Cirrhotic (Hepatic) Lobular Glomerulonephritis

Correlation of Ultrastructural and Clinical Features

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IT IS WELL RECOGNIZED, although not commonly appreciated, that some patients with chronic liver disease such as cirrhosis may exhibit clinical and laboratory manifestations of renal insufficiency. Alterations of certain parameters of renal function including glomerular filtration rate, renal plasma flow, and tubular dysfunction may also be detected in some cirrhotic patients despite the lack of overt evidence of renal failure.[1,2] This has led to the view that persons with cirrhosis are more susceptible to the development of progressive renal failure when episodes known to have an adverse effect on renal function are superimposed on the cirrhotic state.[2] The relative infrequency of overt renal failure in patients with cirrhosis might, however, be considered as evidence against the significance of such "preparatory" physiologic alterations in this regard.

Although pathologic changes have been observed in the kidneys of patients with cirrhosis, these are not universal. Crowson and More,[3] as well as Baxter and Ashworth,[4] have described tubular degenerative changes in kidneys from patients with cirrhosis or other hepatic disorders. Descriptions of nodular glomerulosclerosis in nondiabetic cirrhotic patients by Horn and Smetana[5] and Raphael and Lynch,[6] and of intercapillary glomerulonephritis in 12% of 60 cirrhotic patients examined at necropsy by Patek, Seegal, and Bevens,[7] indicate the occurrence of a glomerular defect in this disorder. Fisher and Hellstrom[8] and Bloodworth and Sommers[9] described the presence of basement-membrane and mesangial thickening in 25% and 77%, respectively, of unselected patients with cirrhosis examined at necropsy. Fisher and Hellstrom[8] also noted glomerular proliferative changes, and considered the lesion distinctive but not specific for cirrhosis. Jones, Rao, and Braunstein[10] subsequently noted this glomerular alteration in some control subjects, although it was more frequent in patients with cirrhosis. There was no correlation of this glomerular alteration, previously designated as membranous and proliferative glomerulonephritis of hepatic cirrhosis or hepatic glomerulosclerosis,

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nor were any particular hepatic change or clinical manifestations apparent. Because of this, as well as the similarity of many of the biochemical and clinical manifestations of cirrhosis and glomerulonephritis,[11] some investigators have attributed little significance to these renal lesions in cirrhosis.[12]

More recently, Sakaguchi *et al.*[13] detected by electron microscopy mild glomerular changes in patients with acute liver disease such as hepatitis, and more advanced changes in patients with cirrhosis. Although they commented upon the presence of glomerular lesions in the absence of renal manifestations, pertinent clinicopathologic correlations were not performed. Similar lesions were also noted in rats with cirrhosis induced by carbon tetrachloride or ethionine.[14]

The purpose of this investigation was to examine by electron microscopy intra vitam renal biopsies from patients with cirrhosis who exhibited overt manifestations of renal insufficiency, and to compare the findings with those obtained from examination of biopsies of cirrhotic patients in whom evidence of renal dysfunction was minimal or lacking. The prospective nature of this investigation might be expected to provide pertinent information allowing for further characterization of the renal lesions observed in patients with cirrhosis and their clinical significance.

Material and Methods

Renal tissue was obtained from 12 patients with Laennec's (nutritional) cirrhosis by intra vitam percutaneous biopsy with a Menghini needle. Diagnosis of cirrhosis was verified in all instances by prior biopsy of the liver with a Vim-Silverman needle. The pertinent clinical and biochemical features of the cases are annotated in Tables 1 and 2. The 4 patients comprising Group I exhibited renal insufficiency characterized by decreased glomerular filtration rate as measured by creatinine clearance and elevation of BUN. Examination of urinary sediment in these patients frequently revealed erythrocytes, erythrocyte casts, and birefringent crystals. Gross hematuria was also noted in 2 (Patients 1 and 2). Proteinuria was marked in all, and serum cholesterol was elevated in 1. Hypoproteinemia was noted in 3, and gamma-globulin content was greater than albumin in serum electrophoretograms of all 4. In Group I, hypertension occurred in Patients 2 and 3, and ascites was present in Patients 1 and 2. Serum bilirubin, BSP retention, and estimated duration of cirrhosis was greater in these 4 patients than in the remaining 8 of Group II. None in Group II revealed abnormal renal function tests, inversion of gamma globulin:albumin ratios, or abnormal protein excretion. Serum cholesterol was elevated and total serum protein decreased in only 1 (Patient 9).

In all patients, ASO titers were negative or insignificantly elevated. Tests for lupus erythematosus (L.E.) including demonstration of antinuclear antibody were also negative in those in whom they were performed (Patients 1, 2, 9, and 10). A second renal biopsy was performed in 2 of the patients with renal insufficiency (Patients 1 and 2) 6 months and 1 year, respectively, after the onset of renal insufficiency and the initial biopsy. No significant change in the clinical or laboratory manifestations was apparent in Patient 2, whereas laboratory evidence of renal failure appeared to be more pronounced in Patient 1 at the time of the second biopsy.

All tissue was either immediately minced into 1-mm. cubes and fixed in toto in 1% osmium tetroxide buffered with veronal acetate, pH 7.4, or—as in Patients 2, 3, 4, 5, 7, 8, and 9—was longitudinally bisected. One portion of the latter tissue was then minced and immersed in osmium tetroxide as above, and the other either frozen on dry

Table 1. Clinical Features and Liver Function Tests in Patients with Cirrhosis

Patient No.	Age/Race	Duration of cirrhosis (yr.)	B. P. (mm. Hg)	Bilirubin (mg./100 ml.)	Ceph. floc.	BSP (%)
			GROUP I			
1	49 W	8	160/78	1.2	4+	16
2	49 N	7	170/104	1.7	4+	30.8
3	38 W	7	150/100	2.0	4+	32.5
4	54 W	6	130/80	3.8	4+	23.5
			GROUP II			
5	48 W	1	160/80	1.7	4+	14
6	51 W	1½	110/70	0.7	2+	8.8
7	51 W	¼	100/70	0.5	3+	5.5
8	41 W	2½	150/80	0.8	4+	10
9	52 W	1¾	140/70	0.9	2+	10
10	47 N	2	150/85	1.0	3+	15.5
11	49 W	1½	135/70	0.9	3+	8.6
12	51 N	2½	120/80	1.2	3+	12

