Kidney International, Vol. 67 (2005), pp. 987–1001

Evolution of nephrotic-associated focal segmental glomerulosclerosis and relation to the glomerular tip lesion[1]

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Evolution of nephrotic-associated focal segmental glomerulosclerosis and relation to the glomerular tip lesion.

Background. Several entities or variants within focal segmental glomerulosclerosis (FSGS) have been described, but their changes with time and interrelationships are undetermined.

Methods. Changes with time were studied in two series of segmental sclerosing lesions in the nephrotic syndrome, one of 22 specimens from ten patients in a trial, the other of 176 specimens from 121 consecutive patients.

Results. The earliest lesions were probably all at the tubular origin, equivalent to the tip variant of FSGS. In some patients, lesions remained at this site, but progression to renal failure was accompanied by morphologic progression, with development of lesions at various sites, equivalent to FSGS, not otherwise specified (NOS). Progression was more likely if there were large lesions, abnormal mesangium, and extensive acute tubular damage. Patients with lesions at the tubular origin at presentation had a shorter duration of symptoms and less chronic renal damage than those with multiple lesions, were more likely to have a complete response of the nephrotic syndrome, and were less likely to progress to renal failure. Recurrent nephrotic syndrome occurred in 12 of 14 allografts at risk, and was usually accompanied by lesions at the tubular origin, then multiple lesions.

Conclusion. At least some patients with FSGS (NOS) have evolved from the tip variant. The tip variant has been considered a distinct entity. Another interpretation is that it includes two conditions, one an early form of classic FSGS, and the other closely related to minimal change nephropathy (MCN), equivalent to the glomerular tip lesion as originally defined.

The term focal segmental glomerulosclerosis (FSGS) has been applied to segmental sclerosing lesions in different circumstances, such as in the nephrotic syndrome, nonnephrotic proteinuria, states of reduced renal mass, and various glomerular disorders. There is recognition that several morphologic entities have been included in FSGS [1]. Whether these are variants of a single condition has not been determined, nor has the relation between them. In particular, there has been little work on their changes with time.

The hypothesis of this study was that there were changes with time in segmental sclerosing lesions in the nephrotic syndrome. Our investigation was of two series of patients who had more than one specimen. The first series comprised patients with repeat specimens in the United Kingdom Medical Research Council (MRC) 1960 trial of steroids in the nephrotic syndrome [2]. Advantages of this series were that renal biopsies were collected without reference to the original diagnosis, patients who had a relapse usually had a repeat biopsy, and among later specimens were autopsy kidneys, which were virtually unobtainable afterwards. The second series comprised patients selected from all those with the nephrotic syndrome seen at one nephrology unit in 18 years, and had advantages that it was larger and more recent. Neither series included children under 13 years old.

METHODS

Repeat specimens in the MRC trial

In this trial, there were renal biopsies from 125 patients aged at least 15 years, with edema, at least 5 g proteinuria per 24 hours, and serum albumin concentration under 30 g/L [2]. Of 26 who had repeat specimens available for study [3], 16 were excluded with membranous nephropathy ($N = 8$), minimal change nephropathy (MCN) ($N = 5$), subendothelial membranoproliferative glomerulonephritis (MPGN) ($N = 2$), and severe late damage ($N = 1$). The ten patients studied had two renal biopsies ($N = 4$), a biopsy and an autopsy ($N = 4$), three biopsies ($N = 1$), and two biopsies and an autopsy ($N = 1$). One slide, usually with one section, was restained with periodic acid-methenamine silver (PA-silver), and examined for these features [4, 5]: number

[1] **See Editorial by Haas, p. 1188.**

Key words: nephrotic syndrome, focal segmental glomerulosclerosis, glomerular tip lesion, renal transplantation, recurrent nephrotic syndrome.

Received for publication July 1, 2004
and in revised form August 19, 2004
Accepted for publication October 7, 2004

of glomeruli, number of glomeruli with identifiable tubular origin, number of globally sclerosed glomeruli, and whether mesangium appeared normal; appearance and size of segmental lesions, their position related to tubular origin and hilum, and number of glomeruli affected; and marked acute tubular damage, detected mainly as flattened epithelium, affecting at least a fourth of proximal tubules. Mesangium was considered normal if the amount of matrix and number of cells were not increased in comparison with those in reference glomeruli, for instance, in thin glomerular basement membrane disease. A large lesion occupied at least one third of the tuft. Epithelial changes in segmental lesions were defined as any changes in visceral epithelial cells, including crowding, swelling, vacuolation, and granulation. Any of the following features were called multiple lesions: (*1*) at least one lesion away from the tubular origin, such as at the hilum or mid tuft, and/or (*2*) lesions extending from tubular origin to hilum, and/or (*3*) lesions at various sites in glomeruli. Sections of autopsy kidneys were examined for a difference between outer and inner cortex, by drawing a line to split the cortex into two zones, counting glomeruli with segmental or global sclerosis, and expressing these as percentages of all glomeruli. A difference between the zones of at least 15% in either count was arbitrarily considered significant. Glomerular area was measured by an approximate method [6]. The index of chronic damage was calculated to measure damage as a proportion of cortical cross-sectional area [7]. Patterns of change in segmental abnormalities were identified.

Repeat specimens in the later series

Cases were selected from middle of 1985, following another study [8], to the end of 2003, from 730 consecutive patients aged at least 13 years with the nephrotic syndrome (edema, serum albumin concentration under 30 g/L, and proteinuria, at least 3.5 g/24 hours, or ratio of urinary albumin to creatinine concentrations of at least 300 mg/mmol). Patients were excluded with membranous nephropathy ($N = 218$), MCN ($N = 122$), diabetic glomerulopathy ($N = 65$), lupus nephritis ($N = 59$), amyloid ($N = 51$), acute postinfective glomerulonephritis ($N = 25$), MPGN ($N = 25$), IgA nephropathy/Henoch Schönlein nephritis ($N = 24$), light chain glomerulopathy ($N = 6$), vasculitic glomerulonephritis ($N = 4$), collapsing glomerulopathy ($N = 3$), eclamptic glomerulopathy ($N = 3$), immunotactoid glomerulopathy ($N = 3$), and cryoglobulinaemic glomerulonephritis ($N = 1$). This left 121 patients with at least one renal biopsy containing at least one segmental lesion. On electron microscopy, none had Alport syndrome or other identifiable inherited disorder. Of these 121 patients, 30 had more than one specimen, including specimens of renal allografts. Twenty-one had two biopsies, two had three, and seven had various biopsies ($N = 13$), nephrectomies ($N = 3$), allograft biopsies ($N = 15$), and allograft nephrectomies ($N = 6$). No autopsies were available. On every biopsy, there were at least six slides, with about six serial sections per slide. Sections were examined as in the MRC series. Nephrectomy kidneys were studied in the same way as MRC autopsy kidneys. Clinical features included treatment with immunosuppressive drugs (steroids, azathioprine, cyclosporine, cyclophosphamide, or mycophenolate mofetil), development of end-stage renal failure (ESRF), and nephrotic recurrence after transplantation. Response of proteinuria was incomplete, if persistently abnormal, or complete, if normal, either total below 0.2 g/24 hours or albumin/creatinine ratio below 3.0 mg/mmol. Renal status at follow-up was defined as well (normal function, and no proteinuria, as defined for complete response), or proteinuria, including the nephrotic syndrome (with normal function), or renal impairment (serum creatinine over 130 μmol/L, irrespective of proteinuria). Other outcomes were ESRF (onset of permanent dialysis), and death before dialysis, with either normal function or renal impairment. Outcomes were mutually exclusive.

Statistical methods

Wilcoxon's rank sum test was used to assess differences in the MRC series in glomerular area, index of chronic damage, and proportions of glomeruli with global sclerosis and segmental lesions. The *t* test was used to assess these factors in the later series, and also age, duration of symptoms, serum creatinine concentration, and length of follow-up. Survival rates to the earlier of ESRF or death, and to ESRF alone, were studied by the Kaplan-Meier method and log rank test, and by the life-table method. Spearman's coefficient was used to assess correlations between outcome and various factors. The Cox proportional hazards model was used to study the effect of different patterns of lesions on outcome, after controlling for these factors: index of chronic damage, proportion of glomeruli with global sclerosis, and proportion with global sclerosis and segmental lesions. The conventional value of $P < 0.05$ was considered significant.

