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Glomerular and proximal tubular morphology after single nephron obstruction

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Glomerular and proximal tubular morphology after single nephron obstruction. This study examined the effect of blocking proximal tubule lumens on glomerular and early proximal tubular morphology. Single nephrons in the rat kidney were blocked with wax by micropuncture. After one day, one week, or one month of obstruction, the kidneys were fixed with glutaraldehyde by intravascular perfusion, and nephron structure was examined by light and electron microscopy. Following obstruction, glomerular changes developed more slowly than tubular changes. After one day, the only change noted in some glomeruli was the presence of inflammatory cells. The only tubule change upstream to the block was a focal loss of apical microvilli. This is in contrast to the severe damage previously reported (Evan, Tanner: *Kidney Int* 30: 818–827, 1986) in downstream proximal tubule segments at this time. After one month of obstruction, glomerular size was decreased and the glomerular filtration membrane was abnormal. Tubular cell size was decreased, apical microvilli were lost, basolateral interdigitations were reduced, and mitochondria were fewer and abnormally oriented. Interstitial fibrosis was present. Changes in nephron structure develop slowly after obstruction, perhaps because continued filtration and reabsorption maintain nephron integrity. Eventually, blocked nephrons atrophy, probably because of reduced blood flow, disuse, and inflammatory responses.

Obstruction of tubule lumens occurs in a variety of kidney diseases, including acute renal failure [1, 2], obstructive uropathy [3], cystic kidney disease [4, 5], glomerulonephritis [6], and multiple myeloma [7]. It is often difficult to discern the effects of obstruction alone, because other damaging influences are usually present in renal disease. The purpose of the present study was to examine the effects of obstruction of single tubules on glomerular and proximal tubular morphology in otherwise normal kidneys.

We have previously shown that when single proximal tubules are obstructed by a solid wax block in rats, the downstream proximal tubule segment is severely damaged after one day [8]. The damaged segment shows extensive necrosis, but also shows signs of cell regeneration; subsequently it atrophies. During the course of that study, we casually observed changes in upstream tubule segments and in the glomerulus. To examine more carefully the morphological effects of prolonged tubule obstruction on early proximal tubule segments and the glomerulus, we undertook the present study. Changes after one day of obstruction were mild, and no cell necrosis was observed at this time. Over the course of a month, cells of the glomerulus and the early proximal tubule lost many of their specialized features, and the nephron decreased in size. Uncomplicated, prolonged tubule obstruction produces glomerular atrophy and atrophy of the proximal tubule both upstream and downstream to a block. The upstream tubule changes are milder and develop more gradually than in downstream tubule segments [8], perhaps because continued filtration and reabsorption help to preserve tubule integrity.

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Methods

Experiments were done on 12 male Munich-Wistar rats (Harlan, Indianapolis, Indiana, USA), weighing 186 to 276 g. The procedure for blocking single tubules was as follows: The rat was anesthetized with sodium pentobarbital (40 mg/kg body wt) and was placed on a heated animal board. Rectal temperature was kept at 37 to 38°C. The left kidney was exposed by a flank incision, and was supported in a micropuncture cup. Sterile saline (0.9% NaCl) was periodically dripped onto the kidney surface to prevent drying. One to five glomeruli were observed on the kidney surface. To identify tubule segments belonging to surface glomeruli, we injected into Bowman's capsule a minute amount of sterile saline, stained with 1 g/liter FD & C Green No. 3 dye, via a sterilized 4 to 6 μm tip diameter micropipette. The lumen of the proximal tubule belonging to the glomerulus became green for a few seconds, and then the tubule was punctured and blocked with wax. The wax was a low melting point (42 to 44°C) paraffin (E. Merck, Darmstadt, FRG), that had been stained with 1% oil red 0 dye. It was injected through a 12 to 15 μm tip diameter, sharpened micropipette, as described by Gutsche et al [9]. Stable, solid wax columns in the tubule lumen were estimated to be about 300 μm in length, and complete obstruction of the tubule lumen was demonstrated by collapse of downstream segments. A drawing of the kidney surface was made, so that the blocked nephrons could be located later. Finally, the kidney was replaced in its original position, and secured to the body wall by a suture passing through some of the perirenal connective tissue. The incision was closed by suturing the muscle layers with silk thread, and by apposing the cut skin edges with metal clips. The rats were

allowed to recover from anesthesia and were housed in individual cages.

