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Electron Microscopic Observations of the Kidney in the Generalized Shwartzman Reaction*

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Summary. Sequential changes in the kidney during the generalized Shwartzman reaction were studied electron microscopically. The first anatomical change was infiltration of neutrophils into the glomerular capillaries. Endothelial damage was not noticeable until the capillaries were filled with fibrin deposits. Fibrin appeared in the mesangium at almost the same time as in the capillary lumina, traversing through the endothelial fenestrae. Endothelial damage was more common in the mesangial portion than in the peripheral portion of the capillaries. Severe mesangiolysis developed after loss of endothelial cells had been followed by massive penetration of intracapillary contents. Later, signs of repair were evident in some parts of the damaged endothelium. The development of cortical necrosis coincided with the appearance of mesangiolysis and arteriolar thrombotic lesions.

Key Words: Endotoxin – Intravascular coagulation – Glomerular ultrastructure – Mesangiolysis – Renal cortical necrosis.

Introduction

The generalized Shwartzman reaction is a pathologic entity most readily produced by two successive injections of bacterial endotoxin. A necessary condition for the development of this reaction is disseminated intravascular deposition of fibrin leading to occlusion of small blood vessels in many organs. In the kidney, this change is particularly severe and causes bilateral renal cortical necrosis, which has been regarded as the *pathognomonic* lesion of the reaction (Thomas and Good, 1952). There have been a few reports dealing with the ultrastructure of the kidney in this reaction (Bohle et al., 1958; Pappas et al., 1958; McKay et al., 1966), but they have contributed little to disclosing the

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sequential changes in the kidney. The study presented here was undertaken to perform detailed observations on the glomerular events in the development of the generalized Shwartzman reaction. The results obtained may be helpful for further understanding of certain renal disorders in which intravascular coagulation may be closely related to the evolution of glomerular lesions.

Materials and Methods

Male albino rabbits weighing 2.0 to 2.8 kg were injected with one or two doses of 0.04 mg/kg of endotoxin (lipopolysaccharide from E. coli 026: B6, Difco Lab. Detroit, Michigan, USA) intravenously. Eighteen animals were killed 1, 3, 8 and 24 h following one injection of endotoxin. Seventy animals were given two doses of endotoxin 24 h apart and killed 30 min, 1, 2, 3, 4, 6, 9, 12, 24, 48 and 72 h after the second injection. Fourteen animals died during the experiment.

Specimens for electron microscopy were fixed in 3% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4, for 3 h at 4°C. They were postfixed in 1% osmium tetroxide for 1 h. After dehydration with graded ethanols, they were embedded in Epon 812. The sections were stained with uranyl acetate and lead citrate and examined with JEM 100 C electron microscope. Another portion of the tissue was fixed in 10% formalin for light microscopic observation.

Results

No fibrin thrombi were detected in the period following the first injection of endotoxin. Small numbers of neutrophils and a few platelets appeared in the glomerular lumen, but no distinct changes were observed in the endothelial, epithelial or mesangial cells, nor in the basement membrane. The glomerular changes after the second injection of endotoxin will be described in two phases, related to the development of cortical necrosis after 9 h.

After 30 min to 6 h

Light Microscopy. The number of neutrophils in the glomerular lumen had increased by 2 h. Neutrophils were observed singly or accumulated in a line in the peripheral part of the glomerulus. Fibrin could be detected as early as 2 h and became abundant between 4 and 6 h. In addition, infiltration of mononuclear cells with irregularly indented nuclei was conspicuous in some animals. The capillary lumen became distended and was engorged by fibrin thrombi or erythrocytes after 4 to 6 h. At this time tubular degeneration was unremarkable, and the interstitium and blood vessels appeared to be normal.

Electron Microscopy. Infiltrating neutrophils were always found in the capillary lumen (Fig. 1a). Most were normal in appearance, but some contained various vacuoles (Fig. 1b). In addition, a few fragmented neutrophils could be seen in the glomeruli especially after 30 min to 1 h (Fig. 1c). There was, however, no definite structural damage to the endothelial cells with the exception of transient microvilli formation. Platelets also appeared in the glomeruli, but

