Evidence Suggesting Persistence of Nephritogenic Immunopathologic Mechanisms in Patients Receiving Renal Allografts

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Abstract Direct immunofluorescent (IF) examinations and elutions were performed on native kidneys and allografts of 24 patients undergoing renal transplantation. Immunoglobulins (Ig) were detected by IF on native kidneys of 12 of the 24; 11 of the 12 later had Ig localized to allograft glomeruli by direct IF. In addition, three other patients also developed Ig deposition on allograft glomeruli, although direct IF of native kidneys was negative. Elution studies indicated: (*a*) that linear Ig deposition on allograft glomeruli was the result of antiglomerular basement membrane (GBM) antibodies, (*b*) Ig localizing to allograft glomeruli in many of these patients was the result of persistent immunopathogenetic mechanisms existing at the time of allograft placement, and (*c*) occasionally, kidneys negative for Ig localization by direct IF contain elutable nephritogenic antibodies.

INTRODUCTION

Renal transplantation as definitive therapy for patients with end-stage renal failure generally has achieved a high degree of success. The principal cause of graft failure appears to be inadequate suppression of immune mechanisms directed specifically toward the allograft. However, the extent to which glomerulonephritis also may affect an allograft has not been defined. Specific data are lacking regarding the frequency of glomerulonephritis in renal allografts and its impact on the success or failure of otherwise successful grafts. Evidence has been offered that the pathogenesis of glomerulonephritis in grafted kidneys is rooted in persistence of immunopathogenetic mechanisms responsible for the failure of the hosts' native kidneys (1–3).

We undertook a prospective study to address these questions, using immunohistochemical and elution techniques to study both native kidneys and allografts of patients undergoing renal transplantation; 24 patients have been studied. Our results indicate frequent immunoglobulin deposition in glomeruli of allografts; in these patients such deposits usually could be related to nephritogenic immunologic mechanisms antedating the allograft.

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METHODS

Patients. 24 of 31 patients receiving renal allografts at Wilford Hall USAF Medical Center during a 4 yr interval are the subjects of the investigation. The other seven patients transplanted during this period did not have immunohistochemical studies performed on their native kidneys (three patients) or have not had allograft biopsies yet (four patients). Descriptive data regarding the 24 study patients are included in Table I. All patients were treated by standard immunosuppressive techniques; four patients (J. W., M. B., M. C., and T. T.) also received horse antithymocyte globulin (ATG).[1]

Tissue Preparation. Wedge biopsies were performed at surgery or at nephrectomy. Tissues were snap frozen in liquid nitrogen and stored at −20°C until immunofluorescent examinations and/or elutions were performed.

Antisera. Antisera were raised in rabbits to human IgG, M, and A, third component of complement (C'_3) and fibrinogen, and equine globulin. IgG was isolated from pooled human serum as described previously (4), fractionated at half saturation with ammonium sulfate, and chromatographed on diethylaminoethyl (DEAE) cellulose equili-

[1] *Abbreviations used in this paper:* ATG, antithymocyte globulin; GBM, glomerular basement membrane; HA-anti-HA, histocompatibility antigen; IF, immunofluorescent; Ig, immunoglobulin; KFab, kidney-fixing antibody; PBS, phosphate-buffered saline.

