The Glomerulus in Man One Hour after Transplantation

An Electron Microscopic Study

Richard J. Weymouth, MD, PhD, Hugo R. Seibel, PhD, Hyung M. Lee, MD, David M. Hume, MD, and G. Melville Williams, MD

ULTRASTRUCTURAL STUDIES of the transplanted dog kidney have been reported[9,15]. The ultrastructure of the human kidney, normal and pathologic, has also been described[2,3,6,8,12,13,20]. Porter *et al*[16] have described the ultrastructural changes in human renal allografts and a single isograft, 20–30 months following transplantation. The variable glomerular changes involved all cellular components as well as the basement membrane. In a more recent report, Porter *et al*[17] described densities in the glomerular basement membrane and postulated that the prognosis of the graft may depend upon the reversibility of the injury associated with the subendothelial densities. Hamburger, Crosmier, and Dormont[5] have described changes which were observed 1–3 and 6–20 months after transplantation, consisting of a mononuclear infiltration, general modification of the intercapillary space, and "slight modification" of the epithelial cells.

Sequential ultrastructural observations of the transplanted kidney in man are rare and the changes associated with its immediate response to the recipient's environment have not been described. We have found these early changes to be impressive and this report considers their clinical relevance.

Materials and Methods

Biopsies from 19 patients who underwent kidney transplantation are described. All patients were hospitalized at the Clinical Transplant Center at the Medical College of Virginia. The details of surgical technique and an early immunosuppressive program have been described previously.[7] The total time of renal ischemia in related living donors varied between 15–30 min, while in cadaver donors, about 40–50 min elapsed between the application of the arterial clamp on the renal artery in the donor and the establishment of free blood flow through the recipient's kidney. Kidneys removed from related living donors as well as from cadaveric donors were

From the Departments of Anatomy and Surgery, Medical College of Virginia, Virginia Commonwealth University, Richmond.

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Address for reprint requests: Dr. Hugo R. Seibel, Department of Anatomy, Medical College of Virginia, MCV Station, Richmond, Va 23219.

perfused with 500 cc of Ringers-Lactate at 10°C containing 10,000 units of heparin and 25 gm of human albumin. Wedge biopsies were taken within 1 hr from the time of completion of the vascular anastomoses, and in five instances, biopsies were also taken from the donor kidney just prior to removal, so that direct comparisons were possible.

The tissue for electron microscopic study was fixed immediately in cacodylate-buffered 3% glutaraldehyde and cut into 1mm cubes; postfixation occurred in 2% phosphate-buffered osmium tetroxide.[18] Following dehydration in a graded series of ethyl alcohol, the tissues were embedded in DER 332.[11] Ultrathin sections were cut on LKB Ultratome III or Porter-Blum MT-II microtomes, stained with uranyl acetate and/or lead citrate, and examined with an RCA EMU 3G electron microscope.

Results

Normal (Donor) Glomerulus

The structure of the normal human glomerulus was studied in five instances. The majority of the ultrastructural features were similar to published descriptions.[1,4,10,21] In these 5 patients (E.B., W.C., R.C., J.L., and V.M.) the endothelium was normal with no thickening, distinct, regular pores, and no arcades; the basement membranes were normal showing regular thickness (2900–3500 Å) and no densities; podocytes showed distinct pedicels with no fusion; inflammatory cells were normal, there were no polymorphonuclear leukocytes, and no fibrin; and only Patient J.L. showed a trace of debris in the Bowman's space.

The endothelial cells lined the capillary lumen as a very attenuated layer in most areas (Fig 1). Characteristic pores in the thin, peripheral cytoplasm were regularly present. The endoplasmic reticulum was quite inconspicuous and ribosomes were associated with it or appeared free in the cytoplasmic matrix. The mitochondria were small (about 3000 Å), and were localized in the area of the nucleus, with few parallel cristae invaginating into the mitochondrial matrix. In this same area, a few parallel lamellae and vesicles which represented the Golgi apparatus, were observed.

The basement membrane was a homogenous, regular layer in most areas and measured approximately 3000 Å in width (Fig 1). It appeared to consist of three layers—a denser, wider internal structure (lamina densa), with less dense layers on each of the epithelial and endothelial surfaces (lamina rara interna and externa). These three layers varied only slightly in density or thickness in most of the capillary loops of the donor glomeruli.

The epithelial cells (podocytes) conformed generally to the descriptions of Trump and Benditt.[21] However, in some areas the cisternae of the endoplasmic reticulum appeared more vesicular and dilated than

was previously reported. Also, finely granular, cytoplasmic condensations were apparent in many of the pedicels, especially in the juxtabasement membrane area. The foot processes were distinct (Fig 1) and frequently invaginated into the less dense lamina on the epithelial surface of the basement membrane. Fat droplets and multivesicular bodies were rare.

"Debris," consisting of desquamated cells and large membrane-limited inclusion bodies, was present within Bowman's space in 1 patient (J.L.). Various cellular organelles were described within the limiting membrane—normal-appearing and degenerating mitochondria, rough and smooth endoplasmic reticulum, and cytosomes. The number of organelles varied considerably, but in most glomeruli there were infrequent cellular particles and inclusion bodies within the urinary space. Capillary inclusions—polymorphonuclear leukocytes, desquamated cells —were infrequently observed.

One-hr Biopsy

Profound endothelial alterations were observed in the 1-hour biopsies from those cases which developed renal malfunction (Table 1). The ultrastructural changes appeared to be similar in most cases. Hypertrophy and hyperplasia of the endothelial cells were noted frequently. This often took the form of cytoplasmic arcades which were much more complex and voluminous than those observed in normal (donor) human renal tissue (Fig 6 and 7); endothelial pores were noticeably absent in most areas. Frequently the endothelial cells and complex processes appeared to occlude the capillary lumen. The hypertrophied endothelial cells often exhibited an enlargement and dilatation of the rough endoplasmic reticulum and an increase in free ribosomes (Fig 5). When considering the 9 cases of early rejection, the endothelium appeared normal in only 1 patient (J.L.). The glomeruler endothelium of the 1-hr biopsies from the 10 patients which demonstrated prompt renal function and continued to maintain normal function 2–37 months following transplantation was usually similar to normal human glomerular endothelium (Fig 3), (Table 1). In a few cases, minimal thickening of the endothelium and a decrease in the number of pores were observed (Fig 2 and 4).