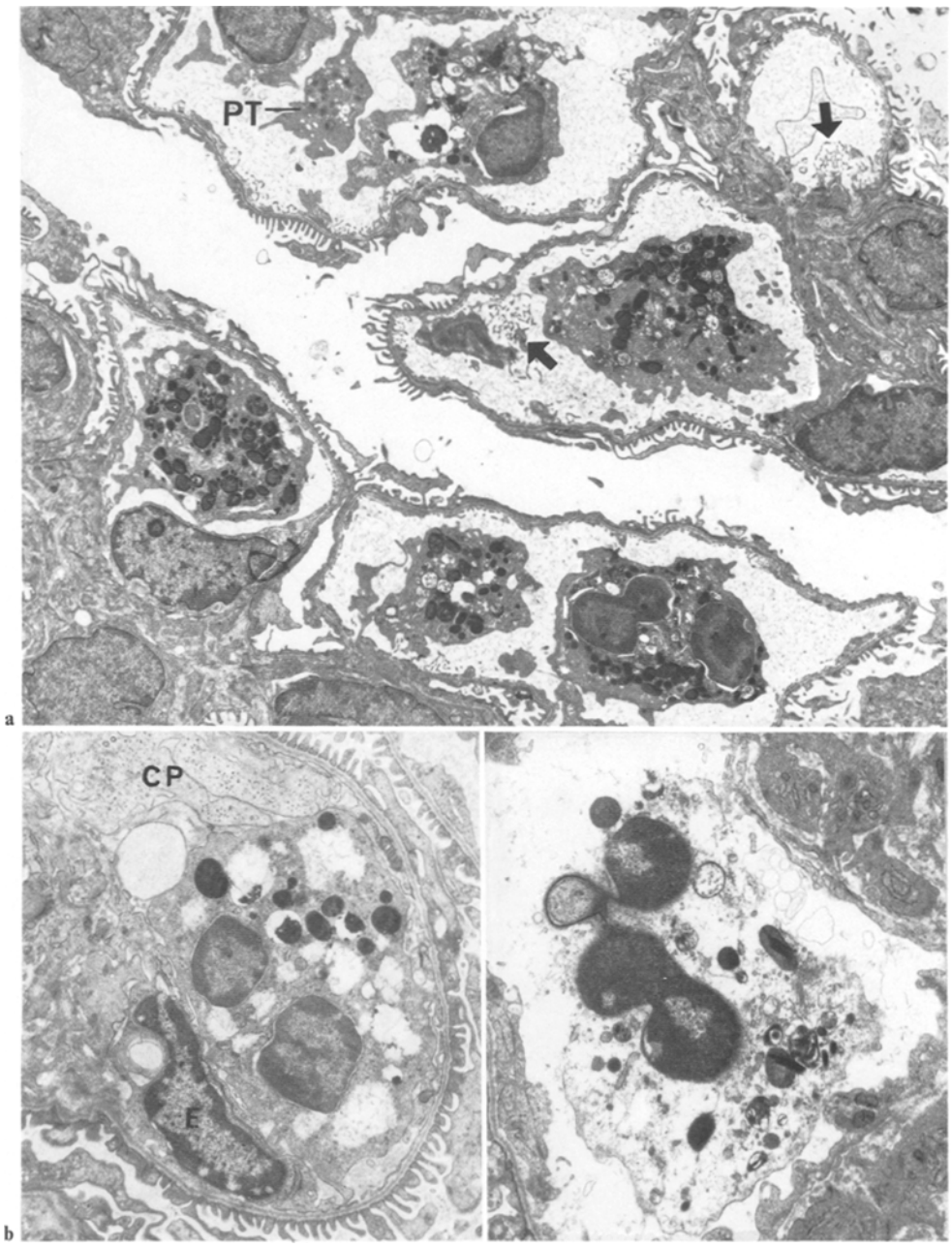


Fig. 1. a Accumulation of neutrophils in the glomerular capillary lumina. The cytoplasm of endothelial cells show microvillus formation (arrows). *PT*, platelet. 1 h after the second endotoxin injection. ×4800. **b** A neutrophil observed 30 min after the second endotoxin injection contains many vacuoles in its cytoplasm. Specific granules appear to be decreased in number. *E*, endothelial cell; *CP*, cytoplasmic processes of a monocyte. ×3900. **c** A neutrophil showing a gapping defect in its cell membrane at which cytoplasmic constituents appear to be partially disgorged. 30 min after the second endotoxin injection. ×6500

their number was small in general. None of them showed any evidence of viscous metamorphosis.

Fibrin appeared in the glomeruli as early as 2 h (Figs. 2–4). At beginning it seemed to precipitate freely in the capillary lumina, often associated with platelets or platelet fragments (Fig. 2). In addition, neutrophils and mononuclear cells were often seen around small deposits of fibrin, conceivably showing the process of engulfing this material (Figs. 3, 4). Specific granules of neutrophils were variably decreased in numbers and there was occasional diminution or loss of electron density of glycogen granules. The migrant mononuclear cells showed many characteristic features of blood monocytes as described previously (Shigematsu, 1970; Kondo et al., 1972; Watanabe and Tanaka, 1976). The cell surface showed irregular cytoplasmic protrusions toward fibrin deposits and there were numerous pinocytotic vesicles and vacuoles in the cell periphery. Electron dense granules (sometimes membrane bound), resembling lysosomal granules, intermingled with fibrin strands (Fig. 4). These cells were located in the capillary lumen often compressing the endothelial cell cytoplasm and not situated under the endothelium or in the mesangium.

Fibrin was seen under the endothelium and in the mesangial areas at almost the same time as in the capillary lumina (Figs. 2, 3). It appeared noteworthy that fibrin permeated the mesangial matrix more prominently than the subendothelial space at the peripheral part of the capillary loops. Mesangial cell cytoplasm was often swollen and contained some fat vacuoles, but phagocytosis of fibrin was inconspicuous. The basement membrane showed no obvious abnormalities. Fibrin was not seen in Bowman's space.

After 9 to 72 h

Light Microscopy. After 9 to 12 h cortical necrosis became evident. The glomeruli were markedly enlarged and the distended capillaries were occluded by fibrin thrombi or aggregated erythrocytes. Large amounts of eosinophilic material with or without erythrocytes were occasionally noted in Bowman's space. Proteinaceous casts were often present in the necrotic tubuli. Arterioles and interlobular arteries were simultaneously occluded by fibrin and platelets thrombi with transmural penetration of erythrocytes.