TABLE I

Clinical and Donor Data of 24 Patients Receiving Renal Allografts

Initials	Sex	Age	Native kidney clinical diagnosis	Allograft donor	Antigenic disparity	Interval from transplant to biopsy	Fate of patient	Fate of allograft	Uncorrect. G. F. R. (Ccr)	Comments
									ml/min	
J. J.	F	22	CGN	Mother	0	8, 17 mo	A	F	49	
S. M.	F	29	CGN	Sister	0	29 mo	A	F	90	
J. W.	F	22	CGN	Father	1	7 mo	A	F	48	
L. R.	F	19	INT	Cadaver	ABO Mismatch	1 mo	A	N		
L. G.	F	12	CGN	Mother	1	8 mo	A	F	42	
J. F.	M	7	RPN	Cadaver	2	10 days 5 wk	A	N		Nephrotic syndrome
K. Y.	F	18	CGN	Sister	0	9 mo	A	F	68	
L. T.	M	8	CGN	Cadaver	2	2 wk 3 mo	A	N		Nephrotic syndrome
M. Br.	F	32	Hered	Mother	1	6 mo	A	F	38	
J. B.	F	28	CGN	Cadaver	3	9 wk	A	N		
E. S.	F	25	CGN	Mother	2	6, 15 mo	A	F	66	
G. M.	F	47	PY	Cadaver	2	10 days	D	N		
P. T.	F	38	PY	Cadaver	2	7 days 6 mo	D	F	37	Nephrotic syndrome
M. C.	F	28	PY	Brother	2	3 wk	D	N		
B. S.	F	36	PY	Cadaver	ND	4, 29 mo	A	F	37	
D. L.	F	29	PY	Mother	2	5 mo	A	F	36	
K. J. W.	F	21	RPN	Cadaver	2	12, 27 mo	D	F	24	
M. J.	F	32	CGN	Cadaver	2	6 mo	A	F	60	
C. C.	F	47	NS	Cadaver	3	3 wk	A	N		
T. T.	M	8	DYS	Mother	2	5 mo	A	F	30	
K. M.	M	2	DYS	Cadaver	2	6 wk 14 mo	A	F	45	
M. Bu.	F	49	PY	Sister	0	6 mo	A	F	47	
S. S.	F	22	PY	Mother	0	6 mo	A	F	70	
G. S.	F	29	CGN	Cadaver	2	22 mo	D	F	35	

Abbreviations used in this table: A, alive; CGN, chronic glomerulonephritis; D, dead; DYS, renal dysgenesis; F, functioning; Hered, hereditary nephritis; INT, interstitial nephritis; N, nephrectomy; NS, hypertensive vascular disease with nephrosclerosis; PY, chronic pyelonephritis; RPN, rapidly progressive glomerulonephritis.

brated with 0.01 M phosphate buffer, pH 8.0. IgM was isolated from myeloma sera by ammonium sulfate precipitation, Pevikon block electrophoresis (5), and DEAE chromatography. IgA was also fractionated from myeloma serum by ammonium sulfate precipitation, DEAE chromatography in Sorensen's buffer using a concave salt gradient between 0.01 and 0.3 M, pH 8.0, and subsequent Pevikon electrophoresis. C'_3 was the gift of H. J. Müller-Eberhard;[2] fibrinogen was isolated by the technique of Kekwick, Mackay, Nance, and Record (6). Antisera harvested from immunized rabbits were tested for monospecificity by double diffusion in 0.5% agarose plates and by immunoelectrophoresis; all antisera were absorbed with immunoglobulin light chains. Globulin fractions of these antisera were fluoresceinated by the dialysis method of Clark and Shepard (7) and subsequently rechromatographed on DEAE (8) at pH 7.4.

[2] Scripps Clinic and Research Foundation, La Jolla, Calif.

Measurement of IgG concentrations. Immunoglobulin concentrations of eluates were measured by radial immunodiffusion by the technique of Fahey and McKelvey (9).

Immunoelectrophoresis. Immunoelectrophoresis was performed on glass slides in 1% agarose in barbital buffer, pH 8.2, Mu = 0.04; conditions for study were 5.5 V/cm² for 40 min at room temperature.

Immunofluorescent microscopy. Immunofluorescent microscopy was performed by the technique of Coons and Kaplan (10), using a Leitz Ortholux microscope (E. Leitz, Inc., Rockleigh, N. J.), HBO 200 W mercury vapor lamp, UGI exciter filter, and K430 barrier. Specificity of fluoresceinated reagents, controls for direct and indirect fluor testing, and performance of antiglomerular basement membrane (GBM) antibody assay were performed as described previously (11, 4).

Elutions. Elution of antibody globulin from native and allograft kidney tissue was done using a 0.02 M citric acid buffer, pH 3.2 (12, 13). Cortical sections were homogen-

TABLE II

Direct Immunofluorescent Examination Results of Native Kidney and Allograft Biopsies: Glomerular Observations

