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Evolution of Recurrent Lobular Glomerulonephritis in a Human Kidney Allotransplant

Combined Light-, Immunofluorescence-, and Electron Microscopic Studies of Serial Biopsies

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Summary. Recurrent lobular glomerulonephritis in an allotransplanted kidney was studied by light microscopy, immunofluorescent techniques and electron microscopy. Three successive biopsies of the graft and the nephrectomy of the transplant were performed. The histological and clinical evolution of the lobular glomerulonephritis of the graft paralleled that of the lobular glomerulonephritis of the donor kidney. The clinical evolution of the recurrent lobular glomerulonephritis in the grafted kidney of the recipient was comparable to that of the original lobular glomerulonephritis, of the recipient's own kidney. Serial biopsies showed that immunoglobulin deposits appeared prior to cellular proliferation. This observation is consistent with the hypothesis that immune complexes have a primary role in the pathogenesis of human glomerulonephritis.

Recurrent glomerulonephritis may be a major cause of transplant failure, if immunosuppressive therapy is withhøeld from patients receiving transplants from identical twins (Glassock *et al.*, 1968; Merril, 1969; Merrill, 1971). In renal allografts glomerular lesions may result either from chronic rejection (Hamburger *et al.*, 1965; Porter *et al.*, 1967; Hamburger *et al.*, 1968) or from recurrence of the patients original disease (Merrill, 1971). Also, a "de novo" glomerulonephritis has been reported in a renal allograft (Merrill, 1971).

Lobular glomerulonephritis is the rarest form of diffuse glomerular disease (Habib, 1970), and its very characteristic histological pattern is particulary useful for studying the question of the recurrence of glomerulonephritis. Four cases of recurrent lobular glomerulonephritis have been reported with a histological pattern similar to that of the patient's original glomerulonphritis and with a rapid evolution toward renal insufficiency (Hamburger *et al.*, 1964; Porter *et al.*, 1968; Rowlands *et al.*, 1970; Rossmann *et al.*, 1970).

The present paper describes a fifth case of recurrent lobular glomerulonephritis in which serial biopsies allowed study of the natural history of the disease from the very beginning to the ultimate destruction of the allografted kidney.

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Material and Methods

Histopathology. Specimens were obtained from the host's own kidney, from the three subsequent biopsies of the graft, and from the nephrectomized graft, and all were prepared for light-, immunofluorescence-, and electron microscopy as outlined below.

Light Microscopy. A portion of each specimen was fixed in 12% formalin or in Duboscq-Brasil solution (biopsies), processed, and embedded in paraffin. Sections cut at 2–3 μ were stained with Masson's trichrome stain, hematoxylin-eosin (H & E), periodic acid Schiff (P.A.S.), periodic acid silver-methenamin (P.A.S.M.) and Weigert's stain for elastic tissue.

Electron Microscopy. Another portion of each biopsy, and a portion of the nephrectomized graft were cut into 1-mm fragments, fixed for 30 min in 1% osmium tetroxide, buffered with 0.1 M sodium potassium phosphate, followed by fixation for 2 h in 3% glutaraldehyde buffered with 0.1 M sodium potassium phosphate. These were then postfixed for 1 h in 1% osmium tetroxide and, finally, embedded in Epon 812. Ultrathin sections were cut on a Reichert ultramicrotome and stained with either uranyl acetate or uranyl acetate and lead citrate. These specimens were examined and photographed using a Philips EM 200 electron microscope. In addition ultrathin sections were impregnated with a solution of silver-methenamin after periodic oxidation (Movat, 1961). Some of these sections were also mounted on glass slides for examination with a light microscope.

Immunofluorescence Microscopy. A third portion of each biopsy was rapidly frozen in a solution of isopentane cooled with liquid nitrogen. Sections from these blocks were cut in a cryostat microtome at 3 μ, picked up on glass slides, and fixed by immersion in acetone for 15 min. Antisera were then applied for 30 min and slides were washed three times in phosphate buffered saline at pH 7.2, as described elsewhere (Berger, 1971). The following sera were utilized: Goat anti-human IgG, IgA, IgM, β 1 C globulin, and albumin, and rabbit anti-human fibrin. All sera were obtained from the Hyland Laboratories, Los Angeles. Both immunoelectrophoresis and double diffusion showed these to be strong and specific.

Observations and photographs were made with a Leitz Ortholux microscope using an HBO-200 W mercury light source.

List of abbreviations used in the figures. *B* Basement membrane, *C* Capillary lumen, *D* Electron dense deposits, *Ec* Endothelial cell, *Ep* Epithelial cell, *Mc* Mesangial cell, *Ma* Mesangial area (intercapillary space), *Mm* Mesangial matrix, *H* Hump, *R* Red blood cell, *U* Urinary space, *W* White blood cell.

Clinical Observation

A male patient, Guy F., born in 1943, was admitted in February 1968 for kidney transplantation to the Department of Nephrology of the Necker Hospital (Prof. J. Hamburger). Proteinuria was first discovered in 1959 during a routine medical examination, but arterial hypertension, renal failure and edema were absent at that time. In 1961, an increase in proteinuria to more than 2.5 g/24 h was observed along with signs of nephrotic syndrome and microscopic hematuria. Arterial hypertension and chronic renal failure occurred in 1965. In August 1967 the blood pressure was 220/120 mm Hg and total blood urea was above 350 mg/100 ml. After peritoneal dialysis the patient was discharged from the hospital with a low protein, low sodium diet, and with the anti-hypertensive drugs Alpha-Methyl-Dopa and Guanethidine. Two additional peritoneal dialyses were done in December 1967 and February 1968.

When hospitalized, on February 20, 1968, the patient was 167 cm tall and weighed 67 kg. The blood pressure was 220/120 mm Hg, and he had palpebral edema without edema of the lower limbs. Physical signs of peripheral cardiac failure were absent, but the electrocardiogram revealed a left ventricular hypertrophy. Fundoscopic examination showed bilateral papillary edema, multiple hemorrhages and exudates. Urinary output was 1.1 litre/24 h, microscopic hematuria 65000 R.B.C/min, proteinuria 2.9 g/24 h, and urinary urea output 6.95 g/24 h.

The first hemodialysis on February 26, 1968, was followed by six additional hemodialyses prior to the renal transplantation on march 21, 1968. The recipient received 4 mg/kg body weight of azathioprine per day for one week in preparation for transplantation. At transplantation,

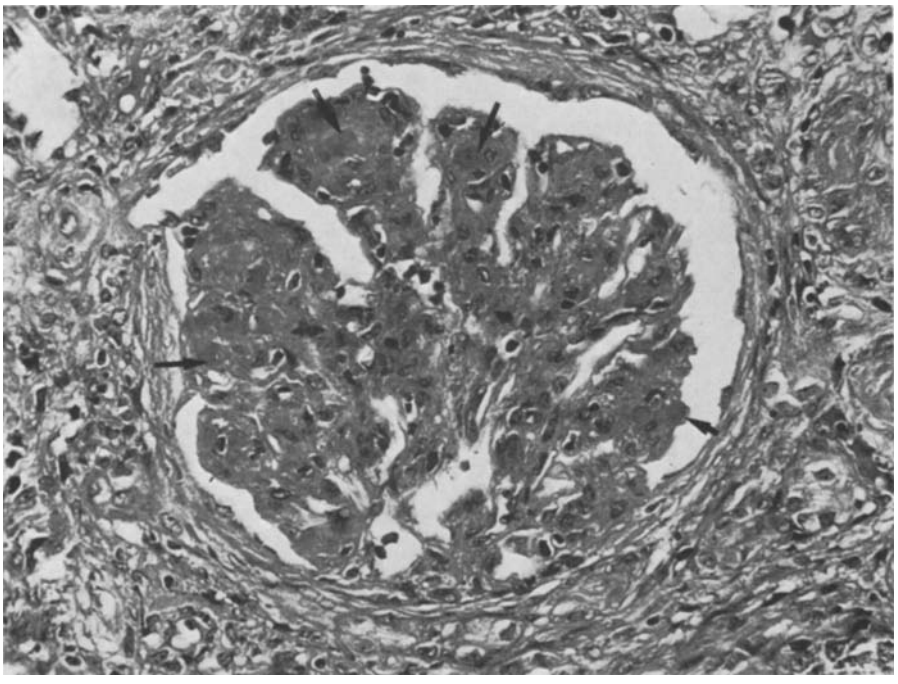


Fig. 1. Host's nephrectomized right kidney. Chronic lobular glomerulonephritis. The tuft is divided into several lobules, each of which is distended by a proliferative central hyaline nodule displacing and obstructing the lumina of the capillary loops toward the periphery of the lobules. There are voluminous areas of fibrinoid material in the centers of proliferation (↗). Light microscopy: Masson Trichrome. ×450

nephrectomy of the right kidney was performed, and the histological examination revealed a chronic lobular glomerulonephritis (Fig. 1).