RESULTS

Repeat specimens in the MRC trial

Patients fell into two groups, differentiated by findings in the last specimen (Table 1). MRC1 to MRC5 formed one group. These had segmental lesions in the first biopsy that were all at the tubular origin when their position could be determined, with foamy intracapillary cells or hyaline material or mixtures, and adhesion between basement membranes of capillary loops and Bowman's capsule (Fig. 1A to C). Epithelial changes were

Table 1. Findings in specimens from ten patients in the Medical Research Council (MRC) trial

Case number in current series	Gender; age at initial biopsy; treatment group	Specimen; time after first specimen; if autopsy, cause of death; time of end-stage renal failure, if relevant	Number of glomeruli in biopsy	Number of tubular origins in biopsy	Segmental lesions; number and percentage of affected glomeruli, exclusive of globally sclerosed glomeruli; size; appearance; if autopsy, uniformity of changes in cortex	Site of segmental lesions; position undetermined if tubular origin and hilum not seen	Definitely normal mesangium	Glomerular area μm^2	Globally sclerosed glomeruli; number %	Index of chronic damage%	Extensive acute tubular damage
MRC1	F; 24; prednisone	1st biopsy	26	4	2, 8%; small; foamy and hyaline	Tubular origin	Yes	21226	0	0	Yes
		2nd biopsy; 2 years	28	4	3, 11%; thin and small; hyaline and sclerosed	Tubular origin	Yes	20725	0	2	No
MRC2	F; 42; not known	1st biopsy	51	12	9, 18%; small; foamy + epithelial changes	8 tubular origin, 1 origin and hilum not seen	No	27386	1, 2%	0	No
		2nd biopsy; 3 years	60	8	9, 17%; 7 small; hyaline and sclerosed; 2 large; foamy and hyaline	7 tubular origin, 2 origin and hilum not seen	Yes	25273	6, 10%	4	No
MRC3	F; 58; prednisone	Biopsy	11	2	2, 20%; small; foamy and hyaline	Tubular origin	No	22184	1, 9%	5	No
		Autopsy; 3 months; cause of death, pneumonia; not on dialysis	—	—	Thin and small; hyaline and sclerosed; outer cortex 18%, inner cortex 14%	Tubular origin	No	28811	Outer cortex 6%, inner cortex 4 %	4	No
MRC4	M; 64; not known	1st biopsy	30	4	2, 7%; small; foamy and hyaline	Tubular origin	No	27907	2, 7%	3	No
		2nd biopsy; 2 years	6	3	3, 50%; small; hyaline	Tubular origin	No	22061	0	3	No
		3rd biopsy; 4 years	37	4	5, 15%; small; 4 hyaline, 1 foamy + epithelial changes	3 tubular origin, 2 origin and hilum not seen	No	23657	4, 11%	1	No
MRC5	F; –; not known	1st biopsy	3	1	1, 33%; small; hyaline	Tubular origin	No	21827	0	2	No
		2nd biopsy; 2 years	31	5	3, 10%; thin	Tubular origin	Yes	22139	1, 3%	1	No
MRC6	M; 16; prednisone	Biopsy	13	2	0	—	No	22488	0	0	No
		Autopsy; 2 years; cause of death, bleeding gastric ulcer; on dialysis 1 year 9 months after biopsy	—	—	Various sizes; foamy and hyaline and sclerosed; outer cortex 53%, inner cortex 55%	Various; tubular origin in some, multiple in others	No	23522	Outer cortex 10%, inner cortex 0 %	73	Yes; renal vein thrombosis
MRC7	M; 41; control	1st biopsy	6	2	0	—	No	20739	0	5	Yes
		2nd biopsy; 2 weeks	5	2	1, 20%; large; foamy + epithelial changes	Tubular origin	No	25964	0	1	Yes
		Autopsy; 4 years; cause of death, renal failure; on dialysis 2 years 6 months after 1st biopsy	—	—	Various sizes; foamy and hyaline and sclerosed; outer cortex 51% inner cortex 43%	Various; tubular origin in a few, multiple in most	No	37756	Outer cortex 46%, inner cortex 52%	98	Yes
MRC8	M; 47; control	Biopsy	11	4	4, 36%; large; foamy + epithelial changes	3 tubular origin, 1 origin and hilum not seen	No	21559	0	0	Yes
		Autopsy; 2 months; cause of death, renal failure; on dialysis 1 month after biopsy	—	—	Various sizes; mostly large, foamy; a few hyaline and sclerosed; outer cortex 20%, inner cortex 51%	Various; tubular origin in many, nearly global in a few	No	22338	Outer cortex 2%, inner cortex 11%	13	Yes

Table 1. continued.

Case number in current series	Gender; age at initial biopsy; treatment group	Specimen; time after first specimen; if autopsy, cause of death; time of end-stage renal failure, if relevant	Number of glomeruli in biopsy	Number of tubular origins in biopsy	Segmental lesions; number and percentage of affected glomeruli, exclusive of globally sclerosed glomeruli; size; appearance; if autopsy, uniformity of changes in cortex	Site of segmental lesions; position undetermined if tubular origin and hilum not seen	Definitely normal mesangium	Glomerular area μm^2	Globally sclerosed glomeruli; number %	Index of chronic damage %	Extensive acute tubular damage
MRC9	M; 59; prednisone	Biopsy	34	8	10, 33%; large; foamy + epithelial changes	7 tubular origin, 3 origin and hilum not seen	No	22879	4, 12%	3	Yes
		Autopsy; 1 year; cause of death, myocardial infarct; on dialysis 1 month after biopsy	—	—	Various sizes; some thin; others foamy and hyaline and sclerosed; outer cortex 29%, inner cortex 49%	Various; tubular origin in some, multiple in others	No	22530	Outer cortex 11%, inner cortex 5%	37	No
MRC10	M; –; not known	1st biopsy	29	11	20, 69%; large; foamy + epithelial changes	11 tubular origin, 9 origin and hilum not seen	No	27309	0	3	Yes
		2nd biopsy; 6 months	17	2	10, 63%; various sizes; foamy and hyaline and sclerosed	Various; tubular origin in 2, multiple in 8	No	19756	1, 6%	92	Yes

sometimes seen (Fig. 1B). Later specimens were at a median of 2 years after the first. These retained the adhesion, sometimes just a thin band, often with hyalinosis and sclerosis, and with little change in the position of lesions, proportion of globally sclerosed glomeruli, and index of chronic damage (Fig. 1D to F). In the autopsy kidney (MRC3), there was little difference between inner and outer cortex.

MRC6 to MRC10 formed the other group. In their first biopsy, they had either lesions all at the tubular origin when their position could be determined, or no lesions (Fig. 2A to C). The last specimens were at a median of 1 year after the first and showed multiple lesions. There was variability in number, size, and appearance of lesions, with a higher index of chronic damage, and more globally sclerosed glomeruli (Fig. 2D to F). Appreciable differences between outer and inner cortex were noted in two of four autopsy kidneys. In MRC8 and MRC9, there were more segmental lesions in the inner cortex, and these were larger than in the outer cortex.

None of MRC1 to MRC5 was on dialysis at the time of the last specimen, although at least four of MRC6 to MRC10 were. On clinical and morphologic grounds, MRC1 to MRC5 were nonprogressive while MRC6 to MRC10 were progressive. In initial biopsies, there were no significant differences between these groups in proportion of globally sclerosed glomeruli, glomerular area, or index of chronic damage. The progressive group had large lesions initially in three cases, and in the second biopsy in MRC7. The progressive group also had a higher proportion of glomeruli with lesions (means 32% vs. 17%) ($P < 0.05$). The only initial biopsy to have normal mesangium, MRC1, was in the nonprogressive group, and two others in this group had normal mesangium later. Extensive acute tubular damage was seen in one nonprogressive case and four progressive, and so were epithelial changes.