Table 2. Renal Function and Biochemical Changes in Patients with Cirrhosis

Patient No.	Cholesterol (mg./100 ml.)	BUN (mg./100 ml.)	G.F.R. * (ml./min.)	Protein (gm./24 hr.)	Serum protein (gm. %)		
					Total	Albumin	Gamma globulin
			GROUP I				
1	376	54	32	5.1	4.5	0.9	2.07
2	224	32	32	1.9	6.6	1.9	3.0
3	216	38	41	1.26	5.3	1.7	2.42
4	290	46	42	3.2	5.3	1.46	3.94
			GROUP II				
5	350	9	92	0.04	5.3	2.9	1.63
6	190	8	108	0	7.2	3.88	1.72
7	132	8	106	0	6.3	3.21	1.94
8	165	14	114	0	7.6	3.8	2.82
9	170	15	108	0	6.4	3.4	1.6
10	185	10	98	0.05	6.8	3.5	1.55
11	150	9	110	0	7.1	3.6	1.3
12	165	12	101	0	6.6	3.0	1.7

* Glomerular filtration rate—creatinine clearance.

ice (Patients 2, 3, 8, and 9) or fixed in Zenker's acetic fluid (Patients 4, 5, and 7). Osmium-fixed tissue was dehydrated and imbedded in Maraglas. Thin (2 μ) and ultrathin sections were prepared with a Porter-Blume ultramicrotome. The former were stained with warm crystal violet and the latter were examined either unstained or after staining with lead citrate with a Philips EM 200 electron microscope. At least 3 glomeruli from each patient were available for study. The width of the lamina densa in each subject was expressed as the average thickness of at least 75 measurements of this structure at sites in free capillary loops remote from the mesangium. This represented the space between clearly defined plasma membranes of epithelial foot processes and endothelial cytoplasm.

Quick-frozen tissue was sectioned in a cryostat at $-20°$ C., stained with anti-human γ and β_{1C} globulins conjugated with fluorescein isothiocyanate, and examined by fluorescence microscopy.

Results

Light Microscopy

Sections of Zenker-fixed, paraffin-imbedded, and plastic-imbedded renal tissue from cirrhotic patients without evidence of renal insufficiency (Group II) revealed moderate mesangial thickening with variable extension of fibrillary mesangial material into free capillary loops of glomeruli in all but 3 patients (10, 11, and 12). These alterations were more pronounced and accompanied by increased numbers of glomerular endothelial and/or epithelial cells (Fig. 1) in patients with renal insufficiency (Group I).

Electron Microscopy

The ultrastructural appearance of kidneys from 3 patients with cirrhosis without renal dysfunction (Group II) was considered comparable to that of normal controls of similar age. Glomeruli of kidneys from the remaining members of this group exhibited mesangial thickening characterized by an increase in basement membrane-like material as well as cells (Fig. 5). In some instances (Patients 5, 7, and 9) fibers measuring 350 Å in width with a periodicity of approximately 550 Å were noted among the bars of mesangial matrix (Fig. 2). Glomerular epithelium was generally slightly increased in size, with prominent coarse endoplasmic reticulum, Golgi structures, RNA particles, and cytoplasmic vacuoles. Occasional round or oval bodies bounded by a solitary membrane and a matrix of homogeneous or fibrillar electron-dense material and lipofuscin droplets were also observed within the epithelial cytoplasm. Blunting, fusion, and focal loss of epithelial foot processes appeared pronounced in only Patient 5 of this group. Large, laminated bodies measuring up to 7500 Å (Fig. 3 and 5) were observed in the mesangium or Bowman's capsule in Patients 5, 6, 7, and 8. The electron-dense laminations appeared to be comprised of aggregates of granules measuring approximately 100 Å. Emission spectros-

copy revealed very small but comparable amounts of silver, copper, and other trace elements in blocks of kidney from the patients with cirrhosis in whom these laminated bodies were found, as well as in controls without renal disease or such inclusions. In 2 instances (Patients 5 and 7) the lamina densa and mesangium contained rare, irregularly shaped or elongated, moderately electron-dense deposits within its endothelial and midportions. These appeared to blend with the matrix of the lamina densa (Fig. 4). The deposits comprised 2 types of granules. The most abundant, which was fine, measured 35–50 Å. The rarer granule was more electron-dense and measured 100 Å. At high manifestations it was noted to be a tetrad comprised of smaller subunits measuring 40 Å and was indistinguishable from samples of horse ferritin (Nutritional Biochemicals) examined at comparable magnifications (Fig. 4). Uninvolved areas of the lamina densa of free capillary loops measured 3763 Å ± 604 Å. Glomerular endothelium appeared unaltered. Epithelium of proximal convoluted tubules occasionally contained cytosomal inclusions similar to those noted in the glomerular epithelium.

These mesangial, glomerular, and tubular epithelial changes were qualitatively similar but more severe in the kidneys from the cirrhotic patients with renal insufficiency in Group I (Fig. 6 and 7). Periodic fibers were noted in the mesangium of Patients 1 and 2. All specimens in this group contained focal deposits within the mesangium and lamina densa. These were found most frequently in the endothelial aspect of the lamina densa (Fig. 8) less commonly in its midportion, and only rarely beneath the epithelium. Wrinkling and occasional longitudinal splitting of the lamina densa were evident. In some instances, portions of this structure appeared to surround endothelial cytoplasm. The width of the lamina densa was greatly increased at sites of deposit. However, its thickness was variable in uninvolved areas, measuring 6394 ± 3000 Å ($p < 0.05$ compared with width of uninvolved lamina densa of Group II). Glomerular endothelial cells were large and were often increased in number (Fig. 10). Folds in their plasma membranes often resulted in intercellular spaces or lacunae, and large cytoplasmic vacuoles were occasionally noted. Their cytoplasmic organelles were often prominent. In 1 specimen (from Patient 12), rounded bodies measuring up to 1000 Å were noted in spaces between endothelium and the lamina densa (Fig. 9). Their matrix was either electron-dense or lucent.

No difference in ultrastructural appearance of the first and second biopsies was appreciated in Patient 1. The second biopsy in Patient 2 revealed more frequent and larger intramembranous deposits than had been encountered in the biopsy performed 1 year previously.