After 24 to 48 h cortical necrosis became confluent, typically occupying most of the width of the cortex, though thin surviving areas were usually found immediately under the capsule and at the corticomedullary junction. The glomeruli showed various changes such as severe congestion, thrombosis or frank necrosis. The arteries and arterioles were also necrosed and thrombosed. Infiltration of neutrophils was often conspicuous in the affected zone. Calcium deposition occurred in the necrotic cortex after 48 to 72 h.

Electron Microscopy. Thromobotic lesions occluding the lumina of glomerular capillaries included partially or completely degranulated platelets, erythrocytes, neutrophils and some undeterminable cellular fragments (Figs. 5, 6). Fibrin rarely showed periodicity and was revealed either as a fluffy or closely packed

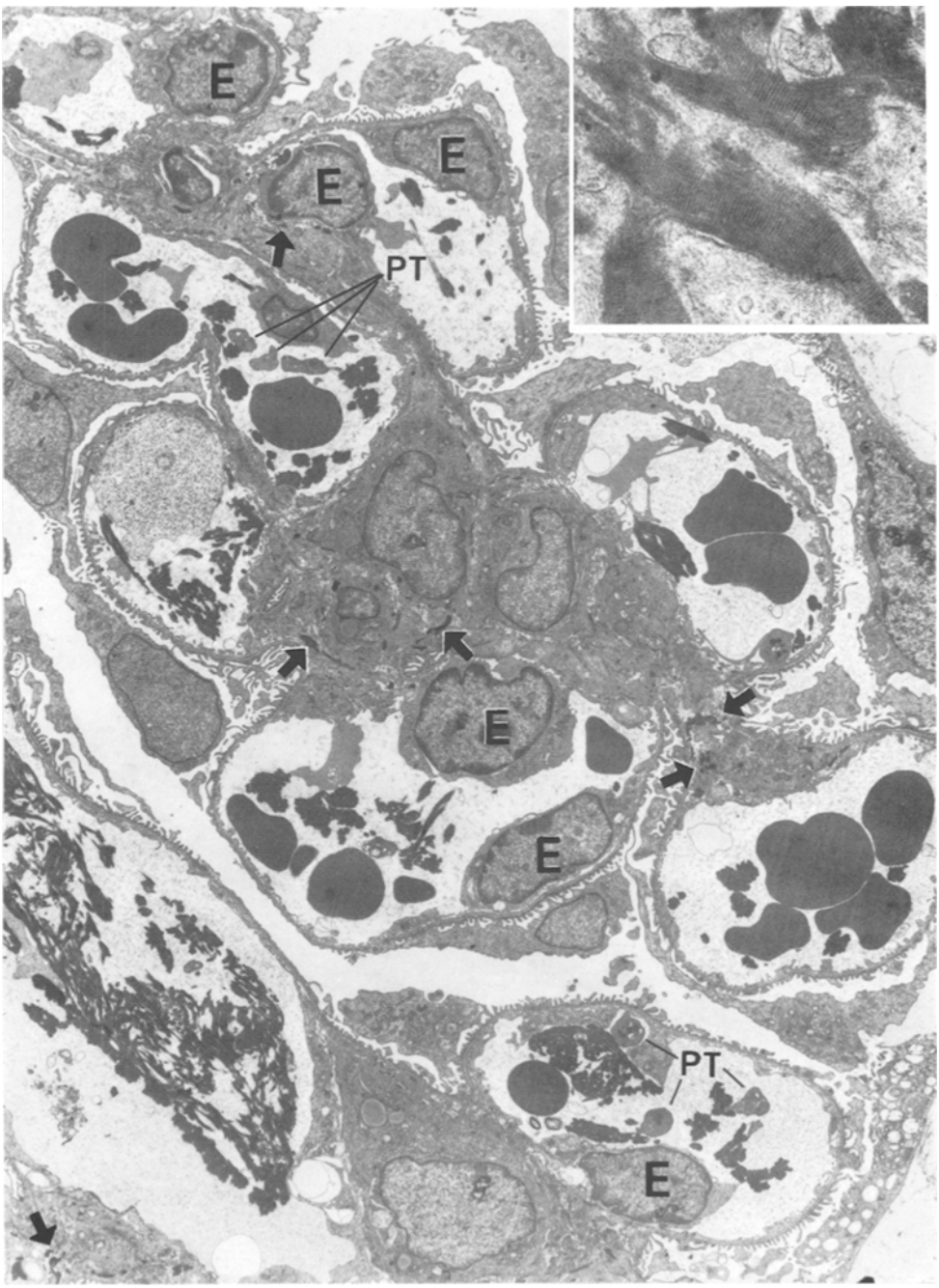
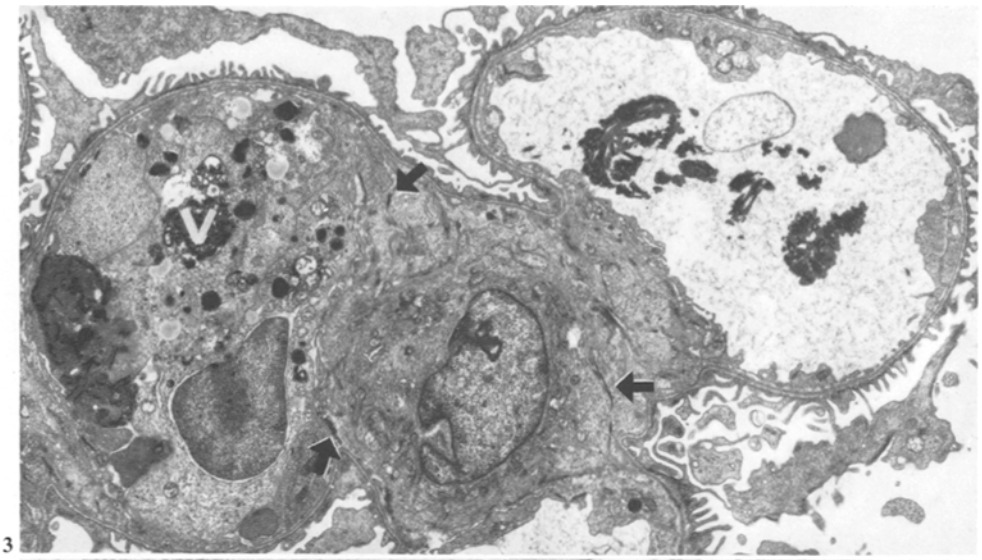


