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Data compiled during the 1970s and early 1980s indicated that during these periods, membranous nephropathy was the most common cause of unexplained nephrotic syndrome in adults, followed in order of frequency by minimal-change nephropathy and focal segmental glomerulosclerosis (FSGS). However, we and others recently reported an increase in the incidence of FSGS over the past two decades, and the number of cases of FSGS diagnosed by renal biopsies in these centers now exceeds the number of cases of membranous nephropathy. Nonetheless, as a substantial fraction of patients with FSGS do not have the nephrotic syndrome, it remained unclear as to what extent the relative frequencies of FSGS and other glomerulopathies as causes of the nephrotic syndrome have changed over this time. To address this concern, we reviewed data from 1,000 adult native kidney biopsies performed between January 1976 and April 1979 and from 1,000 biopsies performed between January 1995 and January 1997, identified all cases with a full-blown nephrotic syndrome of unknown etiology at the time of biopsy, and compared the relative frequencies with which specific diseases were diagnosed in these latter cases between the two time intervals. The main findings of this study were that, first, during the 1976 to 1979 period, the relative frequencies of membranous (36%) and minimal-change (23%) nephropathies and of FSGS (15%) as causes of unexplained nephrotic syndrome were similar to those observed in previous studies during the 1970s and early 1980s. In contrast, from 1995 to 1997, FSGS was the most common cause of this syndrome, accounting for 35% of cases compared with 33% for membranous nephropathy. Second, during the 1995 to 1997 period, FSGS accounted for more than 50% of cases of unexplained nephrotic syndrome in black adults and for 67% of such cases in black adults younger than 45 years. Third, although the relative frequency of nephrotic syndrome due to FSGS was two to three times higher in black than in white patients during both study periods, the frequency of FSGS increased similarly among both racial groups from the earlier to the later period. Fourth, the frequency of minimal-change nephrotic syndrome decreased from the earlier to the later study period in both black and white adults. Fifth, the relative frequency of membranoproliferative glomerulonephritis as a cause of the nephrotic syndrome declined from the 1976 to 1979 period to the 1995 to 1997 period, whereas that of immunoglobulin A nephropathy appeared to increase; the latter accounted for 14% of cases of unexplained nephrotic syndrome in white adults during the latter study period. Finally, 10% of nephrotic adults older than 44 years had AL amyloid nephropathy; none of these patients had multiple myeloma or a known paraprotein at the time of renal biopsy.

Data compiled during the 1970s and early 1980s indicate that during these periods, membranous nephropathy was the most common cause of unexplained nephrotic syndrome in adults, followed in order of frequency by minimal-change nephropathy and focal segmental glomerulosclerosis (FSGS). However, we and others recently reported an increase in the incidence of FSGS over the past two decades, and the number of cases of FSGS diagnosed by renal biopsies in these centers now exceeds the number of cases of membranous nephropathy. Nonetheless, as a substantial fraction of patients with FSGS do not have the nephrotic syndrome, it remained unclear as to what extent the relative frequencies of FSGS and other glomerulopathies as causes of the nephrotic syndrome have changed over this time. To address this concern, we reviewed data from 1,000 adult native kidney biopsies performed between January 1976 and April 1979 and from 1,000 biopsies performed between January 1995 and January 1997, identified all cases with a full-blown nephrotic syndrome of unknown etiology at the time of biopsy, and compared the relative frequencies with which specific diseases were diagnosed in these latter cases between the two time intervals. The main findings of this study were that, first, during the 1976 to 1979 period, the relative frequencies of membranous (36%) and minimal-change (23%) nephropathies and of FSGS (15%) as causes of unexplained nephrotic syndrome were similar to those observed in previous studies during the 1970s and early 1980s. In contrast, from 1995 to 1997, FSGS was the most common cause of this syndrome, accounting for 35% of cases compared with 33% for membranous nephropathy. Second, during the 1995 to 1997 period, FSGS accounted for more than 50% of cases of unexplained nephrotic syndrome in black adults and for 67% of such cases in black adults younger than 45 years. Third, although the relative frequency of nephrotic syndrome due to FSGS was two to three times higher in black than in white patients during both study periods, the frequency of FSGS increased similarly among both racial groups from the earlier to the later period. Fourth, the frequency of minimal-change nephrotic syndrome decreased from the earlier to the later study period in both black and white adults. Fifth, the relative frequency of membranoproliferative glomerulonephritis as a cause of the nephrotic syndrome declined from the 1976 to 1979 period to the 1995 to 1997 period, whereas that of immunoglobulin A nephropathy appeared to increase; the latter accounted for 14% of cases of unexplained nephrotic syndrome in white adults during the latter study period. Finally, 10% of nephrotic adults older than 44 years had AL amyloid nephropathy; none of these patients had multiple myeloma or a known paraprotein at the time of renal biopsy.

