Virchows Arch. A Path. Anat. and Histol. 371, 5—14 (1976)

Recurrent Glomerulonephritis in Human Renal Homografts*

Hugo R. Seibel, Richard J. Weymouth**, Shirley S. Craig, and William H. Sterling

Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Virginia

Received March 3, 1976

Summary. Recurrent glomerulonephritis in kidneys transplanted to glomerulonephritic recipients is becoming more obvious. It has been suggested that the disease process which caused the original disease in the recipient is also operative in the transplanted tissue. This study compared the ultrastructure and immunofluorescence of the native kidneys of four patients with their respective sequential, transplant biopsies. In each case, subepithelial humps and IgG, characteristic of a complex type of nephritis, were observed in both the original diseased kidneys and in the transplants. This would indicate that the immunopathologic process which caused the original glomerulonephritis and led to transplantation is also operative in the transplanted tissue.

Key words: Glomerulonephritis — Renal — Homograft.

Recurrent glomerulonephritis in human renal transplants is becoming increasingly apparent. The question whether the immunopathologic process which caused the lesion in the recipients' original kidneys may repeat itself in the transplanted renal tissue has not been answered. Great advances in prolonging graft survival have been made in the areas of immunosuppression and histocompatibility matching; these advances may leave recurrent nephritis as the major complication of renal transplantation for the treatment of glomerulonephritis.

Glassock et al. (1968, 1967) reported the recurrence of glomerulonephritis in eleven of seventeen twin renal grafts, correlating rejection with the duration of the nephritis in the recipient. Porter et al. (1967, 1968) described recurrent nephritis of an antigen-antibody complex type in three homografts of seventy-one cases. In another series of thirty-nine renal allografts, Dixon et al. (1969) described thirteen cases with anti-GBM nephritis and twenty-six grafts with complex type nephritis. Of the former, seven patients demonstrated immunohistological evidence of recurrent nephritis, and of the latter, six patients demonstrated definite evidence of recurrent complex-type nephritis. Dixon et al. (1969) suggest that the frequency of recurrent nephritis may be greater than previously reported, and that recurrences may be confused with graft rejection.

It seemed important, in order to confirm or deny the recurrence and frequency of glomerulonephritis in renal homografts, to compare the ultrastructure of sequential biopsies removed from the transplanted kidney with the ultrastructure of the recipient's original kidney. Immunofluorescent evaluation of these biopsies was also carried out and reported in detail (Bryant et al., 1972).

* Supported by NIH, U.S. Public Health Services Grant A108150-03

** Present address: School of Medicine, University of South Carolina, Columbia, South Carolina 29206, USA

Materials and Methods

Biopsies from four patients who had glomerulonephritis and underwent renal transplantation are described; the original diagnosis having been made on a pathologic (light microscopy) and clinical analysis. All patients were hospitalized at the Clinical Transplant Center at Virginia Commonwealth University. The details of surgical technique and early immunosuppressive program (Hume et al., 1966), as well as techniques employed for EM study (Weymouth et al., 1970), have been described previously.

All patients at the time of transplantation are free of infection, have undergone hemodialysis, and are being treated with Imuran and prednisone. Patients are treated postoperatively with prednisone, Imuran, diet, radiation therapy, and dialysis. Wedge biopsies for the purposes of ultrastructural and immunofluorescent studies were taken from: (1) recipients original diseased kidney (nephrectomy biopsy); (2) control biopsies from the donor kidney just prior to removal so that direct comparisons were possible; (3) one-hour from the time of completion of the vascular anastomoses; and (4) open percutaneous biopsies were obtained sequentially during regular followups (12–20 weeks).

Results

Nephrectomy Biopsies (Glomerulonephritis)

Significant and similar endothelial cell alterations were observed in all of the biopsies from the four patients (Figs. 1, 5, 7). Hypertrophy and hyperplasia of these cells, often to the extreme of luminal occlusion, were noted frequently, and endothelial pores were decreased. The endothelial "expansion" frequently took the form of voluminous cytoplasmic arcades.

