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Anatomy of the renal interstitium

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The interstitium of the kidney comprises the extravascular intertubular spaces of the renal parenchyma, with their attendant cellular elements and extracellular substances. As we define it here, the interstitium is bounded on all sides by tubular and vascular basement membranes. This suggests including the lymphatics within the interstitium. That the vascular compartment on the other hand should be distinguished from the interstitium—in contrast to what is often assumed—is suggested by evidence of significant solute polarization between capillary plasma and the interstitium [1].

The interstitium of the kidney is not a simple passive space in which the "true" functional units—nephrons and vessels—are embedded. Rather, it mediates and in fact modulates almost all exchange among the tubular and vascular elements of the renal parenchyma; along with segmental specialization of the nephron, it underlies the functional zonation of the kidney; it probably influences glomerular filtration through its effects on tubuloglomerular feedback; it decisively affects growth and differentiation of parenchymal cells; it determines the compliance of the peritubular microvasculature; the cells of the interstitium produce a variety of local (autocoid) and systemic hormones; and alterations in the interstitium contribute to the clinical manifestations of renal disease.

This review will deal with the various cellular and extracellular elements of the renal interstitium under normal conditions. The studies on which our conclusions are based were conducted principally in experimental animals, in particular the rat.

Subdivisions of the renal interstitium

As shown in Table 1 the renal interstitium may be divided into cortical and medullary compartments with several subdivisions each.

Peritubular interstitium

In the cortex the peritubular interstitium must be distinguished from the periarterial connective tissue sheaths. The peritubular interstitium comprises the spaces between tubules, glomeruli and capillaries; the subcapsular interstitial spaces are part of it. In the peritubular interstitium of the cortex a narrow and a wide interstitium have been described (Fig. 1) [2], the former accounting for 0.6% of the cortical volume, the latter for 3.4%. The narrow interstitium is that space in which the outer surface of a capillary is "directly related" to a neighboring tubule. This has been estimated to apply to 54% (in another study 67%; [2]) of the total cortical peritubular capillary surface, whereas 26% of the tubular surface is directly juxtaposed by peritubular capillaries [3]. The capillary endothelium shows evidence of a complementary structural polarity: fenestrated areas are asymmetrically distributed, with twice as great an area of fenestrated capillary surface facing neighboring tubules across a "narrow" as across a "wide" interstitium [2]. Subdivision of the cortical peritubular interstitium into those parts found in the labyrinth and in the medullary rays of the cortex may be important with respect to adenosine production by cortical interstitial cells [4] (vide infra).

Periarterial connective tissue

The periarterial connective tissue forms a fluid-rich loose connective tissue sheath which surrounds the intrarenal arteries and contains the lymphatic vessels of the kidney (Fig. 2) [5–7]. The periarterial sheath extends distally along the intrarenal arteries as far as the afferent arteriole, where it becomes quite attenuated. It is particularly abundant around the arcuate and cortical radial arteries. The periarterial connective tissue sheathes communicate freely with the peritubular interstitium.

The lymphatic capillaries begin within these sheaths about at the level of the cortical radial arteries in smaller species, more distally in larger ones; lymphatics do not in general penetrate the renal parenchyma proper [6–8]. The lymphatic vessels possess an open endothelium and lack a complete basement membrane. The lymphatic vessels converge along with the intrarenal arteries to emerge at the renal hilus. Substances in the interstitium may enter the sheath and flow with the lymph toward the renal hilus. Toward the hilus, the renal veins begin to be incorporated in the sheath.

Glomerular and extraglomerular mesangium

The glomerular and the extraglomerular mesangium may be considered to be special interstitia inasmuch as their cells are embedded in abundant extracellular matrices, which communicate with each other and (the latter) with the cortical interstitial spaces. "Resetting" of the TGF in response to changes in volume and composition of the interstitial fluid probably occurs via this route [9]. Mesangial and extraglomerular mesangial cells are generally considered as having a common origin with vascular smooth muscle cells. They may thus be regarded as a type of perivascular cell. Because of the special character of these interstitia they will not be considered further here.

Table 1. Renal interstitium

Cortical
Peritubular (wide/narrow)
labyrinth
medullary rays
Periarterial
(incl. lymphatics)
Special interstitia
Extra- and intraglomerular mesangium
Medullary
Outer stripe
Inner stripe
Vascular bundle
Interbundle region
Inner medulla

Medullary interstitium

In the medulla, three types of interstitial space can be distinguished [10], corresponding roughly to that of the outer stripe/vascular bundle, that of the interbundle region of the inner stripe, and that of the inner medulla. The first is a narrow, sparse interstitium occupying 3 to 5% of outer stripe volume (Fig. 3) [11]. The somewhat greater interstitial volume of the interbundle region of the inner stripe (10% in the rat) is about equal to that of the cortical interstitium. The most distinctive type of regional interstitium is that found in the inner medulla. Here the interstitium comprises a much larger part of the total tissue volume and in addition unique interstitial cells characterize this region (Fig. 4). Lymphatic vessels are absent from the entire medulla [6, 8].

As suggested above, the relative interstitial volume is quite differently developed in different parts of the kidney with a pronounced axial gradient from cortex to medulla. Stereologic estimates of the peritubular interstitial volume in experimental animals range from 7 to 9% of total parenchymal volume in the cortex to 30 to 40% in the inner medulla [3, 11–13]. Values for interstitial volume are quite similar among species as diverse as the Wistar rat, the rabbit and the desert rodent *Psammomys obesus*. Measurement of the functional interstitial volume of the rat kidney [14], on the other hand, has revealed a volume equivalent to 13.1% of the total kidney volume under control (antidiuretic) conditions. That this value significantly exceeds the stereologically derived values for accessible interstitial volumes (3 to 5% of the cell-free interstitial space of the cortex and outer medulla) [12] makes clear that the functional interstitium includes more than just the peritubular spaces [15, 16]. The periarterial connective tissue sheaths in fact may account for half of the entire interstitial volume [5].

Elements of the renal interstitium

The renal interstitium is composed of cells and extracellular fibrillar structures, proteoglycans, glycoproteins and interstitial fluid (Table 2).

In the peritubular interstitium of the cortex, interstitial cells often fill the irregular spaces between tubules and vessels. The density of interstitial cells increases with increasing total interstitial volume. Compared to the cortex, interstitial cells are quite rare in the outer stripe and the vascular bundles, while they are relatively abundant in the inner medulla. At the ultrastructural level the interstitial cells of the kidney have been studied by several authors [17–20]; however, it is still not clear how many and which types of interstitial cells are present in the kidney [21–23].