The donor was the patient's father, Paul F., born in 1916. His creatinine-clearance was 122 ml/min. Compatibility was satisfactory, that is, the blood types of donor and recipient were both 0Rh +, and the only leukocyte antigens identified in donor and recipient, HL-A and Da 15, were identical.

Following the transplantation, the recipient received 3 mg/kg body weight of azathioprine per day. Urin output on day-1 was 5.0 litres and 2.4 litres on day-2.

The plasma-creatinine decreased from 14.7 mg/100 ml to 1.9 mg/100 ml in 48 h.

On day-4, a rejection crisis of average intensity occurred and responded to corticosteroid treatment. Nonetheless, because of the appearance of steroid diabetes, corticosteroid dosage was rapidly reduced. On April 25 (35th postoperative day) a second transplant crisis occurred which again reacted favorably to an increased dose of corticosteroids.

The First Renal Biopsy was done on May 10, 1968, and the patient was discharged on June 4, 1968. On June 25, 1968, three months after transplantation the patients general condition was satisfactory, that is, the creatinine-clearance was 68 ml/min, plasma-creatinine 1.7 mg/100 ml, proteinuria nil, urinary R.B.C output 3600/min, and an intravenous pyelography was normal. The arterial blood pressure at that time was 175/100 mm Hg under treatment with Alpha-Methyl-Dopa and Guanethidine as noted above. This treatment was continued for the rest of his life. On September 4, 1968, four months after transplantation, proteinuria was noted for the first time at 1.5 g/24 h, and a starch gel electrophoresis revealed a selective pattern. Urinary R.B.C. output was 480000 per minute, and creatinine-clearance was 70 ml/min.

On September 24, 1968, due to the persistent selective proteinuria and the microscopic hematuria, *a Second Renal Biopsy was performed.* Observations in the following months were:

1. Elevation of proteinuria to more than 3 g/24 h in November 1968 and to 5 g/24 h in February 1969.
2. Persistence of microscopic hematuria of 200000 and 500000 R.B.C./min.
3. Minimal degradation of renal function with a creatinine-clearance of 66 ml/min in October 1968 and in February 1969.
4. Persistence of arterial hypertension of 170/100 mm Hg to 200/120 mm Hg.

In May 1969, while still receiving azathioprine at 3 mg/kg body weight per day and prednisone at 0.5 mg/kg body weight per day the patient developed edema of the lower limbs and a biological nephrotic syndrome (total serum protein 4.6 g/100 ml, and albumin 2.4 g/100 ml). Creatinine-clearance was 48 ml/min, and hemoglobin was less than 10 g/100 ml.

On June 9, 1969, a Third Renal Biopsy was done. Subsequent evolution was marked by progressive aggravation of renal failure, elevation of proteinuria to 10 g/24 h, accentuation of the nephrotic syndrome, and more severe hypertension and anemia. Immunosuppressive therapy was stopped on April 1, 1970, when the plasma-creatinine reached 11.6 mg/100 ml, and regular hemodialyses were started on April 10. On April 23, 1970, *Nephrectomy of the Transplant* was performed. The patient remained in relatively good health for 15 months after which his blood pressure became quite, elevated and he died after several episodes of generalized convulsions. Permission for post-mortem examination was refused.

Histopathological Observations

First Biopsy

Light Microscopy. The segment was small and contained only four glomeruli, which appeared normal (Fig. 2). A very moderate subcapsular band of interstitial fibrosis with atrophy of the tubules and infiltration by round mononuclear cells was observed. In the rest of the segment the tubules were normal and there was minimal fibro-edema and rare inflammatory monocytes. Arteries and arterioles presented no anomaly.

Immunofluorescence. No fixation of any anti-serum was observed.

Electron Microscopy. Intercapillary spaces appeared normal at lower magnification, $\times 5000$ (Fig. 3). Mesangial cells were normal and were surrounded by membranoid substance of normal thickness. However, at higher magnifications, many small, finely granular areas of high electron density, perhaps corresponding to small deposits of fibrinoid substance, were seen under the basement membrane of the intercapillary spaces (Fig. 4). Capillary walls seemed to be normal morphologically. Basement membranes were regular with normal thickness and density. Their inner surface was covered by the "lamina fenestrata" of the endothelium which was fine and regular and the pores of which showed no anomaly. A discreet fusion of the epithelial foot processes was noted in some capillary loops.

Second Biopsy

Light Microscopy. The biopsy peace contained 25 glomeruli of similar appearance. Intercapillary spaces were slightly enlarged by fibrinoid, acidophilic, refractive and PAS-positive deposits, but with no associated proliferation of mesangial cells (Fig. 5). A basophilic hypertrophy of the podocytes was also observed. The tubules were generally normal except for some localized fatty lesions on the basal part of the epithelial cells. The interstitium was interspersed with small areas of fibro-edema, some of which contained a small number of mononuclear cells. A few arterioles revealed small subendothelial hyaline deposits.

Immunofluorescence. Fixation of IgG, IgM, and β1C globulin antisera were observed on the deposits in the intercapillary spaces.

Electron Microscopy. Intercapillary spaces, at low magnifications, appeared slightly enlarged, and no mesangial cell proliferation was noted. The trabeculae were thicker and longer than normal. Channels of membranoid substance were more abundant than in the first biopsy, and large dense, fine granular areas of fibrinoid substance were found under the basement membrane of the intercapillary spaces. This topography was clearly visible after silver impregnation. Studies of serial sections, 400 ultrathin sections of the same glomerulus,

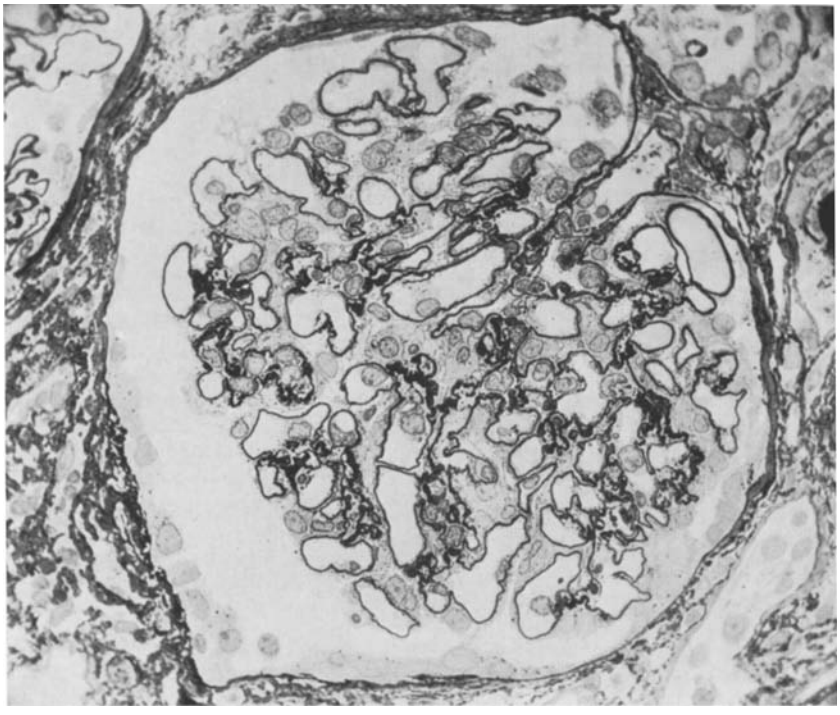


Fig. 2. First biopsy of the transplant, 2 months after transplantation. The glomerulus appeared normal (ultrathin electron microscope section impregnated with silver-methenamin after periodic oxidation, mounted on slide). Light microscopy: ×670

clearly indicated that some of these deposits originated from the intercapillary regions along the basement membranes of the peripheral capillary loops, and became progressively slimmer but still remained in contact with the cytoplasm of mesangial cells (Fig. 6). In these instances, the deposits and the mesangial cytoplasm infiltrated between the basement membrane and the endothelial cells bordering the capillary lumen.