The basement membrane appeared much more variable (3000–20,000 Å) in diameter in 8 of the 9 patients who developed early renal malfunction. This structure contained more endothelial inclusions, and alterations in thickness and density were more frequently noted. In many areas, definite lamina densa and rara could not be discerned due to

Table 1. Ultrastructural changes

Patient	Recipient's disease	Typing	Donor	Endothelium	Basement membrane	Podocytes	Inflammatory cells, fibrin	Bowman's Space
Patients with excellent early and late clinical course								
E.B.	Chronic nephritis	A	Cad	±, minimal thickening	±, minimal change in thickness and density	0, as normal	0	+, debris
F.C.	Pyelonephritis	A	RLD	0	0	0	0	0
W.C.	Chronic glomerulonephritis	B	RLD	±	0	0	0	debris
R.C.	Chronic pyelonephritis	C	RLD	0	0	0	few PMN's	0
C.J.	Renal failure, result of toxemia of pregnancy	A	Cad	±	±	0	few PMN's	debris
V.M.	Pyelonephritis	C	RLD	±	0	±, minimal fusion	few PMN's	debris
N.Mc.	Bilateral glomerulonephritis	—	RLD	±	0	0	0	0
R.M.	Chronic pyelonephritis	A	RLD	±	0	0	0	debris
C.O'B.	Glomerulonephritis, pyelonephritis	—	RLD	+	±	0	0	0
P.W.	Chronic glomerulonephritis	—	RLD	0	0	0	0	0
Patients with early rejection*								
W.D.	Pyelonephritis, hydronephrosis, nephrocalcinosis	—	Cad	+++, arcades, thickened, few pores	++, irregular in thickness	0	PMN's	debris
S.G.	Pyelonephritis, nephrocalcinosis	—	Cad	+++	+++	++, fusion of pedicels	PMN's, fibrin	debris
W.J.	Chronic pyelonephritis	D	RLD	+++	++	+	PMN's	debris
N.K.	Glomerulonephritis, chronic pyelonephritis	—	RLD	+++	+++	++	PMN's	0
J.L.	Chronic pyelonephritis	C	RLD	0	0	±	few PMN's	debris
E.Mc.	Polycystic kidney disease	—	Cad	++	++	+	few PMN's	0
C.R.	Pyelonephritis	—	RLD	++	+	0	0	debris
S.S.	Glomerulonephritis	C	RLD	++	++	+	0	debris
C.S.	Pyelonephritis, hydronephrosis	—	Cad	+++	+++	++	PMN's, fibrin	debris

* Serum creatinine less than 1.5 mg % in 2 days; no rejection crisis in first 2 weeks; kidney still functional 2–37 months after transplantation.

0, normal, no change; Cad, cadaver; +++, max change; RLD, related living donor; ++, lymphocyte antigen typing; based on results obtained from testing with 84 antisera; A, less than 5% major mismatches; B, more than 5% major mismatches but no definite units of major group mismatches; C, 1 unit major group mismatch with less than 25% major mismatches; D+, 1½ major group mismatched with less than 25% major mismatches; D, 2 units major group mismatches or more than 25% major mismatches.

what appeared to be a markedly thickened and/or edematous basement membrane (Fig 7). Neither discrete subendothelial nor subepithelial densities were present. However, irregular granular inclusions, varying in size, density, and location were observed in the basement membrane of some glomeruli (Fig 9 and 10). The ultrastructural changes in the basement membrane were observed in the same cases which exhibited changes of the endothelium and which were discussed previously (Table 1). Only in patient J.L., where no significant endothelial changes were observed, was the basement membrane also normal. The glomerular basement membrane usually appeared normal in the 10 patients who exhibited prompt functioning and continued to maintain their first transplant (Fig. 3, Table 1).

The pedicels appeared broad and confluent more frequently in those cases which developed renal malfunction (Fig 6, 7, Table 1). The rough and smooth endoplasmic reticulum of the podocytes in many glomeruli was also more vesicular (Fig 5), and the ribosomes were increased in number in these same 9 cases. Cytoplasmic condensations, observed primarily in the pedicels, were similar to normal renal tissue. The podocytes, organelles, and foot processes usually appeared normal in the 10 cases which demonstrated an excellent early and late clinical course (Table 1). Large, membrane-limited, inclusion bodies or remnants of desquamated cells (Fig 2), similar to those described in normal tissue, were observed within Bowman's space in 10 of the 19 transplant cases. This material often literally occluded this space and was more pronounced than in the normal renal tissue. When considering the amount and morphology of the debris in Bowman's space, no significant differences could be ascertained between the 9 patients who developed renal malfunction and the 10 who did not. However, the debris was noted more in cases which developed malfunction.

Polymorphonuclear leukocytes were observed more frequently in the 1-hr biopsies than in normal renal tissue, often to the extent of near occlusion of the capillary lumen. The spatial arrangement between leukocytes and endothelial cells was of varying degree—from close approximation of the cytoplasmic processes to what appeared to be cytoplasmic continuity between the two cell types. Certainly this adherence of the leukocyte to the endothelial cell was most intimate in those areas of endothelial arcading (Fig 7). The leukocytes were more frequently observed in biopsies from those patients which developed renal malfunction (W.D., S.G., W.J., N.K., J.L., E.Mc., C.S.) (Fig 8) as compared to the biopsies from patients which had functioned normally (R.C., N.Mc., W.M.) where "few PMN's" were reported.