	Direct immunofluorescent examinations of native kidneys						Direct immunofluorescent examinations of renal grafts					
Initials	IgG	IgM	IgA	B1C	Fibrinogen	Pattern of Ig deposition	IgG	IgM	IgA	B1C	Fibrinogen	Pattern of Ig deposition
J. J.	−	+		—		G	−	+	−	+	−	G
							−	+	−	+	+	G
S. M.	+					G	+	+		+	+	I
J. W.	+	+/−	−	+/−	−	G	+	+	−	+	−	G
L. R.	+	−	−	−	−	L	+	−	−	+	+	L
L. G.	+	−	−	+	−	L	+	+	−	+	+	L
J. F.	+	+	+	+	+	I	+	−	−	+	+	L
							+	−	−		+	L
K. Y.	+	+	+	+	−	I	+	+	−	+	+	L
L. T.	+	+	−	+	+	I	+	+	−	+	+	L
M. Br.	+		−	+	−	I	+	−	−	+	+	I
J. B.	−	+	−	−	−	I	+	−	−	+	−	I
E. S.	−	+	−	+	−	I	−	+	−	−	−	I
G. M.	−	+	+/−	+	+	I	−	−	−	−	−	
P. T.	−	−	−	−	−		+	−	−	+	+	L
M. C.	−	−	−	+	−		+	−	−	+	−	L
B. S.	−				−		+					G
							+	+		+	−	G
D. L.	−			−	−		−	−		−	−	
K. J. W.	−			+			−	−		−	−	
							−	−	−	−	−	
M. J.	−	−			−		−	−	−	−	+	
C. C.	−	−	−	−	−		−	−	−	+	−	
							−	−	−	−	+	
T. T.	−	−	−	−	−		−	−	−	−	+	
K. M.	−			−	−		−	−	−	−	+	
M. Bu.	−	−	−	−	−		−	−	−	−	−	
S. S.	−			−	−		−	−	−	−	+	
G. S.	−	−	−	−	−		−	−	−	−	−	

Abbreviations used in this table: G, granular; I, indeterminate; L, linear.

ized in cold, isotonic phosphate-buffered saline (PBS), and fast sedimenting debris washed extensively. Elutions were carried out at 37°C for 2½ h; after elution the debris was separated by centrifugation, the eluate neutralized with 1 N NaOH, dialyzed against PBS, fractionated at half saturation with ammonium sulfate, and concentrated by negative pressure ultrafiltration before other studies.

Paired-label isotope experiments. To measure the per cent kidney-fixing antibody (KFab) content of selected eluates, paired-label studies were done by modification of the technique of Pressman, Day, and Blau (14). Eluates were radiolabeled with ^{125} or ^{131}I by the method of McConahey and Dixon (15). Control IgG from normal serum treated with 0.02 M citrate for 2½ h at 37°C was labeled with the alternate isotope. Simultaneous intravenous injections of mixed eluate and control protein were made into squirrel monkeys; animals were given potassium iodide in their drinking water and sacrificed 72 h after injection. After perfusion with PBS, kidneys were removed and homogenized in a Waring blendor (Waring Products, Div., Dynamics Corp. of America, New Hartford, Conn.); fast sedimenting debris was washed and counted for ^{125} and ^{131}I activity in a well counter using sodium iodide crystal and dual channel spectrometer. Per cent KFab was calculated as published previously (13, 16).

Histocompatibility typing. Typing was done by the lymphocyte microcytotoxicity assay technique; antisera were obtained from the National Institute of Allergy and Infectious Disease.[3] Quality of match is indicated in Table I.

RESULTS

Immunofluorescent (IF) examinations of native kidneys: glomeruli. As indicated in Table II, 12 (of 24) patients had immunoglobulin (Ig) localized to glomeruli of native kidneys before or at the time of transplantation. The pattern of Ig deposition was clearly linear in two cases, granular in three, and indeterminate in seven. The

[3] Dr. Donald Kayhoe, National Institute of Allergy and Infectious Disease, Bethesda, Md.

TABLE III

Direct Immunofluorescent Examination Results of Native Kidney and Allograft Biopsies: Blood Vessels

	Direct immunofluorescent examination of native kidneys					Direct immunofluorescent examination of renal allograft				
Initials	IgG	IgM	IgA	B_1C	Fibrinogen	IgG	IgM	IgA	B_1C	Fibrinogen
J. J.	−	+		−		−	+	−	−	−
						−	+	−	+	+
S. M.	−					−			−	−
J. W.	−	−	−	−	−	+	−	−	+	−
L. R.	−	−	−	−	−	−	−	−	−	+
L. G.	−	−	−	−	−	−	+	−	+	+
J. F.	−	−	−	+	−	−	−	−	+	+
						−	−	−		+
K. Y.	−	−	−	+	−	−	−	−	−	−
L. T.	−	−	−	−	−	−	−	+	+	+
M. Br.	−	−	−	+	−	−	+	+	+	+
J. B.	−	+	−	−	−	+	+	−	+	+
E. S.	−	+	−	−	+	−	+	−	+	+
G. M.	−	−	−	−	+	−	−	−	−	+
P. T.	−	−	−	−	−	−	−	−	−	−
M. C.	−	−	−	−	−	−	+	−	+	−
B. S.	−			−		−				
						−	−		+	−
D. L.	−	−		−		−	−	−	−	−
K. J. W.	−	−				−	−		−	−
						−	−	−	−	−
M. J.	−	+				−	+	−	+	−
C. C.	−	−	−	−	−	−	+	−	+	+
						−	+	+	+	+
T. T.	−	−	−	−	−	−	−	−	+	−
K. M.	−			−	−	−	+	−	+	+
M. Bu.	−	−	−	+	−	−	−	−	+	−
S. S.	−	−	−	−	−	−	+	−	+	−
G. S.	−	−	−	−	−	−	−	−	−	−