Fibroblast-like cells

The fibroblast-like cells of the cortical interstitium are extensively branched, with long, often sheet-like processes (Figs. 2 and 5). Their cytoplasm generally contains an abundant rough endoplasmic reticulum. Mitochondria, Golgi complexes and lysosomes are regularly encountered; microfilament bundles may be prominent in the peripheral cytoplasm and in the processes. Lipid droplets are occasionally found. These fibroblast-like cells clearly also represent the predominant cell type in the outer medullary interstitium. Together with the lipid-laden cells of the inner medulla, the fibroblast-like cells of the cortex and outer medulla have been classified as type I interstitial cells of the kidney [19].

Lipid-laden interstitial cells

In the inner medulla, the predominant intrinsic interstitial cells, lipid-laden interstitial cells, have several unique characteristics (Figs. 4, 6 and 7) [17, 19, 24, 25]. They contact and/or connect loops of Henle and vasa recta, characteristically spanning these axial structures like the rungs of a ladder. In cross sections through the medulla they appear star-shaped, and may have close structural relations to several thin limbs and capillaries [25]. They increase in number toward the tip of the papilla. They have specialized composite junctional connections to each other [26], but not to the thin limbs or capillaries from which they are separated by a basement membrane. They contain numerous homogeneous osmiophilic lipid droplets; hence they are called lipid-laden interstitial cells. They have an abundant RER with cisternae which are often dilated and filled with flocculent material (Fig. 7a). Special tubular cytoplasmic inclusions (cylindrical bodies) have been described in these cells (Fig. 7c) [17, 24, 27]. The function of these structures is unclear. A cytoskeleton is especially well developed in their most peripheral cell processes (Fig. 7b). In addition to microtubules, microfilament bundles often fill the traversely running cell processes. Mediated by the plasma membrane these microfilament bundles appear to anchor in the basement membranes of loops of Henle and vasa recta (but not collecting ducts). As can be deduced from cell culture experiments, these cells possess receptors for angiotensin II and bradykinin [28, 29]. In the outer medulla transitional forms between the fibroblast-like cells of the cortex and the lipid-laden cells of the inner medulla may be found [19].

Macrophages

Macrophages (histiocytes) are found in all renal zones (Fig. 8) [25, 30]. They appear to be the major fraction of type II interstitial cells described by Bohman [19] and of the "mononuclear" cells described by Bulger and Nagle [18]. These cells generally have a rounded shape. They demonstrate primary and secondary lysosomes and characteristic surface folds, which are especially prominent if they are encountered in the activated state. Their phagocytic capacity is well demonstrated by the uptake of iron dextran when given in low doses [30]. They have been found to be abundant in the inner stripe and the outer parts of the inner medulla, and less frequent in the outer stripe

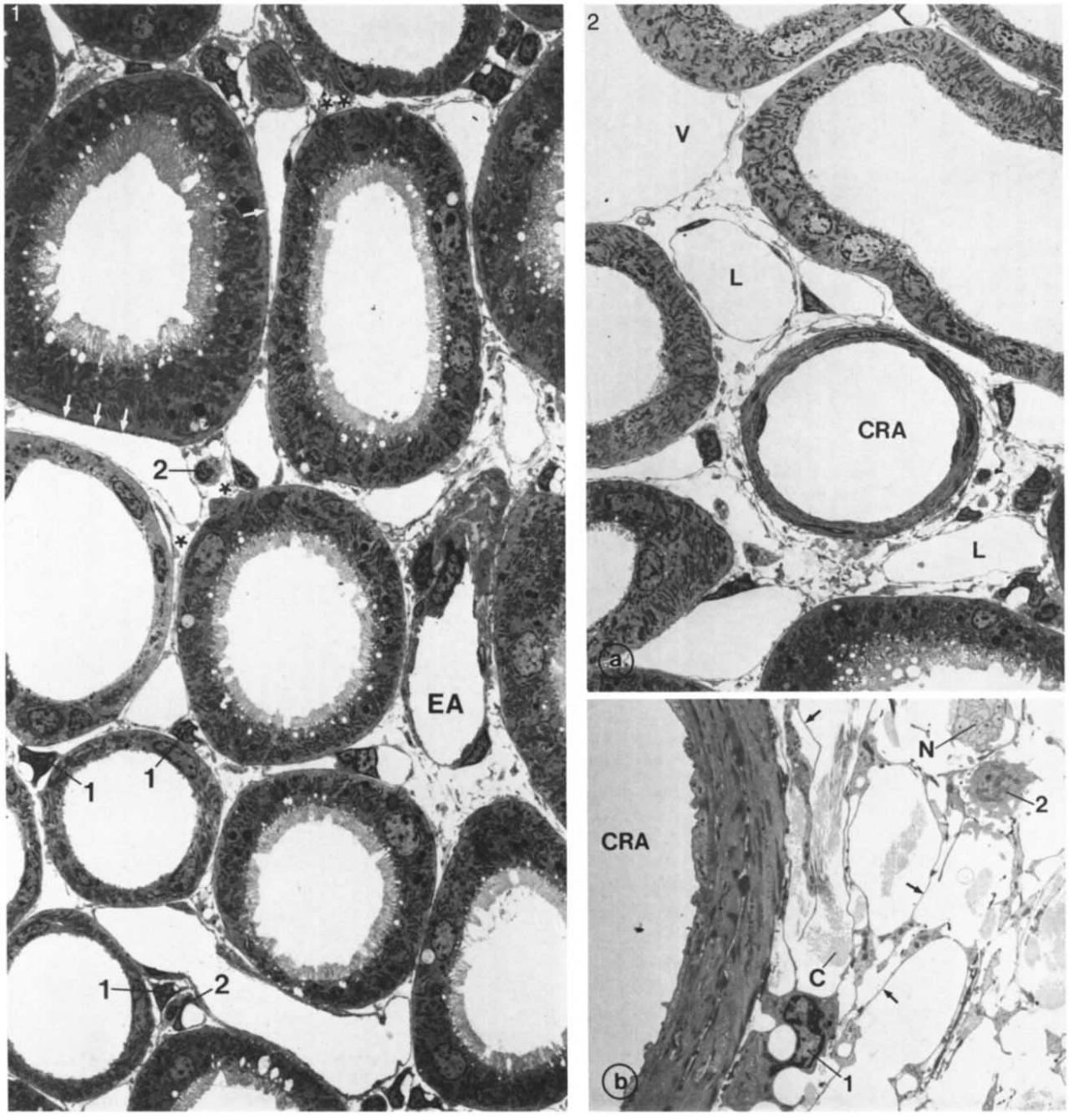

Fig. 1. *Peritubular interstitium of the cortex with narrow (arrows) and wide (stars) portions.* Around the efferent arteriole (EA) the interstitium is somewhat more extensively developed. Interstitial cells are of two types: fibroblast-like cells (1; type I interstitial cells) and rounded cells (2; type II interstitial cells) are seen. Rat kidney; TEM; ×~1,000

Fig. 2. *Periarterial interstitium of the cortex.* **(a)** Cross section through a cortical radial artery (CRA); the vessel is surrounded by wide interstitial spaces which also contain lymphatic capillaries (L). V, vein. **(b)** Periarterial connective tissue sheath around a cortical radial artery (CRA). Wide interstitial spaces subdivided by processes (arrows) of fibroblast-like cells (1). The round interstitial cell (2) appears to be a macrophage. N, nerve; C, collagen. Rat kidney; TEM; (a) ×~980; (b) ~2,720

and the cortex [30]. Cells of this type are often found in close structural association to a fibroblast-like cell (Fig. 8) [19].