Juxtaglomerular cells were available for evaluation in Cases 1, 3, 4, 5, 8,

and 9. True secretory granules were extremely sparse in the cell cytoplasm which contained numerous lipofuscin bodies.

Immunofluorescent studies revealed focal localization of γ globulin within the basement membrane in all cases studied by this technique but β_{1C} globulin was not found.

Discussion

The findings in this prospective study provide information concerning the clinical and functional significance of the renal lesions described that had been lacking in previous light- and electron-microscopic investigations. Although the mesangial and glomerular epithelial changes were qualitatively comparable in both groups of patients, they were more pronounced in those with renal insufficiency. Deposits within the glomerular lamina densa and mesangial matrix were infrequent and subtle in patients without renal failure but pronounced in patients with impaired renal function. Endothelial alterations appeared only in those biopsies from cirrhotic patients with renal failure. A close correlation was also observed between the degree of renal involvement and duration as well as severity of the cirrhosis, which was reflected by the magnitude of cephalin flocculation, Bromsulphalein, and bilirubin retention. Sakaguchi *et al.*[13] have commented upon the occurrence of milder renal alteration in patients with such acute hepatic disease as viral hepatitis than in those with cirrhosis. They also noted a progression of the severity of comparable lesions in rats with cirrhosis induced by the administration of ethionine or carbon tetrachloride.[14] Although the glomerular lesions were qualitatively and quantitatively similar in a second biopsy performed in 1 patient 6 months after recognition of renal failure in this study, examination of the kidney in another example 1 year later disclosed more pronounced change. This information indicates that cirrhosis may be associated with morphologically demonstrable renal lesions which in some instances may progress sufficiently to provoke renal insufficiency. However, that these events are not universal is apparent from the normal-appearing renal biopsies in some patients with cirrhosis who failed to exhibit manifestations of renal insufficiency. The reason for this inconsistency and the precise mechanisms responsible for the selectivity of renal disease in these patients are unclear. Nevertheless, the recognition of uniform, qualitatively similar glomerular changes in both groups of patients studied tends to minimize the view relating the onset of renal failure in patients with cirrhosis to the superimposition of intercurrent incidents on existing physiologic abnormalities known to influence renal function adversely in the cirrhotic patient.[2]

The renal lesions observed in these patients do not appear specific. The mesangial and glomerular epithelial changes observed in those cirrhotic patients without renal failure may be recognized in a variety of unrelated disorders. Although the large subendothelial granules have been considered unique for hepatic glomerulosclerosis by Sakaguchi *et al.*,[13] we have found such deposits in only 1 of the patients with renal failure and in none of those with intact renal function. Similarly, the large laminated bodies, which were found in both groups of patients, have not to our knowledge been described in association with other primary glomerular diseases in man. Nevertheless, they lose their specificity when it is appreciated that identical structures have been encountered in glomerular as well as eccrine basement membranes in an example of generalized argyria by Prose.[15] He regarded them as analogous to Liesegang rings, which are supposedly formed by the precipitation of ions diffusing through gels. Their precise identification and their significance in the kidneys of some patients with cirrhosis is at present unknown. Emission spectroscopy of samples of kidneys with these bodies revealed no differences in their silver or copper content from that noted in control specimens. The distribution of the intramembranous deposits distinguish the lesion from that of poststreptococcal glomerulonephritis.[16–18] Further, none of the patients studied exhibited significant ASO titers. Some features, notably the endothelial proliferation and the location and appearance of the membranous deposits, are not too dissimilar from those encountered in L.E.[16–18] and idiopathic membranous glomerulonephritis.[16,19–21] Patients with these disorders frequently exhibit some manifestations of the nephrotic syndrome, which were also noted in the cirrhotic patients with advanced renal lesions in this study. However, the marked mesangial alterations allow for the distinction to be made between the lesion observed in the cirrhotic patient from L.E. and the more familiar type of idiopathic membranous glomerulonephritis. Also, L.E. tests including investigation of the antinuclear factor were negative in all cirrhotic patients in which these examinations were performed, including those with renal insufficiency.

On the other hand, our observation of both the prominent mesangial alteration accompanied by a normal-appearing lamina densa, or rarely subtle involvement of this structure, which might be considered characteristic of the early lesion in these cirrhotic patients, and of its progression resulting in more pronounced membranous and capillary changes is in accord with the interpretations of Habib *et. al.*[22] and Galle *et. al.*[23] concerning the ultrastructural evolution of the so-called lobular glomerulonephritis of Allen.[24] Recognition of collagen-like fibers in the mesangium

in the lesion investigated in this study represents another similarity to so-called lobular glomerulonephritis. Clinically, all of the cirrhotic patients with advanced renal lesions and insufficiency in this study exhibited either microscopic or gross hematuria, a finding considered by Habib *et al.*[22] to be constant in patients with lobular glomerulonephritis. Although identification of the glomerular lesion in cirrhosis as lobular glomerulonephritis suggests that this group of patients may be particularly susceptible to this form of renal disease, it appears equally tenable at present to contend that cirrhosis may represent one of its possibly several etiologies.

Absolute identification, as well as elucidation of the pathogenesis of the intramembranous deposits encountered in these kidneys from cirrhotic patients, would add greatly to a better understanding of the nature of their renal disease. Unfortunately, information about this is limited and somewhat speculative. The results of immunofluorescent studies have revealed that the deposits observed, at least in some examples of idiopathic membranous glomerulonephritis,[25,26] experimental glomerulonephritis[27] and serum sickness,[28] and poststreptococcal glomerulonephritis[29] may represent antigen-antibody complexes. Identification of the deposits in the cirrhotic patients with these complexes represents an attractive hypothesis, particularly since some evidence has been presented to suggest that autoimmune reactions may participate in the evolution of the cirrhotic process.[30–33] It might be expected that if complexes were indeed formed, at least some might be lodged within the lamina densa, resulting in an autologous immune-complex disease of the kidney.[34] Yet we, as well as Sakaguchi *et al.*,[13] have failed to detect complement within the renal lesions of patients with cirrhosis. Although this does not unequivocally exclude the presence of small quantities of such complexes or negate their role in the initiation of basement-membrane damage, it has prompted us to explore an alternate possibility in order to account for these deposits. Except for the recent study by Faith and Trump,[18] few investigators have provided qualitative information concerning the ultrastructural appearance of such deposits. Faith and Trump[18] observed dissimilarities between the intramembranous deposits encountered in L.E., in which the deposits are finely particulate, preeclampsia, in which they are fibrillar and flocculent, and acute glomerulonephritis, in which they are coarse and very dense. The pathogenetic significance of these differences is, as yet, not evident. Nevertheless, the composition of the finely particulate, intramembranous deposits observed in the glomeruli of these patients with cirrhosis appear identical to those observed in other examples of lobular glomerulonephritis from patients without cirrhosis who were available for study, and include the presence of rare ferritin particles.

