Kidney transplant nephrotic syndrome: Relationship between allograft histopathology and natural course

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Kidney transplant nephrotic syndrome: Relationship between allograft histopathology and natural course. We analyzed clinical and pathologic data from 36 recipients of 38 renal allografts who developed nephrotic syndrome following transplantation. Three groups were identified on the basis of histologic changes in the graft, and each group had a distinct clinical course. Nine grafts (23.7%) had recurrent glomerulonephritis (GN) (5 membrano-proliferative, 4 focal glomerulosclerosis) and developed nephrotic syndrome at 5.1 months (mean) posttransplant. Renal function deteriorated rapidly, with a 2-year graft survival of 29.7%. Four grafts (10.5%) with de novo GN (3 epimembranous, 1 minimal change) developed nephrotic syndrome at 32 months posttransplant, and all functioned for more than 3 years. Twenty-five grafts (65.8%) had allograft glomerulopathy with the onset of nephrotic syndrome at 9.1 months posttransplant and a 2-year graft survival of 66.6%. The differences in duration of graft function between grafts with allograft glomerulopathy and recurrent GN (P < 0.01) and in graft survival rates at 2 years among the three groups (*P* < 0.05) are statistically significant. This analysis indicates that allograft glomerulopathy is the most common cause of kidney transplant nephrotic syndrome. Membranoproliferative GN and focal glomerulosclerosis may recur soon after transplantation and rapidly progress to renal failure in marked contrast to grafts with either de novo epimembranous nephropathy or minimal glomerular change, lesions that are compatible with prolonged graft function.

Syndrome néphrotique du rein transplanté: Relations entre l'histopathologies de l'allogreffe et l'évolution. Nous avons analysé les dossiers cliniques et anatomo-pathologiques de 36 receveurs de 38 allogreffes qui ont développé un syndrome néphrotique après transplantation. Trois groupes ont été identifiés sur la base des modifications histologiques de la greffe et chaque groupe a eu une évolution distincte. Neuf greffes (23,7%) ont eu une récidive de glomérulonéphrite (GN) (5 membrano-prolifératives, 4 gloméruloscléroses focales) et ont développé un syndrome néphrotique 5,1 mois (moyenne) après la transplantation. La fonction rénale s'est détériorée rapidement, avec une survie de la greffe à 2 ans de 29,7%. Quatre greffes (10,5%) atteintes de GN nouvelle (3 extra-membraneuses, 1 à modifications minimes) ont développé un syndrome néphrotique 32 mois après la transplantation et ont toutes fonctionné plus de 3

ans. Vingt cinq greffes (65,8%) ont eu une glomérulopathie de greffe avec l'installation d'un syndrome néphrotique à 9,1 mois après la transplantation et une survie de la greffe à 2 ans de 66,6%. Les différences de durée du fonctionnement de la greffe selon l'atteinte par une récidive de GN ou une glomérulopathie de greffe (*P* < 0,01) et dans la survie des greffes à 2 ans dans les trois groupes (*P* < 0,05) sont statistiquement significatives. Cette analyse indique que la glomérulonéphrite de la greffe est la cause la plus répandue de syndrome néphrotique du rein transplanté. La GN membrano-proliférative et la glomérulosclérose focale peuvent récidiver précocément après la transplantation et progresser rapidement vers l'insuffisance rénale à la différence des greffes atteintes de néphropathie extramembraneuse ou de modifications minimes, lésions compatibles avec une fonction prolongée de la greffe.

Proteinuria and nephrotic syndrome frequently occur in recipients of kidney transplants. Proteinuria in the immediate postoperative period commonly recedes, and neither its amount nor duration has any prognostic significance [1, 2]. Some transplant recipients, however, continue to have or subsequently develop heavy and persistent proteinuria during later stages of their posttransplant course. The incidence of established nephrotic syndrome in recipients of renal allografts [3, 4] or isografts [5] approaches 30%. The causes of transplant nephrotic syndrome have been attributed to allograft glomerulopathy[1] [3, 4], recurrent or de novo glomerulonephritis (GN) [5–9], renal vein thrombosis [10, 11], and reflux nephropathy [12]. Although kidney transplant nephrotic syndrome has been the subject of intensive clinical investigation, few attempts have been made to correlate its natural

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[1] The term "allograft glomerulopathy" is used here to describe nonspecific histopathologic changes in renal allografts of unknown etiology, but presumably due to chronic allograft rejection.

course with histopathologic alterations in the allografts and in the original kidney disease. To determine the natural course of kidney transplant nephrotic syndrome and its relation to underlying pathologic processes, we analyzed clinical and pathologic data from 38 renal allografts in 36 patients with posttransplant nephrotic syndrome.