Repeat specimens in the later series (30 patients)

These 30 patients were divided on the basis of findings in their initial specimen into 15 with segmental lesions all at the tubular origin, ten with multiple lesions, and five with no segmental lesions (Table 2). There were nonsignificant differences between patients with lesions at the tubular origin, and those with multiple lesions, in age at the time of the first specimen (means 30.7 vs. 37.9 years), duration of symptoms (0.2 vs. 2.0 years), serum creatinine concentration (107 vs. 204 μmol/L), glomerular area (28641 vs. 24246 μm^2), and proportion of glomeruli with segmental lesions (24.1% vs. 43.8%). Those with lesions at the tubular origin had a significantly smaller index of chronic damage (2.0% vs. 28.1%) ($P < 0.03$), and a significantly smaller proportion of globally sclerosed glomeruli (0.6% vs. 23.3%) ($P < 0.02$).

Of the 15 with lesions at the tubular origin, two (cases 1 and 4) had only lesions at the tubular origin in their

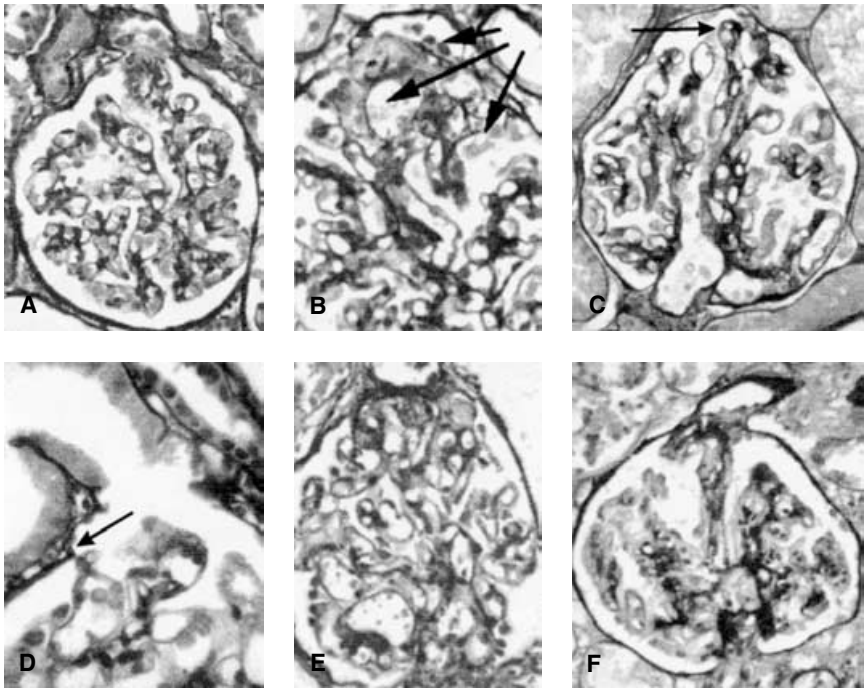

Fig. 1. Findings in three patients in the Medical Research Council (MRC) series who did not progress. (*A*) MRC1, first biopsy. There is a segmental lesion at the tubular origin. (*B*) MRC2, first biopsy. A lesion at the tubular origin has foamy intracapillary cells. Visceral epithelial cells (arrows) are crowded on the surface and vacuolated. (*C*) MRC3, biopsy. There is an adhesion between tuft and Bowman's capsule at the tubular origin (arrow). (*D*) MRC1, second biopsy, 2 years later. There is a thin adhesion (arrow) at the tubular origin. (*E*) MRC2, second biopsy, 3 years later. There is a hyaline lesion at the tubular origin. (*F*) MRC3, autopsy, 3 months later. There is a sclerosed lesion at the tubular origin.

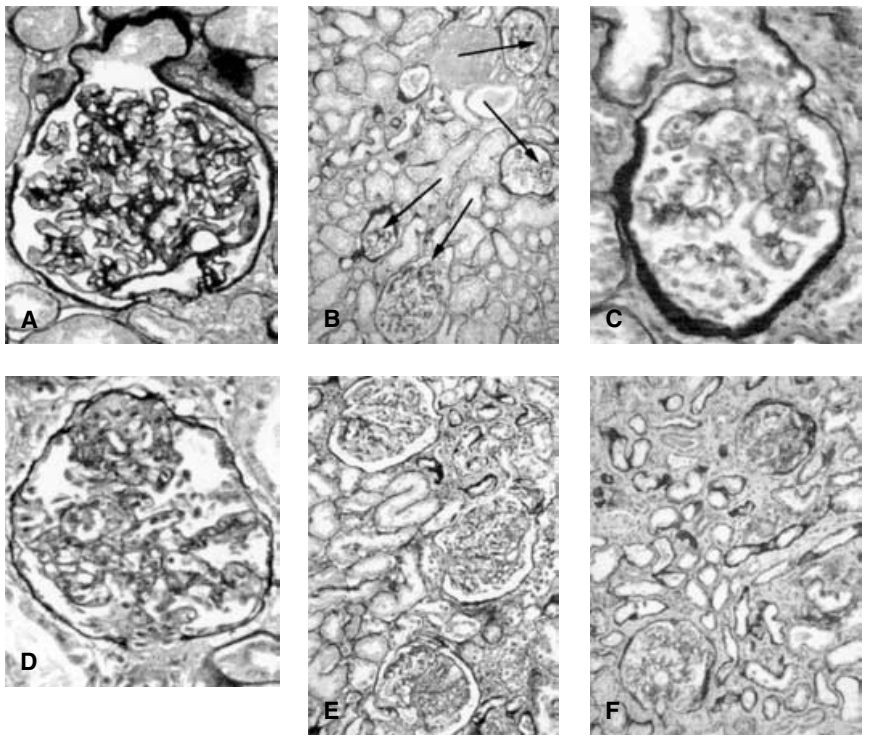

Fig. 2. Findings in three patients in the Medical Research Council (MRC) series who progressed. (*A*) MRC6, biopsy. There is no segmental lesion but mesangium appears mildly increased. (*B*) MRC9, biopsy. Four glomeruli (arrows) have lesions at the tubular origin. There is extensive acute tubular damage and mild tubular atrophy. (*C*) MRC10, first biopsy. There is a large lesion at the tubular origin. (*D*) MRC6, autopsy, 2 years later. There are multiple segmental lesions. (*E*) MRC9, autopsy, 1 year later. Glomeruli have multiple lesions. There is tubular atrophy. (*F*) MRC10, second biopsy, 6 months later. Glomeruli have multiple lesions. There is marked tubular atrophy.

second biopsy, and these were thin adhesions (Fig. 3A and B). Both had been treated with steroids and cyclosporine, and were well, at 29 and 7 years, respectively, after the first biopsy. The other 13 patients all progressed to have multiple segmental lesions, seen in specimens at a median of 1.7 years after the first. Eleven were treated with combinations of immunosuppressive drugs and two with steroids alone. There were significant increases in the index of chronic damage (2.3% to 47.6%) ($P < 0.001$) and proportion of globally sclerosed glomeruli (0.7% to 28.0%) ($P < 0.005$), with a nonsignificant increase in the proportion of glomeruli with segmental lesions (26.1% to 41.5%) (Fig. 3C to F). The outcome was persistent proteinuria in six, including three with the nephrotic