After one day, one week, or one month, the kidneys were fixed with 1% glutaraldehyde in Tyrode's solution by arterial perfusion through a retrograde aortic cannula, exactly as described before [8]. A small block of tissue containing the surface glomerulus was serially sectioned, starting from the surface of the kidney. We also serially sectioned nearby outer cortical glomeruli in the same tissue blocks. Seventeen obstructed surface glomeruli and five unobstructed surface glomeruli were studied by light and transmission electron microscopy.

For light microscopy, thin (1 μm) Epon-embedded sections were stained with basic fuchsin. For transmission electron microscopy, ultrathin sections (0.04 to 0.06 μm) were cut with a diamond knife, stained with uranyl acetate and lead citrate, and examined with a Philips 400 electron microscope.

Dimensions of glomeruli and tubules were measured on 1 μm thick sections using an ocular micrometer. Each glomerulus was serially sectioned so that we could determine its midsection. Proximal tubule dimensions, outer diameter (O.D.) and inner diameter (I.D.), were measured on circular profiles of tubules. Glomerular and tubular diameters were measured at angles of 60, 120, and 180°, and the three values were averaged for each glomerulus or tubule. Tubule cell height was calculated as (O.D. − I.D.)/2. Cell cross-sectional area was calculated as $\pi[(O.D./2)^2 - (I.D./2)^2]$. In each tissue block we compared the dimensions of an obstructed nephron with a surface glomerulus to the dimensions of a normal (unobstructed) nephron without a surface glomerulus. This comparison is justified by our finding that there was no significant difference in dimensions between five normal nephrons with surface glomeruli and five outer cortical nephrons without surface glomeruli. Statistical comparisons between nephrons were made by paired *t*-tests.

Results

In Figures 1, 5, 6, 13, and 14, the normal nephrons featured are unobstructed nephrons with surface glomeruli. We found no difference between unobstructed nephrons with surface glomeruli and unobstructed outer cortical nephrons without surface glomeruli, so both groups are considered as normal control nephrons. Both normal and obstructed nephrons were serially sectioned. This allowed us to identify unequivocally tubule segments and the glomerulus belonging to a specific blocked nephron. In a preliminary study on ordinary Wistar rats, we used microdissection after acid treatment to identify blocked nephrons, and obtained essentially the same results [10].

Glomerulus

Figures 1 through 4 show representative light micrographs of glomeruli from Munich-Wistar rats. After one day or one week of tubule obstruction, the glomeruli looked normal. After one month of obstruction, the glomeruli were clearly abnormal (Fig. 4).

Figures 5 through 12 show low and high power transmission electron micrographs from a normal glomerulus, and from glomeruli whose tubules had been obstructed for one day, one week, or one month. The differences in time had no effect on the morphology of unobstructed (normal) nephrons. In the obstructed tubules, after one day of obstruction, the glomerulus appeared normal, except for the presence, in two of four glomeruli, of lymphocytes and neutrophils. These inflammatory cells were attached to the endothelium of the glomerular capillaries. Also, the inflammatory cells were present in the peritubular capillaries adjacent to the parietal layer of Bowman's capsule. After one week of obstruction, similar changes were seen (Fig. 9). After one month of obstruction, major changes in glomerular ultrastructure were observed. The glomerular basement membrane was folded and thickened (Figs. 11, 12). Some visceral epithelial cells had an undifferentiated appearance; they assumed a cuboidal shape, and individual foot processes were lost. Glomerular capillaries appeared to be reduced in number. Capillary lumens were small or collapsed, and they were occasionally blocked by white cells. Cells of the parietal layer of Bowman's capsule and the basement membrane surrounding the capsule were thickened. The interstitium adjacent to the outer layer of Bowman's capsule showed numerous interstitial cells and severe fibrosis.