Methods

Patient population. From May 1963, to December 1976, 599 renal transplants were performed in 520 patients at The New York Hospital-Cornell University Medical Center. Among the 599 renal allografts, 54 instances of nephrotic syndrome (defined as urinary protein excretion of ≥ 3.0 g/day and persisting for at least 6 months) developed in 52 recipients. Tissue specimens of the recipients' native kidneys and allografts were available for pathologic studies from 36 of the patients, involving 38 allografts. These 36 transplant recipients are the subjects of this study.

The patients' ages at the time of transplantation ranged from 8 to 54 years (24 ± [SEM] 5); 24 were males and 12 were females. Twenty-six kidney transplants were from living related donors and 12 from cadaveric donors. None of the patients received kidneys from an identical twin, but two received kidneys from fraternal twins. Two patients developed nephrotic syndrome in two consecutive transplants. Both received first kidneys from living related donors, and second kidneys from cadaveric donors.

Standard surgical procedures including Paquin technique of ureteroneocystostomy [13] were used. All patients received standard regimens of immunosuppressive agents consisting of azathioprine and prednisone beginning on the day before or on the day they received the transplant. At the time of transplant, all patients were given 3 to 5 mg/kg/day of azathioprine and 100 to 200 mg/day of prednisone. Doses of both agents were gradually reduced to 2 mg/kg/day of azathioprine and 5 to 20 mg/day of prednisone. The prednisone dose was increased transiently during episodes of acute transplant rejection to as high as 1,000 mg/day and reduced to maintenance levels within a few weeks. The average daily maintenance dose was 95 mg of azathioprine and 16 mg of prednisone. No patients in this series received antithymocyte globulin.

All patients were followed by the physicians of the kidney center at different time intervals depending on the stability of graft function and patient status. Followup period for the functioning allografts was at least 10 months, and the longest was more than 15 years (38 ± [SEM] 5.5 months). Graft survival is defined as graft function sufficient to sustain health without chronic dialysis. Actuarial survival rates for the grafts were calculated by the life table method.

Pathologic studies. The tissue specimens obtained by either biopsy or nephrectomy were fixed in Bouin's solution, and serial sections 2 to 4 μ thick were stained for light microscopy with hematoxylin and eosin, periodic acid-Schiff, Azan, reticulin stain, and phosphotungstic acid hematoxylin stain. Tissue for immunohistochemical study was processed by standard techniques and stained with fluoresceinated antisera to IgG, IgA, IgM, C3, and fibrinogen. Tissue for electron microscopic examination was processed by standard techniques and embedded in Epon epoxy resin. Representative areas were stained with uranyl acetate and lead citrate, and examined with an RCA electron microscope.

Slides were studied independently by two pathologists (J.M. and M.S.) without knowledge of the clinical history or of the original renal disease. The only information available was that these were from renal transplants associated with the nephrotic syndrome.

Histologic characteristics of chronic allograft rejection were determined by review of material from 12 cadaveric allografts (in recipients whose original kidney diseases were of nonglomerular origins) that functioned between 10 months and 4 years with episodes of clinical allograft rejection, but without proteinuria, and from the information available from literature (5-7, 14-18). Criteria we arrived at for determination of allograft glomerulopathy, recurrent GN, or de novo GN were:

(1) Allograft glomerulopathy. The glomerular changes of allograft glomerulopathy are generally mild and variable. The vascular and interstitial changes are severe or disproportionately more advanced than are the glomerular changes. Findings in the glomeruli by light microscopy include thickening and wrinkling of the capillary basement membranes, increase in mesangial matrix with slight and variable cellular proliferation and contraction of the tufts with solidification and sclerosis. Occasionally, splitting or double contour patterns of the glomerular capillary walls is observed, but these alterations are not associated with appreciable hypercellularity or hyperlobulation. Vascular changes include endothelial cell swelling and proliferation with onionskin change of intima resulting in an obliterative ar-

teriopathy. Interstitial changes are associated with fibrosis, mononuclear cellular infiltrates, and varying degrees of tubular atrophy. By electron microscopy, predominantly subendothelial electron-lucent deposits are seen together with IgM deposits by immunofluorescence techniques.