Table 2. Findings in 30 patients who had more than one specimen

Case number in current series	Gender; age at initial biopsy; duration of symptoms, if known	Specimen; time after first specimen or after transplant	Segmental lesions; site; number and percentage of affected glomeruli, exclusive of globally sclerosed glomeruli; size, appearance; if nephrectomy, uniformity of changes in cortex	Definitely normal mesangium if lesions at tubular origin or if no lesions	Glomerular area μm^2	Globally sclerosed glomeruli %	Index of chronic damage %	Extensive acute tubular damage if lesions at tubular origin; serum creatinine concentration, if known $\mu mol/L$	Immuno suppressive treatment	Response of proteinuria; time after first specimen	Outcome; years after first specimen or after transplant
1	M; 14; 2 months	1st biopsy	t; 1/6; 17%; small, foamy + epithelial changes	Yes	27158	0	0	No	s, 20 years cya, 6 years	Complete at 18 months; 15 relapses	Well 29 years
		2nd biopsy; 13.2 years	t; 2/33; 6%; thin	Yes	29027	0	0	No			
2	F; 15; 4 months	1st biopsy	t; 1/25; 4%; small, sclerosed	No	29561	0	0	No	s, 2 years cp, 6 months cya, 1 year	None	Nephrotic 6.9 years
		2nd biopsy; 3.9 years	m; 5/7; 71%: worse in inner cortex		32613	64	56	73			
3	M; 17; 1 month	1st biopsy	t; 7/29; 24%; large, foamy + epithelial changes	No	25817	0	0	No; 78	s, 6.5 years aza, 7 months cya, 3 years	Complete at 3 years; 5 relapses	Nephrotic 12.1 years
		2nd biopsy; 10.7 years	m; 5/26; 19%		28775	13	8	—			
4	M; 17; 7 days	1st biopsy	t; 1/21; 5%; small, foamy + epithelial changes	No	31634	0	0	No; 73	s, 5 years cya, 1 year	Complete at 2 months; 2 relapses	Well 7 years
		2nd biopsy; 7 years	t; 2/16; 13%; thin	Yes	25256	0	0	No; 86			
5	M; 18; 1 month	1st biopsy	t; 6/17; 35%; large, foamy and hyaline and sclerosed + epithelial changes	Yes	23916	0	15	Yes; 126	s, 2 years mmf, 2 years	Incomplete	Proteinuria 3.6 years
		2nd biopsy; 11 months	m; 9/27; 33%		22257	13	28	68			
6	M; 19	1st biopsy	t; 3/19; 16%; small, foamy and hyaline	No	30451	0	1	No	s; aza; cp	None	esrf 7.1 years; 3 tx
		2nd biopsy; 6.7 years	m; 20/32; 63%		28365	18	8	627			
		3rd biopsy; 7 years	m; 10/15; 67%		33014	21	24	—			
		nx after esrf; 7.2 years	m; outer cortex 58%, inner cortex 52%			Outer cortex 0, inner cortex 37					
		nx of 1st tx; 6 months	t; outer cortex 1%, inner cortex 4%			Outer cortex 9, inner cortex 8					Never functioned, but histologic evidence of proteinuria
		Biopsy of 2nd tx; 3 months	t; 1/32; 3%; small, foamy								Recurrent nephrotic 3 months; tx not removed
		Biopsy of 2nd tx; 6 months	t; 2/10; 20%; small, foamy								
		Biopsy of 2nd tx; 11 months	t; 3/10; 30%; large, foamy and hyaline								
		Biopsy of 3rd tx; 6 months	t; 1/9; 11%; small, foamy								Never functioned, but histologic evidence of proteinuria
		nx of 3rd tx; 6 months	t; small, foamy; outer cortex 3%, inner cortex 6%			Outer cortex 6, inner cortex 2					

Table 2. continued.

Case number in current series	Gender; age at initial biopsy; duration of symptoms, if known	Specimen; time after first specimen or after transplant	Segmental lesions; site; number and percentage of affected glomeruli, exclusive of globally sclerosed glomeruli; size, appearance; if nephrectomy, uniformity of changes in cortex	Definitely normal mesangium if lesions at tubular origin or if no lesions	Glomerular area μm^2	Globally sclerosed glomeruli %	Index of chronic damage %	Extensive acute tubular damage if lesions at tubular origin; serum creatinine concentration, if known $\mu mol/L$	Immuno suppressive treatment	Response of proteinuria; time after first specimen	Outcome; years after first specimen or after transplant
7	F; 25; 1 month	1st biopsy	t; 3/37; 8%; large, foamy + epithelial changes	Yes	22239	0	5	Yes; 215	s, 2 years cya, 7 months	Complete at 4 years; 1 relapse	Renal impairment 10 years
		2nd biopsy; 1.7 years	m; 2/12; 17%		40274	48	67	—			
8	F; 31; 1 month	1st biopsy	t; 2/26; 8%; small, foamy + epithelial changes	No	22374	0	0	No; 79	s, 1 year aza, 1 year cya, 6 months	None	esrf 4, 1 year; tx
		2nd biopsy; 1.9 years	m; 3/3; 100%		18107	0	97	—			
		Biopsy of tx; 10 months	m; 3/3; 100%								Recurrent fiephrotic 10 months
9	M; 31; 6 months	1st biopsy	t; 4/15; 27%; large, foamy + epithelial changes	No	34650	0	0	Yes; 123	s, 1 year aza, 4 months cp, 9 months	Partial	esrf 2.8 years; tx
		2nd biopsy; 1.6 years	m; 3/22; 14%		24484	49	84	—			Recurrent nephrotic 4 months
		Biopsy of tx; 4 months	m; 2/7; 29%								
		Biopsy of tx; 5 months	m; 1/9; 11%								
10	M; 34	1st biopsy	t; 3/4; 75%; large, foamy + epithelial changes	Yes	12795	0	0	No; 85	s, 2 years cp, 2 months cya, 1 year	Partial	esrf 12.8 years; no tx
		2nd biopsy; 12.4 years	m; 2/4; 50%		38256	89	70	800			
11	F; 35; 1 month	1st biopsy	t; 2/6; 33%; small, foamy + epithelial changes	No	23776	0	0	No; 67	s, 10 months	None	Nephrotic 1.5 years
		2nd biopsy; 1 year	m; 2/8; 25%		18913	0	43	151			
12	F; 48	1st biopsy	t; 3/18; 17%; large, foamy and hyaline + epithelial changes	No	23949	5	0	no	s, 4 years aza, 3 years cya, 3 years	None	Renal impairment 3.7 years
		2nd biopsy; 1.6 years	m; 3/5; 60%		30215	38	84	183			
13	M; 48; 1 year	1st biopsy	t; 10/24, 42%; large, foamy	Yes	33563	4	2	Yes; 135	s, 4 years	Partial	Proteinuria 10.3 years
		2nd biopsy; 2.5 years	m; 1/9; 11%		26267	18	7	110			
14	M; 53; 1 month	1st biopsy	t; 4/13; 31%; small, foamy + epithelial changes	No	44729	0	7	Yes	s, 9 months aza, 9 months	Partial	Renal impairment 16.2 years
		2nd biopsy; 1 year	m; 7/32; 22%		34968	11	51	153			
15	M; 54; 1 month	1st biopsy	t; 3/16; 19%; large, foamy + epithelial changes	Yes	42999	0	0	No; 91	s, 14 months aza, 14 months	Partial	Proteinuria 6.4 years
		2nd biopsy; 1.2 years	m; 1/2; 50%		28480	0	0	—			
16	M; 17; 1 month	1st biopsy	m; 5/22; 23%		37438	0	0	70	s, 9 months	None	esrf 2.3 years; 3 tx
		2nd biopsy; 2 months	m; 10/13; 77%		23132	7	15	100			
		Biopsy of 1st tx; 6 months	t; 4/21; 19%; large, foamy + epithelial changes								Recurrent nephrotic 6 months
		Biopsy of 2nd tx; 3 months	t; 7/22; 32%; large, foamy and hyaline + epithelial changes								Recurrent nephrotic 3 months
		nx of 2nd tx; 3 months	t; large, foamy and hyaline: outer cortex 38%, inner cortex 40%			Outer cortex 4, inner cortex 2					
		Biopsy of 3rd tx; 2 months	t; 8/29; 28%; large, foamy + epithelial changes								Recurrent nephrotic 2 months

Table 2. continued.

