Virchows Arch (1987) 411:257–265

Virchows Archiv A

Microvascular injury and repair in acute human bacterial pyelonephritis*

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Summary. Acute inflammatory cell-capillary endothelial cell interactions, related to injury and repair, were investigated light and electron microscopically in acute human bacterial pyelonephritis. In inflammatory infiltrate-adjacent microvessels, the small capillaries were completely occluded by leukocyte plugs and the large capillaries were densely filled with acute inflammatory cells adhering to the endothelium. Severe damage to small and large capillaries was observed around endothelium adherent, degranulated neutrophil granulocytes containing phagocytosed bacteria. There were spaces in the endothelium, degradation of the vascular basement membrane, of the perivascular interstitial matrix and of collagen fibrils, with fibrin deposition and vessel wall fragmentation. In the small capillaries relatively distant from the interstitial infiltrates, emigration of leukocytes was frequently seen. Around the escaping cells the endothelial lining displayed occasional discontinuities, allowing leakage of vascular fluid into the interstitial space. Some small capillaries not related to the infiltrate were occluded by fibrin thrombi with apparent damage to the endothelial cells and disruption of the capillary wall. Various reparative changes were noticed in association with this change including capillary neovascularization. The findings confirm the existence of polymorphonuclear leukocyte-mediated injury of capillaries during the development of inflammatory responses in acute pyelonephritis.

Key words: Acute pyelonephritis – Polymorphonuclear leukocyte – Endothelial cell – Microvascular injury – Microvascular repair

Since renal biopsy is not a diagnostic tool in the analysis of urinary tract infections (Coe 1986) pathological changes in acute bacterial pyelonephritis in man have been described mainly on the basis of necropsy samples (Heptinstall 1983; Bohle et al. 1984; Churg et al. 1985; Rubin et al. 1986). Although Zollinger and Mihatsch (1978) have published electron micrographs illustrating acute pyelonephritis in biopsy material, many phenomena, especially those relating to the development of the inflammatory process in the early phase of the disease, are not fully understood. This is particularly true concerning changes in the microcirculation.

This paper deals with the morphological patterns acute inflammatory cell insert cortical peritubular capillary interactions and related injury and repair in acute human bacterial pyelonephritis. We report the existence of polymorphonuclear leukocyte (PMNL)-associated severe injury of capillaries and the participation of fibrin formation at sites of endothelial damage. Our observations on the inflammatory process in the tubulo-interstitial space will be published separately.

Materials and methods

The biopsy material was obtained from three patients with clinically unexplained acute renal failure.

Case 1. Percutaneous kidney biopsy was performed on a 26-year-old woman with acute renal failure (oliguria, serum creatinine: 14.6 mg/dl) after a one-week history of loin pain,

* Some parts of this paper were presented at the XVIth Congress of the IAP, Vienna, Austria, August 31–September 5, 1986

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vomiting, fever and leukocytosis. Computed tomography confirmed the histological diagnosis and revealed bilateral kidney involvement. *Klebsiella pneumoniae* was cultured from her blood and urine, with a colony count of more than 10^5/ml in the latter. The urinary sediment contained masses of leukocytes and erythrocytes. After a 45-day treatment, the patient recovered. Vesicoureteral reflux, obstruction and malformation of the urinary tract were excluded.

Case 2. A 56-year-old man was admitted with an eight-day history of fever, dysuria and nocturia. On admission, he had a normal-sized prostate, pain on percussion of the costovertebal angles and oliguria (serum creatinine: 6.3 mg/dl). Urinalysis disclosed 3.7 g/24 h proteinuria, heamaturia and leukocyturia. His white blood cell count was 5000/mm^3, with a qualitative shift to the left. On the third hospital day, percutaneous needle biopsy was performed. Five days later the patient died. Autopsy was not carried out.

Case 3. A 73-year-old diabetic woman presented with a sudden onset of septic fever, leukocytosis and anuria (serum creatinine: 14 mg/dl). After admmission, acute abdomen developed. On laparotomy, slightly enlarged kidneys were found. A small renal tissue sample was excised for histological examination. Twenty days later the patient died. Autopsy revealed bilateral severe acute pyelonephritis with multiple necrosis of the renal papillae.

Morphological methods and nomenclature. Tissue specimens fixed for light microscopy in Dubosq-Brazi solution or in 4% formaldehyde were embedded in paraplast. Staining techniques: haematoxylin and eosin, periodic acid-Schiff (PAS), Goldner and Pearse trichrome and Jones-Chromotrope 2R. For electron microscopy, small blocks with or without previous formaldehyde prefixation were fixed in 3% glutaraldehyde, postfixed in 1% osmiumtetroxyde and embedded in Epon 812. Semithin sections were stained with Azur II-methylene blue and with the silver impregnation of Movat. Uranyl acetate and lead citrate contrasted thin sections were examined with an EM 301 (Philips) electron microscope. In case 1, direct immunofluorescence of non-fixed, frozen sections demonstrated fibrin(ogen) perivascularly and in the interstitium (G. Thoenes, München, FRG).