Interstitial dendritic cells

Interstitial dendritic cells are apparently also present in large numbers in the rat [23, 31, 32]. These stellate cells have not been clearly distinguished from the fusiform fibroblast-like cells in cortex and outer medulla. Differentiation between these cell types is difficult, since quite different methods have generally been used to characterize these cells. By immunocytochemistry, it has been demonstrated that the dendritic cells are constitutively Ia^+ (that is, they express MHC class II antigen),

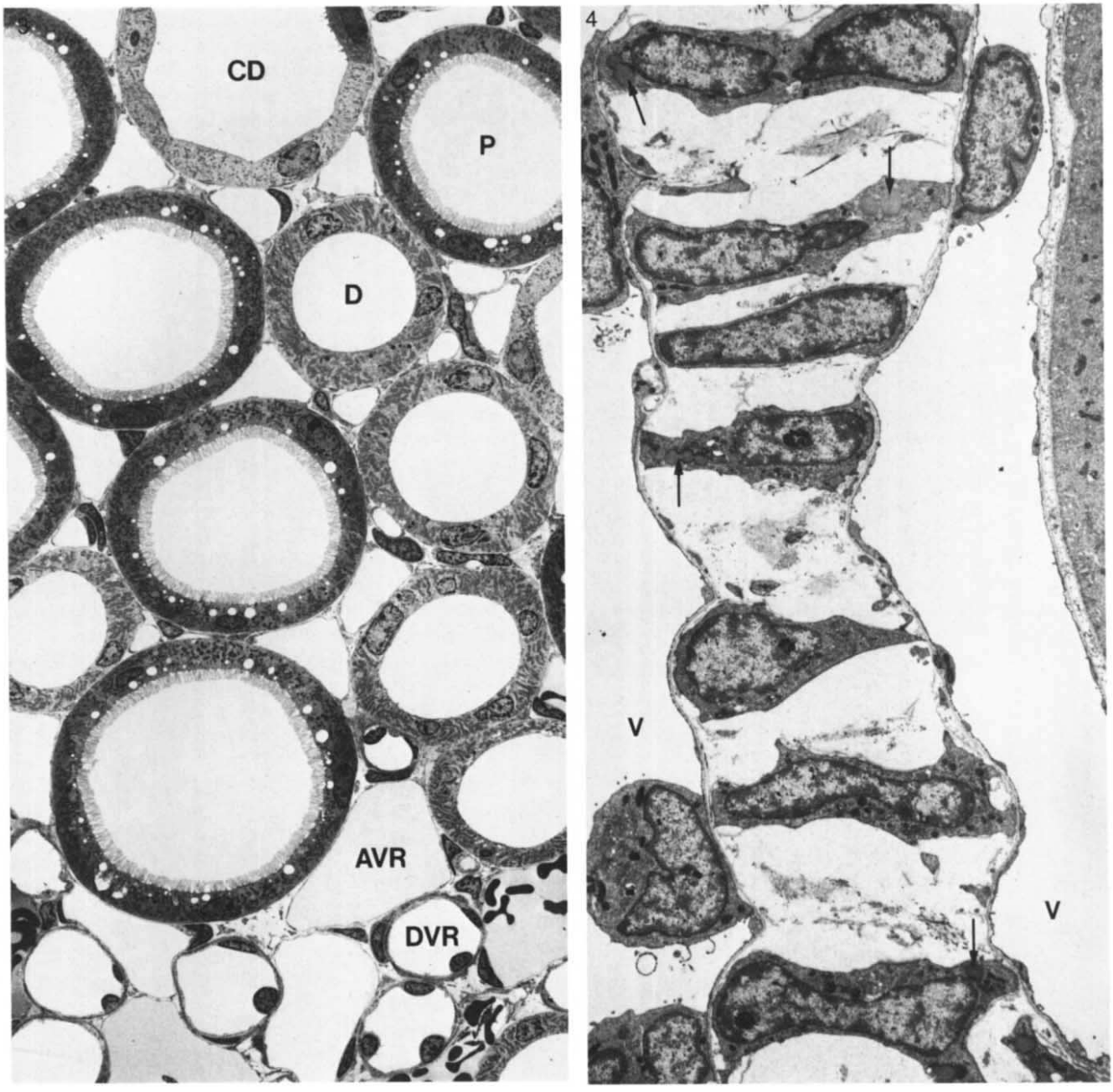

Fig. 3. *Peritubular interstitium of the outer stripe.* Note the sparse interstitial spaces between tubules and capillaries, and between descending (DVR) and ascending vasa recta (AVR) of a vascular bundle. P, proximal tubule; D, distal tubule; CD, collecting duct. Rat kidney; TEM; ×~1,000

Fig. 4. *Inner medulla; longitudinal section.* Wide interstitial spaces are separated by lipid-laden interstitial cells which are arranged like the rungs of a ladder between vasa recta (V) and loops of Henle (in this case: between two ascending vasa recta). Note the lipid droplets (arrows) of these cells. Rat; TEM; ×~1,175

but lack classical macrophage/monocyte surface markers such F_c- or C_3-receptors [23]. They appear, rather, to be the same type of poorly phagocytic Ia^+ antigen-presenting dendritic cells found throughout the interstitial connective tissues of the rat. The similarity in shape and location between type I interstitial cells and MHC II-expressing cells has been previously noted [21]. The dendritic cells have been suggested to be resident in the interstitium for only a few days, since significant tissue depletion occurs within five days of 1000 rad total body irradiation or cyclophosphamide treatment [23, 31], presumably due to failure of radiosensitive bone marrow precursors to replenish dendritic cells which have migrated from the cortical interstitium. On the other hand, Bohman and colleagues [21] have shown that despite the dramatic loss of Ia^+ cells from the renal interstitium after irradiation, the overall volume density of interstitial cells in the cortex and outer medulla remains virtually unchanged, suggesting that the apparent cell loss may actually be loss of cell surface antigen expression. The above-

Table 2. Elements of the interstitium

Cells
Fibroblast-like cells
Lipid-laden interstitial cells
Macrophages and other non-resident cells
Perivascular cells
Extracellular components
Fibrillar structures
Ground substance
Proteoglycans
Glycoproteins
Interstitial fluid

mentioned frequent association of fibroblast-like cells with type II cells (macrophages) may have functional significance, inasmuch as although dendritic cells are excellent antigen-presenting cells, they are not capable of processing particulate antigens themselves, and thus may associate with macrophages in the immune response [33]. Thus much about the origins and nature of Ia^+ cells in the renal interstitium remains to be clarified. In humans the homologous parenchymal dendritic cells express the CD45 common leukocyte antigen and are probably also antigen-presenting cells [34, 35]. Unlike in the rat, in humans most Ia^+ cells of the renal cortex are fixed parenchymal (endothelial) cells. Other leukocytes (such as, plasma cells and mast cells) are also found in lesser numbers in the interstitium.