Case number in current series	Gender; age at initial biopsy; duration of symptoms, if known	Specimen; time after first specimen or after transplant	Segmental lesions; site; number and percentage of affected glomeruli, exclusive of globally sclerosed glomeruli; size, appearance; if nephrectomy, uniformity of changes in cortex	Definitely normal mesangium if lesions at tubular origin or if no lesions	Glomerular area μm^2	Globally sclerosed glomeruli %	Index of chronic damage %	Extensive acute tubular damage if lesions at tubular origin; serum creatinine concentration, if known μmol/L	Immuno suppressive treatment	Response of proteinuria; time after first specimen	Outcome; years after first specimen or after transplant
17	F; 18	1st biopsy	m; 3/14; 21%		13798	13	11	—	s	None	esrf 1.8 years; tx no recurrence 4.9 years
		2nd biopsy; 1.8 years	All globally sclerosed		—	100	97	1132			
18	M; 20	1st biopsy	m; 3/4; 75%		24442	56	77	122	?	None	esrf 0.6 years; tx immediately thrombosed
		2nd biopsy; 0.6 year	m; 1/1; 100%		37064	93	98	1200			
19	F; 22; 6 months	1st biopsy	m; 1/12; 8%		28015	0	1	49	s, 2 years	Partial	Proteinuria 8.8 years
		2nd biopsy; 3 years	m; 1/12; 8%		32240	0	4	—			
20	F; 31; 3.4 years	nx after esrf	m; outer cortex 20%, inner cortex 6%			Outer cortex 79, inner cortex 94			s, 1 year cp, 6 months	None	esrf
		Biopsy of tx; 7 months	t; 2/30; 7%; small, foamy								Recurrent nephrotic 7 months
21	M; 33; 4 months	1st biopsy	m; 17/23; 74%		21261	18	31	165	s, 14 months	None	esrf 1.3 years; tx, no recurrence 1 year
		2nd biopsy; 1 year	m; 4/5; 80%		25130	78	82	—			
22	M; 43	1st biopsy	m; 3/5; 60%		15461	38	28	—	s, 8 months cya, 2 years	None	esrf 3 years; no tx
		2nd biopsy; 3 years	m; 4/7; 57%		19426	75	71	600			
23	M; 46	Biopsy	m; 20/32; 63%		31270	29	76	539	None	None	esrf 0.3 years; tx recurrent nephrotic 1.6 years
		Biopsy of tx; 6 years	t; 4/13; 31%; large, foamy								
		Biopsy of tx; 7.5 years	m; 3/4; 75%								
		nx of tx; 8.6 years	m;outer cortex 30%, inner cortex 12%			Outer cortex 54, inner cortex 74					
24	F; 70; 1 month	1st biopsy	m; 2/4, 50%		19240	50	13	368	s	Partial	Renal impairment 5 years
		2nd biopsy; 2 months	m; 11/39; 28%		21909	59	16	—			
25	M; 72: 9 months	1st biopsy	m; 3/15; 20%		27285	6	16	114	s, 1 month cya, 3 months	Partial; relapse	Renal impairment: 2.1 years
		2nd biopsy; 1 year	m; 1/8; 13%		14578	53	38	210			
26	M; 13	1st biopsy	0/17	Yes	20551	6	0	—	s, 3 years cp, 1 month cya, 1 year mmf, 1 year	Complete at 1 month; 20 relapses	Well 13.9 years
		2nd biopsy; 12.9 years	t; 3/19; 16% thin, 1 calcified	Yes	21151	0	0	no; 74			

Table 2. continued.

Case number in current series	Gender; age at initial biopsy; duration of symptoms, if known	Specimen; time after first specimen or after transplant	Segmental lesions; site; number and percentage of affected glomeruli, exclusive of globally sclerosed glomeruli; size, appearance; if nephrectomy, uniformity of changes in cortex	Definitely normal mesangium if lesions at tubular origin or if no lesions	Glomerular area μm^2	Globally sclerosed glomeruli %	Index of chronic damage %	Extensive acute tubular damage if lesions at tubular origin; serum creatinine concentration, if known μmol/L	Immuno suppressive treatment	Response of proteinuria; time after first specimen	Outcome; years after first specimen or after transplant
27	M; 17; 10 years	1st biopsy	0/11	Yes	26929	0	0	—	s, 4 years cp, 2 months cya, 2 years	Complete with relapses, then none	esrf 6.1 years; 2 tx
		2nd biopsy; 3.1 years	0/13	Yes	19354	7	5	—			
		3rd biopsy; 5.3 years	m; 12/22; 55%		34352	31	37	—			
		nx after esrf; 6.2 years	m; outer cortex 16%, inner cortex 28%			Outer cortex 74, inner cortex 67					
		Biopsy of 1st tx; 1.7 years	m; 1/5: 20%								Recurrent nephrotic 1.7 years
		nx of 1st tx; 2.3 years	m; outer cortex 11%, inner cortex 16%			Outer cortex 56, inner cortex 10					
		Biopsy of 2nd tx; 0.4 year	t; 2/2: 100%; large, foamy								Recurrent nephrotic 5 months
		nx of 2nd tx; 0.5 year	m; outer cortex 0%, inner cortex 19%			Outer cortex 0, inner cortex 0					
28	F; 18; 1 month	1st biopsy	0/9	Yes	32836	0	0	239	s, 5 years cya, 8 months mmf, 1 month	Complete at 2 years relapse	Proteinuria 6.5 years
		2nd biopsy; 0.4 year	t; 2/29; 7%; small, hyaline and sclerosed	Yes	21960	0	0	No			
29	F; 40; 3 months	1st biopsy	0/8	Yes	18546	0	0	78	s, 2 years aza, 2 months cya, 4 years	Partial	Proteinuria 14.1 years
		2nd biopsy; 0.2 year	0/3	Yes	—	0	0	—			
		3rd biopsy; 0.3 year	t; 8/41; 20%; large, foamy + epithelial changes	Yes	28394	9	3	Yes			
30	M; 76	1st biopsy	0/8	Yes	29078	33	18	707	s	Complete relapse	Died at 3.9 years; normal function
		2nd biopsy; 0.1 year	t; 1/13; 8%; small, foamy and hyaline + epithelial changes	No	39838	7	13	Yes			
		3rd biopsy; 1.4 years	m; 1/4; 25%		21334	20	57	200			

Abbreviations are: t, tubular origin; m, multiple; s, steroids; aza, azathromine; cp, cyclophosphimide; cya; cyclosporine; mmf; mycophenolate mofetil; esrf, end-stage renal failure; tx, transplant; nx, nephrectomy. Segmental lesions in the first specimen: Cases 1 to 15, lesions at the tubular origin; cases 16 to 25, multiple lesions; cases 26 to 30, no lesions.