With regard to the nomenclature of microvessels in the cortical labyrinth, we recall (Kriz and Kaissling 1985), that the peritubular capillaries drain directly into the interlobular veins, which start in the superficial cortex and in the midcortex accompanying the coresponding artery. Since peritubular capillaries and interlobular veins have been same wall structure, the differentiation between them by structure is impossible. The diameters of microvessels in semithin sections were therefore measured with an ocular micrometer (Zeiss). Peritubular microvessels approximately 10–50 μm and 75–95 μm in diameter were regarded as small capillaries and large capillaries, respectively. The latter may represent the beginning of the interlobular veins.

Results

The biopsy material was taken from the renal cortex. There was a patchy, but very massive infiltration of the widened interstitium, mainly by PMNLs and macrophages, separating the pertibular capillaries and tubules from each other. Many PMNLs and macrophages contained bacteria. Microhaemorrhages and fibrin deposition often accompanied the cellular exudate. Within the infiltrates, silver impregnation disclosed the focal disappearance of the vascular basement membranes of the microcirculatory bed (Fig. 1). This central zone was surrounded by a zone of markedly dilated peritubular capillaries, in which PMNLs and monocytes accumulated either in the form of tight aggregates completely occluding the lumen of the small capillaries (leukocyte plugs), or in the form of individual cells distributed densely in the lumen of the large capillaries (Fig. 2). In the latter, the cells massively adhered to the endothelium and localized in the vessel wall and in the adjacent perivascular interstitial space. Around them, confluent strands of fibrin were deposited (Fig. 7, inset). Some of the PMNLs which were adherent to the endothelium or located in the wall of the vessel contained numerous engulfed bacteria. In the capillaries adjacent to the infiltrates, the number of erythrocytes was markedly reduced in parallel with the heavy accumulation of acute inflammatory cells.

Frequently, other small capillaries, showing no topographic connection with the interstitial infiltrates, were entirely occluded by fibrin thrombi with severe damage to the capillary wall. At times, fibrin thrombi were encircled by thin protrusions of the endothelial cells.

Within the massive interstitial exudates it was impossible to find the anatomical structures of the microvascular bed in electron microscopy. The microvessels surrounding this central zone could be subdivided into capillaries "adjacent to cellular infiltrates" and "distant from infiltrate". Their endothelial fenestration was rarefied or absent; instead, a continuous layer of endothelial lining was found. Platelets did not participate in any pattern of capillary damage.

Cellular signs of an inflammatory stimulated state were encountered in the aggregated and marginated leukocytes in capillaries next to the cellular infiltrate. In the small capillaries, acute inflammatory cells adhered tightly to each other and to the endothelium, and exhibited a smooth cell surface with only a few small ruffles on the surface membrane (Fig. 3). Some neutrophils contained 3–8 bacteria per section, in lytic vacuoles showing different stages of degradation. The number of lysosomal granules in these cells were markedly decreased, i.e. the cells were "degranulated" (Fig. 5, compare with Fig. 4). At times, especially in the large capillaries, the marginated monocytes exhibited significant phagocytotitc activity. Their phagolysosomes were filled with remnants of whole necrotic cells with amorphous densities, crumpled membranes, or rarely with degrading bacteria. Oc-