On uranyl acetate and lead impregnated sections, the basement membrane of approximately 50% of the capillary loops seemed moderately thickened, to two to three times the normal thickness. The thickening was localized to the endothelial side, and consisted of material with relatively low electron density. Silver impregnations confirmed the integrity of the membrane. The endothelial cytoplasm covering these subendothelial deposits was slightly thickened, and was associated with a disappearance of the pores and an appearance of small, smooth-sided vesicles. In addition, partial fusion of the epithelial foot processes was noted, which was more extensive than in the first biopsy.

Third Biopsy

Light Microscopy. The biopsy peace contained approximately forty glomeruli, which showed diffuse lesions of the intercapillary spaces and capillary walls. Intercapillary spaces were greatly enlarged by fibrinoid, acidophilic, refractive and PAS-positive deposits, membranoid deposits and by the obvious proliferation of mesangial cells. In six glomeruli this cellular proliferation and membranoid deposits extended over complete lobules, suggesting a lobular aspect (Fig. 7). The walls were segmentally thickened by subendothelial deposits. The tubules showed rather diffuse moderate lesions consisting either of an atrophy of the

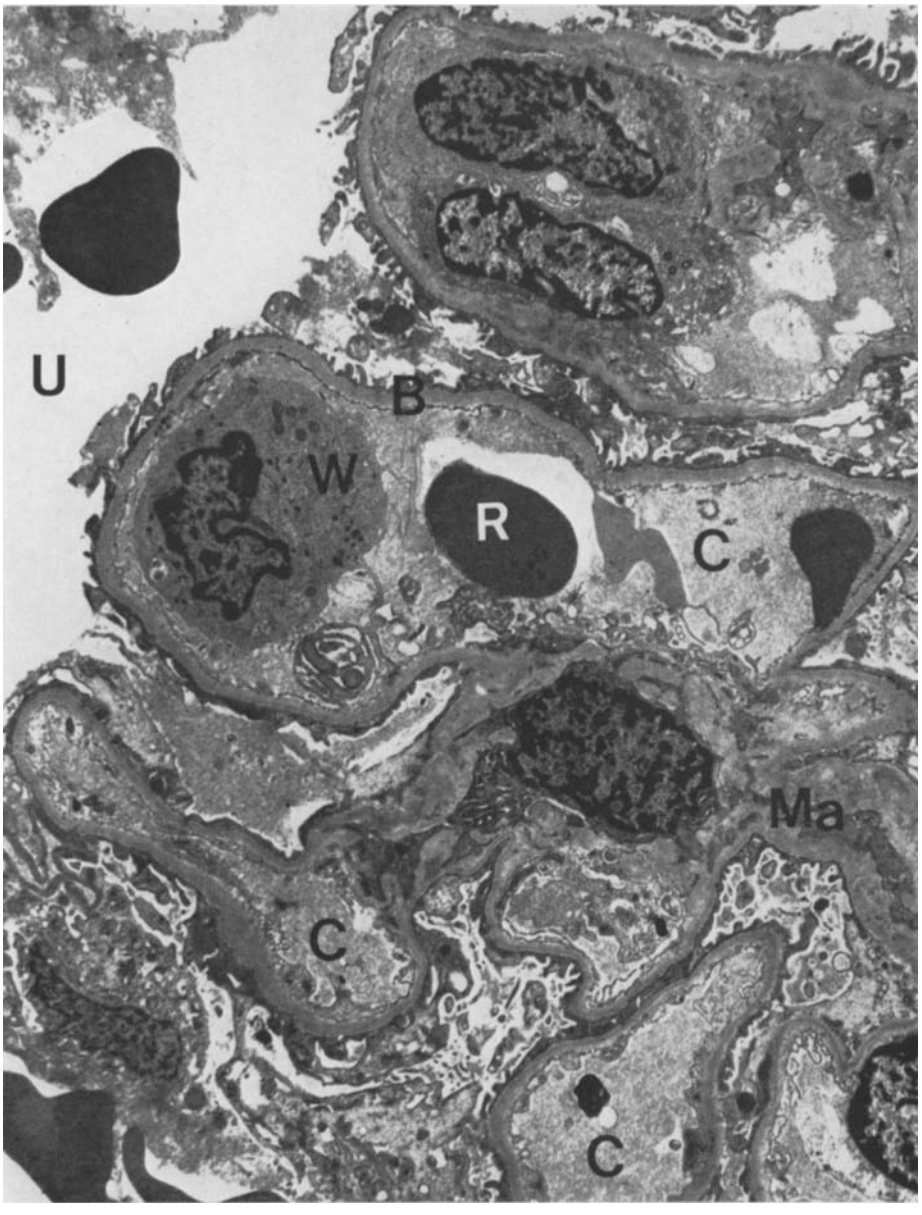


Fig. 3. First biopsy of the transplant, 2 months after transplantation. At this low magnification, the mesangial areas seem normal. The capillary walls are thin; the basement membrane is regular with normal thickness and coated inside by the "lamina fenestrata" of the endothelium. There are several blood cells in the capillary lumina. Electron microscopy: Uranyl acetate and lead citrate. ×4300

epithelium with thickening of the basement membrane or of hyaline droplets in the epithelia cells of the proximal tubules. In the interstitium a moderate irregular fibrosis was noted, but some islets were not affected. Several massive mononuclear infiltrates were observed.