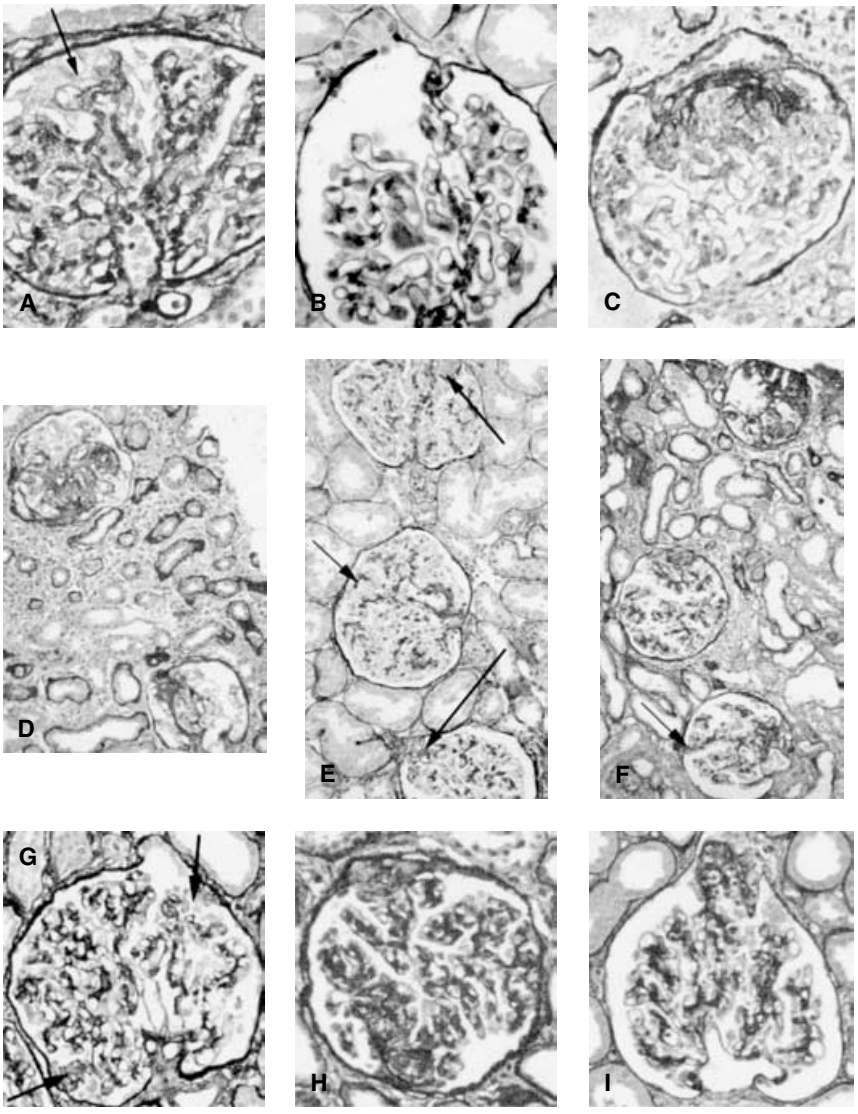

Fig. 3. Findings in four patients in the later series. (*A*) First biopsy. There is a lesion at the tubular origin with epithelial changes (arrow). (*B*) Second biopsy in (A), 13 years later. There is a thin adhesion at the tubular origin. (*C*) First biopsy. There is a large, foamy, hyalinized and sclerosed lesion at the tubular origin. (*D*) Second biopsy in (C), 11 months later. Glomeruli have multiple lesions. (*E*) First biopsy. Glomeruli have lesions at the tubular origin (arrows). (*F*) Second biopsy in (E), 7 years later. Glomeruli have lesions at various positions, including at the tubular origin (arrow). (*G*) First biopsy. There is a lesion away from both tubular origin and hilum, with epithelial changes at the tubular origin (arrows). (*H*) Second biopsy in (G), 2 months later. There are multiple lesions. (*I*) Biopsy of allograft in (G) at 2 months. There is a lesion at the tubular origin.

syndrome, renal impairment in three, and ESRF in four. ESRF was at a median of 5.6 years after the first biopsy.

In ten patients with multiple lesions, the lesions remained multiple in later specimens, with a significant increase in the proportion of globally sclerosed glomeruli (23.3% to 58.1%) ($P = 0.04$) and a nonsignificant increase in the index of chronic damage (28.1% to 52.6%). Five were treated with steroids alone, three had combinations of drugs, one had no immunosuppressive treatment, and treatment was not known in the other one. Seven patients reached ESRF, at a median of 1.3 years after the first specimen.

In five patients with no lesions at first, four were treated with combinations of drugs, and one had steroids alone. Four patients developed lesions at the tubular origin. One of these (case 26) had only thin adhesions, resembling Figures 1D and 3B, and was well at follow-up. Another (case 30) progressed from lesions at the tubular origin to multiple lesions. The fifth (case 27) developed multiple lesions, and reached ESRF at 6.1 years after the first biopsy.

Of 12 patients who reached ESRF, three subsequently had nephrectomy for persistent nephrotic syndrome. In two (cases 6 and 20), segmental and/or global glomerular changes were more marked or more advanced in the inner cortex, and in one (case 27), changes were similar between outer and inner cortex.

Recurrence in renal allografts

There were 15 renal transplants in 10 of 12 patients with ESRF. One graft was lost immediately from venous thrombosis. Clinically evident nephrotic syndrome recurred in 10 transplants, at a median of 5.5 months after transplantation. Two grafts in one patient (case 6) had no useful function, little or no urine output, and no clinically

obvious recurrence, but had evidence of glomerular leak of protein, with effacement of foot processes on electron microscopy, IgG in tubular epithelial cells on immunohistologic study, and high concentration of protein in any urine produced. Of these 12 grafts with proteinuria, nine showed lesions at the tubular origin, with progression to multiple in two (Fig. 3G to I). Three transplants had multiple lesions. In six allograft nephrectomies, segmental and/or global glomerular changes were more marked or more advanced in the inner cortex in two (cases 23 and 27, second graft), more marked in the outer cortex in one (case 27, first graft), and approximately equal in three (cases 6, first and third grafts, and 16, second graft).

Single biopsies in later series (91 patients)

In this group, lesions all at the tubular origin were seen in 61 patients, four with only thin adhesions. In three of the 61, treatment was not known. Four had no steroids or other immunosuppressants. The other 54 were treated with steroids alone (36) or steroids and other immunosuppressants (18), which were combinations of various drugs in seven, cyclosporine in five, cyclophosphamide in three, mycophenolate mofetil in two, and azathioprine in one. Forty-four of 57 with follow-up had a complete response, at a median of 4.5 months after biopsy, and 20 of these had at least one relapse of the nephrotic syndrome. Twenty-four of 57 with follow-up were well, at a median of 6.9 years after biopsy, including three who had no immunosuppressive treatment. Eighteen had proteinuria, at a median of 5.9 years. Nine had renal impairment, at a median of 4 years, and another one developed ESRF at 12.6 years. Five died, at a median of 8.5 years, three with normal function and two with renal impairment.

Of 30 patients with multiple lesions, treatment was not known in six. Fourteen had no steroids or other immunosuppressants. Five others were treated with steroids alone and five with steroids and other immunosuppressants, which were combinations of various drugs in three, and cyclosporine in two. Of 27 with follow-up, none had complete resolution of the nephrotic syndrome. Ten had proteinuria alone, including two with the nephrotic syndrome, at a median of 4.3 years after biopsy. Ten had renal impairment, at a median of 1.8 years. Another one died at 5.5 years, with renal impairment. Six developed ESRF, at a median of 1 year, and one of these had a transplant, lost immediately from venous thrombosis.

The four patients with thin adhesions in their only biopsy, and the three who had these after biopsies either without lesions (case 26) or with lesions at the tubular origin (cases 1 and 4) were similar. All seven had a long history of relapsing, steroid-responsive nephrotic syndrome before the biopsy that showed thin adhesions (median duration 13.2 years), all had a complete response after biopsy, and all were well at follow-up (median 1.4 years).

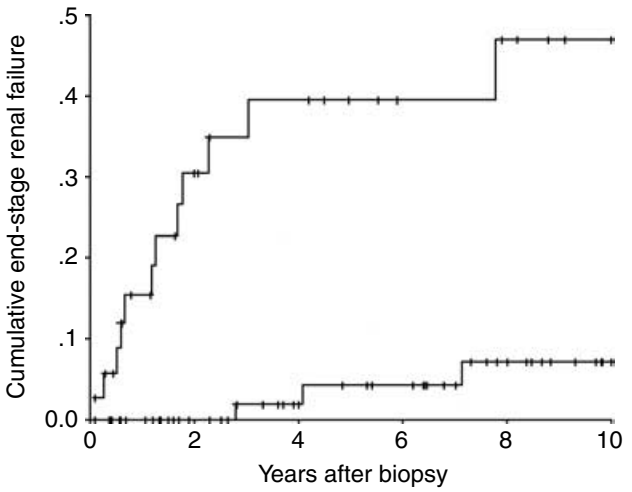

Fig. 4. Survival from the first or only renal biopsy until end-stage renal failure (ESRF) in 72 patients with lesions at the tubular origin (lower line) and 36 patients with multiple lesions (upper line). Marks on lines indicate patients censored at last follow-up, or who died before ESRF. Log rank test $\chi^2 = 22.8$ ($P < 0.001$).