latter classification was necessary due to the far advanced scarring and anatomic distortion of normal glomerular architecture, or because fluorescence was perceptible but not sufficiently distinct to allow confident interpretation of Ig patterns.

Immunofluorescent examination of native kidneys: blood vessels. Ig, B_1C, and/or fibrinogen were observed occasionally in vascular walls, probably of small arterioles, in 9 of 24 native kidneys before allografting. Ig deposits were noted in four kidneys, B_1C in four, and fibrinogen in two (Table III).

Immunofluorescent examinations of allografts: glomeruli. Glomerular-bound Ig was seen in biopsy sections of 11 of the 12 allografts placed into hosts whose native kidneys also had glomerular Ig. The twelfth patient's graft was removed 10 days after implantation and appeared infarcted, the result of a compromised arterial anastomosis; although IF examination was performed, the tissue was necrotic and no localized Ig was observed. In addition, glomerular Ig was seen in grafts of three patients whose native kidneys were negative by IF (Table II). Observed patterns of Ig in allografts were linear in seven kidneys, granular in three and indeterminate in four. Three of these patients had received ATG (patients J. W., M. B., and M. C.); direct IF was negative for horse globulin fixation, as it was also in patient T. T.

Immunofluorescent examination of allografts: blood vessels. Ig, B_1C, and/or fibrinogen were localized in some small blood vessel walls of 18 of 24 grafts inspected. B_1C was observed most commonly, but Ig (usually IgM) and fibrinogen were found frequently also.

Elution studies. Satisfactory elutions from 27 kidneys were performed in 18 of 24 patients: from 14 native kidneys and 13 allografts. Both native kidney and allograft tissue from nine patients were eluted. Tests by indirect immunofluorescence on normal homologous kidney sections indicated the presence of GBM antibody both in eluates of native kidneys and allografts of six patients

TABLE IV

Eluate Concentrations and Results of In Vitro Testing on Normal Homologous Kidney Sections (Anti-GBM Antibody Assays)

	Native kidney eluates						Renal allograft eluates				
Initials	Direct IF pattern	Eluted	Eluate prot conc	Eluate IgG conc	Eluate anti-GBM anti-bodies	Serum anti-GBM anti-bodies	Direct IF pattern	Eluted	Eluate prot conc	Eluate IgG conc	Eluates anti-GBM anti-bodies
			mg/ml	*mcg/ml*					*mg/ml*	*mcg/ml*	
J. J.	G	−				−	G	+			−
S. M.	G	−				−	I	+	2	76	−
J. W.	G	−				−	G	+			−
L. R.	L	+	18	76	+	+	L	+	11	88	+
L. G.	L	−				−	L	−			
J. F.	I	+	22	150	+	+	L	+	15	760	+
K. Y.	I	+		92	+	−	L	+	11	88	+
L. T.	I	+	40	460	+	−	L	+			+
M. Br.	I	−				−	I	−			
J. B.	I	+	25	1,470	−	−	I	+	30	430	−
E. S.	I	+	16	100	−	−	I	+			−
G. M.	I	+	25	260	−	−	Neg	−			
P. T.	Neg	+	10	100	+	−	L	+	50	145	+
M. C.	Neg	+	45	115	+	−	L	+	70		+
B. S.	Neg	−					G	−			
D. L.	Neg	−					Neg	−			
K. J. W.	Neg	−					Neg	+		50	−
M. J.	Neg	−					Neg	−			
C. C.	Neg	+	20	520	−	−	Neg	+	20	100	−
T. T.	Neg	+		200	−	−	Neg	−			
K. M.	Neg	−					Neg	−			
M. Bu.	Neg	+	28		−	−	Neg	−			
S. S.	Neg	+	11	100	−	−	Neg	−			
G. S.	Neg	+	18	520	−	−	Neg	−			

(Table IV). These six patients were patients whose allograft biopsies had linear fixation of IgG. Direct IF examination of native renal tissue from these same patients had shown linear IgG fixation in one, indeterminate patterns in three, and negative IF in two.