Fig. 2. Fibrin precipitates lie free in the capillary lumina. Platelets (*TP*) are trapped in the fibrin strands. Fibrin is also seen in the mesangium (arrows). The endothelial cells (*E*) appear well preserved. The *inset* shows fibrin in the mesangium, with 195 Å periodicity. 3 h after the second endotoxin injection. ×3300; *inset*, ×29,000



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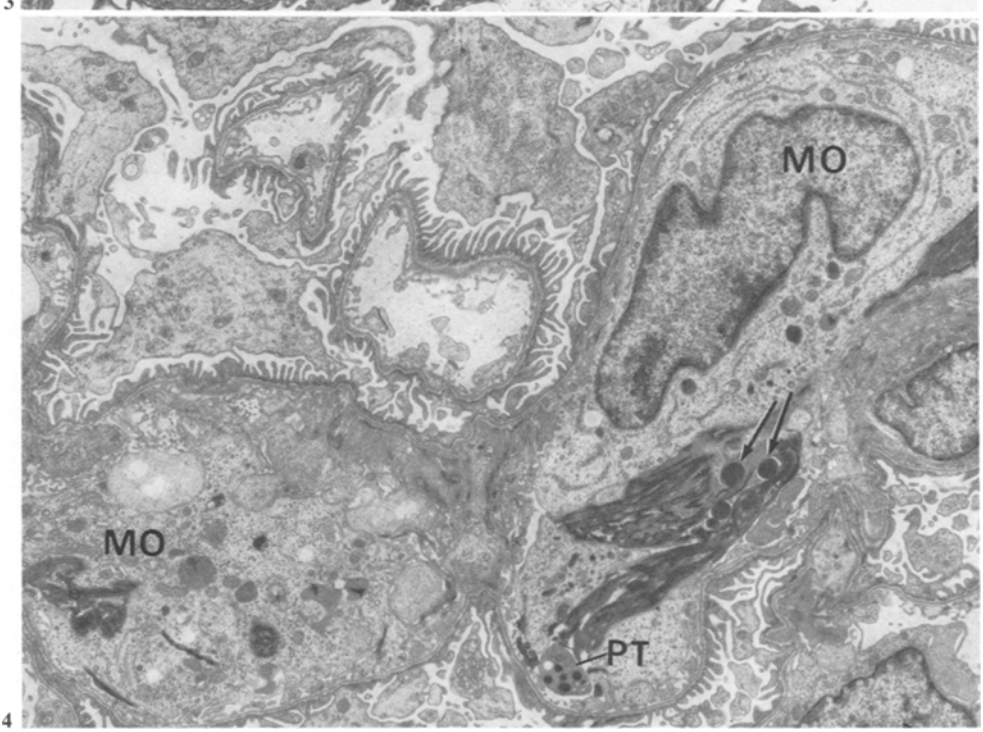

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Fig. 3. A neutrophil showing phagocytosis of fibrin. The specific granules are decreased in number and found mostly near the phagocytic vacuole (*V*). Fibrin strands are seen in the capillary lumen and also in the mesangium (arrows). Note the absence of fibrin deposits in the subendothelial space at the periphery of the capillary. 2 h after the second endotoxin injection. × 5500

Fig. 4. Large mononuclear cells (*MO*) migrating around fibrin deposits. The cell surface shows numerous cytoplasmic protrusions with pinocytotic vesicles and vacuoles. Electron dense granules resembling lysosomal granules are seen intermingled with fibrin strands (arrows). *PT*, platelet. 2 h after the second endotoxin injection. × 5200