In the 91 patients with a single biopsy, there were nonsignificant differences between those with lesions at the tubular origin and those with multiple lesions in age (means 50.6 vs. 49.8 years), serum creatinine concentration (152 vs. 212 μmol/L), and glomerular area (28343 vs. 31074 μm^2). Those with lesions at the tubular origin had significantly shorter duration of symptoms, when the four with thin adhesions were excluded (0.4 vs. 3.5 years) ($P < 0.02$), significantly longer follow-up (6.2 vs. 3.7 years) ($P < 0.03$), significantly smaller index of chronic damage (4.7% vs. 31.7%) ($P < 0.001$), significantly smaller proportion of globally sclerosed glomeruli (4.5% vs. 32.9%) ($P < 0.001$), and significantly smaller proportion of glomeruli with segmental lesions (16.9 vs. 27.4%) ($P < 0.04$).

Later series of 121 patients: Overall outcome and risk markers

After omission from the 121 patients of seven without follow-up, one whose first specimen was nephrectomy after ESRF (case 20), and five with no segmental lesions in their first biopsy (cases 26 to 30), the other 108 were divided into 72 with lesions at the tubular origin in their first or only specimen, and 36 with multiple lesions in their first or only specimen. When the end-point was ESRF or death before ESRF, survival at 10 years after biopsy, computed by the life-table method, was 84% in those with lesions at the tubular origin, and 45% in those with multiple lesions (log rank test $\chi^2 = 17.9$) ($P < 0.001$). This difference was even more marked for ESRF alone, when survival was 94% and 53% respectively (log rank test $\chi^2 = 22.8$) ($P < 0.001$) (Fig. 4).

In the Cox model, after controlling for index of chronic damage, proportion of glomeruli with global sclerosis,

and proportion with global sclerosis and segmental lesions, the position of lesions, whether at the tubular origin or multiple, had no significant independent relation to outcome, nor did any of the other variables.

None of the 36 patients with multiple lesions was well at follow-up, at a median of 2 years after the first or only biopsy. Twelve reached ESRF, at a median of 1.2 years. Eleven had proteinuria, including two with the nephrotic syndrome, at a median of 4.3 years. Twelve had renal impairment, at a median of 2 years. One died with renal impairment at 5.5 years.

In those with lesions at the tubular origin, risk markers for any outcome other than well were analyzed in the first specimen that showed these lesions, based on the findings in the MRC series. There were 71 in this group, 67 with lesions at the tubular origin in their first or only specimen and at least 6 months of follow-up, and four who developed lesions at the tubular origin after a biopsy with no lesions. Twenty-five were well at follow-up, at a median of 7.3 years after the relevant biopsy. Forty-six had any other outcome, at a median of 6.4 years. Twenty-three had proteinuria, including three with the nephrotic syndrome, at a median of 6.1 years. Thirteen had renal impairment, at a median of 4.9 years. Five had ESRF, at a median of 7.1 years. Five died, three with normal renal function, and two with renal impairment, at a median of 8.5 years.

There were nonsignificant differences between those who were well and the others in age at biopsy (means 40.0 vs. 49.8 years), serum creatinine concentration (141 vs. 153 μmol/L), glomerular area (27 377 vs. 28 759 μm^2), and proportion of globally sclerosed glomeruli (3.4% vs. 4.5%). Those who were well had a significantly smaller index of chronic damage (1.8% vs. 5.7%) ($P < 0.01$), and a significantly smaller proportion of glomeruli with segmental lesions (12.2% vs. 21.3%) ($P < 0.02$). There was a correlation between the proportion of glomeruli with segmental lesions and the presence of large lesions ($r = 0.43, P < 0.001$). There was a correlation between any outcome other than well, and the total number from 0 to 3 of presence of three factors, namely, large segmental lesions, mesangial increase, and extensive acute tubular damage ($r = 0.55, P < 0.001$). That is, the more of these factors that were present, the more likely was an outcome other than well. Each of these factors individually had a weaker correlation with outcome. The correlation was not strengthened by inclusion of presence of epithelial changes. These had no significant correlation with outcome.

DISCUSSION

This study showed that there were changes with time in segmental sclerosing lesions in the nephrotic syndrome. These had not previously been investigated in such detail, nor in so many patients with repeat specimens, nor with such prolonged follow-up. This has helped to clarify the relation between some of the entities in a proposed classification of FSGS [1].

Changes with time in segmental sclerosing lesions

In the MRC series, the first lesions in most patients were probably all at the tubular origin. The word "probably" is used for two reasons. One is that glomerular landmarks were not present in every glomerulus and without these the position of lesions could not be definitely determined, but in 36 (72%) of 50 glomeruli with lesions in first biopsies in the MRC series, these were definitely at the tubular origin. In the other glomeruli, the lesions were not shown to be definitely anywhere else, and a position at the tubular origin was not excluded. The second reason to qualify the site of lesions is that the largest number of glomeruli with lesions in any initial MRC biopsy was 20, which is a tiny fraction of all glomeruli in a kidney. There is always the problem that a biopsy may not be representative, and the distribution of lesions may be misleading. There was more certainty about the position of lesions in the later series because serial sections were available. The consistency of the findings in this paper supports the conclusions of another study that used many serial sections to show the relation of early lesions to the tubular origin [9]. Not every lesion could be seen with the tubular opening on the same section, and this explains why a lesion and the opening are shown in some illustrations (for example, Figs. 1A and 2C), but not in others (for example, Figs. 1C and 3A).

Patients in the MRC series who progressed to ESRF showed development of lesions away from the tubular origin, called multiple lesions for convenience. The progressive and nonprogressive groups were too small to be sure whether any differences were due to treatment or lack of it, although at least two in each group had prednisone. Patients in the later series included four with no lesions at first who developed lesions at the tubular origin, one of which progressed to multiple lesions. Among the others with repeat specimens, there were 13 with lesions at the tubular origin which changed to multiple lesions. Progression of lesions was accompanied by increases in the index of chronic damage and proportion of globally sclerosed glomeruli.

These findings are consistent with ideas that the earliest segmental lesions in the nephrotic syndrome are at the tubular origin, and that in some patients, these may progress to multiple lesions, accompanied by development of chronic damage in the kidney, and by a risk of progression to ESRF. An implication is that multiple lesions are late in the course of segmental sclerosing disorders. Not all patients with lesions at the tubular origin showed progression, and some had a change to thin adhesions. This supports the suggestion that lesions at the

tubular origin are permanent, even though their appearance may change [9, 10].

Patients with only one biopsy could not individually confirm these changes with time, but as groups they gave supporting evidence. The group with lesions at the tubular origin had a significantly shorter duration of symptoms than those with multiple lesions, consistent with an earlier clinical stage, and also had a smaller index of chronic damage and proportion of globally sclerosed glomeruli, consistent with an earlier pathologic stage. They were more likely to show a complete response, and many were well at follow-up, using a strict definition of normal renal function and normal protein excretion. Those who were well had longer follow-up than the rest, and so their good outcome was not due to a deceptively short length of observation after the biopsy.

No patient with multiple lesions in the first or only specimen had a complete response, and none was well at follow-up. Patients with multiple lesions were more likely to progress to ESRF, and this was sooner (Fig. 4), consistent with a later clinical stage. The Cox analysis did not show an independent effect on outcome of the pattern of lesions, whether at the tubular origin or multiple, after adjustment for the amount of chronic renal damage, extent of global sclerosis and number of segmental lesions, but equally did not show that these other variables had an independent effect. This was because all these features were correlated with each other. For instance, patients with lesions at the tubular origin had less chronic damage than those with multiple lesions, but the extent of chronic damage did not by itself explain the difference in outcome. Because many patients with multiple lesions had not had an earlier specimen, there is still a possibility that multiple lesions are not always preceded by lesions at the tubular origin, although the current paper shows that lesions at the tubular origin come first in at least some patients.