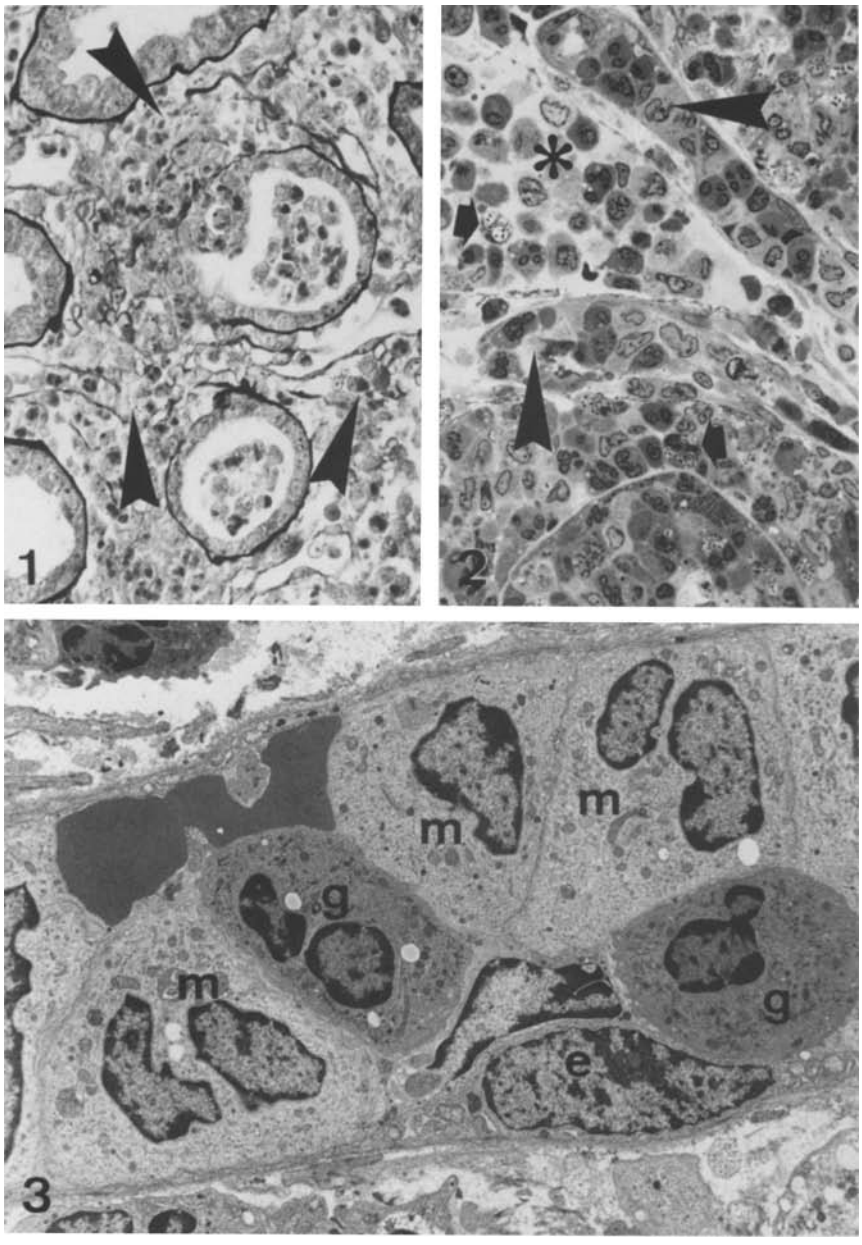


Fig. 1. Focal disapperance of vascular basement membrane of microvessels (*arrowheads*) around and within interstitial inflammatory infiltrates. Two tubules contain granulocytotic casts. Silver impregnation of Jones, × 150

Fig. 2. Infiltrate-adjacent dilated microvessels with low number of erythrocytes. Small capillaries are occluded by leukocyte plugs (*arrowheads*). Acute inflammatory cells accumulated in a large capillary (*asterisk*). Some neutrophils in the interstitium and one in the large capillary contain bacteria (*arrows*). Azur II-methylene blue, × 300

Fig. 3. Tight aggregate of monocytes (*m*) and neutrophil granulocytes (*g*) occlude a small capillary. The vessel wall is intact. *e* endothelial cell, × 4250

casionally, bacterial lying free in the vascular fluid of small capillaries were also observed.

Severe damage to small and large capillaries (Figs. 6 and 7) was detected around degranulated PMNLs containing bacteria adherent to endothelium: gaps or spaces in the endothelial lining (mean-size: 1.05 μm determined on 47 occasions) the lack of vascular basement mebrane and intra- and extravascular fibrin deposition. Cellular swelling, mitochondrial vacuolization, disrupted cell membranes or nuclear changes of endothelial cells indicating cell death (Figs. 6 and 7) were not seen. The intraluminal fibrin clots usually abutted on endothelial cells and on leukocytes adherent to endothelium (Figs. 5–7) and often interrupt the contacts between the vessel lumen and the perivascular space (Fig. 7). In series of thin sections, segments of the large capillaries with massive PMNL and monocyte adherence and fibrin formation showed fragmentation to such an extent that it was difficult to find the remnants of the vessel wall.

Neutrophil granulocytes, monocytes, a smaller number of lymphocytes, plasma cells and a few erythrocytes were distributed in a scattered fashion in the small capillaries distant from infiltrates, usually in loose aggregates of 3–7 cells. The aggregates