Table 1. Glomerular diameters of normal and obstructed nephrons

Duration of obstruction	Normal	Obstructed	Difference
	μm		
One day	124 ± 1.7 (N = 4)	126 ± 2.9 (N = 4)	NS
One week	120 ± 4.5 (N = 5)	119 ± 4.1 (N = 5)	NS
One month	130 ± 3.0 (N = 8)	86 ± 8.6 (N = 8)	$P < 0.001$

Values are means ± SD (number of glomeruli). Normal and obstructed nephrons were compared by paired *t*-tests. NS = not significant ($P > 0.05$)

Measurements of glomerular diameters of obstructed and normal nephrons are presented in Table 1. No significant change in glomerular diameter was recorded after one day or one week of obstruction, but glomerular diameter was markedly decreased after one month of obstruction (Table 1). Assuming that the glomerulus is a perfect sphere, the diameter measurements suggest that glomerular volume was reduced to 29% of normal after one month of obstruction.

Early proximal tubule

Figures 13 to 24 present transmission electron micrographs of proximal segments from control tubules and from tubules which had been obstructed for one day, one week, or one month. All of the tubule segments studied were from the early proximal tubule (S1 segment), and were positively identified because all nephrons were serially sectioned beginning at the glomerulus. Figures 13 and 14 show a normal proximal tubule with features characteristic of an S1 segment [11].

After one day of obstruction (Figs. 15, 16), the only consistently noted change was a focal loss of brush border microvilli. A few inflammatory cells were sometimes present around the tubule. The lack of change in tubule segments upstream to a wax block is in contrast to the striking necrosis in segments downstream to a wax block after one day of obstruction, which we reported earlier [8] and saw again in the present experiments.

Changes after one week of obstruction (Figs. 17–20) varied from nephron to nephron. Overall, the tubule cells had a simplified appearance. Cell height was noticeably reduced. Apical microvilli were lost focally, and the remaining microvilli were shortened. The orientation of the mitochondria was no