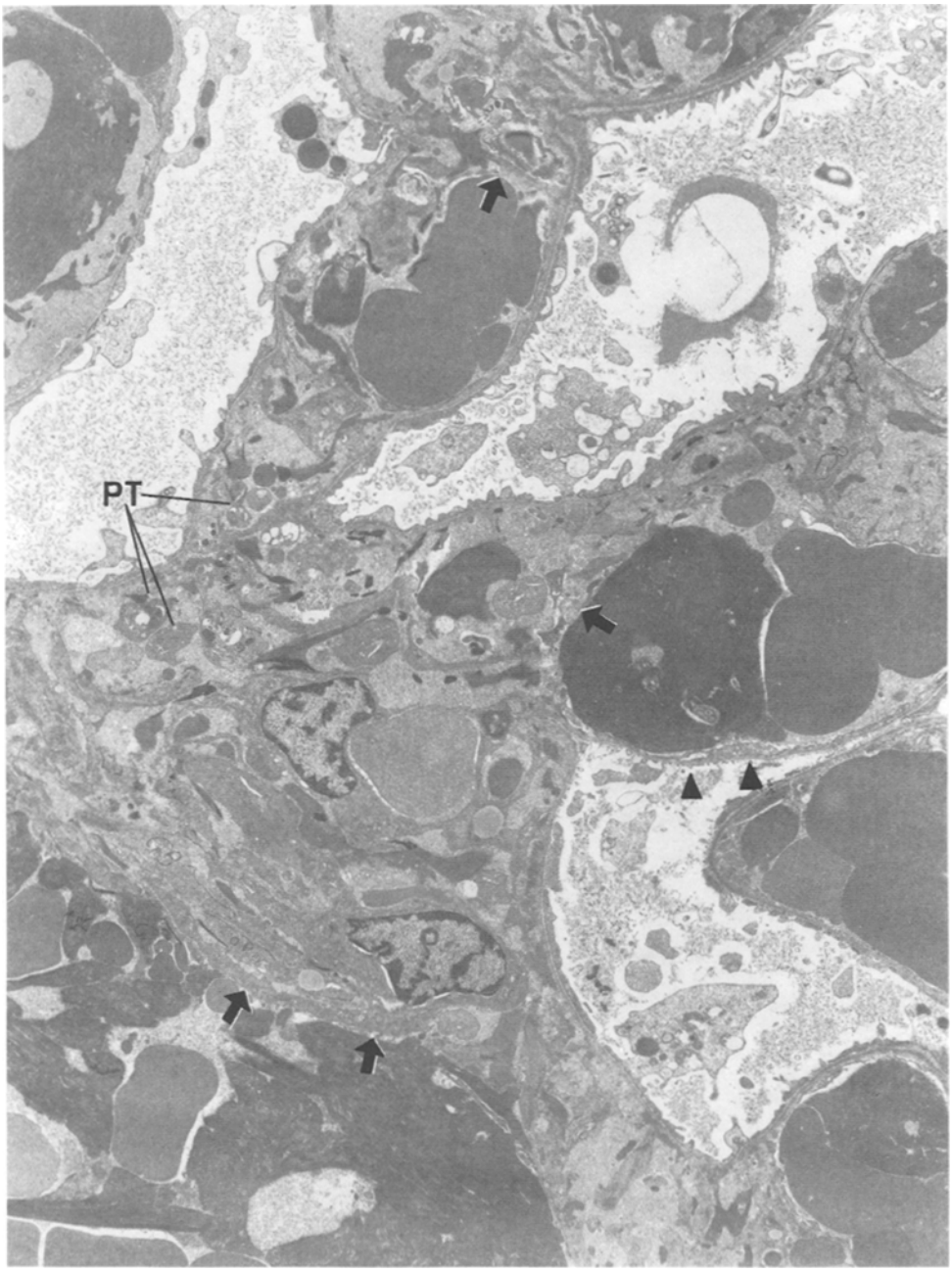
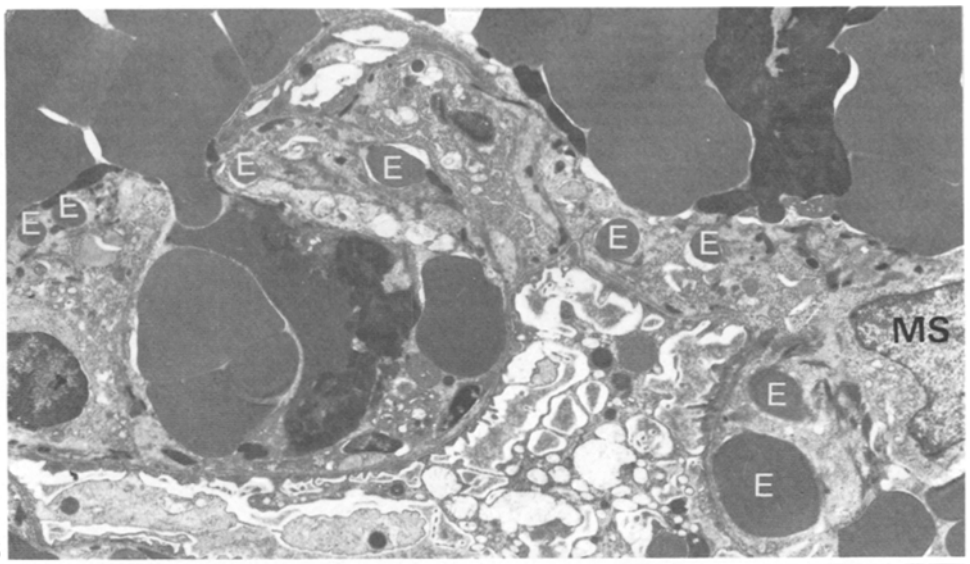


Fig. 5. Aggregates of fibrin and erythrocytes obstruct the capillary lumina. Endothelial layer is widely attenuated and desquamated especially in the mesangial portion (arrows). Note loosening of the mesangial matrix with penetration of fibrin and platelets (*PT*). The epithelial cells show fusion of foot processes or focal detachment from the basement membrane (arrowhead). Flocculent materials are seen in Bowman's space. 9 h after the second endotoxin injection. × 5000