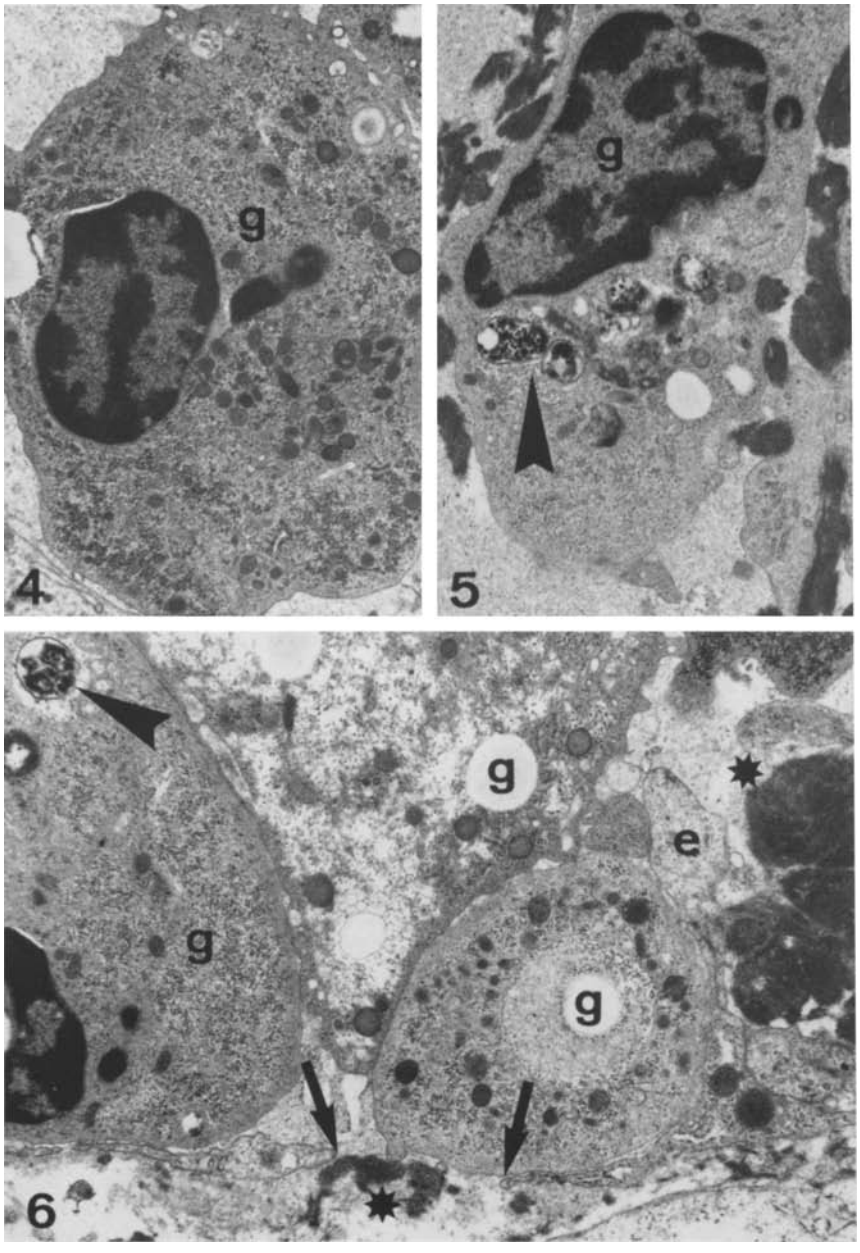


Fig. 4. A glycogen-accumulated neutrophil granulocyte (*g*) from a large capillary. The cell is rich in lysosomal granules. Compare with Fig. 5, ×9000

Fig. 5. A marginated and degranulated neutrophil granulocyte (*g*) containing bacteria (*arrowhead*) from a large capillary. Fibrin strands adhere to the cell membrane. ×8840

Fig. 6. Microvascular injury in a small capillary around endothelium-adhered, variously degranulated neutrophils (*g*): space in the endothelium (*between arrows*), focal disappearance of vascular basement membrane, perivascular interstitial matrix and collagen fibrils, intra- and extravascular fibrin deposition (*asterisk*). *Arrowhead* denotes a phagocytosed bacteria. The endothelium shows no signs of ischemic changes. Along intraluminal fibrin strands, an endothelial cell process (*e*) protrudes into the lumen. ×10830

did not occlude the lumen completely. Rarely, PMNLs contained engulfed bacteria within their phagolysosomes, but microvascular injury could not be observed around them (Fig. 8). Within this zone, inflammatory cell emigration was the most striking feature. Leukocytes adhering slightly to the endothelium either retained their ovoid shape or became flattened along the contacts with the endothelium.

At times, the escaping cell inserted a cytoplasmic process through a gap between the endothelial lining and the basement membrane and crawled into the subendothelial space. Between the emigrating cells and the endothelial lining lifted up by the penetrating pseudopod, there was a close contact (Fig. 9, compare with Figs. 10 and 11). The subendothelially localized leukocyte emigrated into the interstitium through small spaces in the vascular basement membrane. In some electron micrographs, emigration was found next to intercellular junctions.

The anatomical integrity of the capillary was often damaged. The lifted endothelial cell processes around the penetrating pseudopod either seemed to "be broken up" into small fragments (Fig. 10), or were detached from the escaping leuk-