Perivascular cells

Perivascular cells (pericytes) are found in the transitional portion between the cortical efferent arterioles and the peritubular capillaries (Fig. 5b). They are especially abundant in the medulla, where they surround the descending vasa recta [36, 37]. Pericytes are often considered to be a transitional cell type between vascular smooth muscle cells and the fibroblasts of the interstitium. Like vascular smooth muscle cells they are enclosed by a basement membrane.

Extracellular components

The extracellular components of the interstitium comprise a matrix, which may be thought of as a hydrated gel of ground substance within a fibrillar reticulum. The ground substance in turn consists of proteoglycans, glycoproteins, and interstitial fluid. Basement membranes are also considered part of the interstitium.

Several fibers make up the interstitial reticulum. Together with the gelatinous matrix, these provide a very resilient structure, which can perhaps be seen as analogous to man-made composite materials. Typical "interstitial" collagenous fibers (types I, III, and VI) are present in the matrix, both isolated and in bundles (Figs. 2 and 9). Type I collagen forms typical cross-banded fibers of generally more than 30 nm thickness. Type III fibers (10 to 40 nm diameter) and type VI fibers (6 to 10 nm diameter) [38, 39] are both seen often associated with type I fibers. Type III fibers correspond to the classically-described "reticular fibers," which form a network enveloping the tubules and are well demonstrated by silver staining (Fig. 10). Collagen types IV and V are found in the basement membranes. In the multilayered basement membrane of Bowman's capsule they obviously form filamentous structures [40]. In addition, unbanded microfibrils with a diameter of 15 to 30 nm and an electron-lucent core have been described both isolated and associated with interstitial cell processes (Fig. 11) [18, 20]. In the medullary interstitial matrix, Furusato [41] has reported even thinner fibrils (3 to 15 nm in diameter) which appear to underlie a diffuse reticular structure and disappear after treatment with hyaluronidase. In contrast to the subcutaneous interstitium, elastic fibers are not found.

The interstitial fluid together with the glycosaminoglycans (GAG) are responsible for the gelatinous character of the matrix. The content of GAG is high, almost 1% of the dry weight of the medulla in the dog. If hyaluronic acid GAG is uniformly distributed within the interstitial space, its concentration in the medullary interstitium, for example, probably exceeds 2 mg/ml [42, 43].

The several different GAG of the ground substance are present in different proportions in the various regions of the kidney. Their composition has been investigated in most detail in the renal medulla and papilla. In the papilla of the rat [44] the major types of GAG present are hyaluronic acid (34%), heparin (36%) and dermatan sulfate (26%), with much less chondroitin sulfate (4%). An earlier study in the rat [45] indicated a greater proportion of heparan sulfate GAG (51%) in the medulla. In the dog hyaluronic acid may account for a considerably greater proportion (70%) of total medullary GAG [43]. Thus the total renal GAG composition may differ considerably from that found in different parts of the peritubular interstitial matrix itself. "Free matrix granules" [41, 44] seen in the interstitium—often in association with reticular structures—may represent condensed hyaluronate-proteoglycan aggregates, collapsed as part of a macromolecular phase transition during routine fixation. Even the relatively uniform matrix network described by Furosato [41] after treatment with the GAG insolubilizing agent cetyl pyridinium chloride has an appearance which one might expect from a partially collapsed network of such extended aggregates. The composition of the flocculent, basement membrane-like material often seen in the interstitium is currently unknown. It also seems to be contiguous with the microfibrillar reticulum. The appearance of all elements of the matrix is quite dependent on fixation conditions [41]. In well-fixed specimens the ground substance of the interstitial matrix appears to be quite homogeneous.

Various glycoproteins (fibronectin, laminin, and others) are found associated with tubular basement membranes and at other sites in the interstitium. They serve to connect basement membranes to cell membranes as well as to fibrillar structures and GAG of the interstitial matrix [46]. A detailed discussion of these substances is beyond the scope of this review.

Functional significance of the renal interstitium

In the following we will try to summarize the functional relevance of the various interstitial components. Specifically immunological aspects are beyond the scope of this review.

Production and degradation of fibers and ground substance

The fibroblast-like cells in the cortex and outer medulla, and the lipid-laden cells in the inner medulla are responsible for the production of the extracellular material, fibers and ground substance. The well developed rough endoplasmic reticulum of these cells indicates a high rate of protein synthesis, the production of collagenous and non-collagenous extracellular