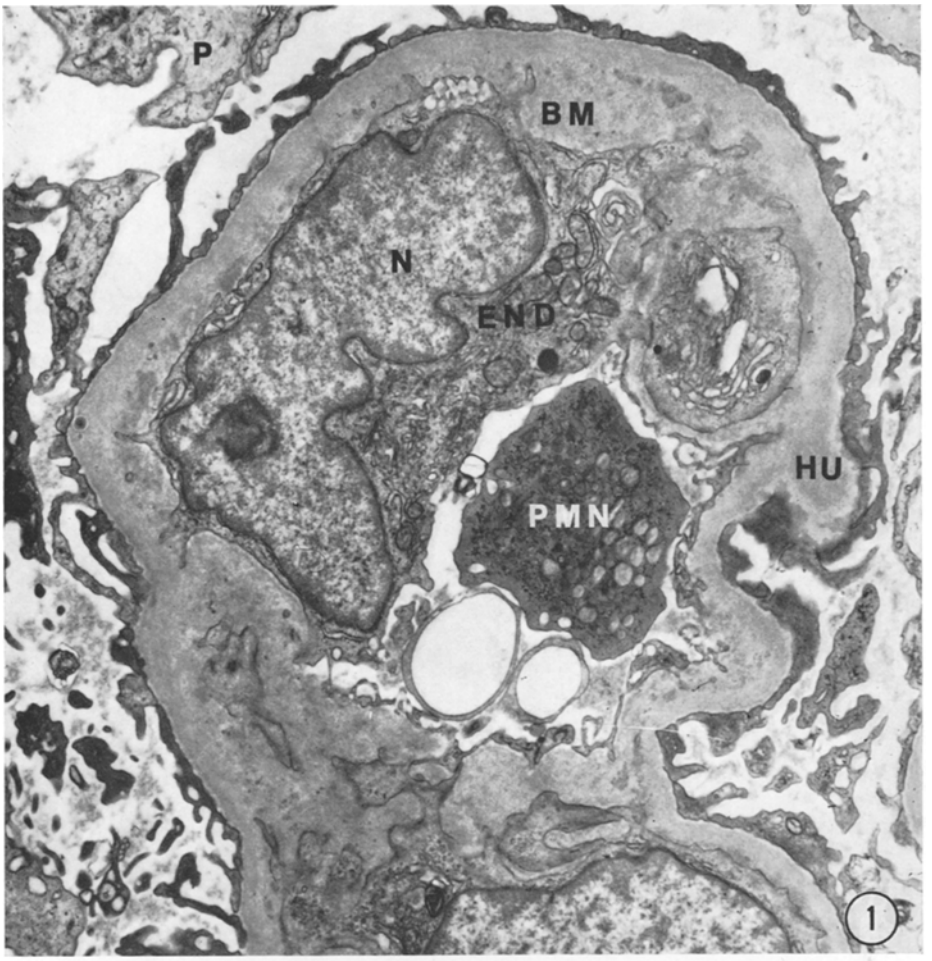
The basement membrane appeared extremely variable in diameter and density in all four cases, ranging from 5,000–20,000 Å; in most areas the three layers were not discernable, being masked by an extreme increase in thickness and/or edema. Neither subendothelial densities nor humps were observed. In some instances electron dense deposits, variable in size, contour and density were observed to be positioned in the middle of the thickened basement membrane (Fig. 1). Perhaps the most striking observation was the appearance of the subepithelial humps in all four cases (Figs. 1, 5, 7). These bodies were hemispherical, consisting of homogeneous electron dense material and situated on the epithelial surface of the capillary basement membrane. The humps were usually focal and seldom confluent in distribution.

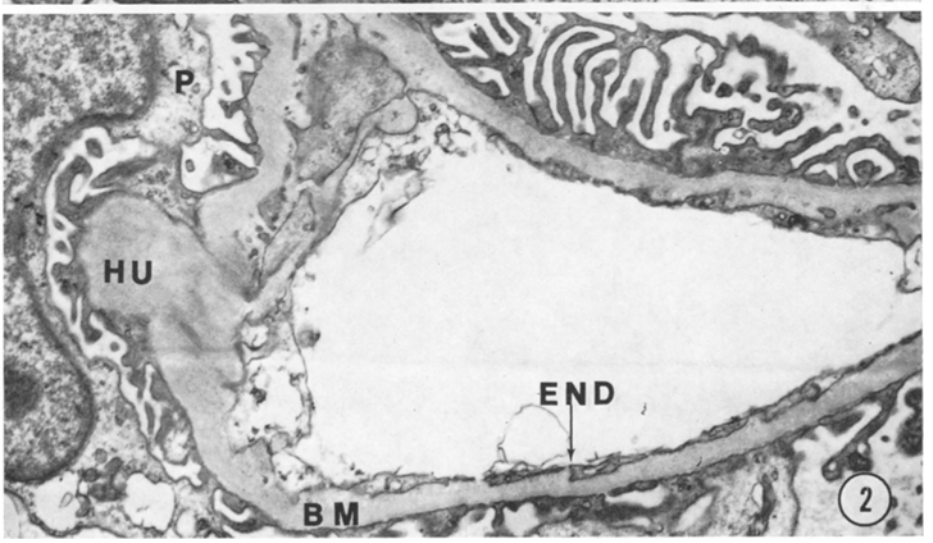
The pedicels appeared broadened and confluent in most areas (Figs. 1, 5, 7). In those locations overlying a subepithelial hump, the pedicels were frequently fused, but delineated pedicels were also present.