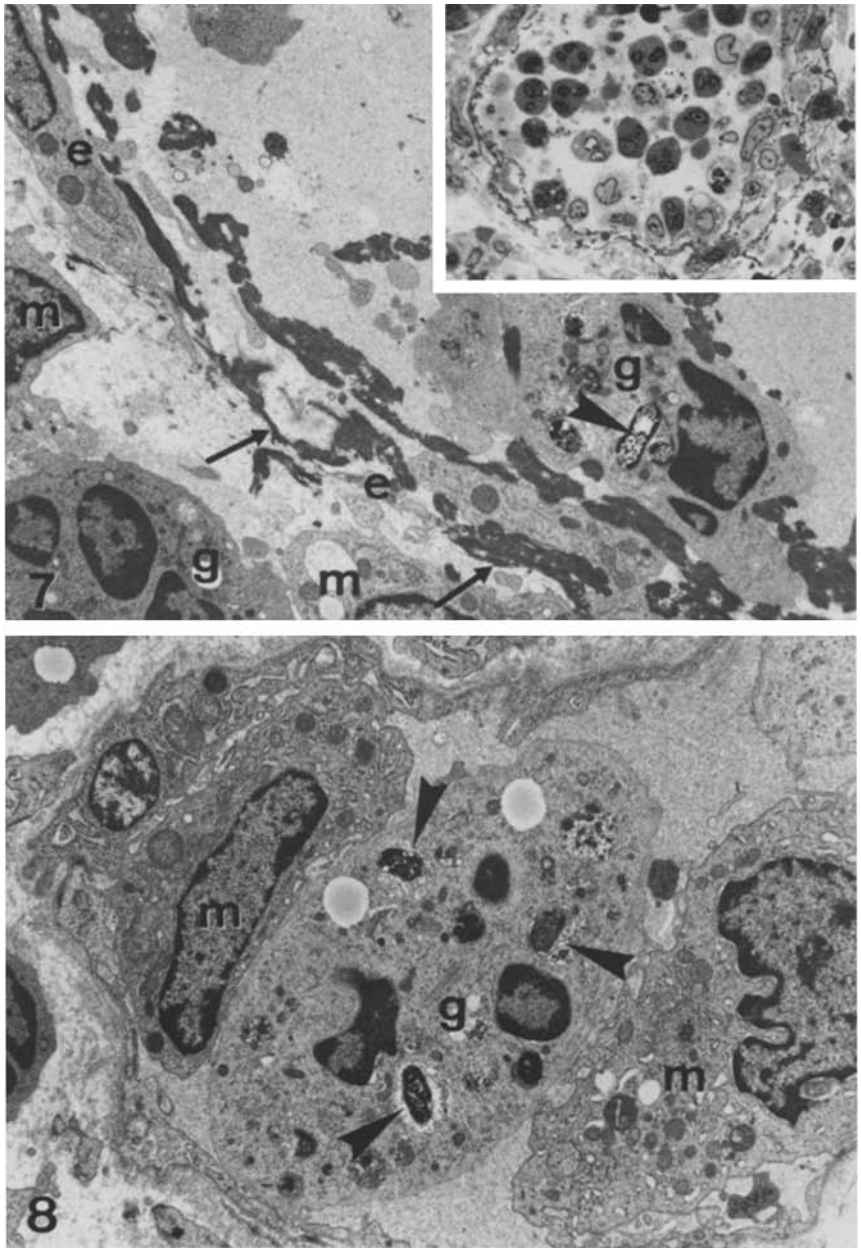


Fig. 7. Microvascular injury in a large capillary (the same vessel is shown in inset). Masses of fibrin strands abut on the fragmented endothelium (*e*), the vessel wall adherent, degranulated neutrophil granulocyte (*g*) with phagocytosed bacteria (*arrowhead*) and interrupt the communications (*arrows*) between the lumen and the partially degrated perivascular connective tissue which contains monocytes (*m*) and a neutrophil granulocyte (*g*). × 5000, inset: Azur II-methylene blue, × 300

Fig. 8. No signs of microvascular injury in an infiltrate-distant small capillary with loose aggregate of two monocytes (*m*) and a neutrophil granulocyte (*g*) containing phagocytosed bacteria (*arrowheads*) × 5780

ocyte, or after penetration, the opened gap did not undergo "resealing" (Fig. 11), resulting in the leakage of vascular fluid into the subendothelial space and through small defects in the vascular basement membrane, into the interstitial space.

In fibrin-plugged microvessels extensive disruption of the capillary walls were noted (Fig. 12). Among densely clumped intraluminal aggregates of fibrin, well-preserved erythrocytes and remnants of a few inflammatory cells were visible. The aggregates caused partial or total sloughing of the endothelial cell bodies from the underlying basement membrane. At sites where fibrin strands closely abutted on the endothelium, the endothelial cell membrane was hardly identifiable (Fig. 12). The cytoplasm of the endothelial cells sometimes showed remarkable swelling. Fibrin strands were also deposited on both sides of the denuded vascular basement membrane (Fig. 12) and on the collagen fibrils in the adjacent perivascular interstitial space.