Eluates tested from two kidneys whose direct IF pattern was granular, from six other kidneys with indeterminate patterns, and seven other kidneys with negative direct IF also were negative for presence of anti-GBM antibody. No extraglomerular vascular fixation of Ig was seen in tests of any of these eluates.

Measurement of kidney-fixing antibody concentrations. Eluates from native kidney and allograft of two patients (L. R. and P. T.) were radiolabeled and studied in paired isotope experiments. Native kidney eluates L. R. and P. T. contained 0.8 and 1.1% KFab, respectively; allograft eluates L. R. and P. T. contained 1.1 and 1.2% KFab, respectively. L. R. had circulating anti-GBM antibodies only in the anephric state, while anti-GBM antibodies were never demonstrated in the serum of P. T.

DISCUSSION

Immunologically-mediated glomerulonephritis might affect a renal allograft in one of three ways: persistence of an active nephritogenic mechanism antedating the graft, elicitation of a nephritogenic mechanism as a consequence of the graft, or new disease whose onset is not the result of graft-specific humoral immune responses.

Numerous studies have reported on some aspect of the pathogenesis of glomerular disease of grafted human kidneys. Studies reported by Glassock, Feldmann, Reynolds, Dammin, and Merrill (17) which describe the development of glomerular lesions in human isografts have been important in establishing the concept of recurrent glomerulonephritis, but data offered do not include immunologic observations regarding the hosts' native kidney disease. Moreover, extensive reports by

Porter et al. (18), Hulme, Andres, Porter, and Ogden (19), Lindquist, Guttmann, Merrill, and Dammin (20), Pasternack and Linder (21), and McKenzie and Whittingham (22), while indicative of frequent allograft glomerular abnormalities by immunohistochemical techniques, have not elucidated the mechanisms of the abnormalities, their frequency in a series of allografts, or established a relationship immunologically to the hosts' underlying native kidney disease.

Survey of one series of long-functioning, living related-donor allografts by immunohistochemical analyses of surgical biopsies indicated a high frequency of immunoglobulin-associated glomerular abnormalities (23). Moreover, the report documented in that group the apparent incidence of linear and other patterns of host immunoglobulin localization, presumptive of anti-GBM, and soluble antigen antibody complex-mediated glomerulonephritis. Nevertheless, this study as the others cited, lacked elution data to confirm the direct immunofluorescent observations, and presented no immunological data regarding the underlying mechanism of disease that destroyed the hosts' native kidneys.

Dixon, Lerner, and McPhaul (1) tabulated data on 16 recipients of renal allografts. They inferred that clinical courses and immunologic data regarding these patients were strongly indicative of persistent immunopathogenetic mechanisms causative of recurrent glomerulonephritis. However, the elution and immunohistochemical studies were incomplete on many of the patients reported, and the group may not be considered representative, inasmuch as they were collected from several different transplantation centers.

The present report provides systematic observations from direct immunofluorescent examinations of host kidneys and allografts of 24 patients transplanted at one institution. These observations indicate that immunoglobulins are found in glomeruli of native kidneys of approximately half of the patients receiving renal allografts at our medical center, and that the risk of apparent immunoglobulin deposition in allograft glomeruli is very high in these patients. 11 of the 12 patients documented to have glomerular-bound Ig of native kidney also developed Ig deposition in glomeruli of their graft. Moreover, 3 of 12 patients in whom direct IF examinations of native kidneys were negative also developed glomerular Ig deposition in their allografts.

Elution studies were crucial in three ways: first, they confirmed that linear Ig deposition in these allografts is the result of anti-GBM antibody. Second, they clarified the significance of direct IF patterns of several kidneys which were interpreted as indeterminate. Three such eluates were demonstrated to contain anti-GBM antibodies although the direct IF was inconclusive, and circulating anti-GBM antibodies were not demonstrable in two. Third, native kidneys of two patients contained elutable anti-GBM antibodies, despite negative IF examination; they also had negative sera when assayed for anti-GBM antibodies. Moreover, in six of the seven cases demonstrated to have linear Ig deposition in glomeruli of their allografts by direct IF, assay of eluates from both native kidneys as well as allografts indicated that the anti-GBM antibody immunopathogenetic mechanism was present antecedent to the transplantation. Renal tissue from the seventh patient was not eluted.