(2) Glomerulonephritis. A diagnosis of recurrent GN was made only when the morphologic pattern in the allografts studied by light microscopic, electron microscopic, and immunohistochemical techniques was similar to that which caused renal failure in the native kidneys. Glomerular changes attributed to recurrent GN were characterized by their severity in contrast to the accompanying interstitial and vascular changes, which tended to be minimal or disproportionately milder than were the glomerular changes. Because focal segmental sclerotic changes due to allograft rejection tend to preferentially involve outer cortical glomeruli (unpublished data) as opposed to juxtamedullary glomeruli as seen in idiopathic focal glomerulosclerosis, we also studied the distribution of the involved glomeruli to aid in differential diagnosis. If the predominant histologic pattern that affected the glomeruli did not resemble those seen in the native kidney, or if the original disease was nonglomerular, then a diagnosis of de novo GN was made.

Approximately two thirds of these specimens were studied by electron microscopy and immunohistochemical techniques. Pertinent information from these morphologic techniques, together with correlations with the clinical course (Fig. 1), was important in the classification of the allograft pathology.

Results

Causes of original kidney diseases. Twenty-eight patients had glomerular diseases whereas 8 had nonglomerular diseases, such as polycystic kidney disease, obstructive uropathy, medullary cystic disease, and tubulointerstitial nephritis (Table 1). Of the 28 patients with glomerular disease, 7 had focal
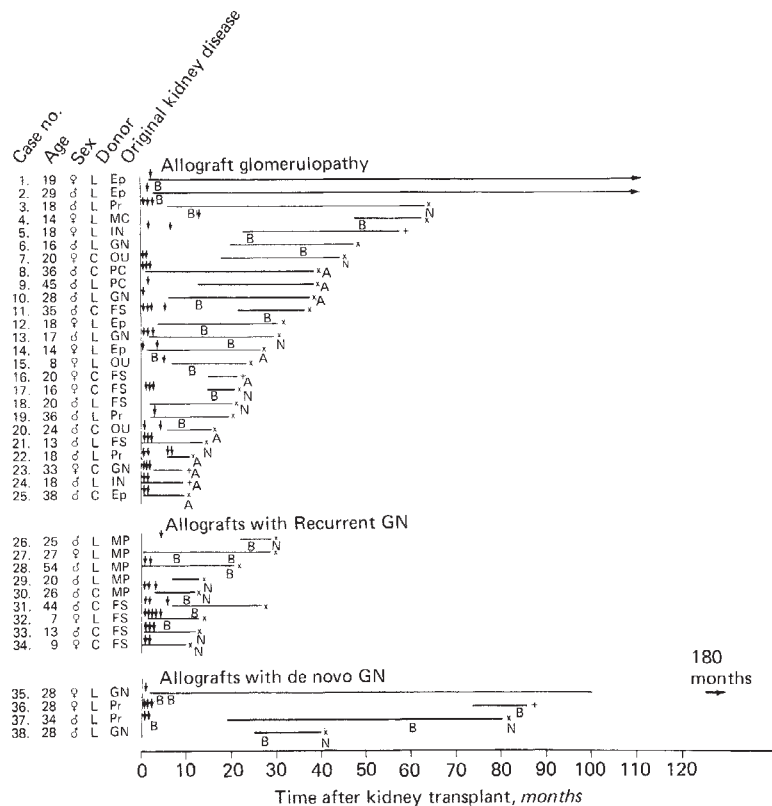
Fig. 1. *Clinical course of individual patients in relation to nephrotic period, episodes of acute rejection, and the ultimate fate of allografts or patients.* The abbreviations and symbols used in this illustration denote the following: —, nephrotic period; x, graft failure; + patient death with functioning graft; ↓, acute rejection; →, graft continues to function; A, autopsy; B, biopsy; C, cadaveric donor; L, living related donor; N, transplant nephrectomy; Ep, epimembranous nephropathy; FS, focal glomerulosclerosis; GN, glomerulonephritides, unclassifiable; IN, interstitial nephritis; MC, medullary cystic disease; OU, obstructive uropathy; PC, polycystic kidney disease; and Pr, proliferative glomerulonephritis.