Multiple lesions only transformed to lesions at the tubular origin in one circumstance, recurrence of the nephrotic syndrome after transplantation. Altogether there were 16 grafts, but two failed immediately and were not at risk of recurrence. Of the other 14, 12 had recurrence. Nine showed lesions at the tubular origin, and two progressed to multiple. This supports ideas that the earliest lesions in the nephrotic syndrome are at the tubular origin, and that multiple lesions develop later but are not necessarily a different condition. The three transplants with multiple lesions in the first biopsy after recurrence may have been biopsied too late to detect the earliest changes, but could also be evidence that multiple lesions can develop without a stage of lesions only at the tubular origin. Recurrence of FSGS in allografts is well known [11], but there was no previous recognition that the first lesions are usually at the tubular origin, nor that lesions may change position.

Relation to other work on FSGS

A proposed classification is to divide FSGS, after exclusion of segmental disorders developing in recognizable conditions such as membranous nephropathy, into five types: (*1*) FSGS, not otherwise specified (NOS); (*2*) perihilar variant; (*3*) cellular variant; (*4*) tip variant; and (*5*) collapsing variant [1]. Collapsing glomerulopathy has such characteristic features that it can be considered a distinct entity, "clinically, pathologically, and epidemiologically different from noncollapsing FSGS" [12], and is uncommon in the United Kingdom (3/730 cases in the later series). For these reasons, this condition was excluded from the current study.

Of the other types, the tip variant is equivalent to lesions at the tubular origin in the current paper, and FSGS (NOS) corresponds with multiple lesions in the current paper. The perihilar variant is common in conditions with a reduced number of functioning nephrons [1], and these rarely present with the nephrotic syndrome [5], which was necessary for inclusion in the current study. The cellular variant has had a change in definition. Originally, this was "hypercellularity in the involved portion of the glomerulus, increased cells in the surrounding Bowman's space, and reactive and proliferative changes in the associated visceral epithelial cells" [13]. In the current study, epithelial changes were common and had no relation to outcome. A later definition of the cellular variant was "at least one glomerulus with endocapillary hypercellularity involving at least 25% of the tuft and causing occlusion of the capillary lumen or lumina" [1]. This description fit many specimens in the current study. The position of lesions was not mentioned in the original definition, and the later definition stressed that the tip variant must be excluded. Possibly, if the consistent relation of the earliest lesions to the tubular origin was not appreciated, these may have been considered to show the cellular variant.

In the later series in the current paper, of 116 patients with segmental lesions in their first or only specimen, 76 (66%) had lesions at the tubular origin. This is a strikingly higher prevalence than reported from the United States, where the tip variant was found in 2% and 17% of cases with segmental lesions [abstracts; Lin J, et al, *J Am Soc Nephrol* 13:452A, 2002; Franceschini N, et al, *J Am Soc Nephrol* 14:285A, 2003]. This discrepancy is partly due to the fact that the current paper was confined to cases of the nephrotic syndrome, but may also reflect different patterns of disease between the United Kingdom and the United States, or different policies about renal biopsy, particularly in the timing of biopsy after the onset of the nephrotic syndrome.

Following the paper by Rich [14], FSGS is frequently said to affect juxtamedullary glomeruli. In the current paper, there were 14 nephrectomy and autopsy kidneys. Segmental and/or global glomerular lesions were more

marked in the inner cortex in six, and this supports the view that the cortex may be affected asymmetrically, at least in some stages. The other kidneys, with a more symmetrical distribution, may have been late, or may have had a modified course because they were grafts, or, in the nonprogressive case MRC3, may not have had the same type of FSGS as the patients of Rich.

Focal means affecting only some glomeruli. A small number of sections, as we studied particularly in the MRC cases, underestimates how many glomeruli contain segmental lesions**.** In serial section studies of some kidneys, segmental lesions were reported in every or nearly every glomerulus, meaning they were diffuse, not focal [9, 15, 16]. In others they were genuinely focal [17]. One reason for this discrepancy may be that different variants of FSGS were studied. Also, unless lesions at the tubular origin are specifically sought, they can be overlooked. In the original MRC trial, a few cases called MCN were found on review to have such lesions [3]. Thin adhesions in particular are likely to be missed or their significance neglected.

Relation to the glomerular tip lesion

The term glomerular tip lesion has been used with three meanings. First, the original definition was the condition in the nephrotic syndrome in which there were segmental lesions at the tubular origin in glomeruli that were otherwise normal [9]. This was presumed to be MCN with segmental abnormalities at the tubular origin [3, 8, 10]. Abnormalities at the tubular origin were common in many disorders such as membranous nephropathy, were not a disease in themselves, and were called tip changes [18]. These were consequences of temporary prolapse of acutely swollen glomerular tufts into the tubular opening [19, 20]. Second, the term glomerular tip lesion was used in another sense by others, who applied it to tip changes in any condition, for instance diabetic glomerulopathy [21]. Another example of this usage is description of the glomerular tip lesion (in the sense of tip changes) in MCN [22]. Finally, the third usage of glomerular tip lesion corresponded with the tip variant of FSGS, and was applied to specimens with tip changes in glomeruli that could have mesangial hypercellularity [1, 23]. This was excluded by the original definition. A group of patients was described who had tip changes in abnormal glomeruli [5]. These were shown to have a risk of progression to more obvious segmental sclerosing lesions, corresponding to multiple lesions in the current paper, and to FSGS (NOS) in the proposed classification [1]. This group was considered to have an early stage of the classical, nephrotic-associated FSGS [5].

One view is that the glomerular tip lesion in the third sense, equivalent to the tip variant of FSGS, and to lesions at the tubular origin in the current paper, is a distinct entity, separate from both MCN and FSGS, but with clinical features closer to those of MCN [23]. If this view is correct, the current paper shows that many patients have a good outcome but that some will progress pathologically and clinically. The overall prognosis is much better than in those with FSGS (NOS).

Another interpretation is possible. This is that the glomerular tip lesion in the third sense, the tip variant of FSGS, and lesions at the tubular origin in the current paper are not one condition, but at least two. The minimum two conditions are MCN plus tip changes, corresponding to the original definition of glomerular tip lesion [9], and an early form of classical, nephrotic-associated FSGS [5].

The evidence that something closely related to MCN is in this group is given by several observations, showing that some patients behaved as though they had MCN. Half the patients in the MRC series did not progress even though they may not have been treated or had similar treatment to some who progressed. Many patients in the later study had a complete response of the nephrotic syndrome, and many had normal renal function and no proteinuria at prolonged follow-up. This included three who resolved spontaneously, without immunosuppression. There were seven patients with thin adhesions at the tubular origin in their last or only biopsy, who had a long history of relapsing, steroid-responsive nephrotic syndrome and a complete response, and were well at follow-up.

Evidence for a condition with a poorer prognosis, resembling the conventional view of nephrotic-associated FSGS [24], is that half the patients in the MRC series progressed, and so did several patients in the later series, both relatively quickly. These developed multiple lesions at medians of 1 year and 1.7 years after the first biopsy. Some in both series progressed despite immunosuppression. The nephrotic syndrome recurred in five allografts in three patients in the later group (Table 2).

If there were two conditions with lesions at the tubular origin, differentiation between them was not easy. Part of the problem was that the effect of immunosuppression on the natural course of these postulated conditions was unknown. There was no single feature that allowed clear distinction between those who had an excellent outcome and those who did not, but three factors, namely, large segmental lesions, mesangial increase, and extensive acute tubular damage, collectively and individually, were more common in those who did badly. These patients also had a higher proportion of glomeruli with segmental lesions, but this was correlated with the presence of large lesions, which were more likely to be seen on a random section. These patients also had a higher index of chronic damage, but the difference was too small to be of practical use.

Whether the tip variant of FSGS [1] is one entity, as others consider it [23], or more than one, as we consider it [5], we have shown that its prognosis is better than that

of FSGS (NOS), that at least some patients with FSGS (NOS) had at an earlier stage shown the tip variant, and that patients with FSGS (NOS) who have recurrence of the nephrotic syndrome after renal transplantation may show the tip variant in the graft.

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