Quantitative kidney-fixing antibody studies carried out in primates with eluates from native kidneys and allografts from two patients indicated that a minimum of 1% of eluted IgG had kidney-fixing specificity. This amount is less than usually eluted from patients with Goodpasture's syndrome, but is compatible with other anti-GBM eluate data (12, 13). Such a content is far in excess of that which has been measured in sera positive for circulating human anti-GBM antibody and many heterologous nephrotoxic sera.

Convincing evidence that immunopathogenetic mechanisms of patients are the same before and after allografting can be offered only with respect to GBM antibody mediation; these antibodies can be dissociated from the insoluble GBM by elution, so as to test them for their specificity. In this series of patients 7 of the 14 with Ig localizing to allograft glomeruli had this mechanism. Demonstration of anti-GBM antibodies in the eluates from the native kidneys of six patients with linear Ig staining allograft glomeruli assures that this humoral system antedated allograft placement. Although not precluding the possibility that allograft sensitization could elicit an augmented anti-GBM antibody response, the latter hypothesis seems unnecesary and cannot be documented in these cases.

Soluble antigen-antibody complexes also can be eluted from pathologic tissues but dissociation of antigen and antibodies to test free antibody specificity and identify antigens remains an unsolved technical problem. However, the demonstration of glomerular lg deposits before as well as after allograft placement in six of the seven patients with nonanti-GBM antibody-mediated glomerular disease suggests that allograft lesions may result from persistence of circulating complexes ongoing antecedent to allografting. This suggestion implies that the antigenic moieties of the complexes are the same. That immunoglobulin classes localized to native kidney and allograft glomeruli are the same in five of the seven patients supports this implication. Nevertheless, patient B. S. had granular Ig deposits in a routine allograft biopsy 6 mo and again 2 yr later, although native kidney had no apparent Ig by direct IF examination. In addition, patient J. B. had IgM localized to native kidney before allografting but IgG localized to allograft glo-

meruli on later biopsy. In these two patients it is reasonable to propose that the Ig localizing to allograft glomeruli resulted from circulating histocompatibility antigen HA-anti HA immune complexes (24, 25). Although our data offer no support in favor of or excluding the possibility, glomerular-bound immunoglobulin of all allografts with non-anti-GBM antibody-mediated glomerular disease might contain HA-anti-HA immune complexes.

Our data, then, are supportive of the hypothesis that immunoglobulin-mediated diseases of renal allograft glomeruli usually are rooted in persistence of immunopathogenetic mechanisms present before the transplantation. They accord well with observations concerning the fate of isografts placed into Lewis rat recipients (Lewis Corp., Woodbury, Conn.) affected by experimental autologous immune complex glomerulonephritis (Heymann nephritis) (26). However, the quantitative impact of these nephritogenic mechanisms on the function and ultimate fate of the renal allografts is harder to define than their persistence. Nevertheless, three patients pursued a florid nephritic course immediately after transplantation, with urinary red cell casts, histologic evidence of fixed glomerular cell proliferation and heavy proteinuria. The graft of one such patient was removed because of the intensity of the nephritis and proteinuria; a second patient died after two bouts of gram negative sepsis which may be related as much to the immunologic susceptibility associated with nephrotic syndrome as to the low dose immunosuppression employed. The third was destroyed by early, intense rejection.

Less certain inferences may be drawn regarding immunofluorescent localization of Ig, B_1C, and fibrinogen in small blood vessel walls. As noted above, 9 of 24 native kidneys of this series contained occasional vascular Ig infiltrates. Such findings were more frequent in allografts examined (18 of 24), were found in grafts whether or not they showed IF evidence of glomerular Ig, and were more frequent and extensive in association with allograft rejections. Eluates tested for non-glomerular vascular fixation were negative. These observations suggest that vascular Ig infiltrates, in contrast to glomerular-bound Ig, more likely result from humoral expressions of allograft immunity (21, 27, 28).

In conclusion, the risk of immunopathogenetic mechanisms causing glomerulonephritis in renal allografts seems proportionate to the presence of an operational nephritogenic mechanism antecedent to and at the time of transplantation. The clinical risk of such an allograft nephritis is probably determined by the quantitative intensity and duration of the humoral mechanisms. Where quantitative expression of the immunopathogenetic mechanisms responsible for glomerular Ig deposition is not great, the fate of the allograft is probably determined more by antigenic disparity and allograft immunity than by the nephritogenic mechanism.

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