It is interesting to note in this respect that 6 of 7 patients (Table 1) that developed early problems and exhibited leukocytes within their glomerular-capillary loops, had as their primary disease, pyelonephritis. Two of 5 patients who had pyelonephritis and whose grafts functioned satisfactorily, also displayed polymorphonuclear leukocytes in their grafts.

The clinical significance of the above, however, is not clear since there is a considerable amount of difficulty in the diagnosis of primary disease at the terminal stage of renal disease, and the number of cases is relatively small. All patients at the time of transplantation are free from infection, have undergone hemodialysis, and are being treated with Imuran and prednisone. Fibrin was observed in only 2 patients (S.G., C.S.); the former represented hyperacute rejection, the latter was transiently anuric, with renal functions within normal limits 5 days post-transplantation (Fig 8).

The results are summarized in Table 1. As noted, six kidneys were cadaveric in source, and 13 were from related living donors. No consistent, significant, cytological differences were noted when only the source of renal transplant was considered.

Discussion

When a kidney is transplanted in man, it would seem reasonable to assume that there must be immediate effects imposed upon the donor renal tissue as a result of the new recipient environment. The ultrastructural changes which may result from this new environment have not been described in early human renal biopsies (1 hr), nor been correlated with a future clinical course of the patient. Porter[16,17] described ultrastructural changes in renal allografts 1¾–2½ years after transplantation. He reported broadening of the pedicels, hypertrophy and hyperplasia of the endothelial cells, an increase in the mesangial matrix and subendothelial densities in these biopsies which were removed months following transplantation. This same investigator[17] associated the amorphous basement membrane densities with incompatibility of host and donor, and suggested that this material may be the deposition of circulating antibodies. An interesting point was that many of these same ultrastructural changes reported by Porter[16,17] were found in the 1-hr biopsies in our series.

The etiology of the glomerular alterations is not clear; however, circulating antibodies may be responsible for these early changes. At this point it is not possible to state the precise nature nor derivation of these antibodies, but they may be a result of the host's original renal disease

(antimembrane antibodies), a new reaction of the host to the graft, or perhaps some other specific or nonspecific process(es). Experiments are in progress in our laboratories to elucidate the above points. Antibodies already present within the host at the time of transplantation and that react with the graft are probably most likely responsible for any early immunologic response in the newly transplanted kidney.

Alterations of the endothelium were observed in 8 of the 9 transplants which developed early renal problems: rejection crises in the first week, acute tubular necrosis, or serum creatinine greater than 1.5 mg % at 2 days. These changes were marked and consisted of endothelial hypertrophy and hyperplasia as well as changes in the cytoplasmic organelles. It would seem unlikely that the cytoarchitectural alterations were due to surgical technique, agonal changes, or perfusion, since the transplants which demonstrated excellent early and late function with minimal to no endothelial changes were treated in the same manner as the transplants which developed early malfunction with endothelial alterations. In only 1 patient (J.L.) did the electron microscopic changes fail to correlate roughly with the clinical course of the patient. In this instance, the creatinine did not return to less than 1.5 mg % until 73 days post-transplantation, and rejection crises were questionable.

Marked variations in density and thickness of the glomerular basement membrane were observed in the same 8 patients who demonstrated endothelial alterations and early renal malfunction. In these cases, the lamina densa and rara appeared voluminous, irregular in contour, and quite edematous in many areas of the glomeruli. The changes usually affected the lamina densa and lamina rara interna more so than the lamina rara externa. As a result, it was frequently difficult to discern the three layers of the basement membrane. Discrete amorphous or granular densities, as described by Porter *et al*,[16,17] were not observed within the basement membrane with any degree of consistency. Infrequently, rather diffuse bodies were apparent within the basement membrane; however, most of these were similar in density and structure to the lamina densa, and in these cases, probably represented fragments of this structure which had become disseminated or altered in cytoarchitectural detail. Basement membrane changes were minimal or were reported as being similar to normal donor kidney in the 10 patients which demonstrated excellent function. Since these transplants were treated identically to the 9 transplants which demonstrated renal malfunction, it would appear that these alterations are not due to technique or to agonal changes, but instead, are due to the new recipient environment of the transplant.

Electron microscopic changes in the endoplasmic reticulum and pedicels of the podocytes were demonstrated also in the majority of cases whose kidney transplants developed early malfunction. The dilatation of the smooth and rough endoplasmic reticulum may represent a nonspecific cytologic alteration; however, the increase in the number of ribosomes is probably indicative of a modification in protein metabolism and synthesis and of a response to this alteration in environment. The remnants of cells, inclusions, or debris which often filled Bowman's space in the 1-hr biopsies probably represent desquamated segments of the podocytes, or portions of the epithelial cells lining the proximal convoluted tubules. Certainly, spatial approximation between extended cytoplasmic processes of the podocyte and desquamated cells was noted. However, the mitochondria and endoplasmic reticulum within these remnants and inclusions closely resembled those observed within the cytoplasm of the cells of the proximal convoluted tubules.

In the majority of previous investigations involving human and canine renal transplantation and chronic rejection crises, the plasma cell and lymphocyte have been the most commonly described and implicated cell types.[5,16,17] In our experience with 1-hr biopsies, the polymorphonuclear leukocytes were the most numerous infiltrative cellular type, and were observed more frequently in those cases which demonstrated early renal malfunction. Only a few plasma cells, lymphocytes, and platelets were observed. There may be a close adherence between the PMN and the glomerular endothelial cell, much like Kountz *et al*[9] described between the plasma and the endothelial cell in the peritubular capillaries of the dog. It would appear that the polymorphonuclear cell is important in glomerular cytological alterations found in human renal transplantation.