As early reparative response, thin endothelial cell protrusions frequently extended toward intraluminal fibrin strands (Fig. 6). These protrusions

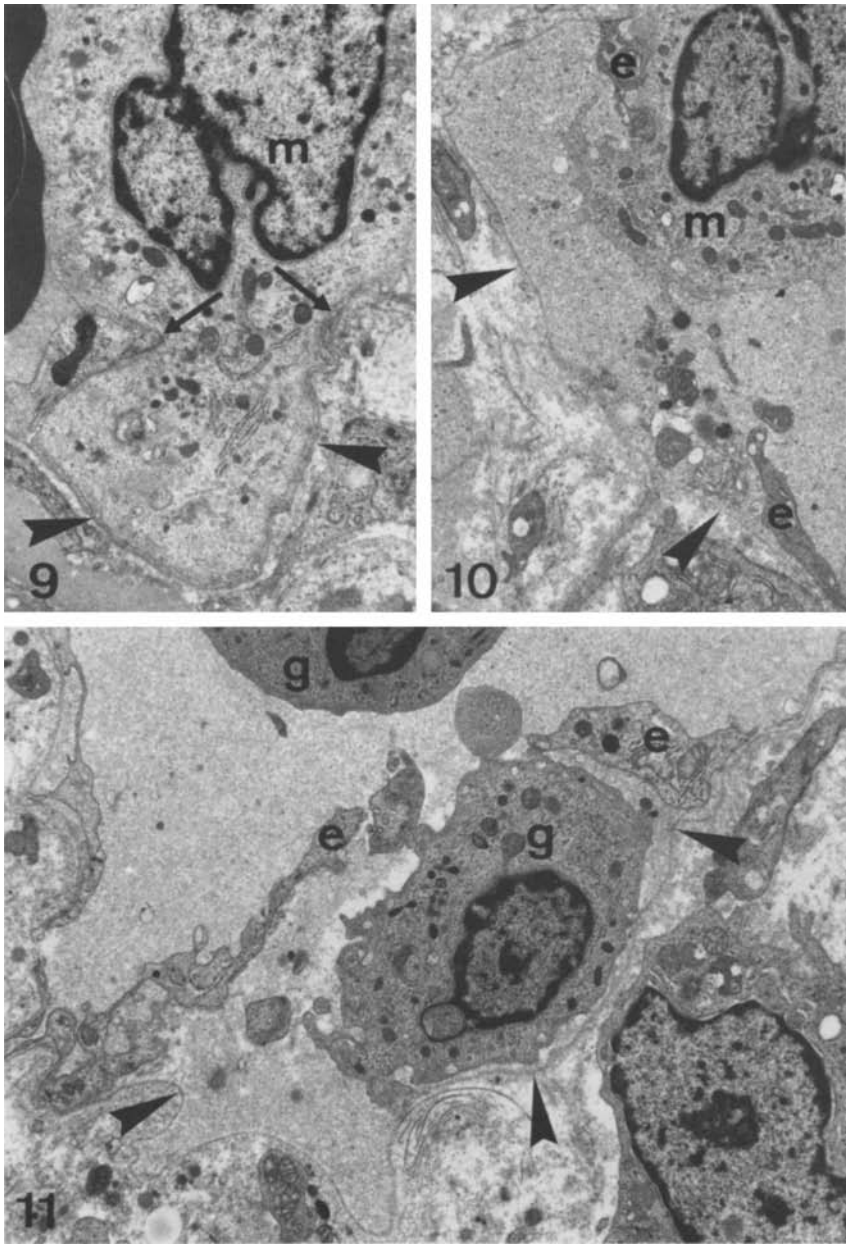


Fig. 9. Monocyte (*m*) emigration from a small capillary. The connection between the endothelial cell and the escaping cell is tight (*arrows*). Arrowheads denote vascular basement mebrane. × 7650

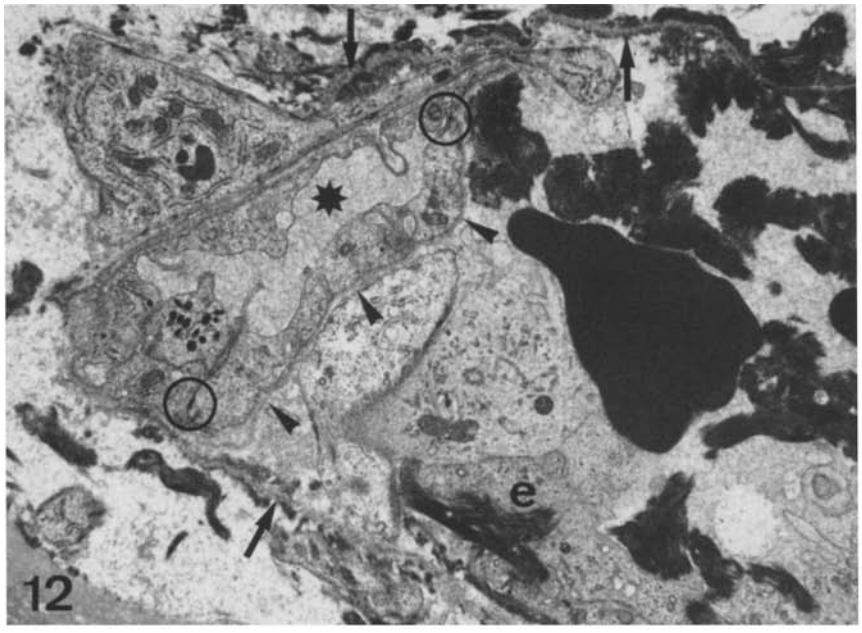
Fig. 10. The endothelial lining (*e*) of the small capillary is broken up around the pseudopod of an emigrating monocyte (*m*). Vascular fluid fills the subendothelial space. *Arrowheads* denote vascular basement membrane. × 5780