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INDEX WORDS: Nephrotic syndrome; renal biopsy; focal segmental glomerulosclerosis; membranous nephropathy; minimal-change nephropathy; IgA nephropathy; amyloid.
recent editions of a number of highly regarded textbooks of nephrology and renal pathology.\textsuperscript{8,10} Recently, however, studies at our center\textsuperscript{11} and that of Korbet et al\textsuperscript{12} in Chicago and D’Agati and colleagues in New York City\textsuperscript{13,14} have indicated a marked increase in the incidence of FSGS over the past two decades, particularly since the mid-1980s. In each of these renal biopsy populations,\textsuperscript{11-14} as well as in Massachusetts,\textsuperscript{15} the incidence of FSGS in adults now exceeds that of membranous nephropathy. However, a substantial fraction of adult patients with FSGS do not have the nephrotic syndrome: this fraction is most often indicated to be between 25% and 35\%;\textsuperscript{16-18} but has been reported to be as high as 44\%.\textsuperscript{6} As such, it remains unclear as to what extent the relative frequencies of membranous nephropathy and FSGS as causes of the nephrotic syndrome have changed over this time. The present study was undertaken to address this question and to determine whether any other significant changes in the profile of glomerular diseases resulting in the nephrotic syndrome in adults have occurred over the past two decades.

**MATERIALS AND METHODS**

**Study Design and Data Collection**

We reviewed the case files of the Renal Biopsy Laboratory of The University of Chicago Medical Center to identify 1,000 consecutive adult (≥18 years old) native kidney biopsy specimens received in this laboratory starting in January 1976 and 1,000 consecutive adult native kidney biopsy specimens received starting in January 1995. These files contain all patient records received with the renal biopsy specimen; a copy of the final biopsy report, which contains pertinent clinical information, descriptions of light microscopic, immunofluorescence, and electron microscopic findings, and the final diagnosis or diagnoses; and prints of electron micrographs. The files also contain notes recorded by the pathologist during telephone conversations held with the appropriate clinicians, who were routinely called to communicate a preliminary and/or final renal biopsy diagnosis.

During this review, we identified all cases in which the patient had nephrotic syndrome of unclear etiology at the time of biopsy, and for these cases recorded the primary renal biopsy diagnosis. Only those cases in which a full-blown nephrotic syndrome was present were specifically identified for inclusion in this study. This syndrome was defined as a 24-hour urinary protein excretion of ≥3.5 g/24 hr, plus peripheral edema and hypoalbuminemia.

When information was missing from the case file, it was requested via a questionnaire sent to the appropriate clinician(s) and/or through telephone conversations with these clinicians. For each case of nephrotic syndrome identified, we also recorded the following information: the patient’s age, sex, and race, and the serum creatinine and 24-hour urinary protein excretion at the approximate time of the biopsy.

Cases in which information present in the case folder and/or obtained through clinician inquiry revealed the patient to have a systemic disease or condition known to be associated with the nephrotic syndrome were excluded from this study. These systemic conditions included diabetes mellitus, systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis, hepatitis B infection, cryoglobulinemia, Henoch-Schönlein purpura, human immunodeficiency virus (HIV) infection, intravenous drug abuse, nephrolithiasis/pyelonephritis, sickle cell disease, prior unilateral nephrectomy, a history of gold or penicillamine therapy, and concurrent malignancy.

All biopsies were interpreted by one of the three renal pathologists who co-authored this paper. In addition to light microscopic examination of hematoxylin-eosin- and periodic acid-Schiff–stained sections for every case, electron microscopy was performed on more than 95% of the biopsy specimens from both time periods studied. During both time intervals studied, it was the standard practice of our laboratory to serially section paraffin blocks of tissue received for light microscopic evaluation in their entirety. Slides were alternately stained with hematoxylin-eosin and periodic acid-Schiff, with every third slide left unstained unless otherwise requested by the pathologist. Immunofluorescence studies (for immunoglobulin G [IgG], IgA, IgM, C3, C1q, fibrinogen, and kappa and lambda light chains where indicated) were performed on more than 95% of cases during the 1995 to 1997 period and on approximately 60% of cases during the 1976 to 1979 period.