Fibrin was observed in only 2 patients, both of whom developed early malfunction of the transplant: S. G. represented hyperacute rejection, whereas C. S. was anuric for 5 days, but following that time, demonstrated excellent renal function. It would be difficult to attach any significance to the presence of fibrin in these 2 cases. Certainly no fibrin was observed in the transplants which functioned well from the beginning; however, there were cases similar to that of C. S. where fibrin was not observed.

As noted in Table 1, it would appear that the source of the donor (cadaveric or related living donor) could not be consistently nor significantly correlated with the ultrastructural changes in the 1-hr biopsies. We are confident in assuming that the ultrastructural changes between the two groups, the 10 patients with excellent early and late clinical

course, and the 9 patients who demonstrated early rejection, are not due to agonal changes nor to technique, since all transplants and biopsies were treated similarly. Therefore, it must be assumed that the kidney transplant in man does react to its early recipient environment and demonstrates ultrastructural glomerular changes in those patients with early renal malfunction (acute tubular necrosis, early rejection, or creatinine greater than 1.5 mg% at 2 days). It is hoped that by studying the serial biopsies of these patients and by correlating the electron microscopic changes with the clinical course of the patient, this specific environmental influence(s) of the recipient on the donor kidney may be elucidated.[19]

Summary

Cytoarchitectural details in glomeruli were observed in 19 kidney biopsies taken 1 hr after transplantation. Bowman's space frequently contained large inclusion bodies. Polymorphonuclear leukocytes were seen in capillary loops in areas where the endothelium was thickened and formed complex processes. The basement membrane was irregular in thickness and contained densities of unknown significance. Fibrin was observed in two biopsies; one kidney never functioned and the other failed to function transiently. The severity of glomerular changes correlated roughly with the future renal function of the graft, suggesting that factors operating acutely in the donor or in the recipient are of greater importance than generally acknowledged.

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[*Illustrations follow*]

Legends For Figures

Key:

BM	Basement membrane	N	Nucleus
BS	Bowman's space	P	Podocyte
C	Cytosome	PED	Pedicel
CL, L	Capillary loop, lumen	PMN	Polymorphonuclear leukocyte
D	Desquamated cell	PO	Endothelial pore
E, END	Endothelium	RBC	Erythrocyte
F	Fibrin	RER, SER	Endoplasmic reticulum
M	Mitochondria		

Fig 1. *(upper)* V. M. Normal donor kidney. Portion of capillary loop lined by attenuated layer of endothelium, with pores *(arrows)*. In most areas, basement membrane is approximately 3000Å in thickness. Pedicels of podocyte are distinct and nonfused. × 9800.

Fig 2. *(lower)* V. M. One-hr biopsy. Patient had excellent early and late clinical course. Basement membrane is uniform in thickness in most areas and quite similar to normal. Endothelium is also similar to normal, with few areas of thickening. Pedicels are distinct and Bowman's space contains many inclusion bodies and/or desquamated cells. × 6750.