Fig. 11. Neutrophil granulocytes (*g*) in a small capillary. The endothelial lining (*e*) above the emigrate granulocyte remained open, allowing leakage of vascular fluid into the subendothelial space. *Arrowheads* denote vascular basement membrane. × 6800

sometimes abutted on each other and intercellular junctions developed. As a result, fibrin aggregates were demarcated from the lumen by 1–3 ring-like layers of the endothelial cell cover (Fig. 13) with the not infrequent formation of basement membrane. Along denuded old vascular basement membranes, small (6–12 μm in diameter) non-fenestrated capillary sprouts were found with well-developed intercellular junctions and thin basement membranes (Fig. 12). The lumina of these vessels were either empty or contained 1–2 mononuclear cells.

Discussion

Capillaries adjacent to infiltrates exhibited a special kind of damage which appeared to be associated with degranulated PMNLs adherent to the endothelium and containing bacteria. Hence the process is likely to be mediated by PMNL-derived factors. Activated neutrophils are able to disrupt endothelial monolayer integrity (Harlan et al. 1985) whereas monocytes cannot (Pawlowski et al. 1985). Since the injection of lysosomal releasate of human PMNLs into the skin of rabbits induced



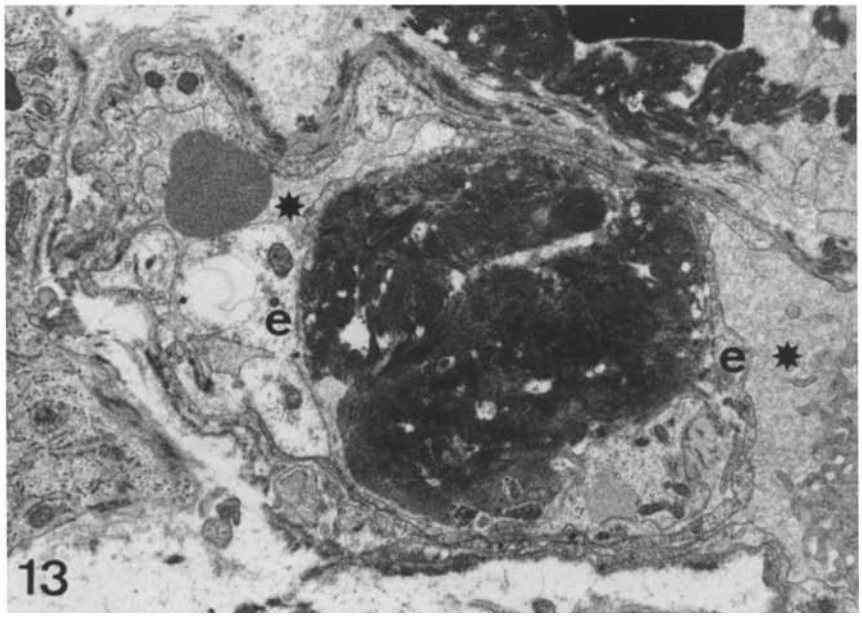


Fig. 12. Disrupted fibrin-plugged small capillary. Along the older vascular basement membrane (*arrows*), a capillary sprout is formed with a narrow lumen (*asterisk*), interendothelial junctions (*rings*) and a thin basement membrane (*arrowheads*). In the right part of the micrograph, remnants of endothelial cells (*e*) can be seen in a close association with fibrin. Compare the sizes of the erythrocyte and the capillary sprout. × 6250

Fig. 13. Endothelial cell processes (*e*) with hydropic changes encircle and demarcate fibrin aggregate from the capillary lumen (*asterisks*). × 7820

almost identical morphological changes in dermal microvessels (Movat and Wasi 1985), we assume that in renal cortical capillaries the extracellular discharge of lysosomal enzymes during phagocytosis of bacteria by neutrophils provides the most important mediators of the PMNL-associated capillary injury in cases of acute human bacterial pyelonephritis. Elastase (Smedly et al. 1986) and collagenase (Weiss et al. 1985) are the likely candidates producing degradation of vacular basement membrane and perivascular connective tissue components (see also Ossana et al. 1986; Weiss et al. 1986). The nearly complete degranulation of neutrophils at sites of microvascular injury indicate a triggered, maximal lysosomal granular discharge, probably related to local hypoxia and monokine stimulation (Klebanoff et al. 1986) acting in concert during the phagocytotic process. The wide area of contact between adherent PMNLs and endothelial cells appears to be essential in the evolution of vascular damage, because we have not found microvascular injury of PMNL derivatives-mediated type in capillaries with loose aggregates of acute inflammatory cells. We must consider the possibility that neutrophils that have already emigrated into the interstitium degradate elements of

the vessel wall from the interstitital side. If this really occurs, we should have found microvascular injury of PMNL-mediatd type other than exclusively in those places were bacterium-laden, degranulated neutrophils adhered to the endothelium. Nevertheless, the degradative capacity of the interstitially localized neutrophils may also play a role in the complete disintegration of the anatomic structures of the microvascular bed.