Their structure is also indistinguishable from the intravascular deposits characteristic of so-called arteriolar hyalinosis,[35] and is considered as evidence relating to their hematogenous derivation.

It appears significant in this regard that all of the patients with cirrhosis who exhibited renal insufficiency and pronounced intramembranous deposits had inversion of their serum gamma globulin:albumin ratios. Indeed, the 2 groups of patients could be distinguished by evaluation of these serum factors. This information provokes the possibility that the deposits may represent such protein trapped within this membranous structure. The presence of a cytofold endothelial system as well as apparent hyperactivity of endothelial cells in this situation may reflect the sequestration of such relatively large molecules from the circulation whether they are immunologic or nonimmunologic in nature, as has been recently proposed by Faith and Trump.[18] It is of interest that intraluminal and rarely subendothelial deposits, as well as evidence of basement-membrane damage, have been noted following the intravenous infusion of large quantities of homologous gamma globulin, but not albumin, in the rat.[36] Michael, Fish, and Good[37] have recently observed by electron microscopy deposits in the mesangium, but not in the lamina densa, in glomeruli of mice following injection of aggregated albumin and globulin. The nephrotoxicity of hypergammaglobulinemic states has recently received attention. Evidence that this plasma protein may produce tubular acidosis has recently been presented.[38] Unfortunately, little information concerning its possible effect on glomerular function is available. Although intramembranous deposits have not been observed in such situations as acute aminonucleoside nephrosis,[39] some examples of lipoid nephrosis,[20] experimental renal vein thrombosis,[40] and multiple myeloma,[41] which are often characterized by a relative or absolute increase in serum globulins, it is noteworthy that such elevations only rarely, if at all, quantitatively exceed those of albumin. Furthermore, the experimental and the clinical situations of globulin increase cited which we have personally studied have been of relatively shorter duration than that in the cirrhotic patients of the present study. It is also germane to note that so-called lupoid, or chronic active hepatitis,[42] a syndrome also associated with extreme hypergammaglobulinemia, as well as some immunologic abnormalities, may be associated with glomerulonephritis in approximately 20% of cases.[33] Glomerulonephritis has been referred to as acute or membranous glomerulonephritis, although ultrastructural studies of the renal lesion have not been recorded.

Despite the purported antagonism between cirrhosis and hypertension,[43,44] 2 of the 4 cirrhotic patients with lobular glomerulonephritis were

hypertensive. The presence of pronounced hypergammaglobulinemia in these patients contradicts the view relating this inverse relationship to the elevated serum globulins encountered in the cirrhotic patient.[45] The similarity of ultrastructural appearance of juxtaglomerular cells in these patients to that noted in individuals with essential hypertension rather than that form of renal hypertension related to the renin-angiotensin-aldosterone system, coincides with the failure experimentally to induce this form of renal hypertension in cirrhotic rats.[44]

Summary

A prospective, correlated ultrastructural and clinical study of renal biopsies from 12 patients with Laennec's (nutritional) cirrhosis was performed. Glomeruli from 5 of 8 with normal creatinine clearance, BUN, urinary sediment, and protein excretion exhibited cellular and membranous mesangial thickening. In several of these, sparse collagen fibers and large laminated bodies were observed within the mesangium, and subtle, finely particulate deposits containing ferritin within the lamina densa. These alterations were qualitatively similar but more pronounced in all 4 of the cirrhotic patients with renal dysfunction, and were more advanced in a second biopsy in 1 of these patients obtained 1 year after initial examination. The duration and severity of cirrhosis was also greater in those patients with functional impairment. Although the glomerular lesion is not specific, and closely resembles the lesion observed in so-called lobular glomerulonephritis in noncirrhotic patients, nevertheless this information strongly suggests that renal failure in some patients with cirrhosis is the result of a progressive glomerular alteration which is in some manner related to the duration and severity of the cirrhotic state.

The nature of the membranous deposits is not established. Immunofluorescence failed to establish their identity as antigen-antibody complexes. Their relationship to the abnormally high serum gamma globulin observed only in those patients with advanced lesions and renal insufficiency is discussed.

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Emission spectroscopy was performed by Dr. E. Hodge of the Mellon Institute of Pittsburgh.

[*Illustrations follow*]

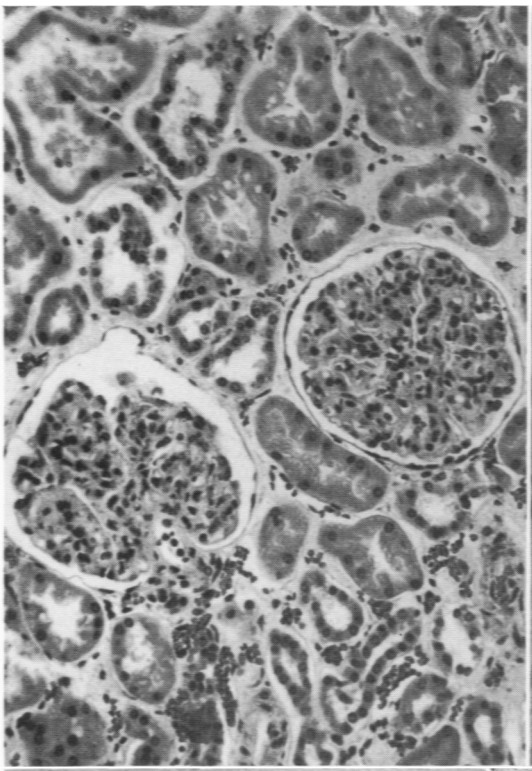
Legends for Figures

Fig. 1. Light microscopic appearance of glomeruli from kidney from Patient 4. Basement-membrane thickening with early lobular transformation and cellular proliferation characterize lesion. Hematoxylin and eosin. × 250.