From the 1,000 consecutive adult native kidney biopsy specimens obtained starting in January 1976 (and ending in April 1979), 199 cases of nephrotic syndrome of unclear etiology were identified. From the 1,000 such biopsy specimens obtained starting in January 1995 (and ending in January 1997), 233 cases of nephrotic syndrome of unclear etiology were identified. This difference may be explained in part by the higher fraction of total adult native renal biopsies performed at The University of Chicago Medical Center, as opposed to at outside referring hospitals, during the earlier time interval (31% v 9% for the 1995 to 1997 period). A high percentage of University of Chicago patients undergoing renal biopsy have a known systemic disease, and a smaller fraction present with idiopathic proteinuria than is the case for patients undergoing biopsies at the referral hospitals, most of which are located in the midwestern United States. For the 1976 to 1979 period, the race of 174 (87%) of the 199 patients studied was known. In addition to the patients of black and white races described in the Results, four patients were Hispanic and five were Asian or Native American. For the 1995 to 1997 period, the race of 213 (91%) of the 233 patients was known; 19 were Hispanic and three were Asian. The numbers of Hispanic and Asian patients were felt to be too few to warrant separate analysis when we considered racial differences in the causes of the nephrotic syndrome.

**Data Analysis**

Distributions of the various renal biopsy diagnoses in the two eras (1976 to 1979 and 1995 to 1997) and among patients of different age groups were compared using Pearson’s chi-
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Table 1. Renal Biopsy Diagnoses in Cases of Adult Nephrotic Syndrome, 1976 to 1979 Versus 1995 to 1997

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Membranous nephropathy</td>
<td>71 (36)</td>
<td>77 (33)</td>
</tr>
<tr>
<td>Minimal-change nephropathy</td>
<td>42 (23)</td>
<td>35 (15)</td>
</tr>
<tr>
<td>FSGS</td>
<td>29 (15)</td>
<td>81 (35)</td>
</tr>
<tr>
<td>Amyloid nephropathy</td>
<td>13 (7)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>MPGN</td>
<td>12 (6)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>10 (5)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>5 (3)</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Focal glomerulonephritis</td>
<td>5 (3)*</td>
<td>0*</td>
</tr>
<tr>
<td>Fibrillary glomerulonephritis</td>
<td>0*</td>
<td>2 (1)*</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>1 (1)*</td>
<td>2 (1)*</td>
</tr>
<tr>
<td>Inadequate biopsy</td>
<td>6 (4)*</td>
<td>1 (&lt;1)*</td>
</tr>
<tr>
<td>All cases</td>
<td>199</td>
<td>233</td>
</tr>
</tbody>
</table>

NOTE. Other diagnoses included (n = 1 each): for the 1976 to 1979 period: nephrosclerosis; for the 1995 to 1997 period, nephrosclerosis, C1q nephropathy. Chi-square analysis showed a significant difference in the distribution of diagnoses between the two periods (χ² on 7 degrees of freedom [χ² = 47.9; P < 0.001]).

* Diagnostic categories pooled for statistical analysis.

RESULTS

Data listed in Table 1 compare etiologies of unexplained adult nephrotic syndrome in our overall renal biopsy population over the two periods of time studied, January 1976 to April 1979 and January 1995 to January 1997. During the former time period, membranous nephropathy was the most prevalent cause of adult nephrotic syndrome, accounting for 36% of cases. As noted in Table 1, this was followed in order by minimal-change nephropathy (23%), FSGS (15%), amyloid nephropathy (7%), MPGN (6%), and chronic glomerulonephritis of unspecified etiology (5%). These data are quite consistent with data compiled in other centers in North America, South America, and Europe before 1986.1-7,12 Comparing findings during the January 1995 to January 1997 period with these earlier data, a highly significant difference in the distribution of diagnoses was detected (see Table 1 footnote). The major changes noted in Table 1 are a marked increase in the fraction of nephrotic adult patients with FSGS and a decrease in the fraction of such patients with minimal-change nephropathy. In our overall renal biopsy population, FSGS is now the leading cause of unexplained adult nephrotic syndrome, overtaking membranous nephropathy by a small margin (35% of cases vs 33%; Table 1).

We also noted a lower fraction of adult nephrotic patients with MPGN (inclusive of subtypes I, II, and III) and with chronic glomerulonephritis of unspecified etiology, and a higher fraction with IgA nephropathy, during the 1995 to 1997 period than during the 1976 to 1979 period. The fraction of patients with IgA nephropathy during the earlier time period may be artificially low (and the fraction with unspecified chronic glomerulonephritis artificially high), however, in that during this time period immunofluorescence studies were performed on only approximately 60% of biopsy specimens received. Of note, five nephrotic patients during the 1976 to 1979 period were diagnosed as having focal glomerulonephritis with electron-dense deposits present ultrastructurally; immunofluorescence was not performed on any of these biopsy specimens. Immunofluorescence studies were also not performed on six of the 10 cases of unspecified chronic glomerulonephritis diagnosed from 1976 to 1979; deposits were also identified ultrastructurally in each of these cases.