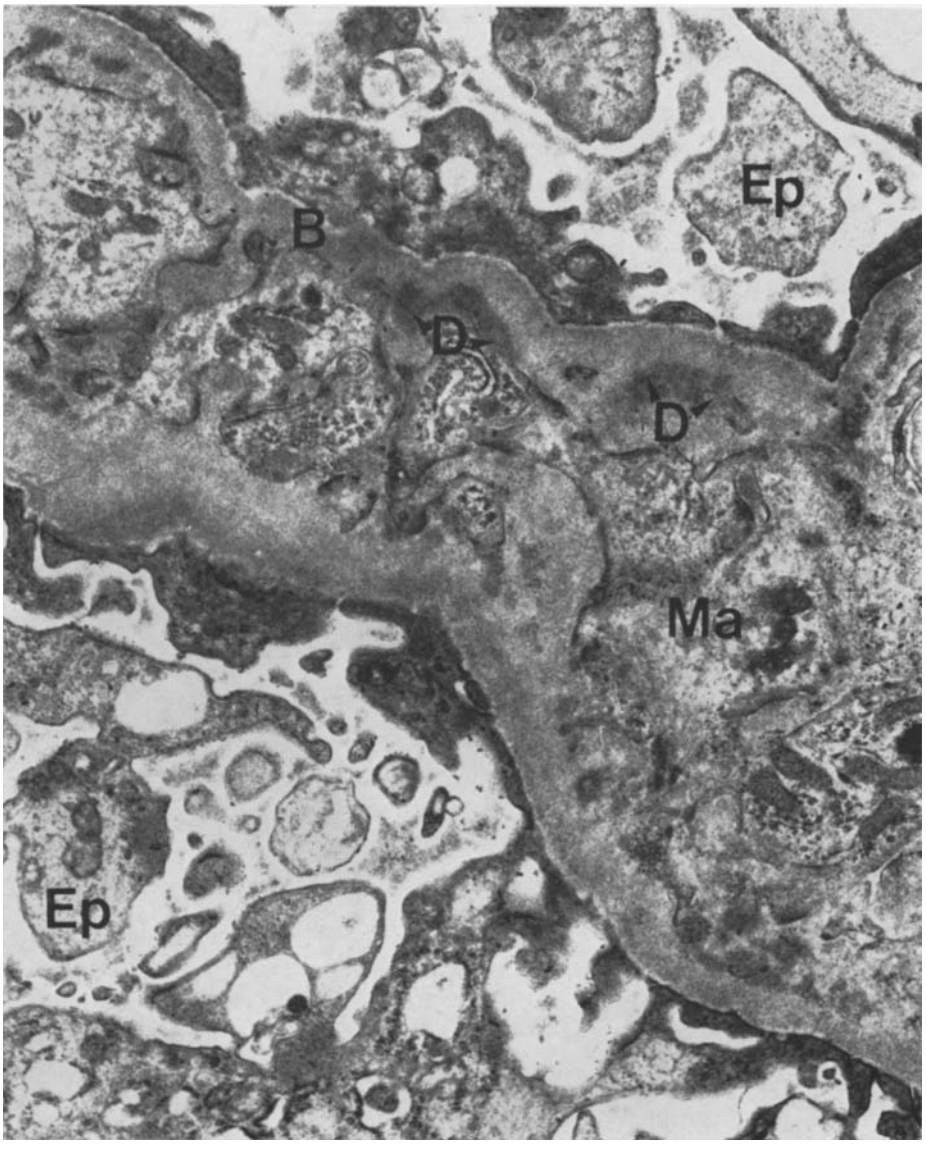


Fig. 4. First biopsy of the transplant, 2 months after transplantation. Detail of a mesangial area showing granular small deposits under the basement membrane. Electron microscopy: Uranyl acetate and lead citrate. ×12760

Many arterioles showed subendothelial hyaline deposits and one interlobular artery had an endarteritis.

Immunofluorescence. IgG, IgM and β1C globulin were found on the deposits of intercapillary and subendothelial topography (Figs. 8 and 9).

Electron Microscopy. Glomeruli examined at low magnification, ×3500, showed mesangial proliferation and an extension of abnormal deposits to most of the peripheral capillary walls (Fig. 10). The proliferated mesangial cells had abundant cytoplasm, which was rich in ergasto-

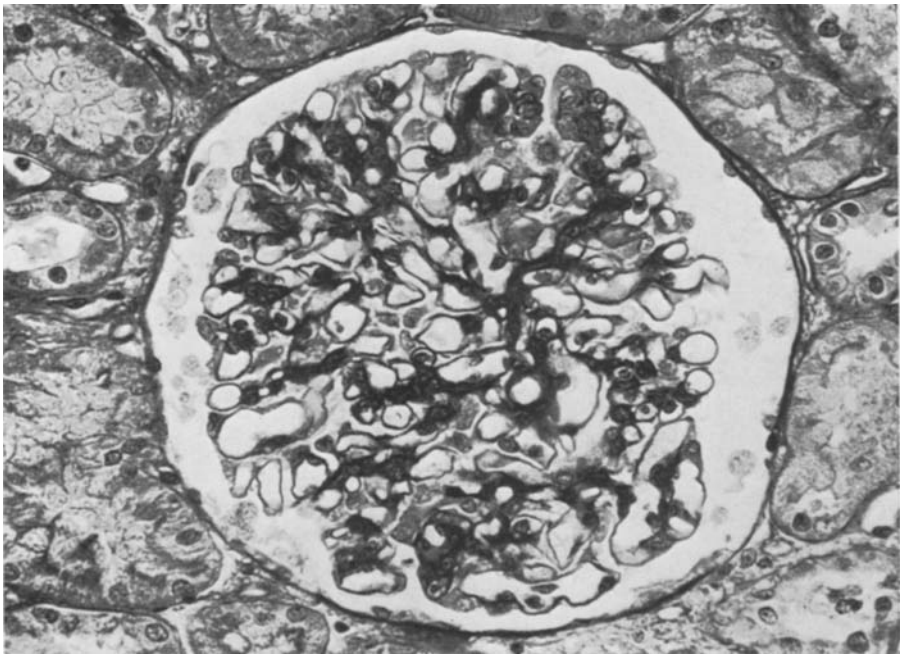


Fig. 5. Second biopsy of the transplant, 6 months after transplantation. The mesangial areas are slightly enlarged by fibrinoid deposits. No mesangial cell proliferation. Capillary walls are normal. Light microscopy: Masson Trichrome. ×450

plasm and mitochondria, and these cells were frequently extended along the capillary walls where they diminished the lumina. These cells were surrounded by abundant archs of membranoid substance which were separated from the capillary lumen by the endothelial cytoplasm. Finely granular, fibrinoid deposits under the basement membranes of the mesangial areas were more abundant than on the preceding biopsy and frequently contiguous to analogous deposits in the peripheral portions of the capillary loops (Fig. 11a). In approximately 80% of the capillary walls the basement membrane examined with uranyl acetate and lead impregnated preparations appeared to be considerably thickened by the deposits on its endothelial side (Fig. 11b). Such deposits were either much clearer than the actual basement membrane, or very dense and finely granular. Silver impregnation showed that the basement membrane was normal and regular. The endothelial cytoplasm was often turgescent and rich in cytoplasmic organelles, but on many capillary loops a normal "lamina fenestrata" was still in contact with the deposits. Epithelial cells showed microvilli and a fusion of the foot processes more evident than in the preceding biopsy.

Transplant Nephrectomy

Light Microscopy. The glomeruli contained diffuse and marked lesions. On most of them, each lobule was distended by a marked proliferative central hyaline nodule with displacement of the capillary lumen to the periphery of the lobule (Fig. 12). The remaining discernible capillary walls were thickened by fibrinoid, acidophilic, refractive and PAS-positive deposits of the subendothelial topography. There were also many fibrinoid deposits in the centers of the nodules. Epithelial cells showed strongly basophilic and hypertrophied cytoplasm, and cellular crescents were found on some glomeruli. Almost all tubules showed an atrophic epithelium, and their lumina were distended and contained many cylinders. A large and diffuse fibrosis with several centers of inflammatory mononuclear cells was noted in the