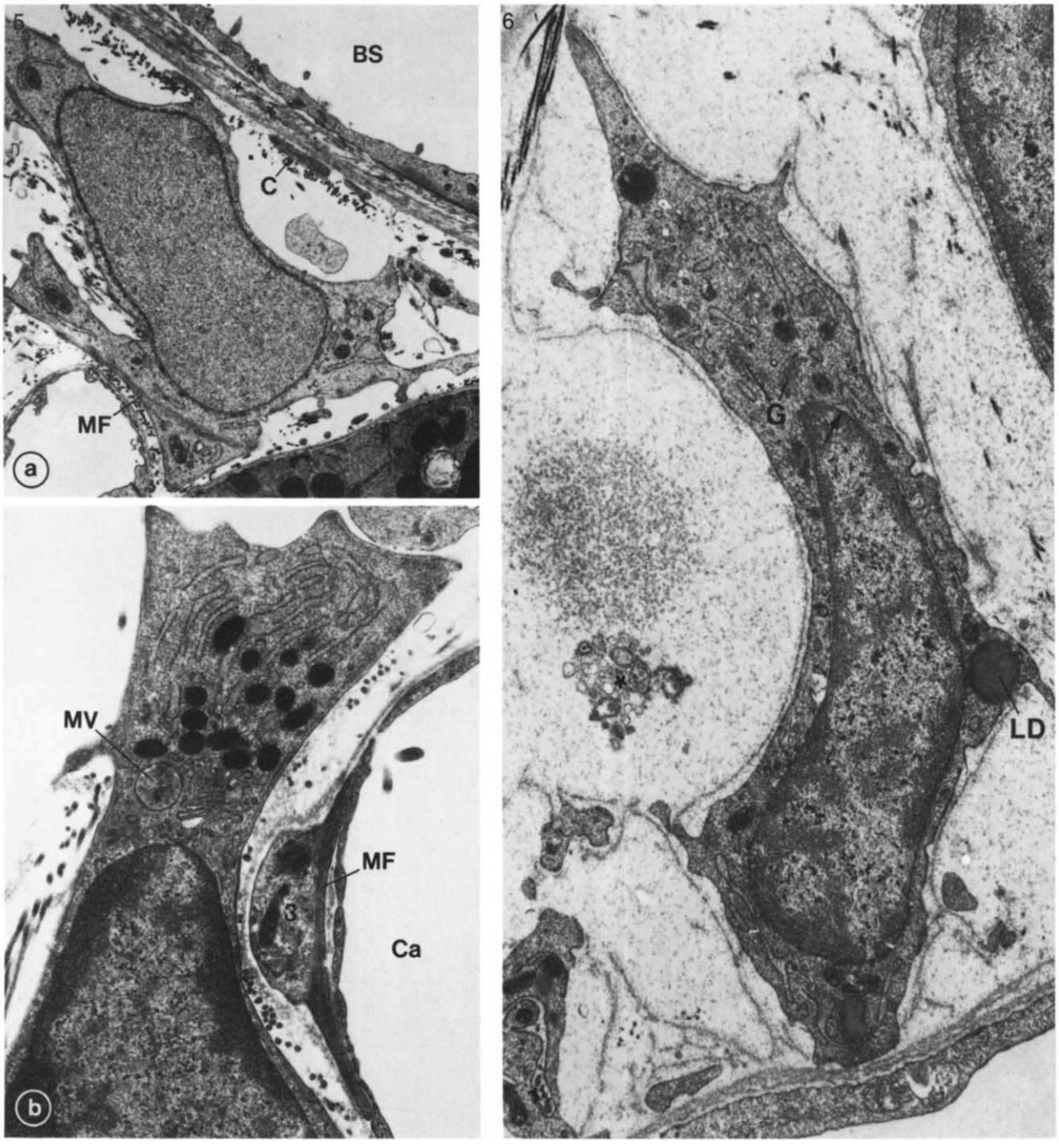

Fig. 5. (a). *Fibroblast-like cell in the cortical peritubular interstitium.* Note the smooth contours of the nucleus, the well-developed rough endoplasmic reticulum, and microfilament bundles (MF). BS, Bowman's space of a renal corpuscle (glomerulus). Note the multilayered basement membrane of Bowman's capsule (stars). **(b)** Part of a fibroblast-like interstitial cell containing a well-developed rough endoplasmic reticulum, several round profiles of mitochondria, a multivesicular body (MV), and Golgi apparatus. In addition, a perivascular cell (3) is seen which contains a microfilament bundle (MF) and is surrounded by a basement membrane. C, collagen fibres; Ca, capillary. Rat kidney; TEM; (a) ×~7,900; (b) ×~18,000

Fig. 6. *Lipid-laden interstitial cell of the inner medulla.* This cell contains a few lipid droplets (LD), and a well-developed, widened rough endoplasmic reticulum. The perinuclear cisternae are often found to be widened (arrow). G, Golgi apparatus. The cell is partly surrounded by basement membrane-like material. Note cell detritus in the interstitium (star). Rat; TEM; ×~13,500

proteins. Widened cisternae of the ER—often seen in cortical fibroblast-like cells—are generally taken as evidence for a very active synthesis. On the other hand, the often extremely widened cisternae of the ER in the lipid-laden interstitial cells in the inner medulla have been interpreted as artifacts [25, 47], since they are frequently found as empty spaces in otherwise