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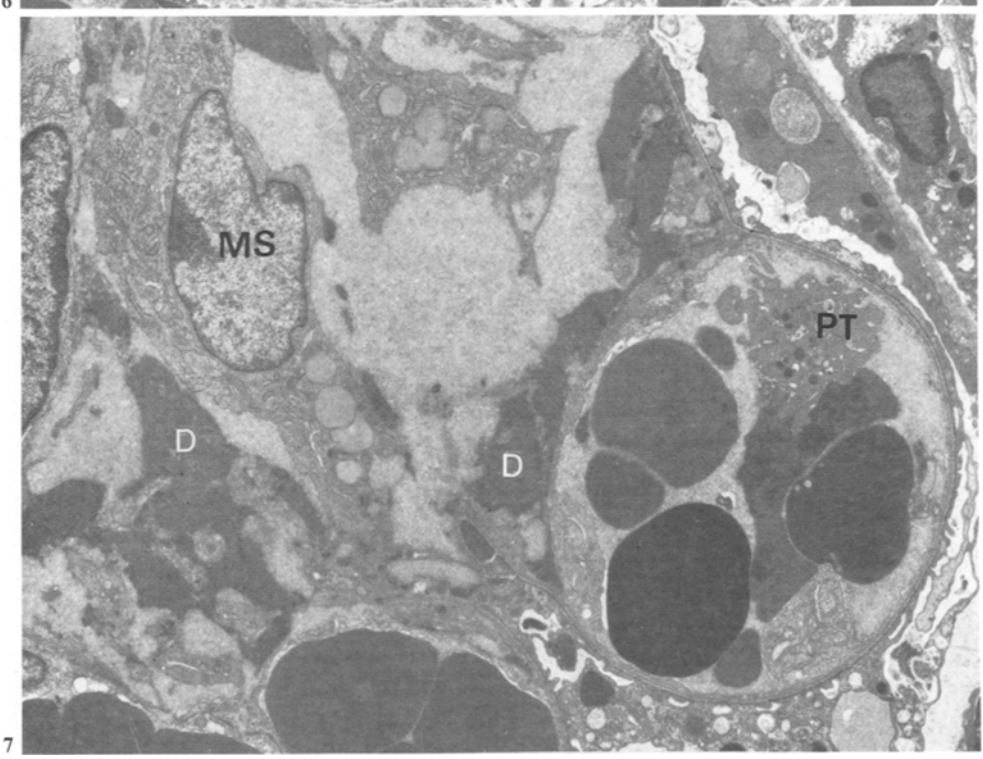

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Fig. 6. Many fragmented erythrocytes (*E*) are seen in the disintegrated mesangium. The epithelial cells show formation of various vacuoles filled with proteinaceous materials. Note necrosis of the endothelial cell layer. *MS*, mesangial cell. 9 h after the second endotoxin injection. ×5100

Fig. 7. Marked disintegration of the mesangial matrix by the imbibition of plasma constituents. Degenerated fibrin or cell debris (*D*) is also seen in the matrix. Fatty vacuoles are present in the mesangial cell (*MS*). The epithelial foot processes are fused. *PT*, platelet. 24 h after the second endotoxin injection. ×6500

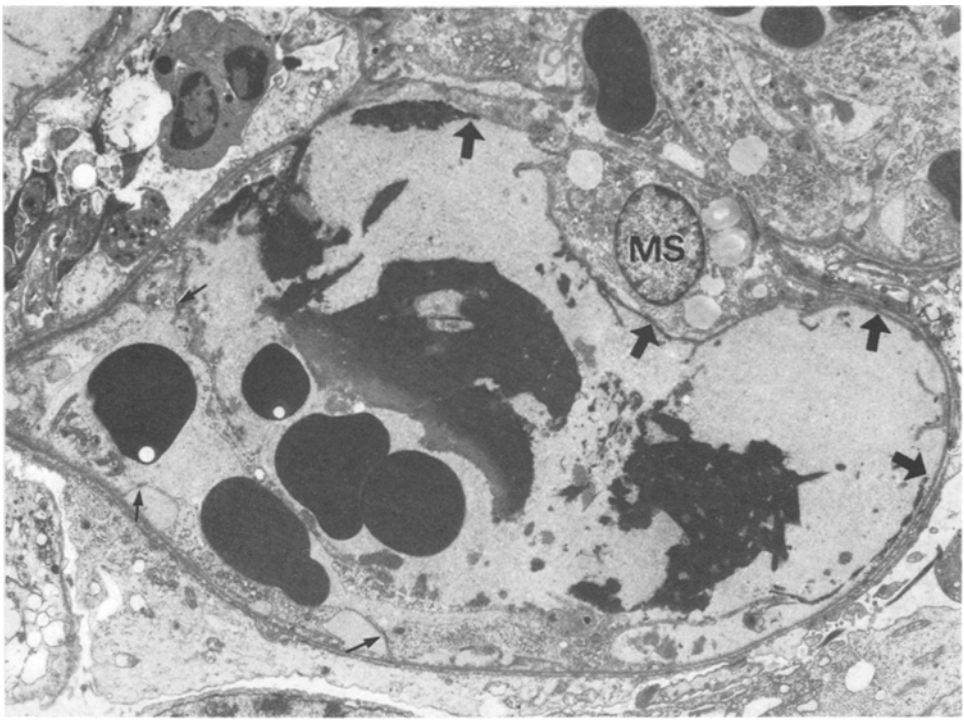

Fig. 8. Irregular bridging of the capillary lumen by the elongated endothelial cell cytoplasm. Small arrows show junctional complexes. Note no endothelial lining, particularly in the mesangial portion (large arrows). Fatty vacuoles are seen in the denuded mesangial cell (*MS*). There are erythrocytes in the mesangium. Fusion of foot processes is seen. A neutrophil, platelets and fibrin are present in Bowman's space (upper left). 48 h after the second endotoxin injection. × 3700