Racial differences in the incidences of adult nephrotic syndrome caused by individual diseases are examined in Table 2. Overall, there was a significant difference in the distribution of diagnoses between black and white patients during both eras studied (χ² = 13.8, P < 0.05).

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>45 (38)</td>
<td>16 (34)</td>
</tr>
<tr>
<td>Minimal-change nephropathy</td>
<td>26 (22)</td>
<td>9 (19)</td>
</tr>
<tr>
<td>FSGS</td>
<td>11 (8)</td>
<td>14 (30)</td>
</tr>
<tr>
<td>Amyloid</td>
<td>8 (7)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>MPGN</td>
<td>0 (8)</td>
<td>0†</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>6 (5)</td>
<td>2 (4)†</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>5 (4)*</td>
<td>0†</td>
</tr>
<tr>
<td>Focal glomerulonephritis</td>
<td>3 (3)*†</td>
<td>1 (2)*†</td>
</tr>
<tr>
<td>Fibrillary glomerulonephritis</td>
<td>0†</td>
<td>0†</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>0†</td>
<td>1 (2)*†</td>
</tr>
<tr>
<td>Inadequate biopsy</td>
<td>5 (4)*†</td>
<td>2 (4)*†</td>
</tr>
<tr>
<td>All cases</td>
<td>118</td>
<td>47</td>
</tr>
</tbody>
</table>

NOTE. Other diagnoses are specified in the footnote to Table 1. Data were analyzed by chi-square test in two ways: comparison of white versus black patients within the same study period and comparison of data from patients of the same race in the two different study periods. "P values for these analyses are listed in the text.

* Diagnostic categories pooled for statistical analysis of racial differences within a single study period.
† Diagnostic categories pooled for statistical analysis of patients of the same race in the two different study periods.

for the 1976 to 1979 period; \( \chi^2 = 27.5, P < 0.001 \) for the 1995 to 1997 period; see Table 2 footnote). Consistent with other studies indicating a high incidence of FSGS among blacks,¹¹,¹²,¹³,¹⁴,¹⁵ we found that the fraction of nephrotic adults with FSGS was two to three times higher among black patients than white patients during both the 1976 to 1979 and 1995 to 1997 study periods. Nevertheless, during the former period, membranous nephropathy was the leading cause of unexplained nephrotic syndrome among both black and white adults. The increase in the relative frequency of FSGS as a cause of the nephrotic syndrome from the earlier to the later study period was, interestingly, similar in these two racial groups, although during the 1995 to 1997 period, membranous nephropathy remained the leading cause of nephrotic syndrome in white adults, whereas among black adults FSGS is now by far the leading cause of unexplained nephrotic syndrome. Overall, the change in the distribution of diagnoses between the two eras was significant in both white (\( \chi^2 = 30.8, P < 0.001 \)) and black (\( \chi^2 = 9.5, P < 0.05 \)) patients.

The observed increase in the relative frequency of FSGS as a cause of the nephrotic syndrome, both overall and in black patients, is in a minor way related to an increase in the incidence of the collapsing glomerulopathy variant of FSGS.²⁶-²⁸ While no cases of this variant were observed during the 1976 to 1979 period, during the 1995 to 1997 period there were seven cases of collapsing glomerulopathy diagnosed in patients with the nephrotic syndrome. These seven cases are included among the FSGS cases listed in Tables 1 and 2. All but one of the patients with collapsing glomerulopathy were black; none was HIV-positive and none of these seven biopsy specimens showed tubuloreticular inclusions ultrastructurally. Thus, collapsing glomerulopathy accounted for 9% of all nephrotic FSGS cases during the 1995 to 1997 period and 16% of all such cases in black patients. We reviewed slides for each case of FSGS diagnosed during both study periods, and in only four cases (two during each study period) did we observe the glomerular "tip" lesion as an isolated finding (ie, in the absence of more "classic" FSGS lesions). These cases are also included among the FSGS cases listed in Tables 1 and 2.

In addition to those noted with FSGS, we observed large racial differences in the relative frequency of IgA nephropathy as a cause of the nephrotic syndrome. As noted above, the frequency of IgA nephropathy as a cause of adult nephrotic syndrome was higher during the 1995 to 1997 period than during the 1976 to 1979
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period. During both time periods, the great majority of cases of IgA nephropathy as a cause of the nephrotic syndrome were seen in white patients, with only a single case (during the 1995 to 1997 period) diagnosed in an black patient (Table 2). These findings are consistent with previous observations that IgA nephropathy is rare in blacks, this is true even of cases of IgA nephropathy that histologically and clinically resemble FSGS. Similar to the findings of Korbet et al., we also observed a trend toward a lower relative frequency of MPGN in black patients compared with white patients (Table 2).

