Table 3 and in Figure 4. In the control specimens, mean glomerular area averaged 11,149 μm². By contrast, the mean area of all sclerotic and nonsclerotic glomeruli of patients with Class 1 was 23,632 μm².

Figure 3. Glomerulus from a patient with Class 3 lesions showing a severe intracapillary hypercellularity with many polymorphs and a moderate diffuse glomerulosclerosis. Note the extensive hyalin changes in the arteriole (hematoxylin and eosin, ×250).

Figure 4. Distribution of glomerular cross-sectional area; only nonsclerotic glomeruli are represented.

<table>
<thead>
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<th>TABLE 3. Glomerular morphometrya</th>
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<tr>
<td>MGA</td>
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<td>MGA ns</td>
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<td>MGA s</td>
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Abbreviations are as follows: MGA, mean glomerular area; MGA ns, mean glomerular area of nonsclerotic glomeruli; MGA s, mean glomerular area of sclerotic glomeruli. Values are in square micrometers.

b P < 0.05 versus Class 2; P < 0.05 versus Class 3; P < 0.05 versus controls.
c P < 0.05 versus Controls.
d P < 0.05 versus controls.
* P < 0.05 versus Class 2; P < 0.05 versus Class 3; P < 0.05 versus controls.
f P < 0.05 versus Controls.
g P < 0.05 versus Controls.
and was significantly higher than that in controls \( (P < 0.05) \). The values of mean glomerular area ranged from 13,996 to 28,077 \( \mu m^2 \). Excluding the mean glomerular area of globally sclerotic glomeruli (average, 15,513 \( \mu m^2 \)), the difference between the mean glomerular area of patients with Class 1 and controls is even higher (25,737 versus 11,149 \( \mu m^2 \)) \( (P < 0.05) \).

In Class 2, the mean glomerular area averaged 16,483 \( \mu m^2 \), ranged from 9,053 to 20,444 \( \mu m^2 \), and was significantly higher than in controls \( (P < 0.05) \). However, the values of the mean glomerular area of patients with Class 2 were significantly lower than those in patients with Class 1 (23,632 versus 16,483 \( \mu m^2 \)) \( (P < 0.05) \). The mean glomerular area of globally sclerotic glomeruli was similar in both Classes 1 and 2 (15,513 versus 14,328 \( \mu m^2 \)) \( (P = 0.2) \). The values of the mean glomerular area of nonsclerotic glomeruli was slightly higher (17,889 \( \mu m^2 \)) but still lower than in Class 1 \( (P < 0.05) \).

In Class 3 patients, mean glomerular area averaged 18,134 \( \mu m^2 \) and ranged from 7,815 to 32,787 \( \mu m^2 \). The value of the mean glomerular area was significantly lower than in Class 1 (18,134 versus 23,632 \( \mu m^2 \)) \( (P < 0.05) \). The mean glomerular area of globally sclerotic glomeruli was 15,515 \( \mu m^2 \) and was not significantly different from that of controls and globally sclerotic glomeruli of Classes 1 and 2 \( (P = 0.68) \). The mean glomerular area of nonsclerotic glomeruli averaged 18,821 \( \mu m^2 \) and was still significantly lower than that in Class 1 patients (18,821 versus 25,737 \( \mu m^2 \)) \( (P < 0.05) \).

Clinical and Laboratory Features

Table 4 depicts the clinical characteristics of different histologic classes at the time of renal biopsy. The patients with Classes 1, 2, and 3 did not show any significant difference in age and in duration of diabetes. In Class 1, the ratio of male to female was 0.3, whereas in Classes 2 and 3, it was 4.3 and 2.4, respectively. Mean serum creatinine, urinary protein excretion, and arterial pressure were not significantly different at time of renal biopsy. Although the follow-up was rather short, patients of Classes 1 and 2 had a progressive worsening of renal function associated with an increase of urinary protein excretion (Table 5). Renal function at follow-up was rather stable, however, in Class 3 patients. Despite the presence of a progressive deterioration of renal function, mean arterial pressure did not increase in any of the classes of patients.

DISCUSSION

At variance with type I diabetes, little information is available on the prevalence and nature of renal damage in type II diabetes \( (15) \). Particularly, it is not clear whether all patients who develop renal damage and eventually renal failure have a pattern of tissue injury similar to that described in patients with type I diabetes. The few available data are very recent. Mogensen et al., studying newly diagnosed non-insulin dependent diabetics, found abnormal excre-

| TABLE 4. Clinical characteristics of the patients population at renal biopsy |
|-------------------------------------------------|----------------|----------------|----------------|
| Class 1                                         | Class 2        | Class 3        |
| No. of Patients                                 | 19             | 16             | 17             |
| Sex (M/F)                                       | 5/14           | 13/3           | 12/5           |
| Age (yr)                                       | 62 ± 12        | 64 ± 8         | 60 ± 8         |
| Duration of Diabetes (yr)                      | 10.2 ± 8.5     | 11.2 ± 9.4     | 7.8 ± 5.8      |
| Duration of Follow-Up (months)                  | 10.8 ± 11      | 12.5 ± 13.4    | 4.2 ± 4.2      |