Fig. 2. Fibers with periodic bands (arrows) and electron-dense body with lucent center exhibiting local invagination are present within mesangial matrix. × 21,000.

Fig. 3. Appearance of laminated, electron-dense body depicted in lamina densa of Fig. 5 and also found in mesangium and Bowman's capsule of other patients. × 97,000.

Fig. 4. Deposit (D) which blends with matrix of lamina densa in glomerulus of cirrhotic patient without renal insufficiency. × 25,000. **Inset.** Small and large particles comprising deposit; one of latter (circle) exhibits tetrad configuration. × 500,000.



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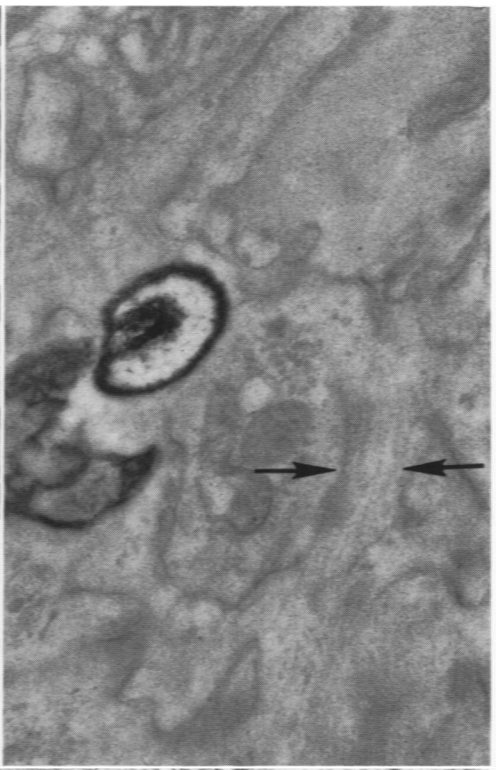

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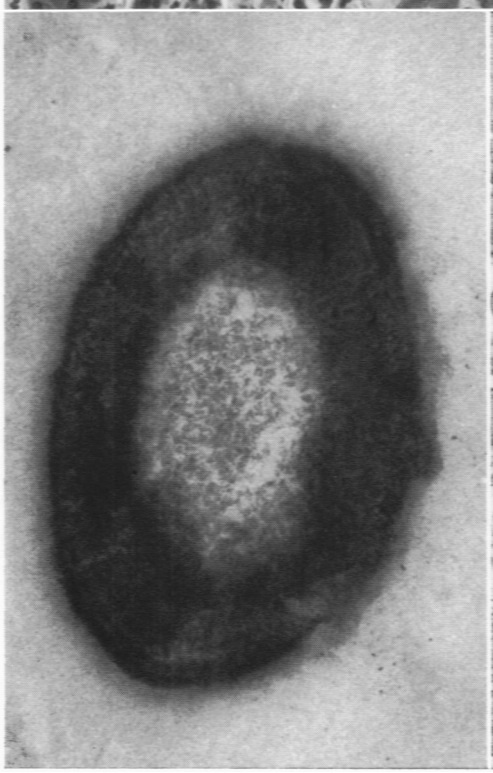

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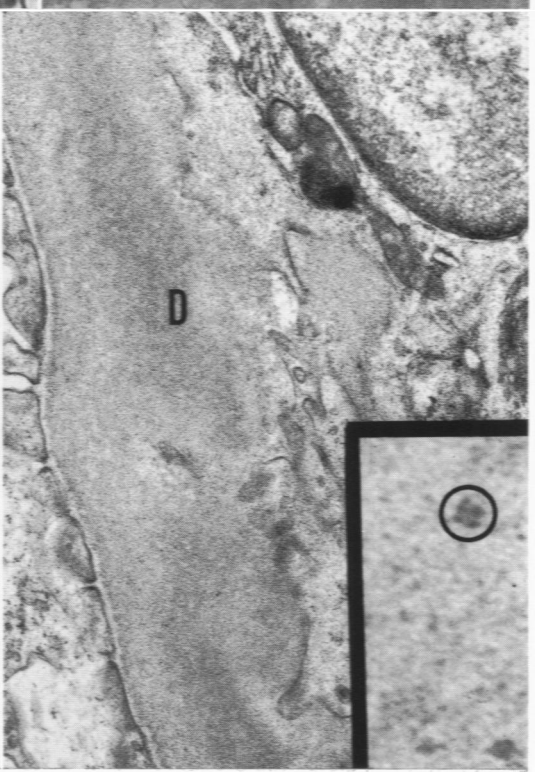