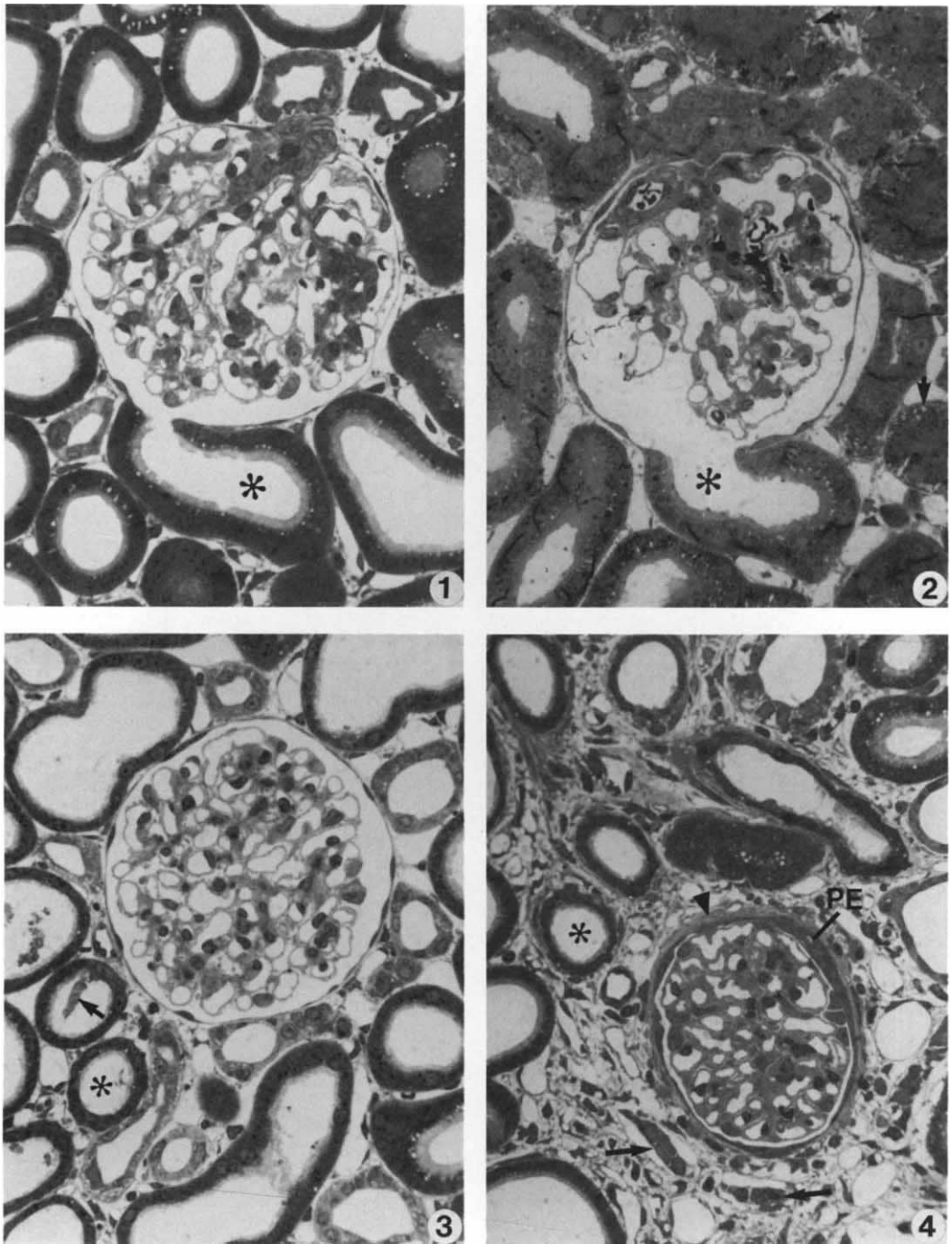
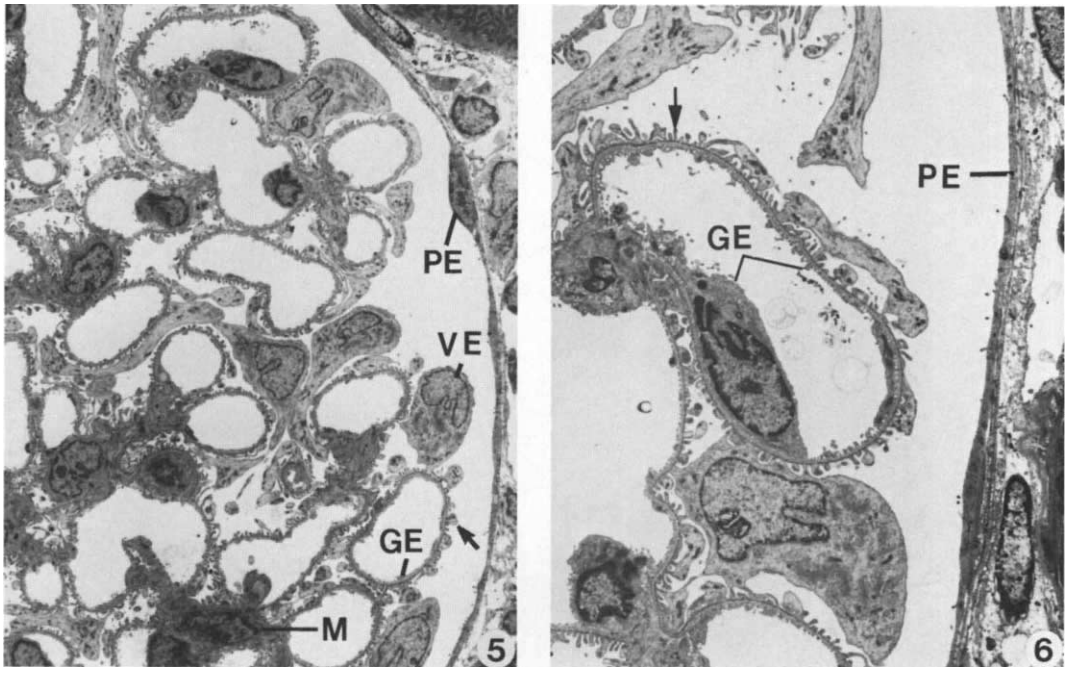