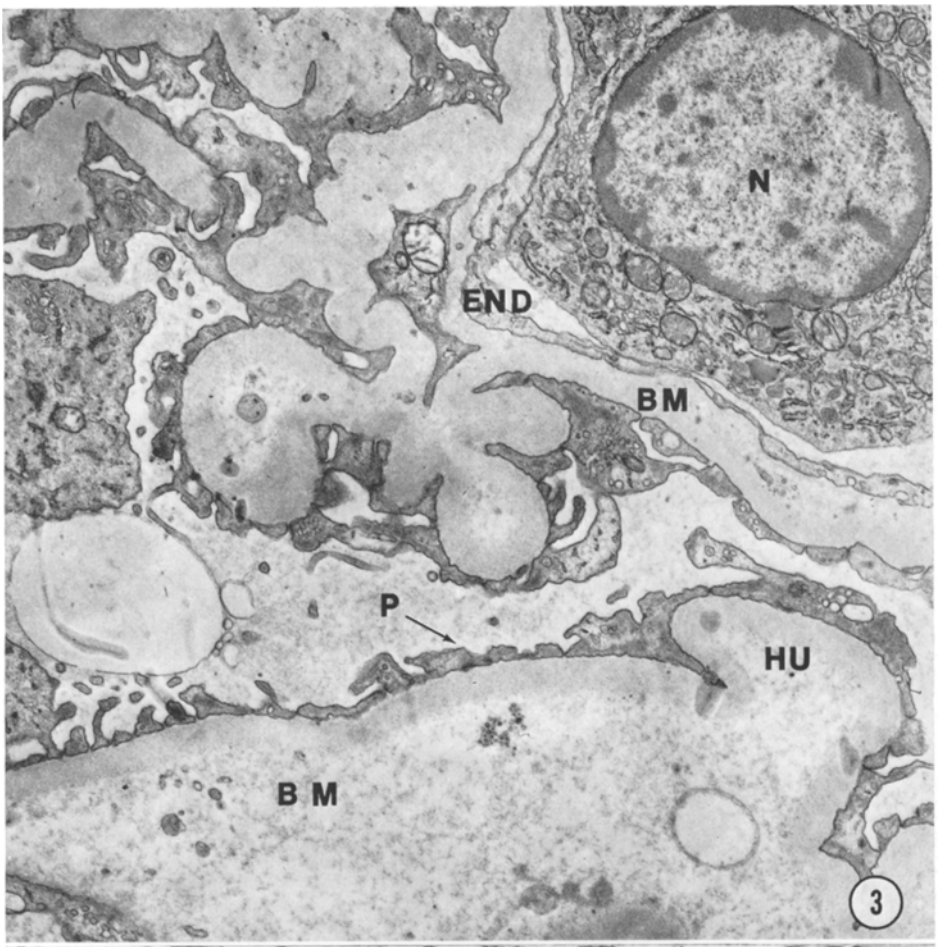
IgG and complement were present in all four cases. IgM was positive in two cases and fibrin in one (Table 1). The distribution and location of these immunoglobulins has been reported previously (Bryant et al., 1972).

Fig. 1. Patient G. L.; Nephrectomy. Endothelial (*END*) hypertrophy almost completely occludes the capillary lumen; the basement membrane (*BM*) demonstrates variations in thickness and density and a subepithelial hump (*HU*). Fusion of the pedicels of the podocytes (*P*) should be noticed. *PMN* polymorphonuclear leukocyte; *N* nucleus. × 8,920

Fig. 2. Patient G. L.; 1 h biopsy. When compared to Figure 1, the basement membrane (*BM*) appears more normal. Although endothelial pores are not obvious, the endothelium (*END*) exhibits little hypertrophy. A subepithelial hump (*HU*) is illustrated. *P* podocyte. × 9,850