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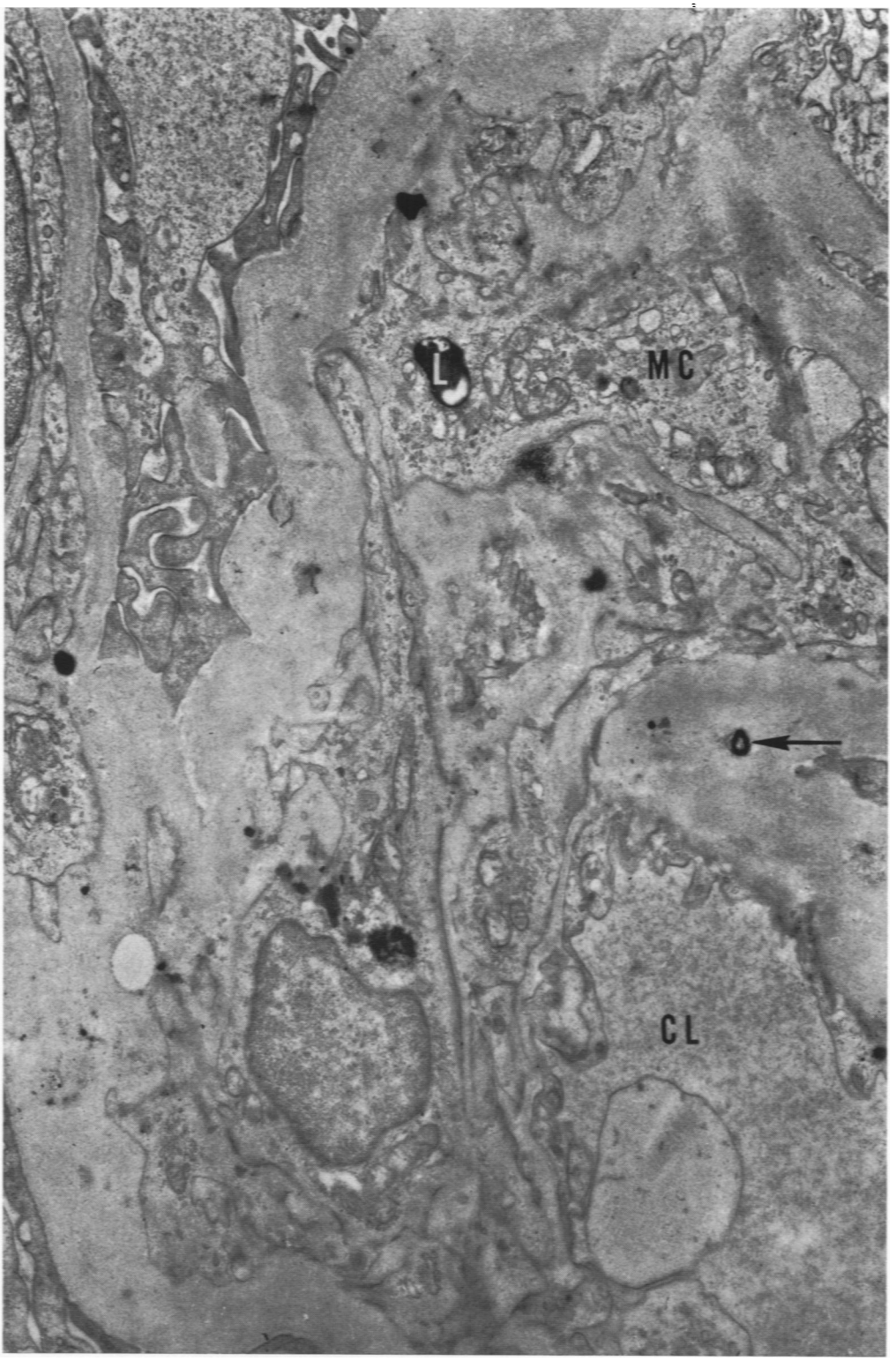


Fig. 5. Increase in mesangial matrix and cells (MC) in cirrhotic patient without renal insufficiency. Lipid droplets (L) are present, as well as dense body (arrow) in lamina densa. × 14,700.

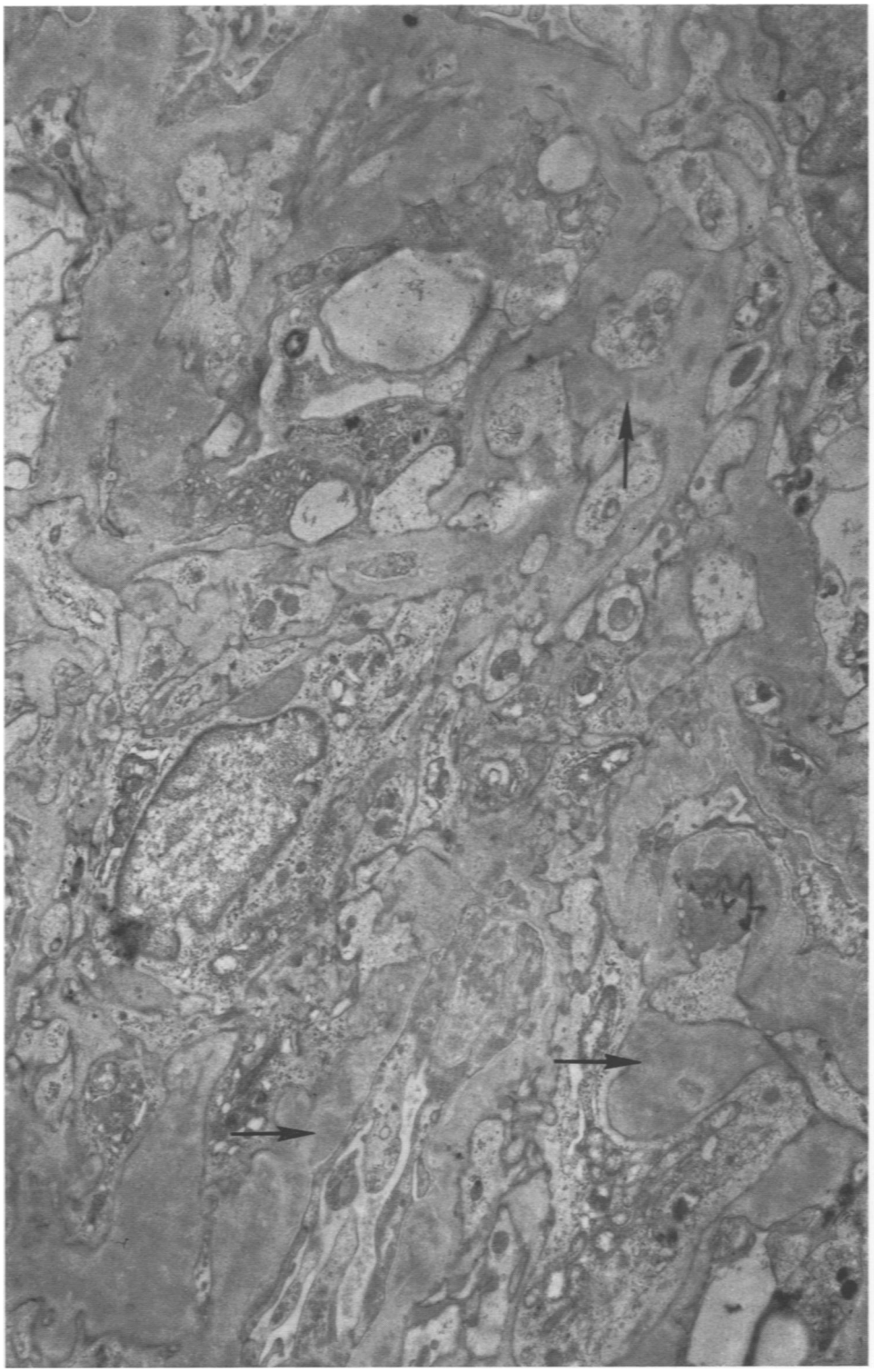
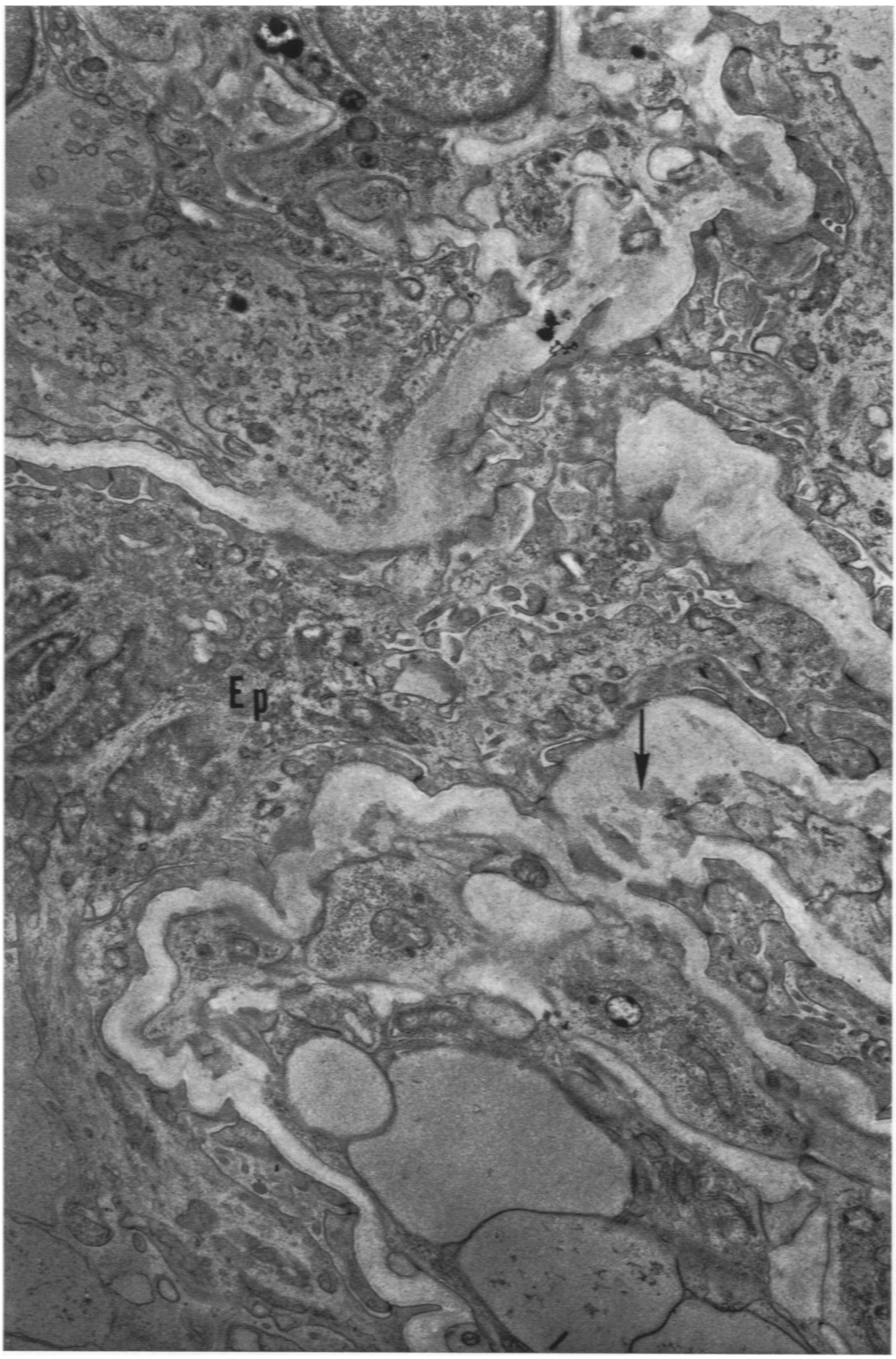