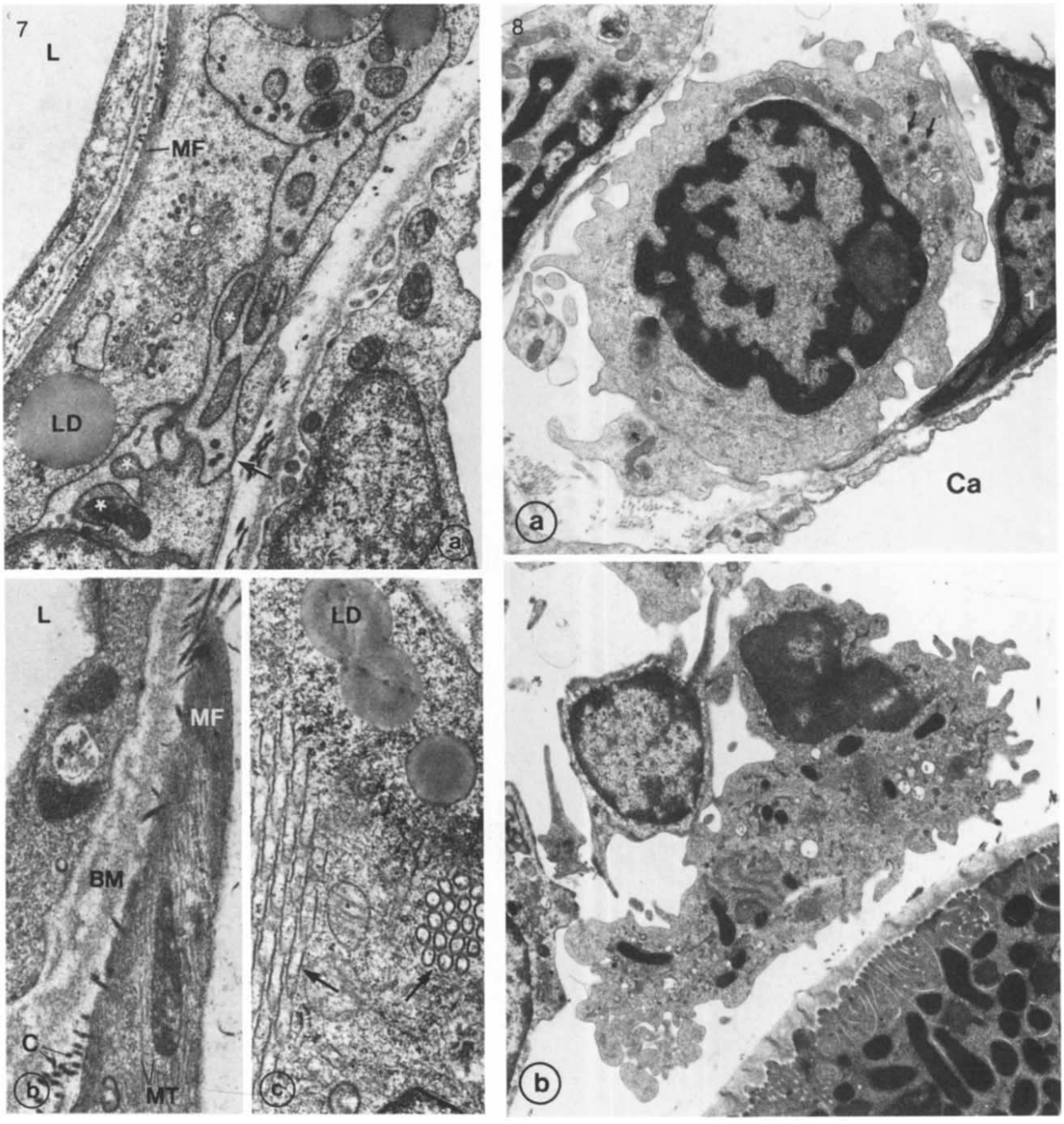

Fig. 7. *Details of lipid-laden interstitial cells.* **(a)** Part of a lipid-laden interstitial cell with conspicuously widened cisternae of the RER; cytoplasmic processes (stars) project into this widened space (arrows). Close applications of the ER-spaces to the plasma membrane (arrow) are often seen. LD, lipid droplet; MF, microfilament bundle. **(b)** Process of a lipid-laden interstitial cell anchoring into the basement membrane (BM) of a loop of Henle (L). The cytoskeleton of this process consists of abundant microtubules (MT) and microfilaments (MF). C, collagenous fibres. **(c)** "Cylindrical bodies" in cross and longitudinal section (arrows). LD, lipid droplet. Rat kidney; TEM; (a) ×~18,000; (b) ×~24,500; (c) ×~21,900

Fig. 8. *Macrophages in the cortical interstitium.* **(a)** Round cell (type II interstitial cell) exhibiting surface folds and numerous primary lysosomes (arrows) typical for macrophages. Adjacent, a fibroblast-like cell (1) is seen. Ca, capillary. **(b)** A macrophage in the activated state. Rat kidney; TEM; (a) ×~12,000; (b) ×~8,500

poorly fixed specimens. However, conspicuously widened cisternae may also be filled with flocculent material and may be found in well fixed (Fig. 7a) [17] and in cultured lipid-laden interstitial cells [44].

The lipid-laden interstitial cells synthesize GAG and probably are the source of most of the hyaluronic acid in the inner medulla [44]. The GAG of the renal interstitium are quite dynamic, with a half-life of just a few days [45]. It is possible

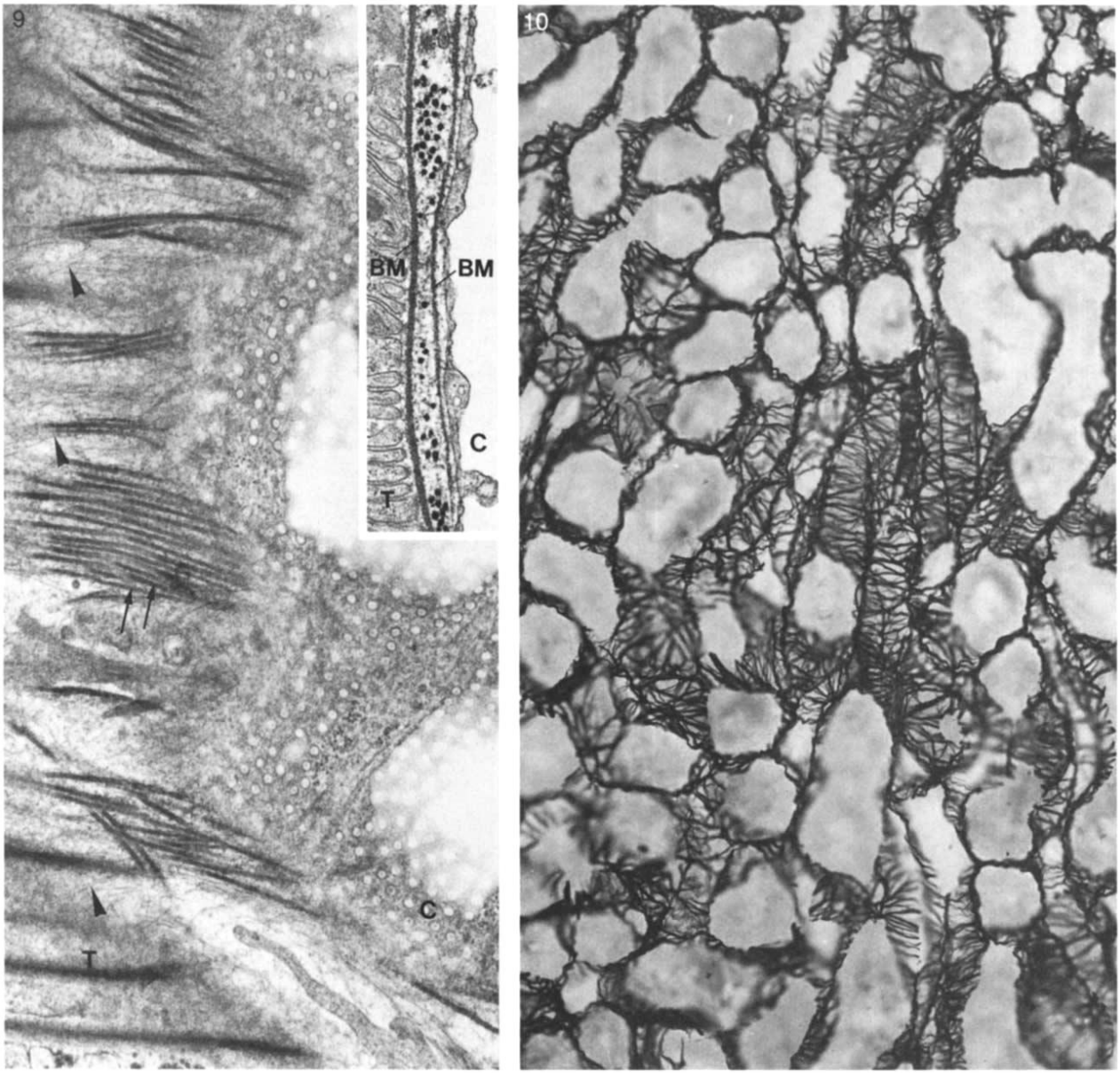

Fig. 9. *Peritubular interstitium of the cortex; tangential section through the interface between a tubule (left) and a capillary (right).* The inset shows a comparable situation in cross section. Between the two basement membranes (BM; clearly discernable in the inset) collagenous fibers (arrows; 30 to 40 nm thick) are seen which probably correspond to the "reticular fibers" shown in Fig. 10. Much thinner fibrils (10 to 15 nm thick; arrow heads) are also encountered. These do not appear to be typical microfibrils (hollow structure; see Fig. 11) but may represent "reticular microfibrils." T, tubule; C, capillary. Rat kidney; TEM; ×~22,800; inset, ×~23,650

Fig. 10. *Longitudinal section through the outer stripe of the rat kidney.* "Reticular fibers" are stained by a silver impregnation technique [78]. The "reticular fibers" surround the tubules predominantly in a circular manner. Photograph provided by Professor T. Ishii, University of Sendai, Japan. Rat kidney; LM; ×~340

that prostaglandins (produced by the lipid-laden cells themselves) regulate GAG production by these interstitial cells inasmuch as fibroblasts in culture both synthesize prostaglandins and respond to them by increased sulfated GAG production [48]. Inhibitor experiments suggest that whereas the fibroblast-like cortical interstitial cells are involved in degradation of sulfated GAG in the cortex and part of the outer stripe of the medulla, in the rest of the medulla macrophage-like cells (type II interstitial cells [19]) and not the lipid-laden interstitial cells are responsible for lysosomal degradation of sulfated GAG [30].