fibrillar and finely granular structured material. Endothelial cells were distorted by the intraluminal contents and displayed severe alteration of the cellular architecture indicating the onset of necrosis in many areas. Damage to the endothelial cells appeared more prominent in the mesangial half of the capillary loop, where the endothelial lining was widely denuded. Hence the mesangial cells and matrix were directly exposed to the capillary lumen. Simultaneously, the mesangial matrix showed edematous swelling or lysis and was invaded by fibrin, varying numbers of platelets and fragmented erythrocytes (Figs. 5, 6). With time lytic process of the mesangial matrix became more prominent owing to accumulation of plasma constituents (Fig. 7). Cytoplasmic processes of mesangial cells became necrotic and were seen floating in the disintegrated mesangial matrix. In contrast, the basement membrane was seen to be fairly well preserved, though apparently stretched and thin. Epithelial cells showed irregular fusion of foot processes, increase of cytosomes and formation of various vacuoles often containing finely granular, sometimes clumpy material (Figs. 5, 6). Local disintegration and desquamation of epithelial cells were also evident (Fig. 5). Eventually Bowman's space was filled with finely granular or floccular material sometimes including fibrin and cellular fragments.

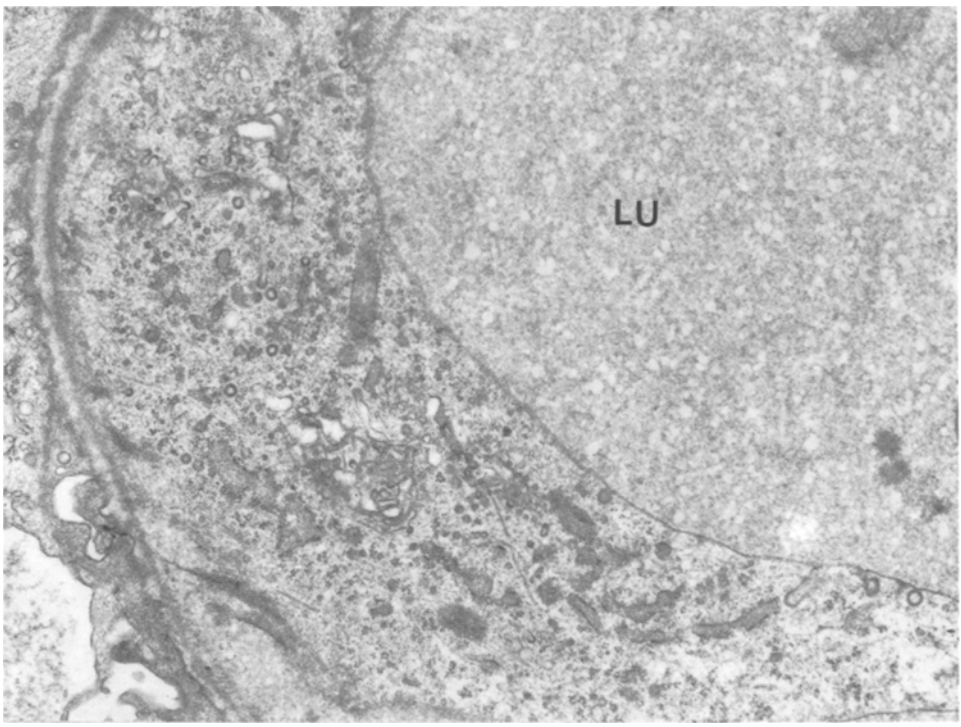

Fig. 9. An endothelial cell layer partially covering the peripheral capillary wall. The cytoplasm is thick and contains prominent Golgi complexes, many ribosomes, coated vesicles, microtubules and pinocytotic vesicles. The capillary lumen (*LU*) is filled with flocculent materials. Epithelial foot processes are fused. 48 h after the second endotoxin injection. × 12,700

In severely affected areas, especially in the 24 and 48 h specimens, definite identification of the mesangium became increasingly difficult and some glomeruli were merely seen as a cluster of blood channels crowded with erythrocytes, thrombi and plasma constituents of an increased density. Erythrocytes were often seen separated by disintegrated cytoplasmic network, conceivably of the mesangial cells. In addition to these destructive changes, signs of repair became evident in the damaged endothelium after 48 h. The thick endothelial layer containing many polyribosomes, vesicles (including coated ones), prominent Golgi complexes and rough endoplasmic reticulum was observed, especially in the peripheral portion of the capillary wall (Figs. 8, 9). Several junctional complexes were found in the adjacent endothelial cells. These endothelial cells extended thin, long cytoplasmic processes toward the opposite side of the capillary wall, forming in this way irregular cytoplasmic bridges across the lumen. In contrast, the mesangial side of the capillary loop often remained denuded and mesangial cells were exposed directly to the capillary lumen (Fig. 8).