We also examined the age distribution of the patients studied, in a manner similar to the study of Korbet et al. in patients with nephrotic-range proteinuria. Both white and black patients who underwent biopsy during the 1995 to 1997 period were older on average (mean age, 49.2 ± 15.9 years) for 124 white patients; 43.8 ± 15.0 years for 68 black patients) than those who underwent biopsy during the 1976 to 1979 period (44.0 ± 18.8 years for 113 white patients; 36.8 ± 15.9 years for 45 black patients); this difference was statistically significant for white patients (P = 0.023 by t-test) but not for black patients (P = 0.069), whose sample size was smaller. The difference in mean age between white and black patients was significant during both the 1976 to 1979 (P = 0.045) and the 1995 to 1997 (P = 0.019) periods.

Table 3 examines the age and racial distributions of patients with specific renal biopsy diagnoses. For the purpose of this table, data from both study periods were combined to avoid comparison of very small numbers of patients with diagnoses other than membranous nephropathy and FSGS and/or excessive pooling of data for statistical analysis (see Materials and Methods). The overall distribution of diagnoses in Table 3 was found by chi-square analysis to be significantly different between patients less than 45 years old and patients at least 45 years old among both white and black patients, although the statistical significance of these differences was lost for all but one comparison (in white patients during the 1976 to 1979 period, see Table 3 footnote) when the data were further stratified according to study period. There was also a significant difference in the distribution of diag-

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. (% of Cases: White Patients</th>
<th>No. (% of Cases: Black Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous nephropathy</td>
<td>44 (40)</td>
<td>16 (26)</td>
</tr>
<tr>
<td>Minimal-change nephropathy</td>
<td>20 (18)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>FSGS</td>
<td>16 (15)</td>
<td>34 (55)</td>
</tr>
<tr>
<td>Amyloid</td>
<td>1 (1)*</td>
<td>1 (2)*</td>
</tr>
<tr>
<td>MPGN</td>
<td>9 (8)</td>
<td>1 (2)*</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>3 (3)*</td>
<td>3 (6)*</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>15 (14)</td>
<td>1 (2)*</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>2 (2)*</td>
<td>3 (6)*</td>
</tr>
<tr>
<td>All cases</td>
<td>110</td>
<td>62</td>
</tr>
</tbody>
</table>

NOTE. Data shown are combined from the 1976 to 1979 and 1995 to 1997 periods and include only adequate biopsy specimens. Other diagnoses include those specified in the footnote to Table 1, as well as fibrillary glomerulonephritis and focal glomerulonephritis of unspecified etiology. Chi-square analysis showed a significant difference in the distribution of diagnoses between patients of the two age groupings for both white patients (χ² = 19.8; P < 0.01) and black patients (χ² = 10.9; P < 0.05), and a significant difference in the distribution of diagnoses between white and black patients of each age grouping (χ² = 36.4; P < 0.001 for <45 years; χ² = 11.6, P < 0.05 for ≥45 years). Although not shown in this table, differences in the distribution of diagnoses between the two age groupings, when stratified by both race and study period and analyzed by Fisher’s exact test (see Materials and Methods), were significant only for white patients during the 1976 to 1979 period (P = 0.010), and not for white patients during the 1995 to 1997 period (P = 0.40) or for black patients during either study period (P = 0.33 for 1976-1979; P = 0.855 for 1995-1997).

* Diagnostic categories pooled for statistical analysis of differences between white and black patients of the same age grouping.

† Diagnostic categories pooled for statistical analysis of age differences within a single racial group.
noses between white and black patients in both age groupings (see Table 3 footnote).

When individual diagnoses were considered, several interesting age-related trends were noted (Table 3). First, among both white and black patients, amyloid nephropathy was a significant cause of unexplained nephrotic syndrome in patients ≥45 years old, accounting for 10% of total cases in this age group but for only 1% of cases in patients younger than 45 years. Each of the patients in the older age group had AL (primary) amyloid, although none was known to have a serum or urine paraprotein or a hematologic abnormality at the time of renal biopsy (see Discussion). Second, in black but not in white patients, FSGS was more prevalent in the younger age group, a finding also noted by Korbet et al. During the 1995 to 1997 period, we found that FSGS accounted for 67% of cases of unexplained nephrotic syndrome in black adults younger than 45 years compared with 44% of such cases in black adults aged 45 years or older. Third, both IgA nephropathy and MPGN, which as noted earlier were observed primarily in white patients, also had a higher relative frequency in younger adults. Finally, we found that the relative frequencies of membranous and minimal-change nephropathies were similar before and after the age of 45 years in both white and black adults.