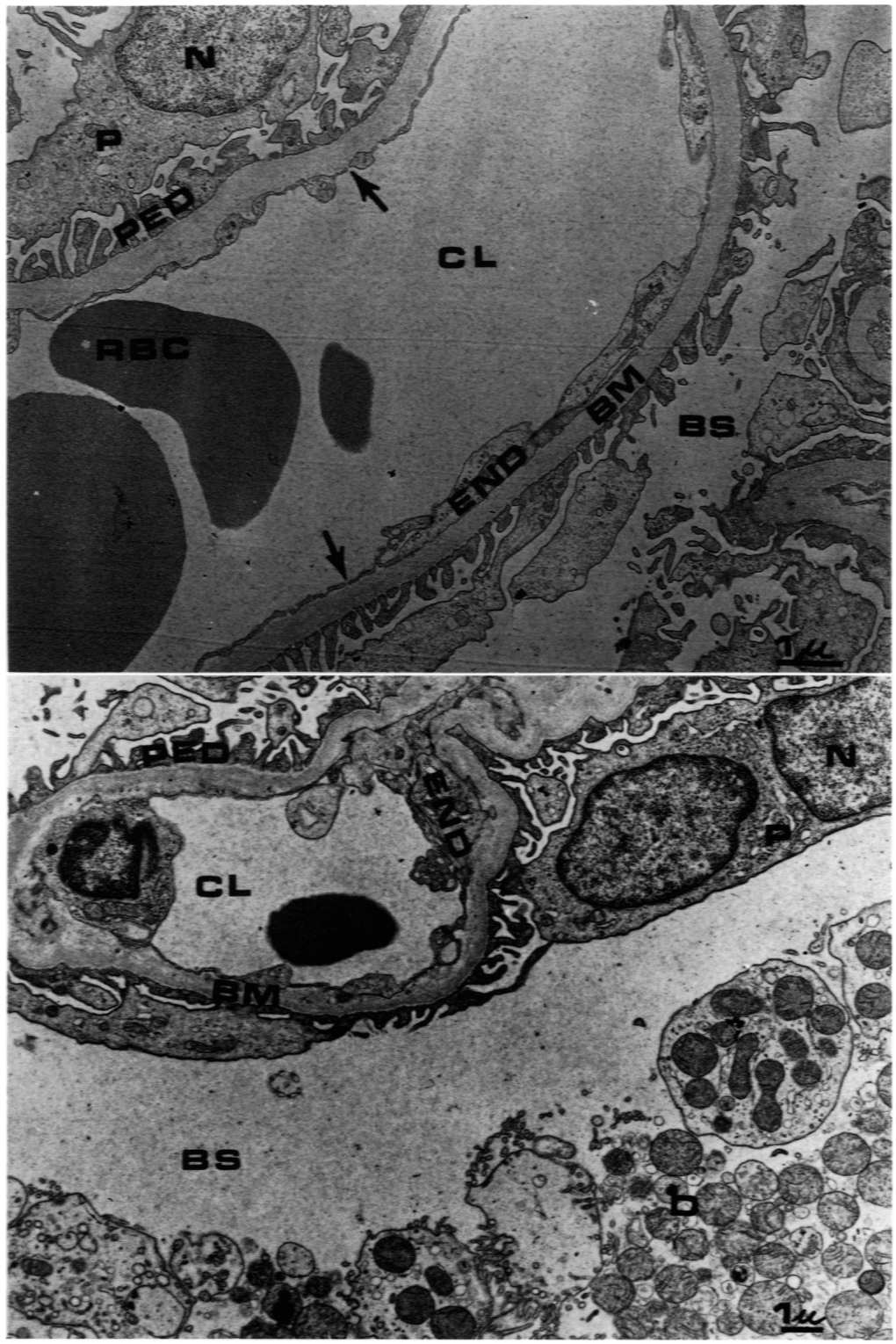
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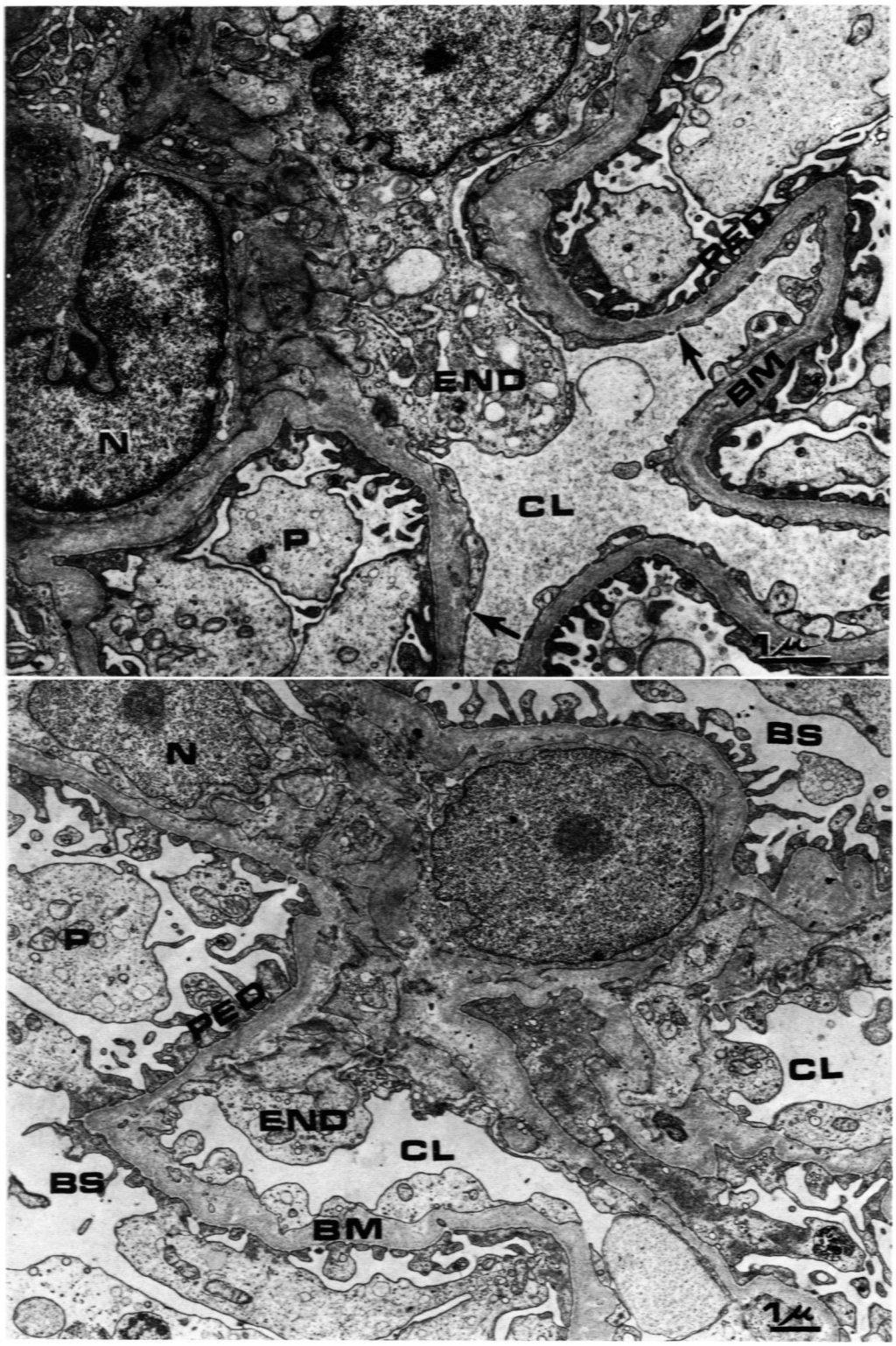
Fig 3. *(upper).* R. C. One-hr biopsy. Patient had excellent early and late clinical course. Basement membrane appears similar to normal (Fig 1) with few areas of thickening and variations in density. Endothelium lines capillary lumen as attenuated layer in which pores *(arrows)* are present. Pedicels of podocytes are nonfused and evident. × 9800.