P
BM
N
END
HU
PMN
1


P
HU
END
BM
2


N
END
BM
P
HU
B M
3

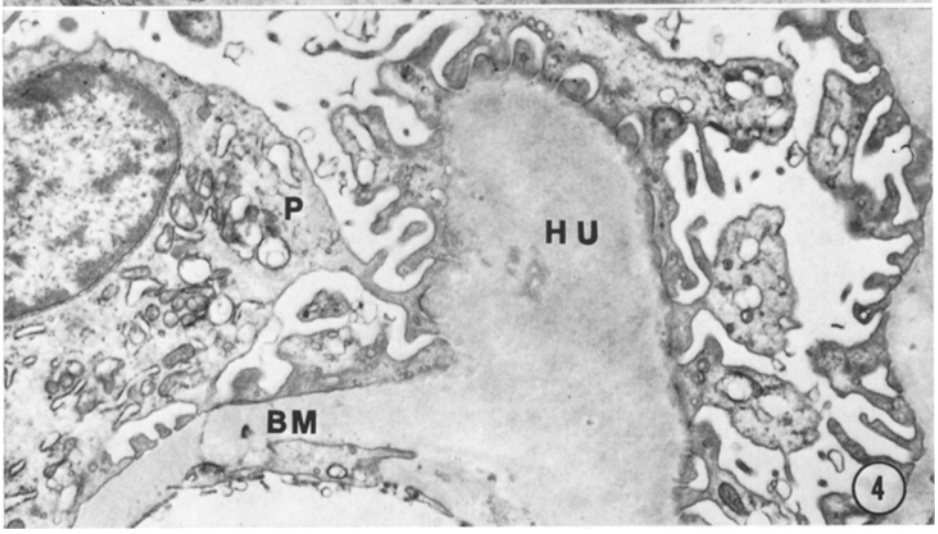

P
HU
BM
4

Table 1. Ultrastructure and immunofluorescent analyses

Patient[a]	Donor	Anephric-weeks	Biopsies			Clinical
			Neph-x	1 h°	Sequential	
G.L.	RLD	0				
					(13 wks)	
Endothelium			3.5	1.5	2.5	(13 wks)
Basement membrane			3	1.5	2	Bun 17
						Cr 0.6
F.E.	RLD	2				
					(12 wks)	
Endothelium			3	2	2.5	(32 wks)
Basement membrane			3.5	2.5	2.5	Bun 16
						Cr 1.0
A.L.	Cad	3				
					(20 wks)	
Endothelium			3	2.5	3	
Basement membrane			3	2.5	2.5	reported not
H.U.	RLD	3				
					(12 wks)	
Endothelium			3	2	3.5	(60 wks)
Basement membrane			3	2	3	Bun = 35
						Cr = 1.7

[a] All four patients were originally diagnosed to suffer from glomerulonephritis; all biopsies exhibited subepithelial humps, and all except the 1 h biopsy of patient G.L. were positive for IgG and complement

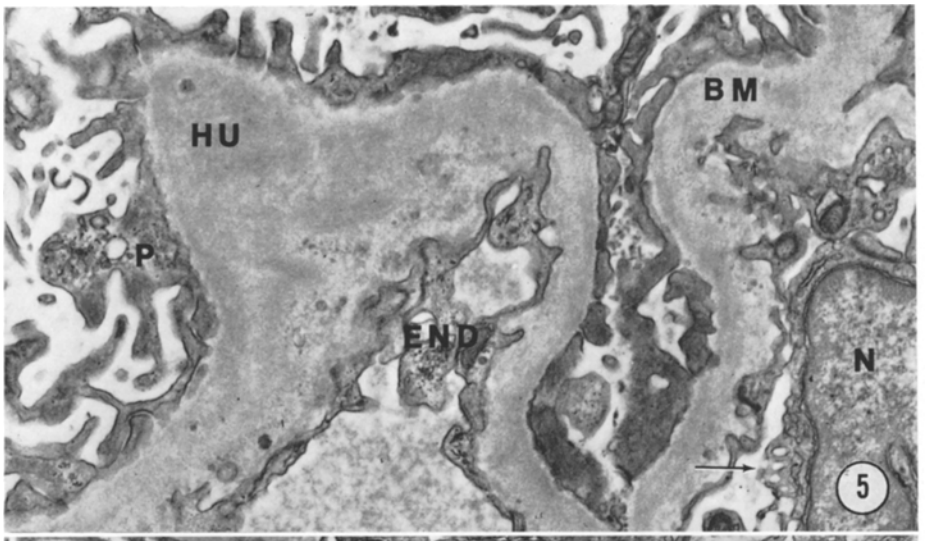
0 = Normal; 4 = maximum change; RLD = related living donor; Cad = Cadaver