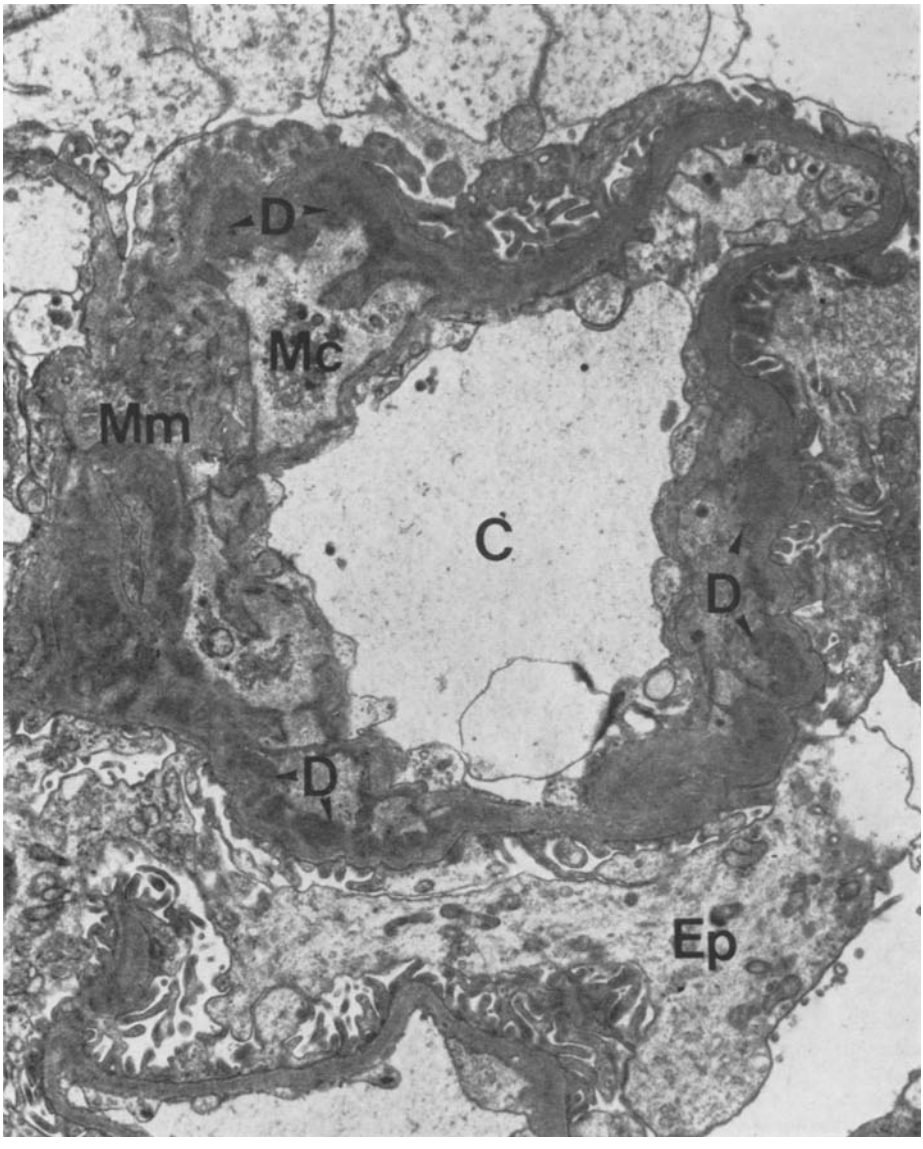


Fig. 6. Second biopsy of the transplant, 6 months after transplantation. Detail of an intercapillary space and a capillary loop. Voluminous deposits of electron dense, finely granular fibrinoid material are visible under the basement membrane of the intercapillary space. These are spread along the capillary wall and accompanied by the cytoplasm of a mesangial cell. In this case the nature of this cell was shown by study of serial sections, as described in the text. Electron microscopy: Uranyl acetate. ×11000

Fig. 8. Third biopsy of the transplant, 15 months after transplantation. Fixation of IgG antiserum on the deposits in subendothelial and mesangial areas. Immunofluorescent microphotography. ×600

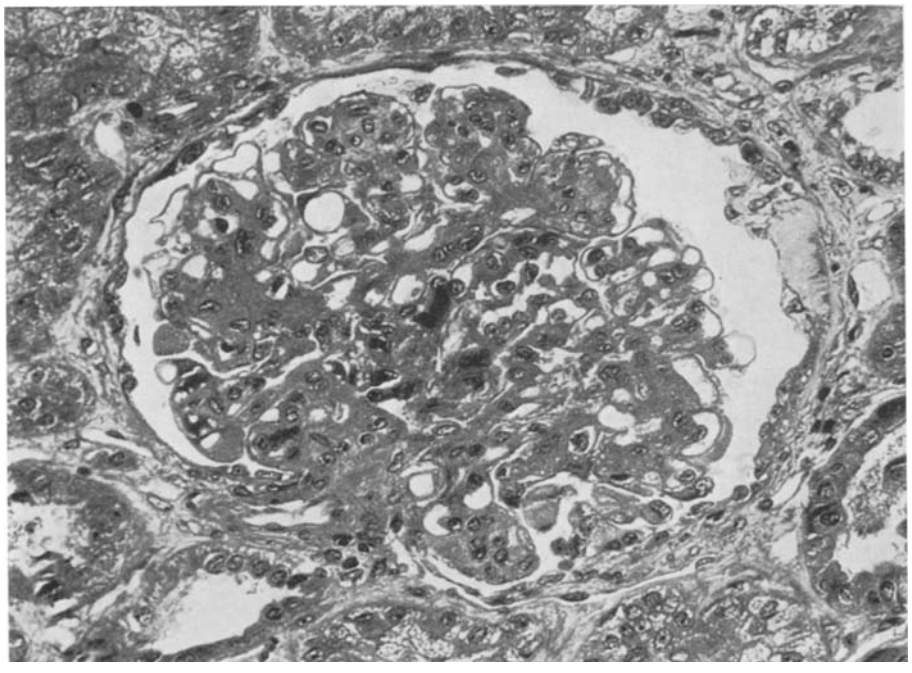


Fig. 7. Third biopsy of the transplant, 15 months after transplantation. Clear proliferation of mesangial cells giving the glomerulus a lobular aspect. There are also many deposits of fibrinoid matter in the intercapillary spaces. Light microscopy: Masson Trichrome. ×450

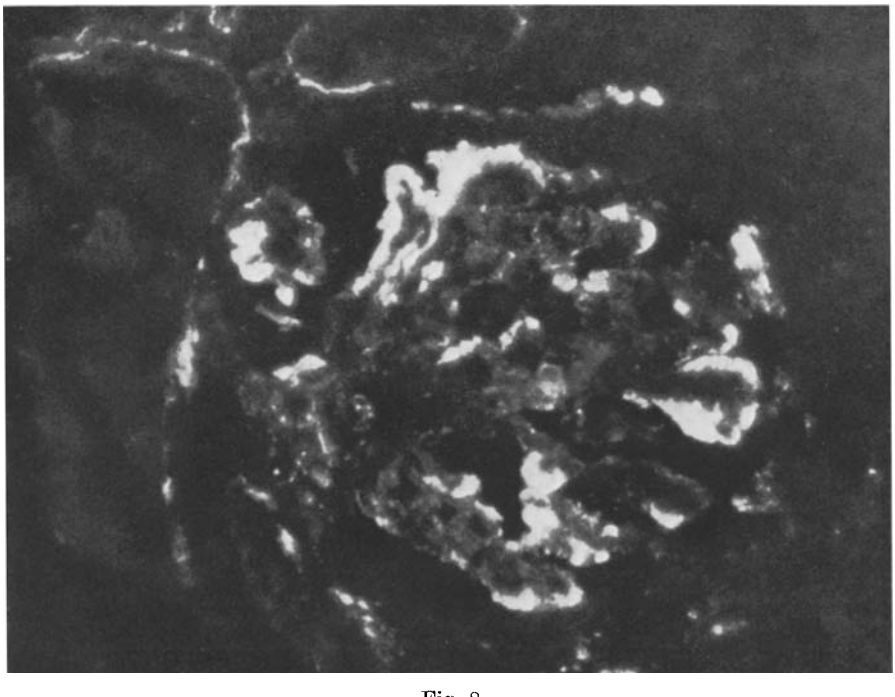


Fig. 8

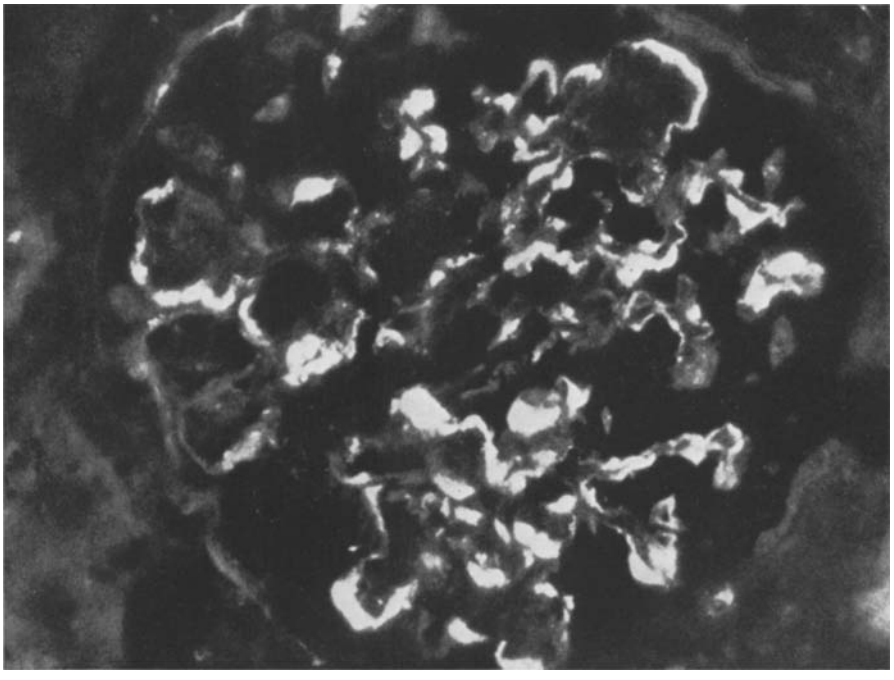


Fig. 9. Third biopsy of the transplant, 15 months after transplantation. Fixation of β1C globulin antiserum on the deposits in subendothelial and mesangial areas. Immunofluorescent microphotography. $\times 600$

interstitium. The arteries showed endarteritis with a slightly foamy aspect, and arterioles showed subendothelial hyaline deposits.