Tissue skeleton/structural support

One of the basic functions of any interstitium is to give structural support to an organ, to its parenchymal and vascular elements. We have not described the coarse connective tissue elements of the kidney, the collagenous capsule and the collag-

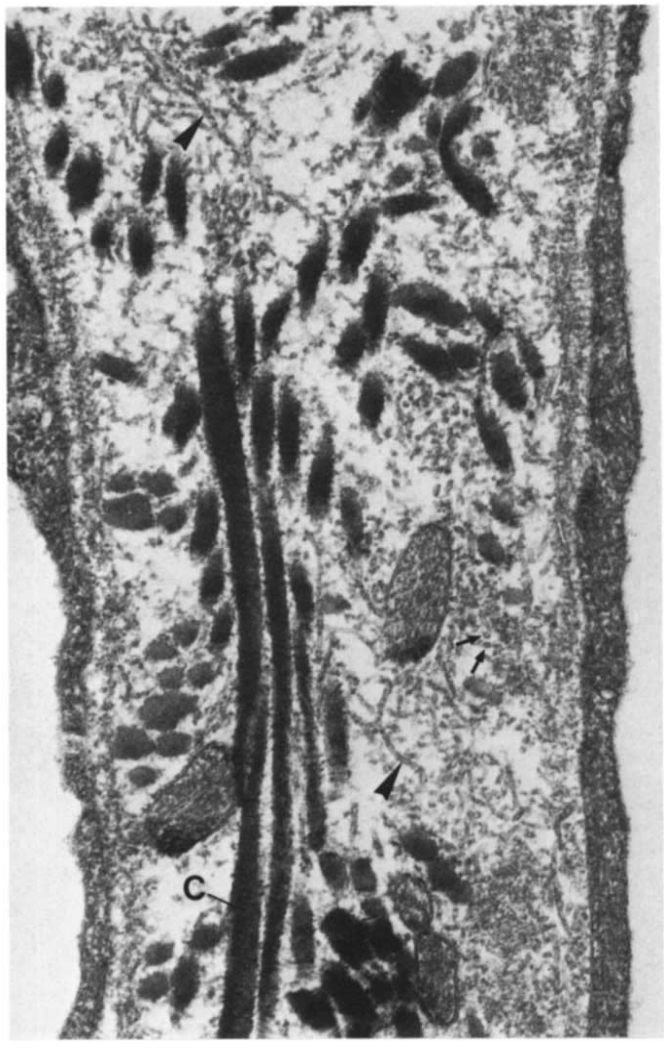

Fig. 11. *Peritubular interstitium of the renal cortex between two capillaries.* In addition to collagenous fibers (C) abundant microfibrils (arrowheads) are frequently seen. These microfibrils can be clearly recognized by their tubular structure (arrows) together with their typical thickness of about 15 nm. Rat kidney; TEM; ×~54,000

enous arches which are anchored in the peripelvic connective tissue and run along the medullary side of the arcuate veins at the cortico-medullary border [49].

The mechanical integration of renal tubules and blood vessels via the interstitium is always mediated through their surrounding basement membranes, which are attached to both cell and matrix via glycoproteins such as laminin and fibronectin, and heparan sulfate proteoglycans [46, 50]. The interstitial matrix supports the renal tubules and blood vessels by virtue of its resilient network of extracellular fibers and ground substance. The finest fibrillar structures (microfibrils, collagen type VI) are anchored in the lamina rara interna in the basement membrane or, in the case of microfibrils, may sometimes be seen to penetrate into the lamina densa [51]. The fibrillar reticulum is connected to the ground substance not simply by steric entanglement with its extended proteoglycans: strong electrostatic interactions appear to bind collagenous fibers to sulfated GAG [52] and specific binding sites between GAG and collagen have even been suggested [53].

In the medulla the interstitial cells themselves also connect the axial tubular and vascular structures to one another. The transversely running microfilament bundles of these cells all terminate in the most peripheral cell processes which anchor in the basement membranes of loops of Henle and vasa recta (although not of collecting duct [25]).

Matrix support is probably particularly important for the delicate tubular structures in the inner medulla, of which the venous blood vessels may be little more structurally than "tunnels in a gel" [54], their compliance characteristics deriving entirely from those of the extracellular substance. This may explain the particular susceptibility of these structures to toxic reactive substances which affect the matrix [55]. Connections to the matrix network probably also help to keep these thin walled structures patent, despite changes in interstitial pressure.

Structural support is also provided by perivascular cells (pericytes), which encircle the precapillary segments of the cortical vasculature and the descending vasa recta in the medulla. These cells are undoubtedly contractile, but—in contrast to vascular smooth muscle cells—they lack direct innervation. They support these vessels in the way smooth muscle cells do in arterioles and arteries [37].

Exchange and insulation

All exchanges among tubules and vessels have to pass through an interstitial compartment; exchange is considered to occur mainly by diffusion. There seems to be no compelling morphologic reason to posit the existence of "free fluid" spaces within the interstitium. When we refer to the interstitial "fluid" this is actually to be understood as the aqueous component of a gel. In addition to the distances between the structures, the properties of this gel, of the ground substance, will have significant effects on diffusional exchange [56], especially in the medulla where it is most highly developed [44].

As already noted, interstitial spaces are quite differently developed in the kidney with respect to site and composition. Narrow interstitial spaces facilitate local exchanges; wide interstitial spaces, on the other hand, allow exchange and equilibration among more distant structures. In the peritubular interstitium of the cortex the "narrow interstitium" would seem to be responsible for most direct exchange between tubule and capillary. Differences in oncotic and hydraulic pressure found in the "narrow" and the "wide" peritubular interstitium in the cortex may account for some of the discrepancies which have arisen in attempts to explain proximal tubular fluid reabsorption in terms of peritubular physical forces [15]. The loss of facilitated exchange across a "narrow" interstitium may be a crucial factor in explaining functional derangements when the interstitium volume increases in some pathological conditions [57].