Discussion

The initial reaction to sequential endotoxin injections was accumulation of neutrophils, followed by progressive intravascular clotting. Most of the neutrophils were well preserved and free from disruption, but a few fragmented cells were detected in the glomerular capillaries. Other neutrophils also showed decrease in the number of specific granules and formation of various vacuoles, and often gained an intimate contact with fibrin deposits.

The role of neutrophils in intravascular clotting has long been a subject of controversy; neutrophils contain many enzymes (Cohn and Hirsch, 1960; Baggiolini et al., 1969), and it is conceivable that many of these enzymes could be involved in the process. Horn and Collins (1968a, b) have considered that the neutrophilic specific granule is the source of the clot-promoting factor operative in this reaction. In fact, it has been recently reported that the neutrophils obtained from rabbits that had received two doses of endotoxin have considerable coagulant activity (Niemetz, 1972; Niemetz and Fani, 1973), although Riddle and Barnhart (1964) have shown that neutrophil granules may participate in dissolution of fibrin. Degranulation of neutrophils is also known to occur during phagocytosis (Hirsch and Cohn, 1960; Zucker-Franklin and Hirsch, 1964; Baiton, 1973). The present observations revealed the intimate relationship of neutrophils to fibrin deposition, but the exact mechanism initiating coagulation remains obscure.

The present study failed to support the opinion that platelets are essential in the activation of massive intravascular clotting (Evans and Mustard, 1968; Margaretten and McKay, 1969; Mustard and Packham, 1970). Aggregation of platelets was not conspicuous in the glomeruli and there was little evidence of viscous metamorphosis or necrosis in the early phase of endotoxemia.

The suggestion that extensive endothelial damage may play a primary role in this reaction remains to be demonstrated. In many experimental conditions, thrombi are considered to form in areas where connective tissue is exposed (Stemerman et al., 1971; Baumgartner, 1974; Mustard et al., 1974). Damage to endothelial cells might be a requisite for the activation of coagulation process by release of tissue thromboplastin (Astrup and Buluk, 1963; Watanabe, 1970) and by the activation of contact factor (McKay et al., 1971). In endotoxin treated animals, endothelial damage prior to fibrin deposition has been observed in the aorta (Spaet, 1970) and mesenteric arteries (McGrath and Stewart, 1969; Stewart and Anderson, 1971). McKay et al. (1966), however, have failed to show it in kidney and lung capillaries. In the present study, glomerular endothelial cells apparently remained unchanged until the capillary lumina were filled with fibrin deposits. Therefore, it appears likely that endothelial damage in the glomeruli is secondary to the ischemia produced by thrombotic lesions, though the possibility still remains that functional alterations of endothelium could occur without definite structural damage.

The major event in the glomerulus was the deposition of fibrin, first noted at 2 h after the second endotoxin injection. From 4 through 6 h the intraluminal glomerular deposits became extensive. Migrant monocytes, neutrophils, and

fibrinolysis might all produce fibrin dissolution, though this was ineffective. In addition, fibrin appeared in the mesangium at almost the same time as in the capillary lumina, firstly traversing through the endothelial fenestrae. Accumulation of fibrin in the subendothelial space at the periphery was an inconspicuous feature. This is in remarkable contrast with other conditions, such as certain forms of glomerulonephritis and toxemia of pregnancy, in which the intraglomerular clotting process was chronic and slowly progressive (Vassalli et al., 1963; Kincaid-Smith, 1973; McKay, 1973; Watanabe and Arihiro, 1975; Watanabe and Tanaka, 1976). In these conditions, granular deposits of fibrin or its derivatives have been shown to accumulate beneath the endothelium closely applied to the glomerular basement membrane.

The sequence of events was characterized by progressive disintegration of the mesangium, similar to that described in the glomerular injury in Habu snake poisoning, refered to as "mesangiolysis" (Kawaji and Ôyama, 1960; Suzuki et al., 1963). The mesangiolysis in Habu snake poisoning is characterized by elective destruction of the mesangial matrix resulting in baloon-like distortion of the tuft structure. In contrast, the lytic process in the present study was most likely provoked by severe endothelial damage induced by intraluminal thrombotic lesions. The dislodgement of the endothelial cells permitted increased permeation of blood constituents, including fibrin and some cellular elements, terminating in extensive mesangial lysis and finally, in necrosis of the glomeruli. A similar lytic process involving the mesangium has recently been observed in immunologically induced, rapidly progressive glomerulonephritis (Kondo et al., 1972; Shigematsu and Kobayashi, 1976). Of particular note here is that varying degrees of thrombotic lesions have been almost always observed in these glomeruli. It is conceivable that lytic or necrotizing processes resulting from intravascular clotting may also be responsible for the induction of such a disorganizing glomerulonephritis, characterized by crescent formation (Vassalli and McCluskey, 1964; Watanabe and Tanaka, 1976).

It is thus concluded that glomerular changes in the generalized Shwartzman reaction are formed by sequential changes, i.e., (1) accumulation or sequestration of neutrophils in glomerular capillaries, (2) intravascular deposition of fibrin promptly invading the mesangium, (3) Severe endothelial damage leading to the mesangiolysis which terminated in necrosis of the glomeruli. It appears noteworthy that the development of cortical necrosis coincided well with that of mesangiolysis and thrombotic arteriolar lesions.

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