Fig. 6. Mesangium from cirrhotic patient with renal insufficiency, containing more matrix and cells than noted in patients without functional impairment as depicted in Fig. 5. Electron-dense deposits (arrows) are scattered throughout matrix. × 9000.

Fig. 7. Portions of capillary loops from glomerulus of cirrhotic patient with renal insufficiency. Epithelial cell (Ep) change is pronounced. Lamina densa, particularly in region of the mesangium, contains dense deposits (arrows). Loops appear to be converted into lobules. × 9000.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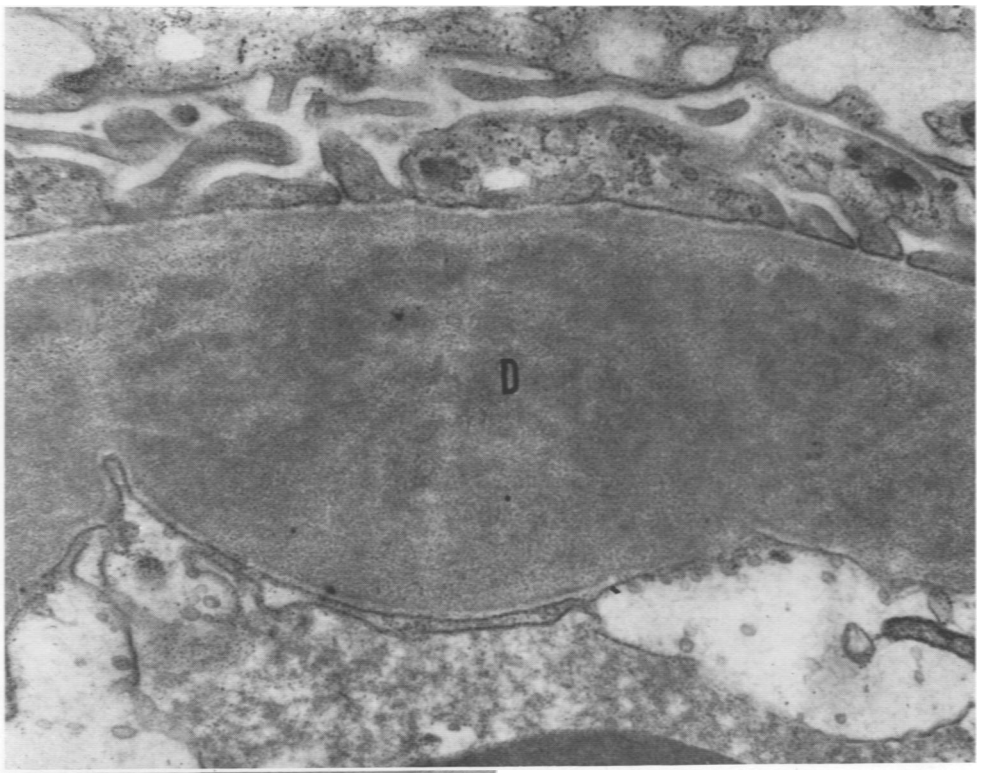