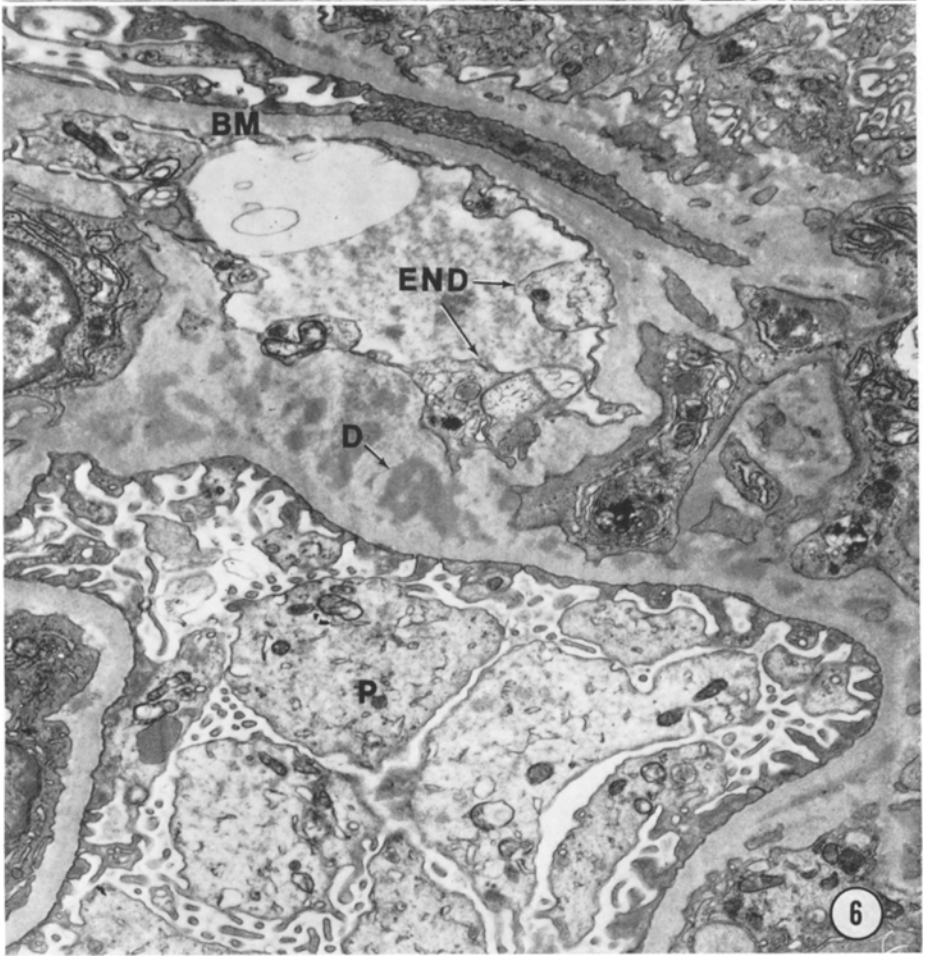
One-Hour Biopsies

To a varying extent, the endothelium and basement membrane approached a more normal cytological appearance in all of these biopsies (Fig. 2). However, in most of the glomerular capillary lumina of all four cases there was noted an increase in size and number of the endothelial cells, as well as thickening of the basement membrane, when compared to the ultrastructure of the normal human glomerulus (Weymouth et al., 1970). Subepithelial humps were observed in all cases; these were similar to those described in the respective nephrectomy biopsies (Fig. 2). IgG and complement were observed in three of the four cases.

Fig. 3. Patient G. L.; 13 weeks posttransplant. Thickening of the basement membrane (*BM*) absence of endothelial pores (*END*), a subepithelial hump (*HU*), and fusion of the pedicels of the podocytes (*P*) are well illustrated. *N* nucleus. × 12,830

Fig. 4. Patient G. L.; 13 weeks posttransplant. A subepithelial hump (HU) is apparent. The pedicels of the podocytes (*P*) are well preserved over the hump. *BM* basement membrane. × 6,430