Table 1. Histopathology of native kidneys and allografts[a]

	Allograft glomerulopathy	Recurrent GN	De novo GN
Glomerular diseases (N = 28)			
FGS (N = 7)[b]	5	4	
Type I MPGN (N = 5)		5[c]	
Epimembranous GN (N = 5)	5		
Proliferative GN (N = 5)	3		2
Unclassifiable (N = 6)	4		2
Nonglomerular diseases (N = 8)	8		
Total (N = 36)	25 (65.8%)	9 (23.7%)	4 (10.5%)

[a] Figures denote number of cases. Abbreviations used are: GN, glomerulonephritis; FGS, focal glomerulosclerosis; MPGN, membranoproliferative GN.

[b] Two of these patients developed nephrotic syndrome in two consecutive transplants.

[c] Although MPGN was a predominant finding in the allografts, 3 of these also had histopathologic changes consistent with allograft glomerulopathy.

glomerulosclerosis (FGS), 5 type I membranoproliferative GN (MPGN), 5 epimembranous nephropathy, 5 proliferative GN, and 6 had unclassifiable glomerular diseases due to either atypical glomerular abnormalities or too advanced glomerular changes. There was no patient with either anti-GBM antibody nephritis or type II MPGN (dense-deposit disease).

Histopathologic findings in allografts. Three major groups of histopathologic abnormalities were identified from the 38 renal allografts. These were allograft glomerulopathy, recurrent GN, and de novo GN (Table 1).

Of 9 allografts transplanted into the 7 patients with FGS, 4 had recurrence of FGS. Two patients with FGS, the only pediatric patients in this series, developed nephrotic syndrome in two consecutive transplants. One had a recurrence of FGS in both allografts whereas the other had chronic rejection only in the first allograft, with a recurrence of FGS in the second.

Of the 5 patients with type I MPGN, all developed a recurrence of the same disease in the allograft. Of these, however, 3 also had histologic changes consistent with allograft glomerulopathy. Three of the patients had normal serum complement levels, and two had persistent hypocomplementemia during the course of their original kidney disease, dialysis treatment, after transplantation, and after transplant nephrectomy.

Although all 5 of our patients with MPGN were classified as recurrent GN, it is frequently difficult in a specific case to be certain that the lesion represents a true recurrence rather than a manifestation of allograft glomerulopathy [16]. This was especially true in 3 of the 5 patients in whom the MPGN was associated with allograft glomerulopathy. Based, however, on findings of similarities with the native kidney lesions and electron microscopic study, as well as serum complement determinations, we concluded that the findings were most compatible with recurrence of MPGN.

All allografts in patients with epimembranous nephropathy revealed allograft glomerulopathy, and none had a recurrence of the original disease.

Of the 5 allografts in patients with proliferative glomerulonephritis, 3 demonstrated allograft glomerulopathy, but 2 developed de novo epimembranous nephropathy with subepithelial deposits. None, however, had a recurrence of the original disease.

Of the 6 allografts in patients whose original diseases were glomerulonephritides that could not be classified, 4 had allograft glomerulopathy only, 1 epimembranous nephropathy with typical subepithelial electron-dense deposits, and 1 minimal change in two open biopsies while the patient was nephrotic. Although we could not be certain of the exact nature of the original glomerular lesions in the latter 2 patients, neither the clinical data nor the pathologic findings were supportive of the diagnosis of epimembranous nephropathy or minimal change disease. Thus, the glomerulopathies found in them represent de novo GN.

All 8 patients with nonglomerular disease revealed only allograft glomerulopathy in their grafts.

None of the patients had vesicoureteral reflux or renal vein thrombosis in the transplanted kidney when these were evaluated by radiographic or pathologic studies (13 nephrectomized specimens and 10 postmortem examinations).

Thus, the histopathologic alterations found in 38 renal allografts from 36 patients with the nephrotic syndrome were attributable to allograft glomerulopathy in 25 (65.8%), recurrent GN in 9 (23.7%), 3 of which also had coexisting allograft glomerulopathy, and de novo GN in 4 (10.5%).