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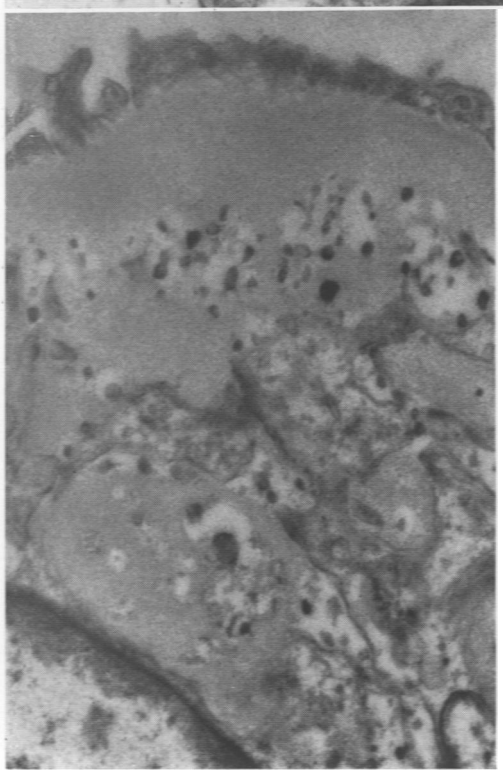

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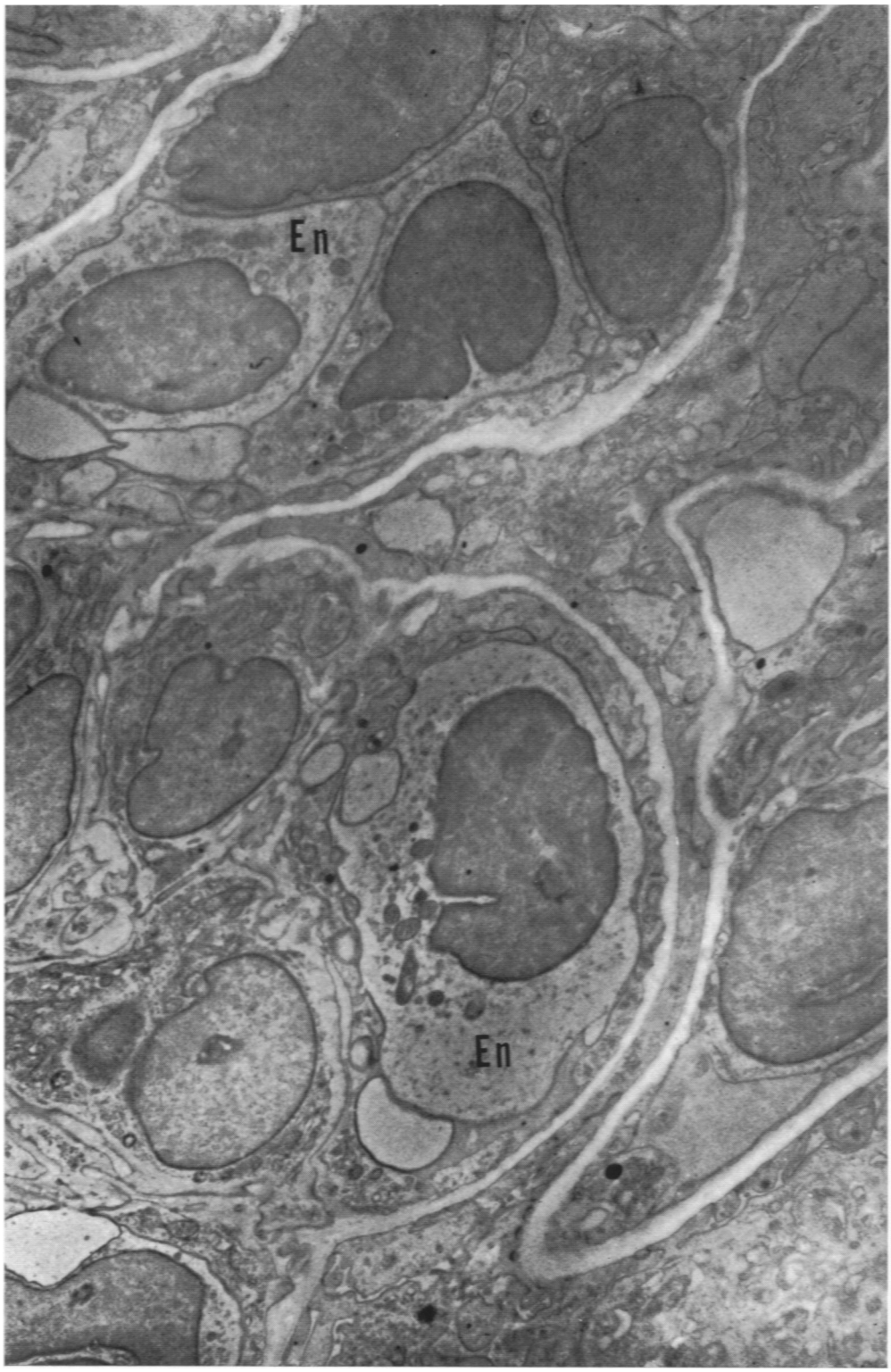
Fig. 8. Deposit (D) in endothelial aspect of lamina densa of cirrhotic patient with renal insufficiency. Accumulation is denser and more discrete than that noted in Fig. 4. × 27,600. **Fig. 9.** Round bodies between endothelium and lamina densa noted in 1 patient with renal insufficiency. × 19,700. **Fig. 10.** Portion of glomerulus from cirrhotic patient with renal insufficiency demonstrating increased numbers of endothelial cells (En). Lamina densa in this area appears unaltered. × 6500.



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