HU
BM
P
END
N
5


BM
END
D
P
6

Sequential Biopsies

In three of the cases (G. L., A.L., H. U.) an increase in the severity of ultrastructural observations, approaching that of the respective nephrectomy biopsies, was observed. In these three cases, when compared to their one-hour biopsies, the basement membrane was thicker and the endothelial cells demonstrated more hypertrophy and hyperplasia, frequently occluding the glomerular lumen (Fig. 6). In one case (F. E.) the glomerular ultrastructure of the twelve week biopsy was similar to the one hour biopsy. Subepithelial humps, similar to those observed in the nephrectomy and one-hour biopsies, were again present in all four cases (Figs. 3, 4, 8). The pedicels appeared more confluent and similar in cytoarchitecture to the nephrectomy biopsies, in all cases (Figs. 3, 4, 6, 8). IgG and complement were observed in all sequential biopsies.

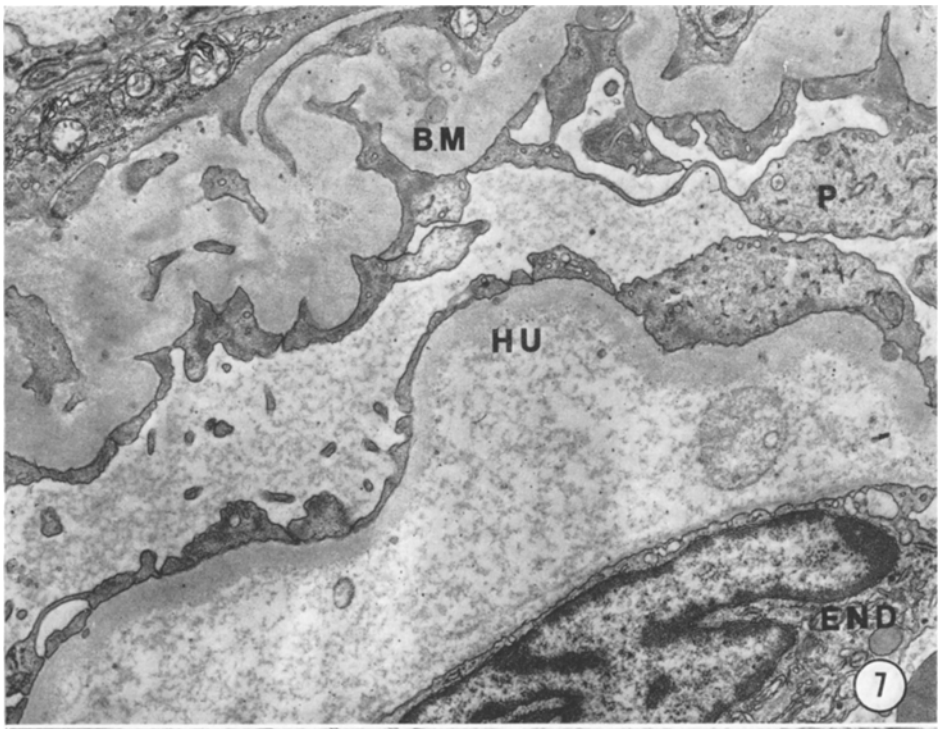
Discussion

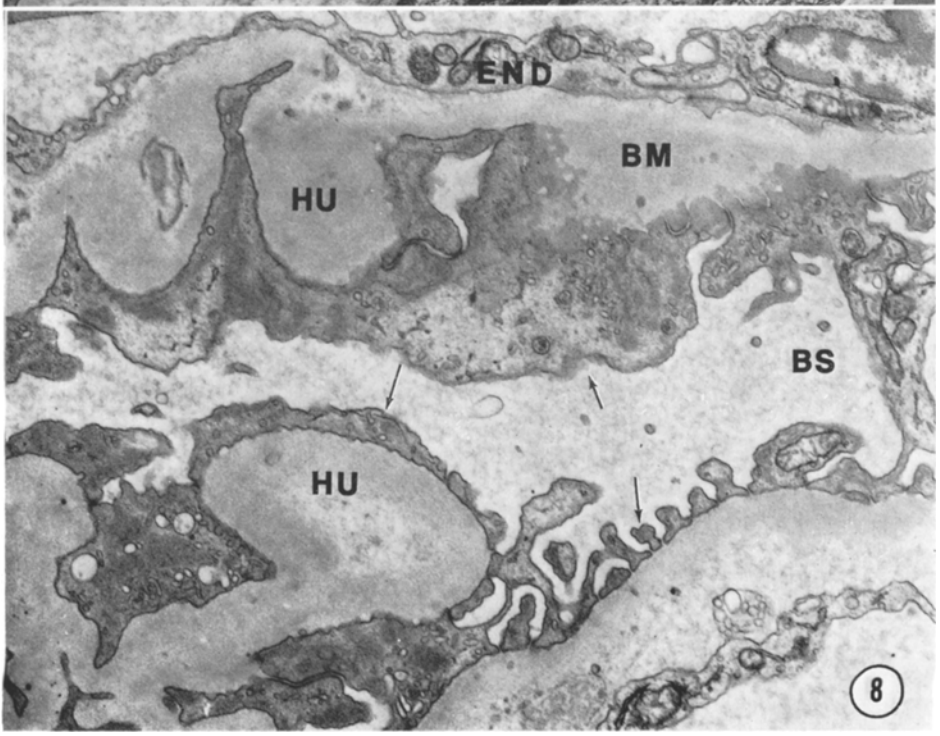
Recurrent glomerulonephritis in kidneys transplanted to recipients who originally had glomerulonephritis is becoming more evident and is a threat to the renal transplants in these recipients. A similar immunopathologic process which caused glomerulonephritis in the native kidney and may be repeated in the recipient, has been postulated. However, a correlative ultrastructural and immulogic study of the sequential transplant biopsies compared to the original glomerulonephritic tissue has not been fully attended to.