Clinical course. The clinical course of individual patients in relation to nephrotic period, episodes of acute rejection, and the ultimate fate of allografts or patients is depicted in Fig. 1. The mean values of the time of onset of nephrotic syndrome from the date of transplantation, the duration of graft function, and actuarial graft survival rates in each group are presented in Table 2. The actuarial graft survival rates are also graphically depicted in Fig. 2. Be-

Table 2. Clinical course of allografts[a]

	Allograft glomerulopathy (N = 25)	Recurrent GN (N = 9)	De novo GN (N = 4)	Statistical significance
Onset of nephrotic syndrome, *months*				
Range	1 to 48	1 to 22	2 to 74	NS
Mean ± SEM	9.1 ± 2.17	5.1 ± 2.26	31.5 ± 15.37	
Duration of graft function at close of study, *months*				
Range	10 to 113	10 to 29	40 to 180	$P < 0.01$
Mean ± SEM	31.2 ± 7.35	16.7 ± 2.37	92.3 ± 25.17	
Actuarial graft survival, % by 2 yr	66.6	29.7	100	$P < 0.05$

[a] *N* denotes number of allografts. GN is glomerulonephritis.

cause the number of patients with MPGN or FGS are small, and their clinical courses are similar, these patients are combined into one group in Table 2 and Fig. 2.

The allografts with recurrent GN (4 with FGS and 5 with type I MPGN) became nephrotic earlier, usually within 6 months of transplant. The clinical course of the disease was rapidly progressive and the duration of graft function was significantly shorter than that of the other allografts. The progression of their original kidney disease from clinical onset to renal failure varied from 6 months to 13 years (54.4 ± [SEM] 7.5 months). Of these 9 patients with recurrent GN, however, 8 became nephrotic within 7 months and all allografts ceased functioning within 3 years after transplantation, irrespective of the duration of their original disease. Thus, there is no correlation between the duration of the original kidney disease and the time of progression to renal failure following transplantation.

In contrast, those allografts with de novo GN became nephrotic 2 to 3 years after transplantation, although one allograft with minimal glomerular change developed nephrotic syndrome 2 months after transplantation. Furthermore, all allografts with de novo GN functioned for at least 3 years, and one even continues to function for more than 15 years.

In grafts with allograft glomerulopathy alone, the time of onset of nephrotic syndrome and duration of graft function were intermediate between those of allografts with recurrent GN and de novo GN.

When the duration of kidney function is estimated by the product-limit method of Kaplan and Meier [19], the patients with allograft glomerulopathy have a significantly longer ($P < 0.01$) duration of kidney function than do patients with recurrent GN. There are, however, too few patients with de novo GN to permit a valid comparison with the other groups. The differences in actuarial survival rates for the grafts at 2 years among the three groups were statistically significant ($P < 0.05$) by the χ^2 test.

Fig. 2. *Actuarial graft survival of allografts.* Figures denote number of patients at risk during each observation period. *N* denotes total number of patients at risk at the beginning of the study.

Discussion

Histopathologic abnormalities in long-term renal allografts have been extensively studied, and histologic similarities between lesions caused by recurrence of original GN and by allograft glomerulopathy, as well as difficulties in differentiating between their lesions, have been emphasized [6, 7, 9, 16, 17, 20–23]. Few studies, however, are available that correlate the course of allografts with different underlying pathologic processes, such as allograft glomerulopathy, recurrent GN, and de novo GN.

Although the histopathologic criteria we used in this study to differentiate allograft glomerulopathy from glomerulonephritis are not absolute, their validity is supported by other studies. Glassock et al
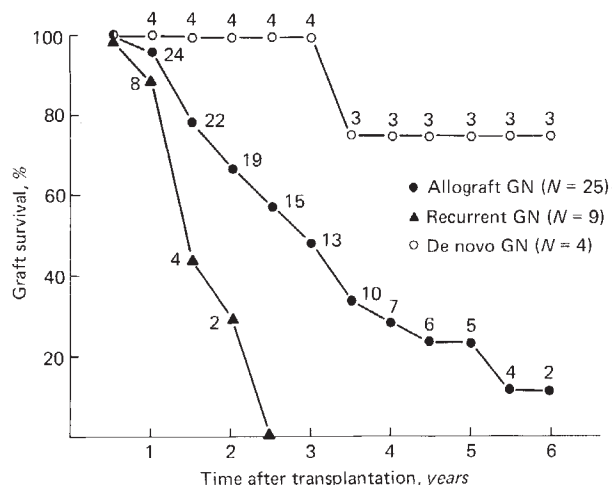
[5] reported 11 cases of recurrent GN in 22 renal isograft recipients. These isografts serve as a prototype of recurrent GN in grafts without additional alterations due to transplant rejection. The predominant histopathologic features of recurrent GN in these isografts were in the glomeruli. Arterial and interstitial abnormalities were minimal, even though the degree of GN was severe enough to lead to renal failure in 5 patients.