The increase in the relative frequency of FSGS as a cause of the nephrotic syndrome has occurred in parallel with a marked increase in the overall incidence of FSGS over the past two decades. In Table 4 illustrates that the fraction of adult patients with FSGS who had a full-blown nephrotic syndrome did not increase, but rather decreased slightly (but not significantly; \( P = 0.50 \) by chi-square analysis), from the 1976 to 1979 period (66%) to the 1995 to 1997 (59%) period. Each of these figures for the fraction of FSGS patients with the nephrotic syndrome is within the range of previous observations in adults (56% to 74%). The fraction of total adult FSGS patients with the nephrotic syndrome is lower than a similar fraction of total adult patients with membranous nephropathy; as such, the total incidence of FSGS in adults now far exceeds that of membranous nephropathy (Table 4; also Haas et al. despite the fact that FSGS only slightly exceeds membranous nephropathy as a cause of the nephrotic syndrome (Table 1, 1995 to 1997). It is also interesting to note that during the 1995 to 1997 period, 20 (18%) of the 109 patients with IgA nephropathy had a full-blown nephrotic syndrome at the approximate time of renal biopsy; this fraction far exceeds the number that can be accounted for by cases of IgA nephropathy with FSGS-like histology (7.4%).

**DISCUSSION**

Previous reports from several centers in the United States, including our own, have indicated that FSGS is now the most prevalent adult nephropathy seen on renal biopsy, having overtaken membranous nephropathy during the past 5 to 10 years. We present data indicating that since the start of 1995, FSGS is the most common cause of unexplained adult nephrotic syndrome in our renal biopsy population, accounting for slightly more such cases than membranous nephropathy. This has occurred despite the fact that only 59% of patients with FSGS in our renal biopsy population during the 1995 to 1997 period had the nephrotic syndrome at the approximate time of renal biopsy, compared with 82% of patients with membranous lesions.

FSGS is now by far the most common cause of unexplained nephrotic syndrome in black adults, accounting for over half of such cases and for two thirds of such cases in black patients younger than...
45 years in our renal biopsy population. Notably, during the late 1970s (January 1976 to April 1979), this was not the case; during this time period, FSGS accounted for 30% of cases of unexplained nephrotic syndrome in black adults and was slightly less prevalent than membranous nephropathy as a cause of the nephrotic syndrome in this population. Even among black adults younger than 45 years, FSGS and membranous nephropathy had equivalent frequencies as causes of unexplained nephrotic syndrome during the 1976 to 1979 period, each accounting for 37% of such cases. While FSGS is still less common than membranous nephropathy as a cause of nephrotic syndrome in white adults, the fraction of nephrotic white adults with FSGS has nevertheless increased substantially from the late 1970s (9%) to the present (25%). Because of racial differences in the incidence of FSGS, which have been well-documented previously, the relative frequencies of FSGS and membranous nephropathy as causes of adult nephrotic syndrome will vary in patient populations of different racial composition. The fraction of blacks in our renal biopsy population, which is approximately 30% at present, has not increased since the mid-1970s. As such, a change in the racial composition of our study population cannot account for the increase in the overall frequency of FSGS noted in a previous study or the increase in the relative frequency of FSGS as a cause of adult nephrotic syndrome found in the present study.

The underlying cause(s) for the marked increase in the incidence of FSGS during the past decade is unclear. Our previous data led us to conclude that this was not related to changes in nephrology or pathology practice with respect to renal biopsies; this will be discussed further below.

On average, patients who underwent biopsy during the 1995 to 1997 period tended to be somewhat older than those who underwent biopsy during the earlier study period, although this would not be expected to increase the frequency of FSGS as a cause of the nephrotic syndrome, since this tends to occur more frequently in younger adults, particularly in blacks. FSGS also appears to be a rather heterogeneous condition, and more than one etiology is likely. For example, substantial evidence now exists for a circulating factor that causes proteinuria in FSGS patients, particularly those who have recurrence of the disease following a renal transplant. However, this factor is clearly not present in all FSGS patients. There are multiple secondary forms of FSGS, including lesions related to intravenous drug abuse, obesity, and extensive nephron loss due to surgery or other renal diseases, such as advanced hypertensive nephrosclerosis.