Fig 4. *(lower)* R. M. One-hr biopsy. Patient with excellent early and late clinical course illustrating minimal ultrastructural changes. Basement membrane is more variable in thickness and density, but probably within normal limits. There is no profound arcading of endothelium, although pores are not distinct in this area. Pedicels of podocyte are not fused and are distinct. × 6500.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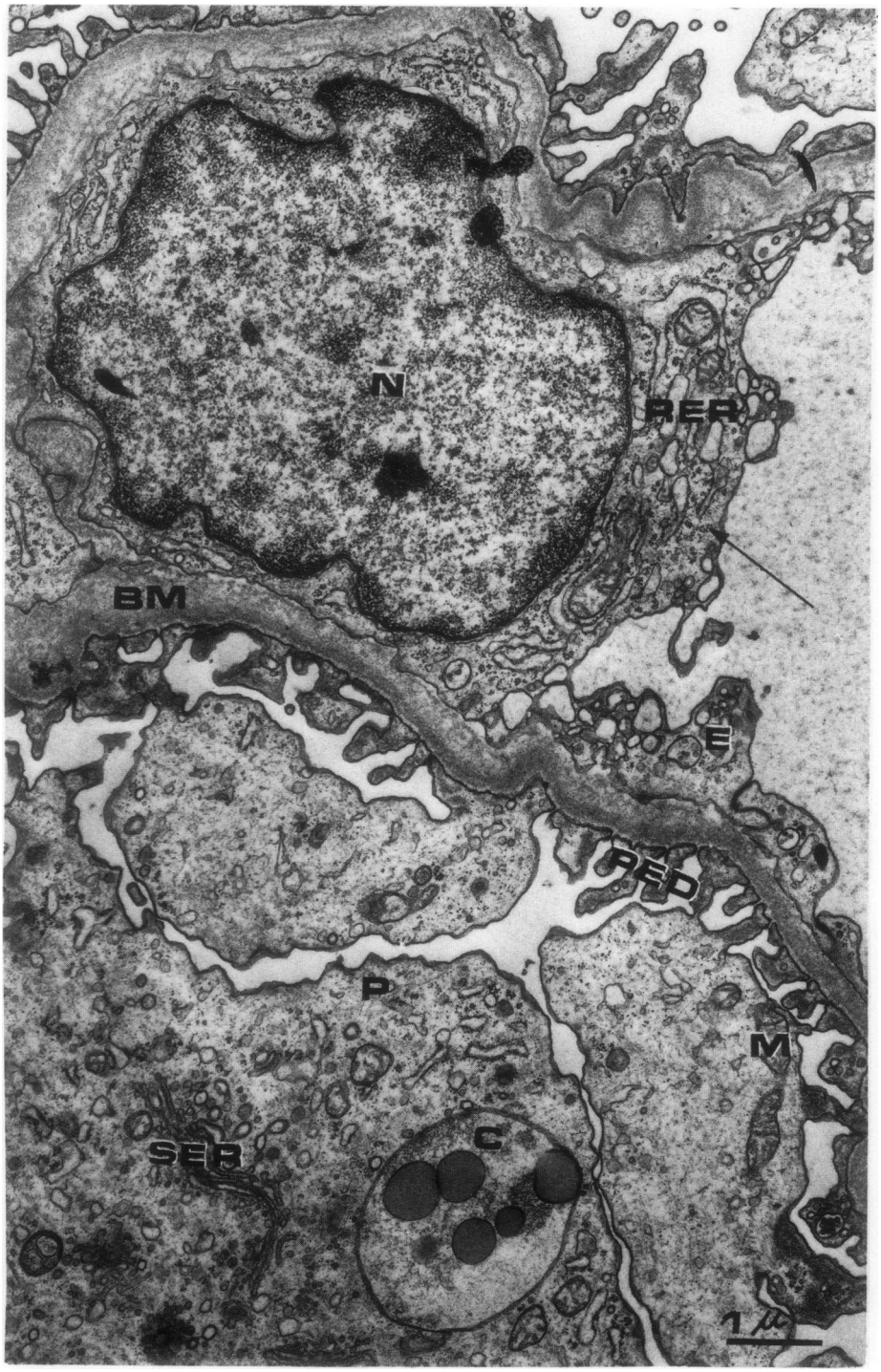

Fig 5. W. J. One-hr biopsy. Patient with early rejection. Lamina rara interna of basement membrane is wider than normal. Dilatation and vesiculation of endoplasmic reticulum of podocyte and endothelial cell are apparent. Increase in free ribosomes *(arrow)* is also demonstrated. × 14,700.