Fig. 1. *Light micrograph of a normal surface renal corpuscle.* The S1 segment of the proximal tubule (asterisk) is seen at the urinary pole of the glomerulus. ×450

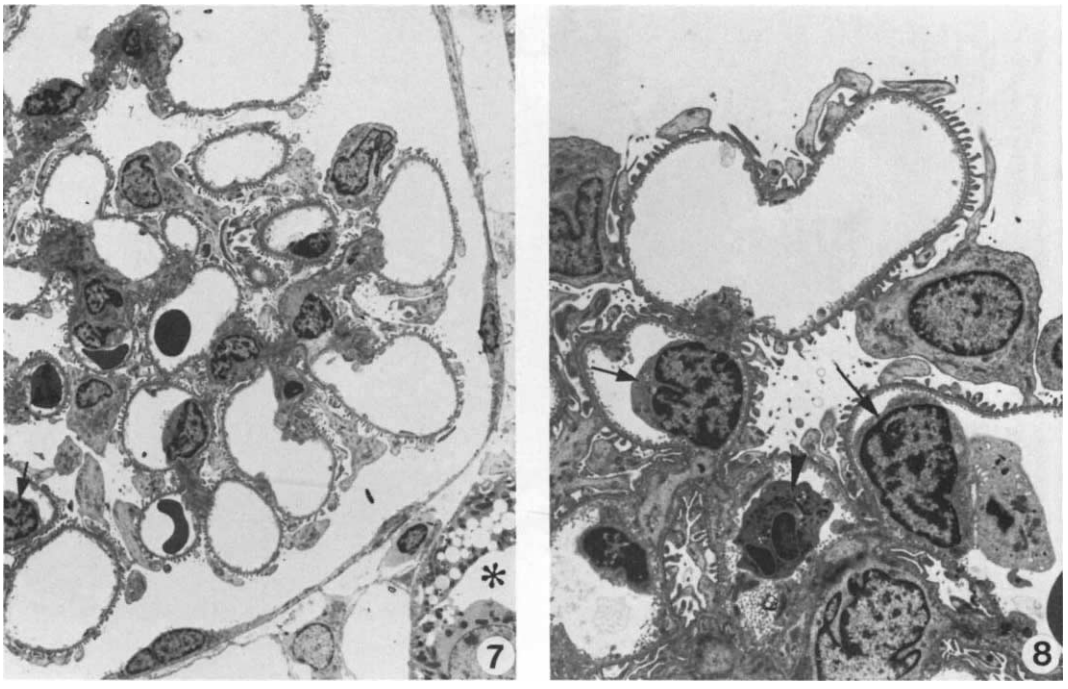
Fig. 2. *Light micrograph of a surface renal corpuscle from a nephron whose tubule lumen had been blocked for one day.* The S1 segment (asterisk) upstream to the block appears normal, as do all cell types of the renal corpuscle. Proximal tubule segments downstream to the block (arrows) show signs of cell injury, as demonstrated by the presence of vacuoles at the basal cell surface. ×450

Fig. 3. *Light micrograph of a surface renal corpuscle from a nephron whose tubule lumen had been blocked for one week.* No obvious changes are seen in the glomerulus at this magnification. Segments of the upstream proximal tubule (asterisk) show a decreased outer diameter, and, in this example, some cell debris (arrow) in the lumen. ×450

Fig. 4. *Light micrograph of a surface renal corpuscle from a nephron whose tubule lumen had been blocked for one month.* The renal corpuscle shows a reduced diameter, increased parietal epithelium (PE) cell height, and a thickened Bowman's capsule basement membrane (arrowhead). Cross sections of the upstream proximal tubule (asterisk) show a reduced outer diameter and cell height. Extensive interstitial cell proliferation and fibrosis are seen to encase the renal corpuscle and proximal tubule of the blocked nephron. The downstream proximal tubule (arrows) shows severe atrophy. ×450