Immunofluorescence. For technical reasons the result could not be interpreted.

Electron Microscopy. Examination at low magnification, $\times 5000$, confirmed the proliferation of the endothelial and mesangial cells. The proliferation of endocapillary cells distended the tuft and partially or completely obstructed the capillary lumina. The mesangial cells were surrounded by voluminous deposits of membranoid substance. The endothelial cells had lobulated nuclei and a large cytoplasm rich in organelles. In the same section, the endothelial cells seemed to be joined without interposition of membranoid substance and appeared to contribute to the obstruction of the capillary lumina.

Dense, finely granular fibrinoid deposits were widespread, especially in contact with cellular proliferation, forming vast areas ringed by the basement membrane, which was still easily recognized on the silver impregnation. Several fibrinoid deposits appeared in the form of rounded areas on the epithelial side of the basement membrane (subepithelial "humps", Fig. 14). All the remaining discernible peripheral capillary loops had very thickened walls, as much as six times the normal thickness, caused by subendothelial deposits of variable density (Fig. 13).

Discussion

In 1964, Hamburger *et al.* reported the first case of recurrent lobular glomerulonephritis, histologically identical to that of the host's own kidney, occurring in a allografted kidney. Three other analogous cases were later described by Porter *et al.* (1968); Rowlands *et al.* (1970); and Rossmann *et al.* (1970). These authors

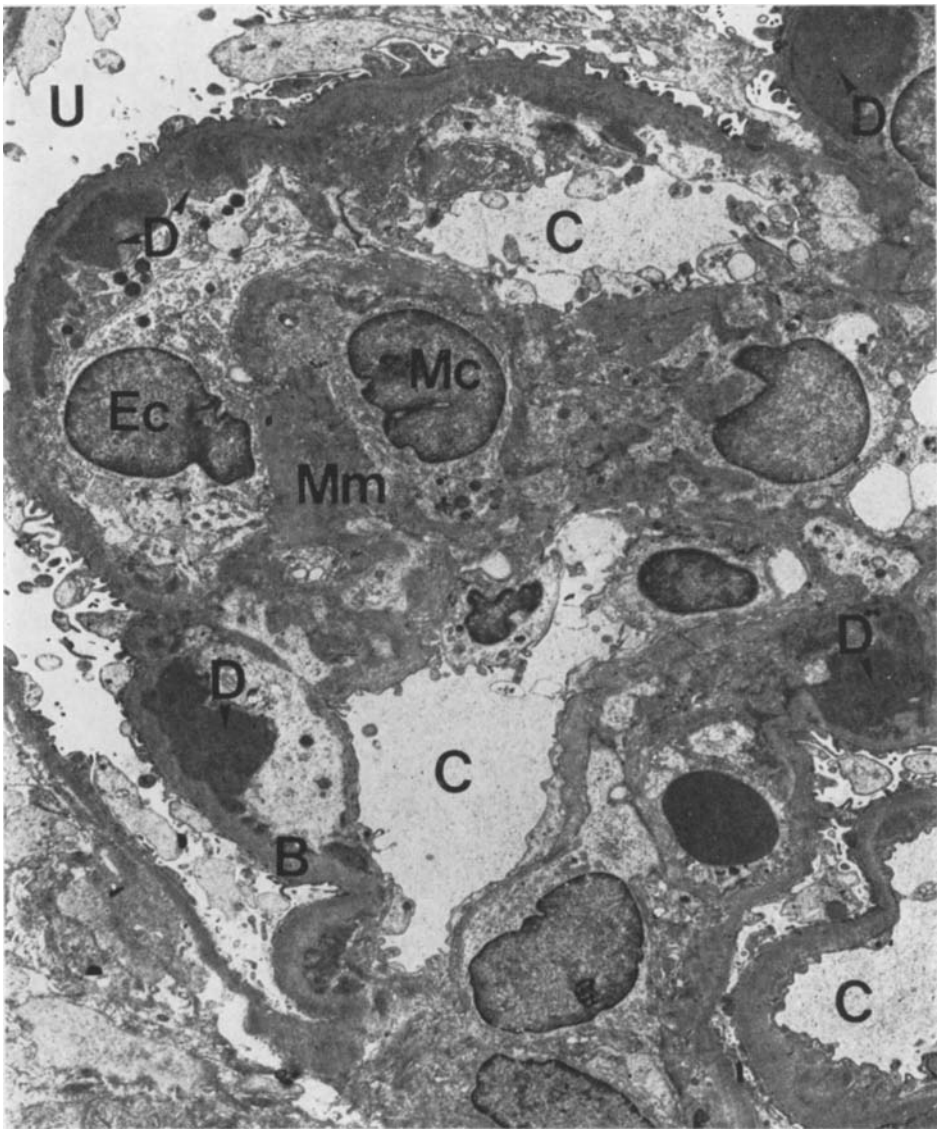
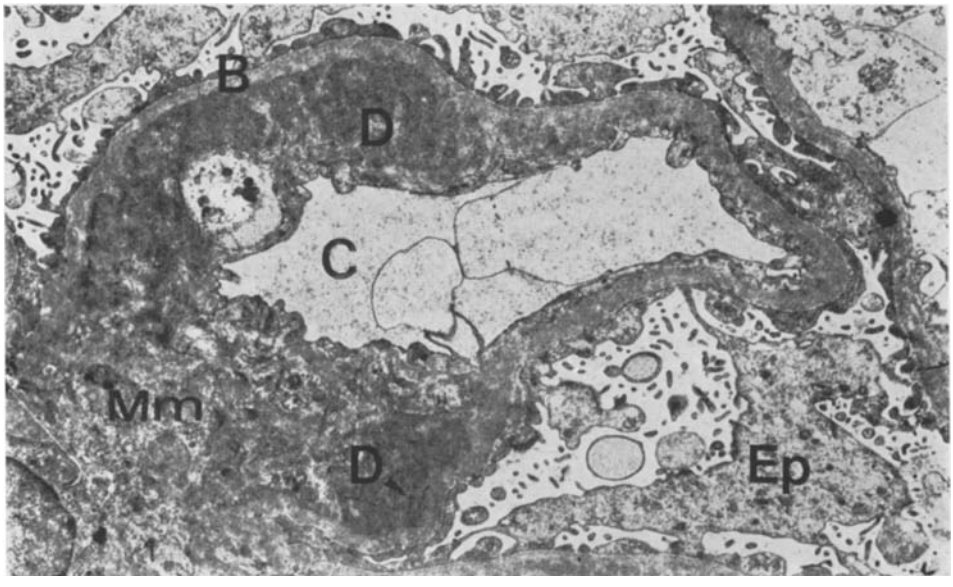
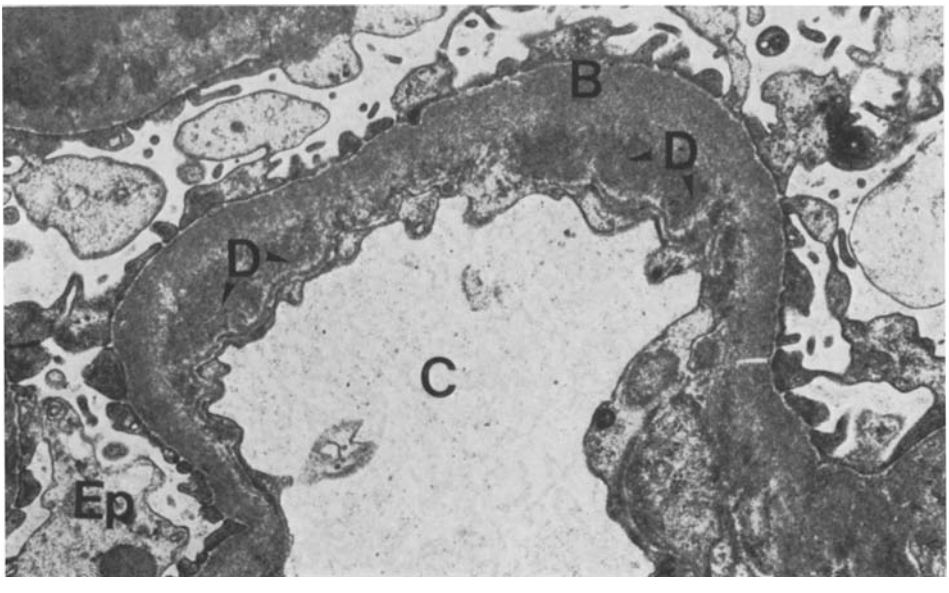