By thoroughly reviewing all case folders and directly communicating with the appropriate clinicians (see Materials and Methods), we attempted to exclude all such secondary FSGS lesions (as well as other secondary causes of the nephrotic syndrome) from the present study, although admittedly complete efficiency in this regard is not possible in a retrospective study such as this in which biopsy specimens were received from many different hospitals and nephrologists. However, with certain specific exceptions (eg, HIV- and heroin-associated lesions), the majority of patients with secondary FSGS do not have the nephrotic syndrome.

A minor component of the observed increase in the relative frequency of FSGS as a cause of the nephrotic syndrome can be accounted for by the collapsing glomerulopathy variant of FSGS. Consistent with findings of others, we did not observe any cases of this variant before 1980, whereas during the 1995 to 1997 period, collapsing glomerulopathy accounted for 9% of our overall cases of FSGS with the nephrotic syndrome and for 16% of such cases in blacks. The frequency with which collapsing glomerulopathy was observed in our renal biopsy population was notably less than that reported by Valeri et al for a population based in New York City. These investigators found this variant of FSGS to account for 24% of their total cases of idiopathic FSGS from 1990 to 1993, and an even higher fraction of nephrotic FSGS patients noting the higher incidence of the nephrotic syndrome in patients with collapsing glomerulopathy (91%) versus "classic" FSGS (60%) reported in their study. In contrast, Korbet and colleagues, in their Chicago-based renal biopsy population, reported a relative frequency of lesions analogous to collapsing glomerulopathy (referred to as cellular lesions of FSGS with diffuse capillary collapse by these investigators) similar to that observed in the present study and in our previous study of adult nephropathies.

Our finding that the relative frequency of ne-
nephrotic syndrome caused by FSGS increased approximately equivalently in black and white patients from the late 1970s to the present is consistent with the hypothesis that a ubiquitous environmental factor or factors may be responsible for much of the increase in the incidence in FSGS in the overall population, with a genetic predisposition to developing FSGS accounting for the higher incidence of this condition in blacks.

Our findings are in general agreement with those of Korbet et al., who examined racial and age-related prevalences of renal biopsy diagnoses in 340 patients with nephrotic-range proteinuria due to a primary glomerular disease during two intervals, 1975 to 1984 and 1985 to 1994. One notable difference in the findings of these two studies is that while we found a higher frequency of FSGS among both black and white patients in our later study period compared with our earlier one, Korbet et al. found that the increased frequency of FSGS observed during the 1985 to 1994 period compared with the 1975 to 1984 period was limited to black patients. However, two important differences in study design may have contributed to this apparent discrepancy. First, Korbet et al. considered patients ≥15 years of age with proteinuria of at least 3.0 g/d, whereas the present study included only patients ≥18 years of age with proteinuria of ≥3.5 g/d, edema, and hypoalbuminemia (ie, a full-blown nephrotic syndrome). In our renal biopsy population, approximately 83% of patients with apparent primary FSGS have nephrotic-range (≥3.5 g/d) proteinuria, whereas only 59% to 66% of these patients have the nephrotic syndrome (Table 4). Thus, a significant fraction of patients included in the study of Korbet et al. would not have met inclusion criteria for the present study. Second, the present study compared renal biopsy findings during two relatively short, noncontiguous time intervals separated by more than 15 years, whereas Korbet et al. compared findings during two consecutive 10-year intervals. Our previous study showed a progressive increase in the relative frequency of FSGS among adult nephropathies between 1975 and 1994, and particularly after 1980. Noting this, it appears that a study comparing findings in two relatively short, widely separated time intervals might represent a more sensitive means of detecting changes in the relative frequency of FSGS in a given study population over the past two decades.

Concurrently with the increase in the frequency of FSGS, both overall and as a cause of adult nephrotic syndrome, we observed a decrease in minimal-change nephropathy and in cases of adult nephrotic syndrome related to the latter condition. A similar decrease was also noted by Korbet et al. This finding raises the obvious questions of whether we, as renal pathologists, are simply better at diagnosing FSGS now than two decades ago, have over time developed a lower threshold for the histologic diagnosis of FSGS, and/or are presently supplied with better renal biopsy samples than we were in the 1970s. In the context of a recent, related study, we reviewed in a blinded manner 40 biopsy specimens from 1974-1975 with a diagnosis of FSGS, minimal-change nephropathy, or membranous nephropathy, and agreed with the original diagnosis on all but one (which was originally interpreted as FSGS, but felt to be minimal-change nephropathy plus nephrosclerosis on review). This would argue against changes in the skill or threshold of the pathologists in diagnosing FSGS leading to the observed increase in the relative frequency of FSGS and concurrent decrease in the relative frequency of minimal-change nephropathy.