Glomerulonephritis appears to be caused by one of two distinct mechanisms. The first of these involves the production of antibodies by the patient, reacting with his own glomerular basement membrane (anti-GBM). Generally speaking, this type of nephritis is characterized by subendothelial deposits of antibody. The deposits resemble those produced by antiglomerular antibodies in nephrotoxic serum nephritis and are located in a fine continous, linear pattern along the inner portion of the glomerular membrane. The second mechanism is dependent upon the production of antibodies by the patient which react with non-glomerular antigens (exogenous or endogenous), resulting in the formation of antigen-antibody complexes and these complexes subsequently being trapped within the glomerular basement membrane. This type of nephritis is characterized by deposits of antigen-antibody complexes along the outer portion of the glomerular basement membrane, giving a lumpy-bumpy appearance to the subepithelial layer. These deposits are identifiable both by electron microscopy and immunofluorescence and are similar to the deposits observed in serum sickness nephritis and acute post streptococcal glomerulonephritis.

Fig. 5. Patient F. E.; Nephrectomy. A subepithelial hump (*HU*) is shown. Pedicels of the podocytes (*P*) exhibit some fusion as well as delineation. There is moderate endothelial arcading (arrow) and a decrease in the number of pores. *BM* basement membrane; *N* nucleus. × 9,350

Fig. 6. Patient F. E.; 12 weeks posttransplant. Deposits (*D*) of irregular shape and density are illustrated within the basement membrane (*BM*). Endothelial (*END*) hypertrophy is noticeable. *P* podocyte. × 10,690


BM
P
HU
END
7


END
BM
HU
BS
HU
8

It would seem, from the literature, that the anti-GBM type of nephritis, with its fine linear and continuous pattern of antibody deposits located along the subendothelial aspect of the glomerular basement membrane, may sometimes be confused with the cytoarchitectural pattern observed in the rejection of renal grafts. In a series of seventy-one renal homografts, Porter et al. (1967, 1968) reported that three of the grafts demonstrated subepithelial deposits and a distribution of IgG typical of complex induced nephritis. These three grafts were considered to present recurrent nephritis; however, comparative studies were not made with the recipients original diseased kidney. Electron microscopic examination revealed that fifty-four grafts contained subendothelial deposits, and forty-nine of the above allografts also demonstrated IgM distributed along the inner aspect of the glomerular basement membrane in a fine, linear pattern. Porter et al. (1968) related these changes to graft rejection since five of the 54 patients had not had glomerulonephritis as their original disease.

In a series of 39 patients with renal allografts, Dixon et al. (1969) reported on the basis of immunohistological evidence, a recurrence of anti-GBM nephritis in seven of thirteen grafts. In the same study, a recurrence of complex type nephritis in six of twenty-six grafts was reported. IgG and C distribution were reported in both anti-GBM and complex nephritis and a correlation between the native kidney and respective allograft was possible. Therefore, Dixon et al. (1969) suggest that the recurrence of glomerulonephritis in renal grafts may be higher than reported by Porter et al. (1967, 1968). Glassock et al. (1967, 1968) described recurrent pathology in eleven of seventeen twin renal grafts, whose original diagnosis was glomerulonephritis. In those cases where recurrent glomerulonephritis was associated with renal failure, both subepithelial and subendothelial deposits of IgG were reported in the isografts, however, no comparative study of the isografts and the original diseased kidney was conducted.