Fig. 10. Third biopsy of the transplant, 15 months after transplantation. General aspect at low magnification showing: 1. Proliferation of mesangial cells surrounded by abundant deposits of membranoid substance producing a slight lobulation of the tuft. 2. Voluminous deposits of fibrinoid substance in the intercapillary spaces and on the subendothelial sides of the walls of the peripheral capillary loops. Electron microscopy: Uranyl acetate and lead citrate. ×2640

concluded that the most probable explanation of the above events was that the lesions of lobular glomerulonephritis, seen in the allografted kidney, were the expression of the transmission of the original lobular glomerulonephritis to the transplant.



a



b

Fig. 11. a Third biopsy of the transplant, 15 months after transplantation. Ultrastructural aspect of an intercapillary space and of a peripheral capillary loop showing large, electron dense deposits much more voluminous than in the second biopsy (Fig. 6), and spread out along the entire circumference of the capillary loop in the form of small subendothelial plaques. Electron microscopy: Uranyl acetate and lead citrate. ×7500. b Third biopsy of the transplant, 15 months after transplantation. Detail of a peripheral portion of a capillary loop. The basement membrane is moderately thickened by subendothelial, electron dense, finely granular deposits. Electron microscopy: Uranyl acetate and lead citrate. ×7300

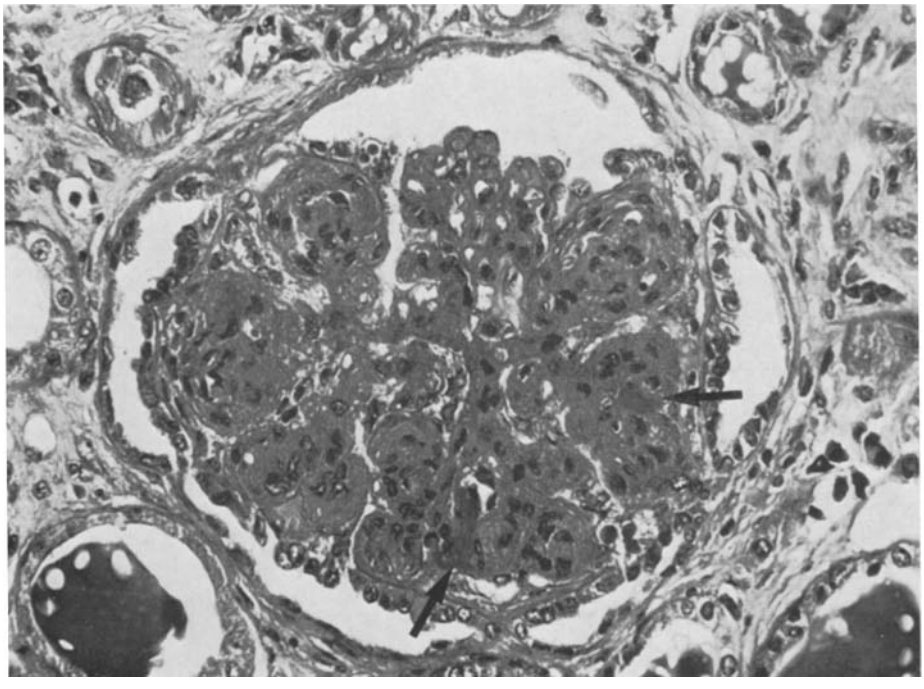


Fig. 12. Nephrectomized transplant, 24 months after transplantation. Typical lobular glomerulonephritis. Each lobule is distended by a proliferative central hyaline nodule displacing and narrowing the lumina of the capillary loops toward the periphery of the lobules. Several large deposits of fibrinoid substance are visible in the centers of the proliferation (↗). Light microscopy: Masson Trichrome. ×450

The present observation supports even more strongly the high probability of transmission of lobular glomerulonephritis to the transplant. Two arguments, one histological, the other clinical, support this probability. The glomerular lesions in the nephrectomized kidney were completely identical to those in the original kidney (Figs. 1 and 12). The lobular glomerulonephritis had characteristic lesions quite different from the glomerular lesions caused by chronic rejection with diffuse, isolated thickening of the capillary walls (Porter *et al.*, 1967). Moreover, there were no signs of interstitial or vascular rejection in the first two biopsies.

From a clinical point of view, there is a remarkable similarity between the observation presented here and those previously published of the four cases of lobular glomerulonephritis in allotransplanted kidneys. There was the same early appearance of proteinuria and the same rapid evolution within two years toward definitive renal insufficiency (Fig. 15). This is not the usual evolution of glomerulonephritis caused by rejection, which is associated with mild proteinuria and relatively slow impairment of glomerular filtration rate (Hamburger *et al.*, 1965; Hume *et al.*, 1970).

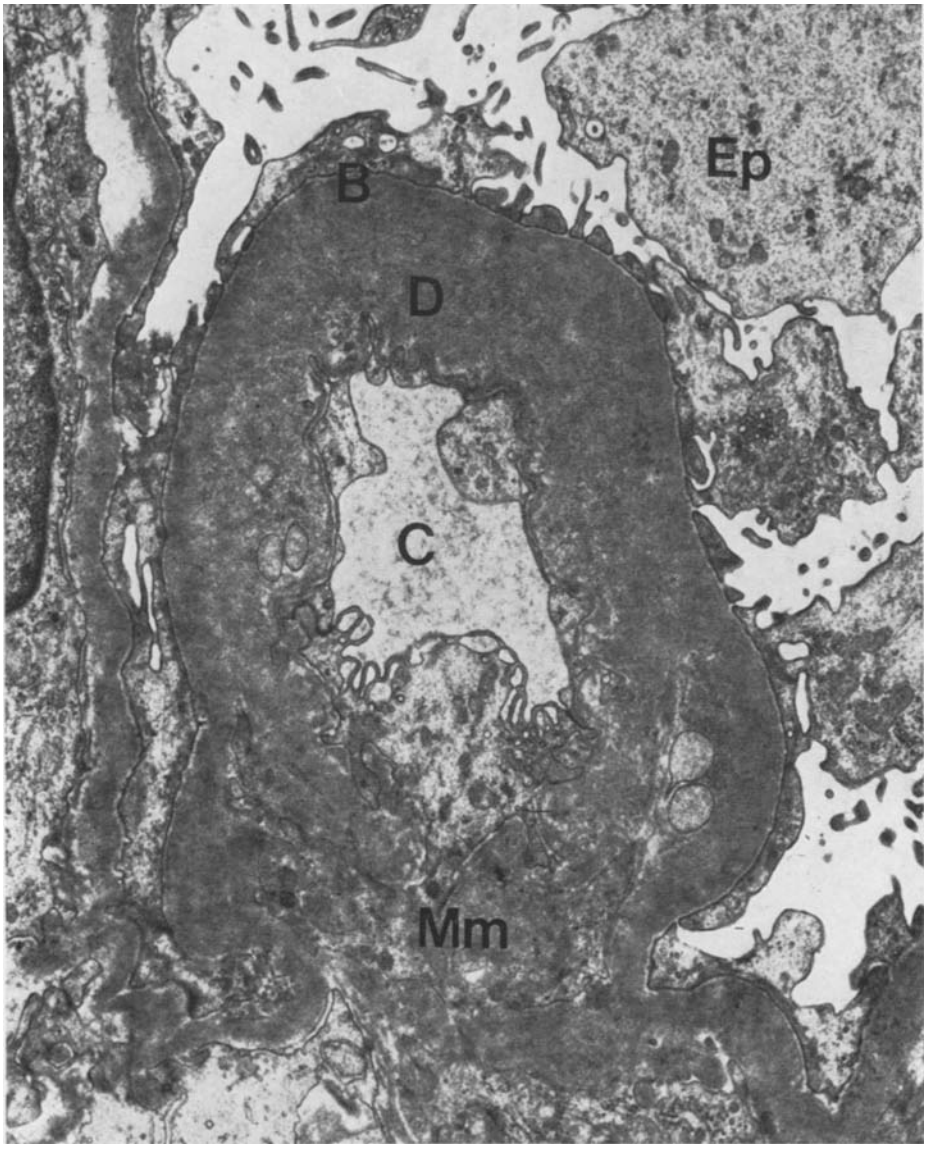


Fig. 13. Nephrectomized transplant, 24 months after transplantation. Detail of a capillary loop. The wall is considerably thickened by a voluminous subendothelial deposit of unequal electron density which greatly reduces the lumen of the capillary loop. Electron microscopy: Uranyl acetate and lead citrate. ×11250