| TABLE 5. Functional parameters                  |
|-------------------------------------------------|----------------|----------------|----------------|
| Class 1                                         | Class 2        | Class 3        |
| Serum creatinine (mg/dL)                        | 2.3 ± 1.9      | 2.7 ± 2.2      | 3 ± 2.7        |
| Urinary Protein excretion (g/24h)               | 3.6 ± 2.1      | 4.9 ± 2.1      | 3.5 ± 2.5      |
| Mean Arterial Pressure (mm Hg)                  | 110.2 ± 10.6   | 108.6 ± 2.5    | 113.2 ± 8.4    |
| Biopsy                                          | Follow-Up      | Biopsy         | Follow-Up      |
| Biopsy                                          | Follow-Up      | Biopsy         | Follow-Up      |
| Biopsy                                          | Follow-Up      | Biopsy         | Follow-Up      |
| Biopsy                                          | Follow-Up      | Biopsy         | Follow-Up      |
cise-induced proteinuria even in patients with a good metabolic control (16,17). Moreover, Hasslacher et al. found that the cumulative prevalence of proteinuria was comparable in type I and type II diabetes (18). More importantly, this latter study showed a comparable cumulative prevalence of renal failure in type I and type II diabetics when permeability to proteins is abnormal (18). Thus, more than 50% of patients with either diagnosis have renal failure after 5 yr from the time of the onset of proteinuria. Similar data have been obtained by Kunzelman et al., studying Pima Indians of southern Arizona—a population with the world’s highest prevalence of a type II—like diabetes not associated with insulin dependency (19).

In 30% of patients with type I diabetes, glomerular volume increases in the early phase of the disease for reasons that have not yet been fully clarified (11). This leads to an increase in glomerular surface area and GFR (20). In recent years, data have accumulated to suggest convincingly that hyperfiltration, at least in type I diabetes, is an early maker of renal disease progression (21,22). Whether glomerular hypertrophy also occurs in type II diabetes has not been established conclusively. Some early studies did not find glomerular hypertrophy and hyperfiltration in type II diabetes, but artifacts related to the technique of paraffin-embedded kidney tissue might have influenced the results (23). A recent study performed on prospectively collected autopsy kidney specimens has used plastic embedding of the samples in order to eliminate or minimize shrinkage (13). The data—analyzed stereologically to further reduce interpretation bias—indicated that glomerular volumes in type II diabetes were normal (13). This conclusion, however, conflicts with the recent evidence of a 50% increase in GFR in newly diagnosed type II diabetics (24). Such a discrepancy is difficult to explain. The issue is further complicated by the fact that a significant percentage of patients with type II, but not type I, diabetes has concomitant nondiabetic renal diseases, i.e., renal vascular disease, chronic glomerulonephritis, and reflex nephropathy, diseases that per se may lead to nephron mass reduction and compensatory increase in the size of remnant nephrons.

The data presented here show that only 37% of patients with type II diabetes—that we define as Class 1—have glomerular hypertrophy invariably associated with severe glomerulosclerosis and exudative lesions of glomerular capillaries and arterioles. Such a pattern is identical to the one of type I patients. In the second group of patients (Class 2), prevailing pathologic findings were chronic vascular (or arteriosclerotic type) and tubulointerstitial lesions, nonspecific findings that may be seen in all cases of chronic renal diseases. In this group of patients, glomerular volumes (albeit higher than normal) were significantly lower than those in Class 1. In the third group of patients, representing the 33% of the entire population we studied (Class 3), renal biopsy pattern was characterized by the presence of diabetic lesions associated with glomerular changes unrelated to diabetes. We cannot exclude that, in the high prevalence of patients with a second glomerular disease, unrelated diabetes may reflect a selection bias, because in general, renal biopsies in type II diabetes are more likely to be taken from patients with more atypical clinical course. This consideration, however, does not necessarily apply to our patients, all of whom have been biopsied on the basis of proteinuria exceeding 0.9 g/24 h. During the last few years, the increasing number of reports on double or superimposed glomerulopathies has led some authors to consider these forms as a separate entity among glomerular diseases (25–28). Double glomerulopathies are detected much more frequently in diabetics (26). Why diabetics are more susceptible to develop a superimposed nondiabetic type of glomerular disease is not known.

Given the heterogeneity of renal biopsy findings, it is not surprising that previous analyses of glomerular volumes in type II diabetes ended up with inconsistent results. Why do only 37% of patients with type II diabetes and nephropathy develop type I diabetic—like lesions? It has been suggested that glomerular hypertrophy in type I diabetes is a compensatory mechanism by which the less-affected glomerulus increase their surface area, thereby vicariously for the already obsolescent glomeruli (29). This may well apply to patients with type II diabetes and Class 1 lesions. It is possible that in patients with Class 2 lesions glomerular volume increase is offset by the concomitant presence of vascular changes. A support to this possibility derives from the observation that the percentage of glomeruli with global sclerosis was higher in Class 2 than in Class 1 patients (42 versus 24%), which might be taken to indicate that chronic vascular damage of arteriosclerotic type is a factor that favors glomerular ischemia and collapse.

Prospective studies are necessary to establish if the three different patterns of injury in type II diabetes are associated with different rates of progression of the disease to end-stage renal failure. Experimental and clinical evidence has accumulated in recent years to indicate convincingly that antihypertensive (30,31) drugs slow the rate of decline of GFR in type I diabetes, and the data would suggest that angiotensin-converting enzyme (ACE) inhibitors are more effective than other antihypertensive molecules (32-34). This has been attributed to the fact that ACE inhibitors have the peculiar property of lowering the increase in intraglomerular capillary pressure that is associated with glomerular hypertrophy and hyperfiltration (22). One can speculate that in type II dia-
betice only the group of patients with glomerular hypertrophy, i.e., Class 1 pattern, may benefit from such therapy. By contrast, patients with Class 2 and vascular lesions may possibly be more susceptible to ACE inhibitor-induced renal ischemia (35,36), as are patients with atherosclerosis or renal artery stenosis. These results would suggest that renal biopsy in patients with type II diabetes and signs of renal damage may offer important insights to understanding the nature of the lesions and may have an effect on prognosis and management.

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