In the four reported cases, glomerulonephritis was the original, primary disease process as determined by clinical and histologic evidence. The nephrectomy biopsies from these four cases also demonstrated ultrastructural subepithelial humps similar to the lesions produced in the complex-type of nephritis. Correlative immunofluorescence studies of these biopsies indicated the presence of IgG and C. In addition, pronounced fusion of the pedicels, thickening of the basement membrane and arcading and hyperplasia of the glomerular endothelial cells was observed. Again utilizing electron microscopy and immunofluorescence, subepithelial humps were observed in each of the respective one hour post-vascular anastomosis and sequential biopsies. These deposits or humps were essentially the same in cytoarchitecture and distribution as those observed in the native kidney of each patient. IgG and C were also detected in these sequential biop-

Fig. 7. Patient A. L.; Nephrectomy. A subepithelial hump (*HU*) is exhibited. *P* podocyte; *END* endothelium; *BM* basement membrane. × 10,150

Fig. 8. Patient A. L.; 20 weeks posttransplant. The basement membrane (*BM*) exhibits variations in thickness and subepithelial humps (*HU*) are illustrated. *END*, endothelium; pedicels of podocytes (arrows); *BS* Bowman's space. × 9,620

sies. Subepithelial humps were present, even at one hour, but cytology of the endothelial cells, basement membrane and podocytes approached a normal appearance. In 3 of the 4 cases the sequential biopsies demonstrated hyperplasia, arcading, hypertrophy of the endothelial cells, thickening of the basement membrane and pedicel fusion which reminded the authors of the native kidneys. Subepithelial humps, IgG and C were consistently present in all of these sequential biopsies. A follow-up of these patients at thirteen to sixty weeks post transplantation indicates that the BUN ranges from 16–35 and serum creatinine from 0.6 to 1.7 mg%. All patients are on immunosuppresive therapy.

Our evidence indicates that complex type of nephritis is recurrent in the allografts of all four patients and probably mediated by mechanisms similar to those in the native kidney.

References

Bryant, C. P., Hume, D. M.: Preliminary observations on 19 human renal transplants: correlation of clinical and immunofluorescent results. Anat. Rec. **172**, 280 (1972)

Dixon, F. J., McPhaul, J. J., Lerner, R.: Recurrence of glomerulonephritis in the transplanted kidney. Arch. intern. Med. **123**, 554–557 (1969)

Glassock, R. J., Feldman, D., Reynolds, E. S., Dammin, G. J., Merrill, J. P.: Recurrent glomerulonephritis in human renal isograft recipients: A clinical and pathologic study. Proc. of the First Int. Congress of the Transplantation Soc., Paris (1967)

Glassock, R. J., Feldman, D., Reynolds, E. S., Dammin, G. J., Merrill, J. P.: Human renal isografts: A clinical and pathologic analysis. Medicine (Baltimore) **47**, 411–454 (1968)

Hume, D. M., Lee, H. M., Williams, G. M., White, H. J. O., Ferre, J., Wolf, J. S., Prout, G. R., Slapak, M., Jr., O'Brien, J., Kilpatrick, S. J., Kauffman, H. M., Cleveland, R. J.: Comparative results of cadaver and related donor renal homografts in man and immunologic implications of the outcome of second and paired transplants. Ann. Surg. **164**, 352–397 (1966)

Porter, K. A., Andres, G. A., Calder, M. W., Dossetor, J. B., Hsu, K. C., Rendall, J. M., Seegal, B. C., Starzl, T. E.: Human renal transplants. II. Immunofluorescent and immunoferritin studies. Lab. Invest. **18**, 159–171 (1968)

Porter, K. A., Dossetor, J. B., Marchioro, T. L., Peart, W. S., Rendal, J. M., Starzl, T. E., Terasaki, P. I.: Human renal transplants. I. Glomerular changes. Lab. Invest. **16**, 153–180 (1967)

Weymouth, R. J., Seibel, H. R., Lee, H. M., Hume, D. M., Williams, G. M.: The glomerulus in man one hour after transplantation. Amer. J. Path. **58**, 84–104 (1970)

Dr. Hugo R. Seibel
Department of Anatomy
Medical College of Virginia
Health Sciences Division
Virginia Commonwealth University
Richmond, Virginia 23298, USA