Our practice of serially sectioning tissue blocks (see Materials and Methods), which should optimize our ability to detect small, segmental diagnostic lesions of FSGS, was not different during the two study periods. Furthermore, although we have not systematically studied this, it is our impression that renal biopsy specimens received during the past several years tend to, on average, contain smaller samples of renal cortex with fewer glomeruli than those received two decades ago, in large part because of the increased use of smaller-gauge biopsy needles and biopsy "guns."

An alternative hypothesis for the decline in the relative frequency of minimal-change nephropathy in our adult renal biopsy population could be that fewer patients with such lesions are actually being subjected to biopsy. In the current medical economic climate, it is possible that a greater percentage of adults who present with idiopathic
nephrotic syndrome without hypertension or impaired renal function are being treated empirically with a course of corticosteroids before a potential renal biopsy, much as is typically done with nephrotic children.

We also observed a lower relative frequency of MPGN (inclusive of all subtypes) and of unspecified chronic glomerulonephritis and a higher relative frequency of IgA nephropathy as causes of adult nephrotic syndrome during the 1995 to 1997 period compared with two decades earlier. The change in the relative frequency of MPGN, but not that of IgA nephropathy, may reflect the overall increase in the age of our renal biopsy population from the earlier to the later study period, as both of these glomerular diseases were noted in association with the nephrotic syndrome more frequently in younger adults (Table 3). The increased frequency of IgA nephropathy and the decreased frequency of unspecified chronic glomerulonephritis as causes of the nephrotic syndrome may be largely artifactual in that immunofluorescence studies were only performed on approximately 60% of renal biopsy specimens received in our laboratory during the 1976 to 1979 period. Nevertheless, in other studies documenting the causes of adult nephrotic syndrome before 1986,1-7 IgA nephropathy is usually not specifically listed and is typically grouped with "other lesions" or "other proliferative glomerulonephritides."

In two of these latter studies, IgA nephropathy was specifically listed among causes of the nephrotic syndrome in adults and accounted for only 0.5% and 2% of such cases, respectively, despite accounting for 10.6% and 15%, respectively, of all diagnoses in these two studies in which immunofluorescence studies were performed on all cases.1,2 In contrast, our data from the 1995 to 1997 period showed that of 109 adult patients diagnosed with IgA nephropathy (10.9% of all adult native renal biopsy diagnoses during this period), 20 (18%) had the nephrotic syndrome, accounting for 9% of all cases of unexplained adult nephrotic syndrome during this period.

Whether this represents a true increase in the frequency of IgA nephropathy as a cause of the nephrotic syndrome, a finding related to renal biopsy practices in our patient population, or both, presently remains unclear. We recently studied 244 cases of IgA nephropathy diagnosed at our center between 1980 and 1994, and found a mean level of proteinuria of 2.9 ± 2.7 (±SD) g/24 hr in these patients.39 However, the 10-year renal survival rate of these patients was only 50% to 60%, which is lower than that observed in most studies of IgA nephropathy (approximately 80%, reviewed by Galla30 and D'Amico31). This suggests that our population of IgA nephropathy patients tended to have more severe and/or advanced disease than most such populations represented in the literature. Indeed, in our study,33 none of the 39 IgA nephropathy patients with the mildest glomerular lesions (histologic subclass I) had nephrotic-range proteinuria.

Interestingly, Korbet et al34 also have noted that IgA nephropathy accounts for a significant fraction of white adults with nephrotic-range proteinuria (7% to 9% overall; 15% in patients less than 45 years old), although this fraction did not change significantly between 1975-1984 and 1985-1994. Thus, our experience, as well as that of Korbet et al,34 suggests that IgA nephropathy should be considered in the differential diagnosis of adult nephrotic syndrome of unknown etiology, particularly in younger patients not of black race, and that all renal biopsies performed on such patients should provide tissue for immunofluorescence studies.

Finally, we found that a significant fraction (10%) of patients at least 45 years of age with unexplained nephrotic syndrome had amyloid nephropathy. Although amyloid is technically not a primary renal disease, we included patients with amyloid nephropathy in the present study of patients with unexplained nephrotic syndrome if at the time of renal biopsy they had no known evidence of a systemic disease related to amyloidosis (eg, rheumatoid arthritis), no known serum or urine paraprotein, and no evidence of a hematologic malignancy. Of the 22 patients with amyloid nephropathy meeting the study criteria, 20 were at least 45 years old, and all of the latter had AL (primary) amyloid. As the majority of patients with AL amyloidosis do not have overt multiple myeloma and 10% to 20% do not have a detectable monoclonal immunoglobulin or light chain in the serum or urine,41 amyloid nephropathy should be considered in the differential diag-
nosis of unexplained nephrotic syndrome in adults older than 44 years.

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REFERENCES