As a control for our study, we reviewed pathologic material from 12 cadaveric allografts that functioned between 10 months and 4 years in patients whose original kidney diseases were non-glomerular. Abnormalities in these allografts are characteristic of allograft glomerulopathy presumably mediated by sensitization to histocompatibility antigens expressed in the grafts with little likelihood of GN. The predominant and characteristic abnormalities in these allografts were obliterative arteriopathy and tubulointerstitial changes with only mild and variable glomerular abnormalities. These findings are consistent with histopathologic findings in chronic allograft rejection described in other studies as reviewed by Rowlands, Hill, and Zmijewski [14], Corson [15] and Cameron and Turner [17].

Chronic kidney transplant nephrotic syndrome has been attributed primarily to allograft glomerulopathy [3, 4], recurrent or de novo GN [5, 9], renal vein thrombosis [10, 11], and reflux nephropathy [12]. Our analysis reveals that allograft glomerulopathy is the single most common cause of nephrotic syndrome, regardless of the nature of recipients' original kidney disease, comprising 65.8% of total renal allografts. Recurrent and de novo GN are less common but not infrequent causes of the nephrotic syndrome comprising 23.7% and 10.5%, respectively. Thus, although other causes might be responsible for transplant nephrotic syndrome in unusual instances, allograft glomerulopathy and recurrent or de novo GN are the major processes responsible for nephrotic syndrome. This observation is consistent with previous reports indicating that allograft glomerulopathy is the most common cause for nephrotic syndrome in allograft recipients, whereas recurrent glomerulonephritis is the most common cause for that in isograft recipients [3–6].

Our results should not be interpreted as indicating the relative incidence of recurrent or de novo GN in transplant recipients, because we analyzed only those patients who became nephrotic. Our findings do indicate, however, that recurrence of GN (particularly MPGN and FGS) and de novo GN do occur and cause nephrotic syndrome in sub-stantial numbers of renal allografts that function for prolonged periods.

Each group of patients has a distinct clinical course. The patients with recurrent GN develop nephrotic syndrome in the early posttransplant period and rapidly progress to renal failure, as compared with those patients with de novo epimembranous nephropathy, in whom nephrotic syndrome develops later in the posttransplant period and the clinical course is slow and indolent. Patients with allograft glomerulopathy alone, however, follow a course that is intermediate between these two extremes. Thus, biopsy studies of allografts from nephrotic patients help to clarify the underlying process causing the nephrotic syndrome, and help to estimate the prognosis of the graft.

The reported incidence of recurrent glomerulonephritis in renal allografts ranges from 5 to 18% [5–7, 9, 17, 20, 21], and the clinical course of such patients is generally reported to be shorter and more rapidly progressive to renal failure than that of the original kidney disease [5, 23]. Our results are consistent with this experience and indicate that recurrence of MPGN and FGS begins early, usually within 6 months, with the onset of nephrotic syndrome. The renal lesion progresses rapidly to renal failure within 3 years after transplantation, regardless of the duration of the original disease or the duration of dialysis treatment prior to the transplantation.