The occlusion of the infiltrate-adjacent small capillaries by leukocyte plugs was a striking feature. Leukocyte plugging can diminish capillary blood flow (Hammerschmidt et al. 1981; Engler et al. 1983), by increasing the capillary vascular resistance (Braide et al. 1984). In experimental pyelonephritis, this resulted in reduction or cessation of capillary perfusion around the inflammatory infiltrates (Hill and Clark 1972). In our material apart from the plugs, the very low numbers of erythrocytes and the absence of platelets at sites of injury suggest no-flow phenomenon and subsequent hypoxia within the zone of infiltrate-adjacent capillaries. Although ischaemic changes in capillary endothelial cells were generally absent, the slight to moderate ultrastructrual signs of hypoxia seen in the proximal tubules confirm the real existence of local tissue hypoxia, which can stimulate the phagocytotic process in PMNLs (Baehner et al. 1977). Reviewing the published electron micrographs on ischaemic injury in the kidney (Thoenes 1964; Reimer et al. 1972; Glaumann et al. 1977; Donohoe et al. 1978; Venkatachalam et al. 1978), it is clear that peritubular capillaries did not exhibit remarkable ischaemic alterations. For this reason we conlcude that the ultrastructural morphology of the capillary endothelium and the local oxygen tension are not directly correlated. Clinically, disturbed capillary perfusion together with other well-known factors, e.g. renal vasoconstriction, tubular obstruction, etc. might contribute to the sudden onset of acute renal failure.

Since we have examined severely affected kidneys from patients with septic state, the coagulative effects of systemic endotoxinemia might have complicated the morphological picture of microvascular injury. For example, the fibrin-plugged capillaries exhibited extensive endothelial cell damage with focal disruptions of the vessel wall, a change resembling that in the kidneys of monkeys induced with infusion of endotoxin (Richman et al. 1980). The deposition of fibrin at sites of microvascular injury of PMNL-mediated type was a constant finding and had some singular characteristics: the intraluminal fibrin clots were closely associated with the endothelial cells and acute inflammatory cells adherent to the vessel-wall and interrupted communication between the capillary lumen and the perivascular space. The absence of platelets does not exclude the participation of platelet-derived phospholipids in the formation of fibrin because degranulated platelets can be easily overlooked. The other possibility is that fibrin was formed *via* an endothelial cell-dependent pathway of coagulation, e.g., by expressing a tissue factor-like procoagulant activity, the initiating cofactor of the extrinsic pathway of coagulation (Bevilacqua et al. 1985; Stern et al. 1985; Nawroth et al. 1986; Nawroth and Stern 1986; Pober et al. 1986). The exposure of the perivascular connective tissue during the degradation of the capillary basement membrane by lysosomal enzymes and oxygen metabolites may further enhance the thrombotic events at sites of microvascular injury.

There is a general agreement that leukocytes emigrate across the endothelium through widened interendothelial junctions (Harlan 1985; Movat 1985). In a recent report (Faustmann and Dermietzel 1985) it was shown that PMNLs escaped from cerebral microvessels *via* a transcellular route. It is difficult to determine the exact route of leukocyte emigration in human material. In some of our electron micrographs emigration was found next to interendothelial junctions, and accordingly we do not exclude the possibility that leukocyte escape in renal cortical capillaries may take place *via* a transcellular route as well. In conncection with emigration, the anatomic integrity of the capillary wall often showed damage, allowing leakage of vascular fluid into the subendothelial space and into the interstitium. We presume that local hypoxia may influence the adhesion of capillary endothelial lining to the underlying basement membrane and in the course of the early events of emigration, the endothelial lining detaches from the capillary basement membrane.

The small capillary tubes with interendothelial junctions of fine basement membrane characteristically found at sites of fibrin thrombi-injured capillaries, usually along remnants of the denuded, old capillary basement membranes, can be regarded as morphological evidence of neovascularization. The remnants of the original basement membrane seem to be important in the induction of capillary neovascularization. It has been shown that microvascular endothelial cells cultured on basement membrane-associated collagens organized into capillary-like tubes with lumina, junctional complexes and basal lamina formation. If microvascular endothelial cells are cultured on interstitial collagens, the cells proliferate and migrate (Madri and

Pratt 1986). Based on these observations we assume that renal cortical capillary endothelial cells can restore injured capillary walls by using the original basement membrane as conducting material.

We conclude that severe damage to cortical microvessels occurs during vascular and cellular responses of acute pyelonephritis and is associated with the adherence of stimulated polymorphonuclear leukocytes to endothelium.

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Accepted January 15, 1987