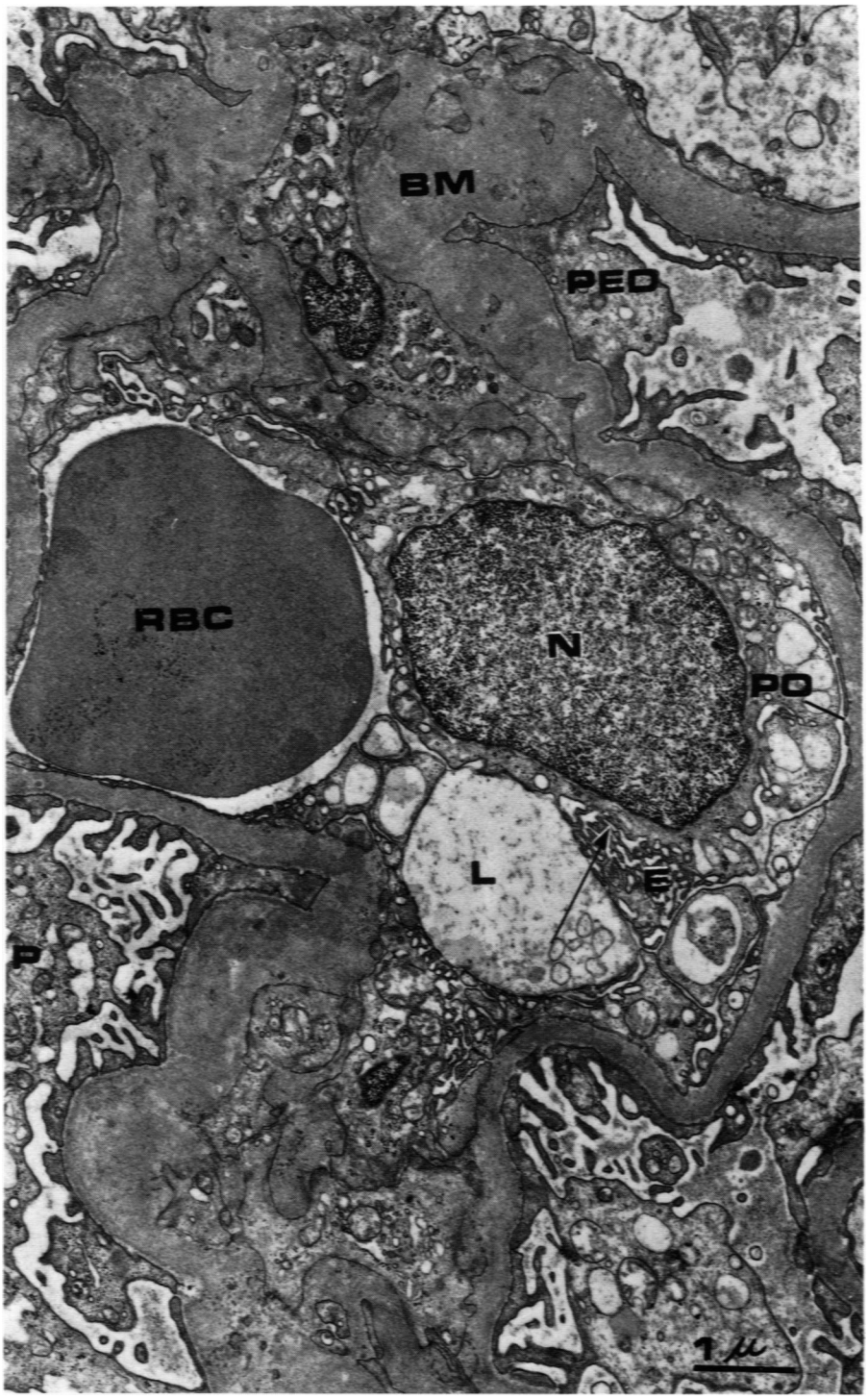

Fig 6. N. K. One-hr biopsy. Patient with early rejection. Hyperthrophied endothelium with arcading *(arrow)* partially occludes capillary lumen. There is considerable variation in density and thickness of basement membrane. Erythrocyte is present. Notice fusion of pedicels. × 13,000.

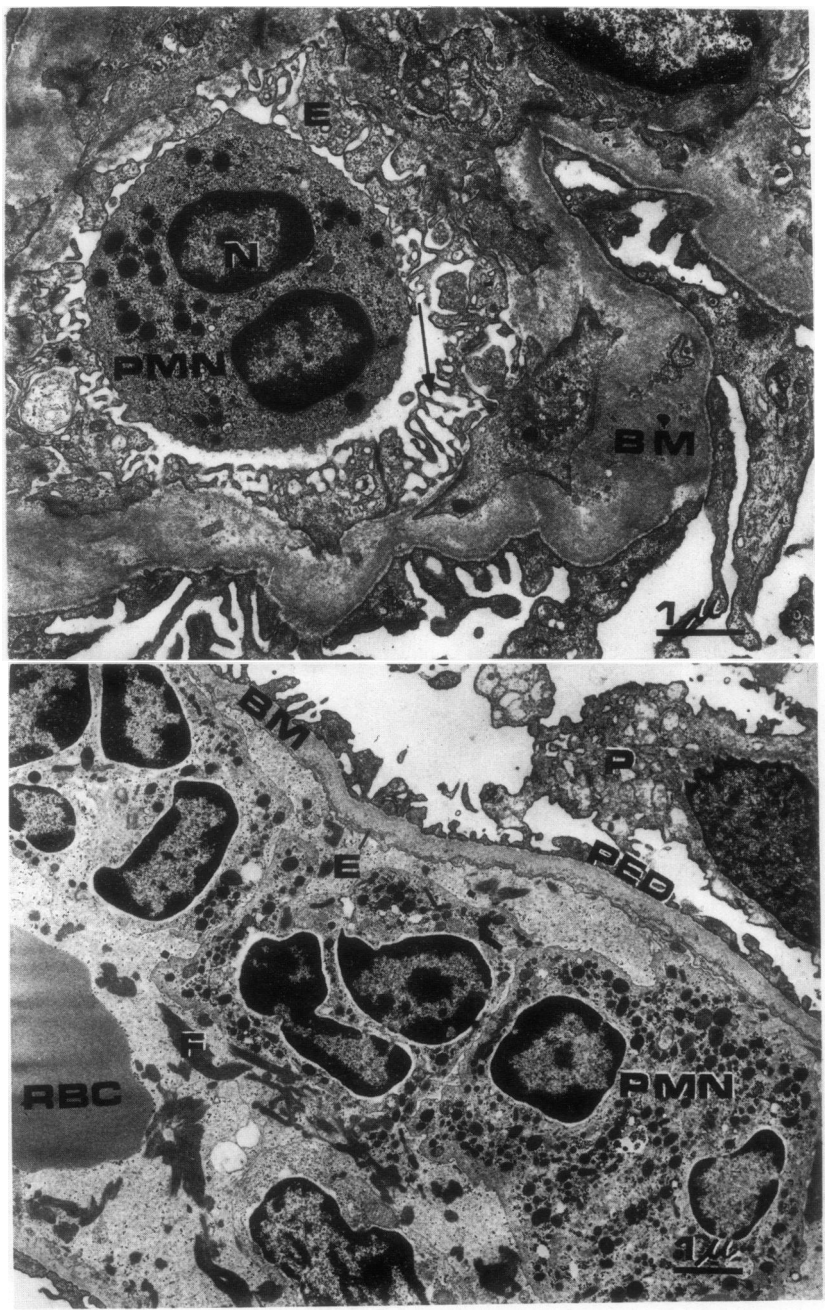

Fig 7. *(upper)* N. K. One-hr biopsy. Patient with early rejection. Glomerular loop contains polymorphonuclear leukocyte. Notice thickening of endothelium, its arcading *(arrow)* and obliteration of pores. Basement membrane exhibits irregularities in thickness and density. Variable proximity of leukocyte to endothelium is well illustrated. × 11,700.