The results presented here are of interest since the evolution of a case of recurrent lobular glomerulonephritis could be studied morphologically and immunohistochemically on four serial histological specimens (Table 1). The first biopsy obtained before the appearance of clinical symptoms showed normal

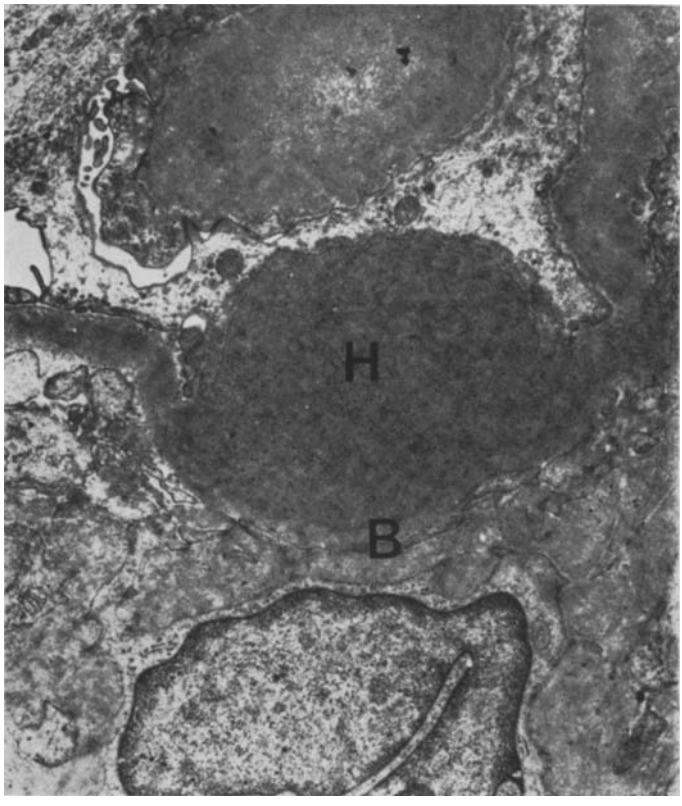


Fig. 14. Nephrectomized transplant, 24 months after transplantation. Hemispheric, electron dense, finely granular deposit on the epithelial side of the basement membrane (hump). Electron microscopy: Uranyl acetate and lead citrate. ×11250

glomeruli, except for small fibrinoid deposits in the mesangial areas which were only observed with electron microscopy. The second biopsy, done shortly after the appearance of proteinuria and hematuria, showed the first important and completely isolated lesion, that is, large abnormal immune deposits mainly located in the intercapillary spaces. The second important pathological process was observed in the third biopsy, ten months after the second biopsy, and consisted of a proliferation of the mesangial cells and the beginning of hyaline nodules. Also the deposits observed in the first and second biopsy showed considerable extension, and their quantity, topography and immunological constitution were completely identical to that observed in a primary lobular glomerulonephritis (Berger *et al.*, 1969, 1971). Studies of the nephrectomized kidney confirmed the evolution of the lesions toward a typical lobular glomerulonephritis. Electron microscopy showed that some deposits were located on the epithelial side of the basement membrane (humps), similar to those reported by Porter *et al.* (1968) in one of their cases of recurrent glomerulonephritis.

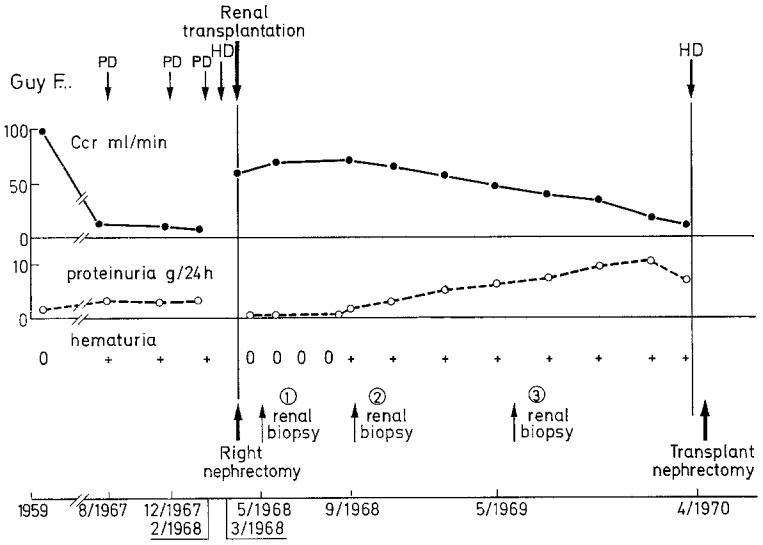


Fig. 15. Clinical evolution of the host's own and the allotransplanted kidney

Table 1. *Histopathology of the kest's own and the recurrent lobular glomerulonephritis in the allotransplanted kidney*

Patient Guy F.	Light microscopy			Electron microscopy				Immunofluorescence		
	Endothelial and mesangial proliferation	Epithelial proliferation	Hypertrophy of mesangial areas	Basement membrane (silver-methenamin impregnation)	Deposits mesangial	Deposits subendothelial	Deposits extramembranous	IgG	IgM	βl-C glob.
Host's own kidney	+++ +++		+++	not done				not done		
First biopsy	—	—	—	nor	+	—	—	—	—	—
Second biopsy	—	—	+	nor	++	+	—	++	+	+
Third biopsy	++	—	++	nor	+++	++	—	+++	+++	+++
Nephrectomy of the graft	+++	++	+++	nor	+++	+++	+	not done		

+ = mild, ++ = moderate, +++ = severe, nor = normal.

It would seem that an Important Conclusion to draw from the Present Evolutionary Analysis of a Recurrent Lobular Glomerulonephritis that Immune Deposits Precede Cellular Proliferation. This has not been clearly shown in other cases of recurrent

lobular glomerulonephritis described in the literature and has never been observed in primary lobular glomerulonephritis because deposits and proliferation occured simultaneously. This observation may be an additional argument in favor of the primary role of the desposits of immune complexes in the pathogenesis of human proliferative glomeruloneplirtis, a role which is well supported by the results from work of experimental glomerulonephritis (Dixon, 1968; Dixon *et al.*, 1971). Considering this hypothesis, the delayed occurrence of cellular proliferation which was seen in the case presented here, could be due to the continuous action of azathioprine or corticosteroid treatment which slows down the sequence of pathological phenomena. This argument however is weak, not only because of the current uncertainty about the action of immunosuppressors or corticosteroids on cellular proliferation (Urizar *et al.*, 1969; Germuth *et al.*, 1968), but also because deposits similar to those which were found on the second biopsy have been observed under immunofluorescence during chronic rejection (Hume *et al.*, 1970; Porter *et al.*, 1968). In this laboratory several transplants showed under immunofluorescence the presence of large deposits in the glomeruli without other associated lesions and without any evolution in the subsequent years. Indeed some deposits even disappeared (Hamburger *et al.*, 1971).

Finally, it should be emphasized that the recurrence of glomerulonephritis lesions can best be differentiated from those observed in chronic rejection by the correlation of clinical, histopathological and immunofluorescent data.

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