The "wide" parts of the peritubular interstitium of the cortex may be suggested to establish an interconnected compartment which freely and extensively communicates with the periarterial connective tissue sheathes. Such a communication has been demonstrated by the distribution of high molecular weight tracers from the subcapsular spaces through the peritubular interstitium into the periarterial sheathes and finally the lymphatics [2]. The relevance of diffusional equilibration within the cortical peritubular interstitium may be small, however, be-

cause of the relative sparsity of these spaces and because of the presence of extensive "mixing" blood flow within the peritubular capillaries.

The most sparsely developed interstitium is found in the outer stripe and within the vascular bundles in the inner stripe. At these sites countercurrent structures are running side by side: ascending and descending vasa recta within the vascular bundles; in the interbundle region of the outer stripe descending tubules (partes rectae of proximal tubules and collecting ducts) and ascending vasa recta [10, 58]. The close juxtaposition of these structures favors countercurrent trapping of solutes in the medulla. Together with the lack of medullary lymphatics, this arrangement establishes the insulation of the medulla. Cortical and medullary interstitia are virtually completely separated.

The interstitium in the interbundle region of the inner stripe is similar to the peritubular interstitium in the cortex, albeit slightly more abundant. In both cortex and the interbundle region the convective element of fluid and solute transport (represented by blood flow in the peritubular capillary plexus) overwhelms the effects of local diffusion across the interstitium. A very narrow, insulating interstitium would be inconsistent with the random, non-countercurrent arrangement of blood flow in this region.

In the inner medulla the interstitium must be assumed to establish rather extensive regions over which tubular and vascular structures exchange and equilibrate with each other. However, the high GAG content of the matrix will limit water and probably also solute movement [59, 60]. It seems reasonable to conclude that there is effectively no bulk flow of water within the interstitial spaces. Together with a relative paucity of laterally running capillary segments there, this means that in the inner medulla most interstitial exchange is mediated by lateral diffusion. Based on dye injection studies the existence of longitudinal "channels" in the interstitial matrix along the collecting ducts and under the papillary epithelium has been proposed [61], but structural studies have so far failed to demonstrate such channels. The orientation and density of lipid-laden inner medullary interstitial cells would also seem to hinder axial diffusion in this region, helping to create lateral medullary microcompartments in which the histotopography establishes specific exchange relations among the tubules and vessels [10]. In addition, other characteristics of the ground substance (such as high negative charge density) may decrease the potential for interstitial stone nucleation and metastatic calcification, despite very high concentrations and long residence times of the reactant species [62].

Lymphatic drainage

The renal cortex has a lymphatic drainage, whereas the medulla does not [6, 8, 16]. The drainage of the cortical interstitium is effected by the periarterial connective tissue sheath [7]. The peritubular interstitium in the cortex freely communicates with these sheathes. Thus, substances from the cortical interstitium may enter the periarterial connective tissue from all sides. Within this tissue, bulk flow outside the lymphatic vessels probably occurs both because there is a hydrostatic pressure gradient from interstitium to hilus (perhaps approximately equal to the gradient within the venous system) and the intrinsic resistance to flow within the loose connective tissue of the sheath is considerably less than that of the peritubular interstitium outside the sheathes. Along the way to the hilus, fluid and solutes may gradually enter the lymphatic vessels. The periarterial connective tissue is also closely related to the intrarenal veins which, given their capillary-like wall structure, may be expected to exchange various substances with the sheath.

In addition to lymphatic drainage, the functions of the periarterial connective tissue sheathes probably include intrarenal distribution of renin and angiotensin [7], and the intrarenal movement of lymphocytes, macrophages, etc. In particular, renin from the granular cells of the juxtaglomerular apparatus is released into the periarterial interstitium [63] from which both the renin and the angiotensin generated by it can gain access to structures at the vascular pole of the glomerulus as well as the renal arteries and veins. Similar considerations may be relevant with respect to the lymphatic distribution of the adenosine formed by fibroblast-like cells within the cortical labyrinth (vide infra).

Hormonal significance of interstitial cells

Interstitial cells of the kidney are involved in the synthesis of several systemic and autocoid hormones. Erythropoietin (EPO) has long been known to be synthesized in the kidney. By in situ hybridization it has recently been shown that the synthesizing cells are located in the cortical peritubular compartment [64, 65]. It remains unclear whether the endothelial cells of peritubular capillaries or peritubular interstitial cells express the erythropoietin mRNA detected in these studies. Only a very small number of peritubular cells express EPO in nonanemic mice; these cells are located in the inner cortex [66]. Increasing EPO production is a result of increasing cell recruitment, not of changes in the level of EPO synthesis within individual cells. Even under conditions of severe anemia, however, it is estimated that less than 10% of interstitial cells express EPO mRNA [66].

Recent studies have also shed light on the renal localization of adenosine production [4, 67]. The enzyme ecto-5-nucleotidase catalyses the cleavage of AMP into adenosine and phosphate. Adenosine from this process is released into the extracellular space. The peritubular localization of this enzyme has been clearly demonstrated; only the interstitial cells, most probably fibroblast-like cells (termed fibroblasts by the authors) of the cortical labyrinth (and not of the cortical medullary rays or the medulla) contained this enzyme. Endothelial cells were negative.

In the kidney adenosine represents an autocoid which contracts the afferent arteriole, inhibits renin release and decreases sodium reabsorption. Since adenosine production increases during hypoxia [68], adenosine has been interpreted as part of an intrarenal mechanism protecting the kidney from hypoxic injury by decreasing the workload of the kidney [69, 70].

The synthesis of both erythropoietin and adenosine is stimulated by hypoxia. Moreover, several studies have suggested that adenosine stimulates erythropoietin production [71, 72]. Thus, it is possible that adenosine represents a transduction signal between the sensor of decreased O_2 availability and the cells responsible for subsequent erythropoietin production. The site of pO_2 "sensation" and EPO production is perhaps not surprising, if the local pO_2 of the renal cortex approximates that of arterial blood as is commonly believed. Given that the

"sensing" system for arterial pO_2 must lie in cells resident in some organ, the best site would seem to be an organ so highly perfused that oxygen tension there reflects arterial pO_2 and not the effects of local metabolism.

In the medulla, the lipid-laden interstitial cells have long been considered to be important for renal medullary prostaglandin production. The lipid droplets of these cells contain polyunsaturated fatty acids which appear to be precursors for prostaglandins and other lipid-derived hormones [73]. In tissue culture these cells have been found to synthesize prostaglandins in increased amounts when exposed to angiotensin II or bradykinin [28, 29]. They produce, as well, an antihypertensive effect when transplanted subcutaneously into several models of hypertension in the rat, possibly due to production of the lipid hormones, medullipin I and II [74, 75]. Differences in the size and number of lipid droplets are observed between salt-resistant and salt-sensitive Dahl hypertensive rats [76] as well as between Brattleboro and normal Long-Evans rats [77], but consistent morphologic differences associated with normal physiologic changes in medullary function have not been demonstrated.

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