Fig 8. *(lower)* S. G. One-hr biopsy. Patient with early rejection. Portion through glomerular capillary loop filled with polymorphonuclear leukocytes, fibrin, and erythrocyte. Endothelium and basement membrane appear normal in this area. Fusion of pedicels should be noted. × 7300.

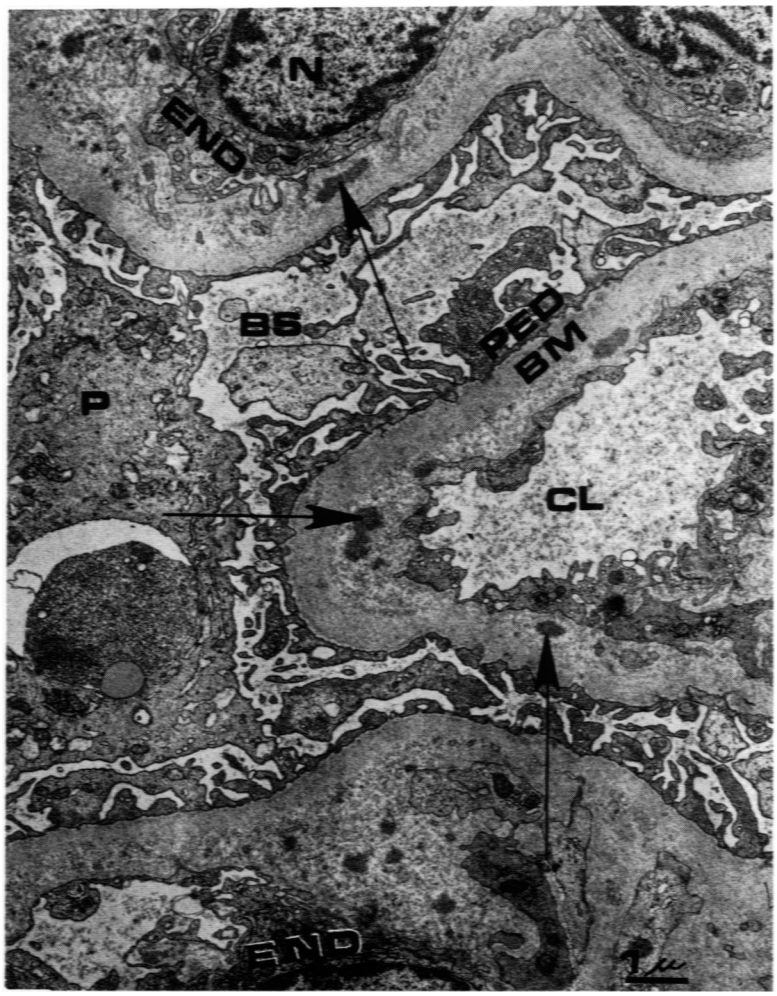

Fig 9. W. J. One-hr biopsy. Patient with early rejection. Basement membrane shows variations in thickness and density and granular deposits (*arrows*) can be pointed out. × 8200.

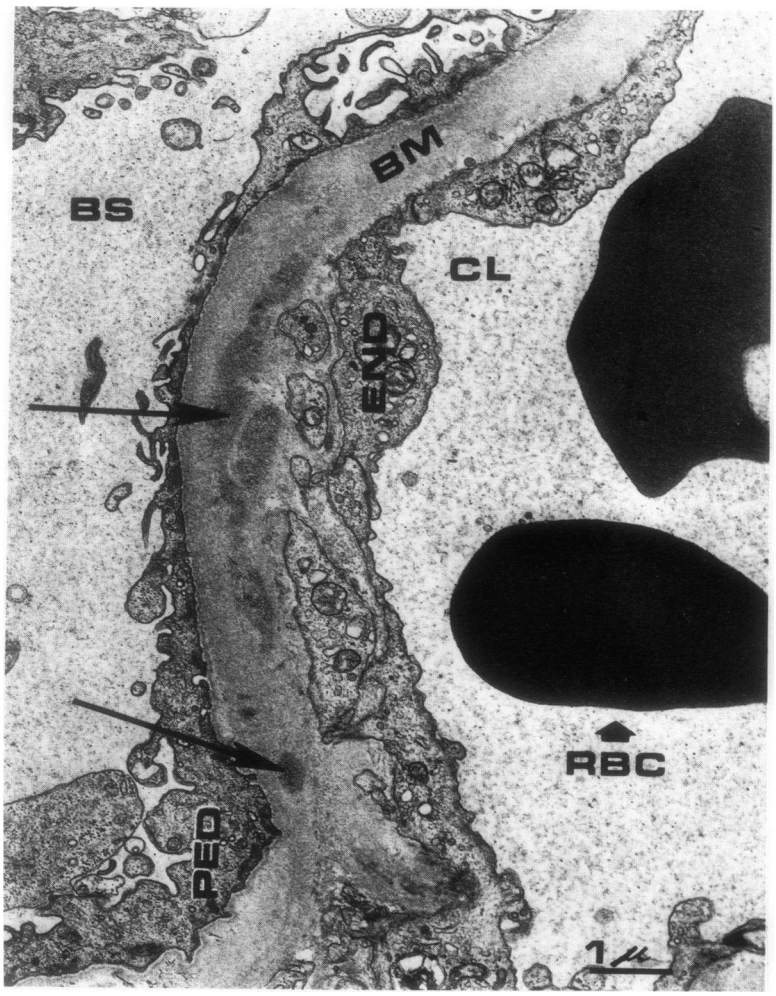

Fig 10. W. J. One-hr biopsy. Patient with early rejection. Basement membrane exhibits deposits *(arrows);* no pores are present due to hyperthrophied endothelium, and red blood cells are present in capillary lumen. Pedicels are fused. × 10,000.