Reasons for the differences in the clinical course of original versus recurrent glomerulonephritis are not immediately evident. Anatomical (size of renal mass) and functional (number of nephron units) factors may play a role. Other factors, however, may be more important, such as the presence of several pathologic processes (allograft glomerulopathy and recurrent glomerulonephritis) and, possibly, the more frequent exposure of the graft to nephrotoxic antibiotics and radiographic contrast agents. The presence of allograft glomerulopathy in addition to recurrent glomerulonephritis, as seen in 3 of 5 allografts with MPGN in this study as well as 3 of 14 allografts with MPGN reported by Berthoux et al [24], might be more detrimental to allograft survival than recurrent glomerulonephritis alone. Beyer et al [25] reported that histologic changes of glomerulonephritis are more severe and rapidly progressive in unilaterally nephrectomized animals than they are in sham-operated animals. The authors speculated that the accelerated course of glomerulonephritis after unilateral nephrectomy is due to a higher density of immune complexes to each remaining nephron as the number of circulating complexes is held

constant but the number of glomeruli is reduced by unilateral nephrectomy, and that glomerular damage is proportional to the concentration of immune complexes impinging on each glomerulus. A similar mechanism could play a role in the accelerated course of recurrent GN in renal allografts.

The presence of nephrotic syndrome in patients with idiopathic MPGN [26] or FGS [27], as well as in transplant recipients [28], has been associated with a poor prognosis. Because this study includes only patients who have had nephrotic syndrome, the clinical course of our patients with recurrent glomerulonephritis may be biased towards a poorer prognosis than it is for patients with recurrent glomerulonephritis without nephrotic syndrome [17]. A patient with recurrent FGS reported by Cameron and Turner, was healthy, however, with good graft function for over 3 years, despite persisting nephrotic syndrome.

Development of de novo [29] as well as recurrence of epimembranous nephropathy [30, 31] has been observed previously, and various viral agents have been suggested as antigenic stimulants for immune complex formation. In this study, there were 3 allografts with epimembranous nephropathy in patients whose original kidney disease was probably not of the same nature. One of these had had chronic hepatitis B surface antigenemia prior to onset of nephrotic syndrome. It is difficult to be certain whether the cases classified as de novo epimembranous nephropathy belong to true de novo glomerulopathies or are related to some other pathologic process. The epimembranous nephropathy in renal allografts could be a renal response to the original nephritogenic stimuli or an example of immune complex nephropathy due to the interaction of alloantigen and alloantibody, thereby representing a form of either recurrent glomerulonephritis or allograft glomerulopathy. Regardless of the precise mechanism responsible for this pattern, the clinical course of allografts with this pattern is strikingly indolent and benign, in sharp contrast to those allografts with recurrent glomerulonephritis. Apparently, the lesion develops some time later in the posttransplant period (2 to 3 years after transplantation), and the allografts maintain stable function for many years thereafter. This observation is consistent with other reports of de novo or recurrent epimembranous nephropathy and is remarkably similar to the natural course of idiopathic epimembranous nephropathy [32]. The benign and indolent course of allografts with epimembranous nephropathy might be due at least in part to immu-

nosuppressive therapy, because such therapy has recently been shown to be helpful in idiopathic epimembranous nephropathy [33, 34].

Allografts with minimal changes have been observed previously and characterized by severe proteinuria and nephrotic syndrome starting within 1 to 2 months after transplantation [8, 9, 35]. Although 3 of these were proven to be cases of FGS in subsequent studies and progressed to renal failure [8], one of them remitted 2 years after transplantation [35]. One of our patients, a recipient of a fraternal twin's kidney, became nephrotic 2 months after renal transplantation. Two kidney biopsies performed while she was nephrotic showed only minimal glomerular changes. Despite severe and prolonged nephrotic syndrome, she has maintained a well-functioning allograft for over 15 years and gave birth to three normal children during this period. Furthermore, she is the only patient in this series in whom proteinuria resolved and who has maintained excellent graft function after a protracted course of nephrotic syndrome.

Allograft glomerulopathy is the most common cause for transplant nephrotic syndrome, and its clinical course is insidious and slowly progressive. As shown in our previous studies [4, 28], the presence of nephrotic syndrome in renal allograft recipients, particularly related donor kidney recipients, is a factor that adversely affects, albeit to a mild extent, their natural courses. Among the nephrotic patients, however, the survival rate of grafts with allograft glomerulopathy is significantly better than that of grafts with recurrent glomerulonephritis. A similar result has been reported previously by Hamburger et al [22] and Starzl et al [36], who have shown that grafts with histologic changes consistent with allograft glomerulopathy tend to have a more favorable prognosis than those with recurrent glomerulonephritides. The grafts with allograft glomerulopathy, however, do ultimately progress to renal failure, and about half cease functioning by 3 years after transplantation.

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