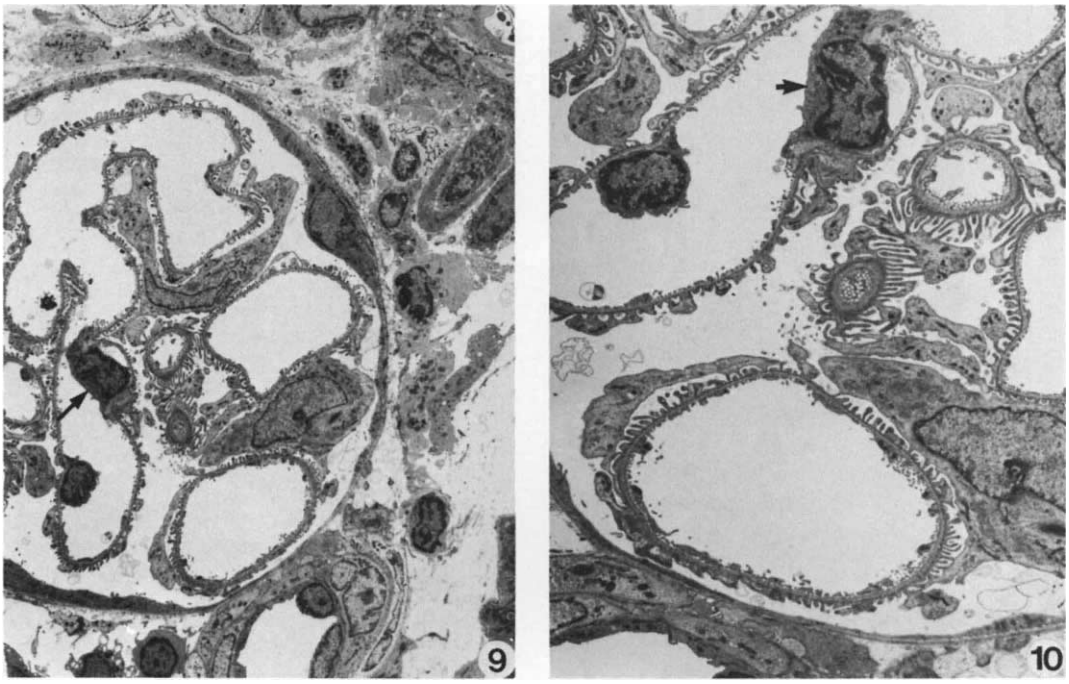


Figs. 5 and 6. *Transmission electron micrographs of a normal (unblocked) renal corpuscle.* The parietal epithelium (PE) is attenuated normally, and the visceral epithelium (VE) possesses numerous foot processes (arrow). The glomerular endothelial cells (GE) are fenestrated and rest on a uniform basement membrane. A mesangial cell (M) is present. Fig. 5: ×1,800, Fig. 6: ×4,000



Figs. 7 and 8. *Transmission electron micrographs of portions of a renal corpuscle from a nephron that had been blocked for one day.* Parietal and visceral epithelial cells and glomerular endothelial cells appear normal. Lymphocytes (arrows) appear to be attached to the glomerular endothelium and a neutrophil (arrowhead) is present in a capillary. The downstream proximal tubule (asterisk) contains damaged cells. Fig. 7: ×1,800, Fig. 8: ×4,000

longer primarily perpendicular to the basement membrane as in the normal tubule cell. No evidence of mitochondrial damage was seen. Large vacuoles were found in some cells. Basal microvilli were lost in some cells. One (Fig. 19) of five nephrons had cell debris in the tubule lumen, and some cell necrosis was seen in the tubule wall of this unusual nephron. Changes in the



Figs. 9 and 10. *Transmission electron micrographs of portions of a renal corpuscle from a nephron that had been blocked for one week.* The only change noted within the glomerulus is the attachment of a leukocyte (arrow) to the glomerular endothelium. The interstitium surrounding the renal corpuscle appears widened and contains numerous inflammatory cells and collagen bundles. Fig. 9: ×1,800, Fig. 10: ×4,000

Table 2. Proximal tubule dimensions of normal and obstructed nephrons

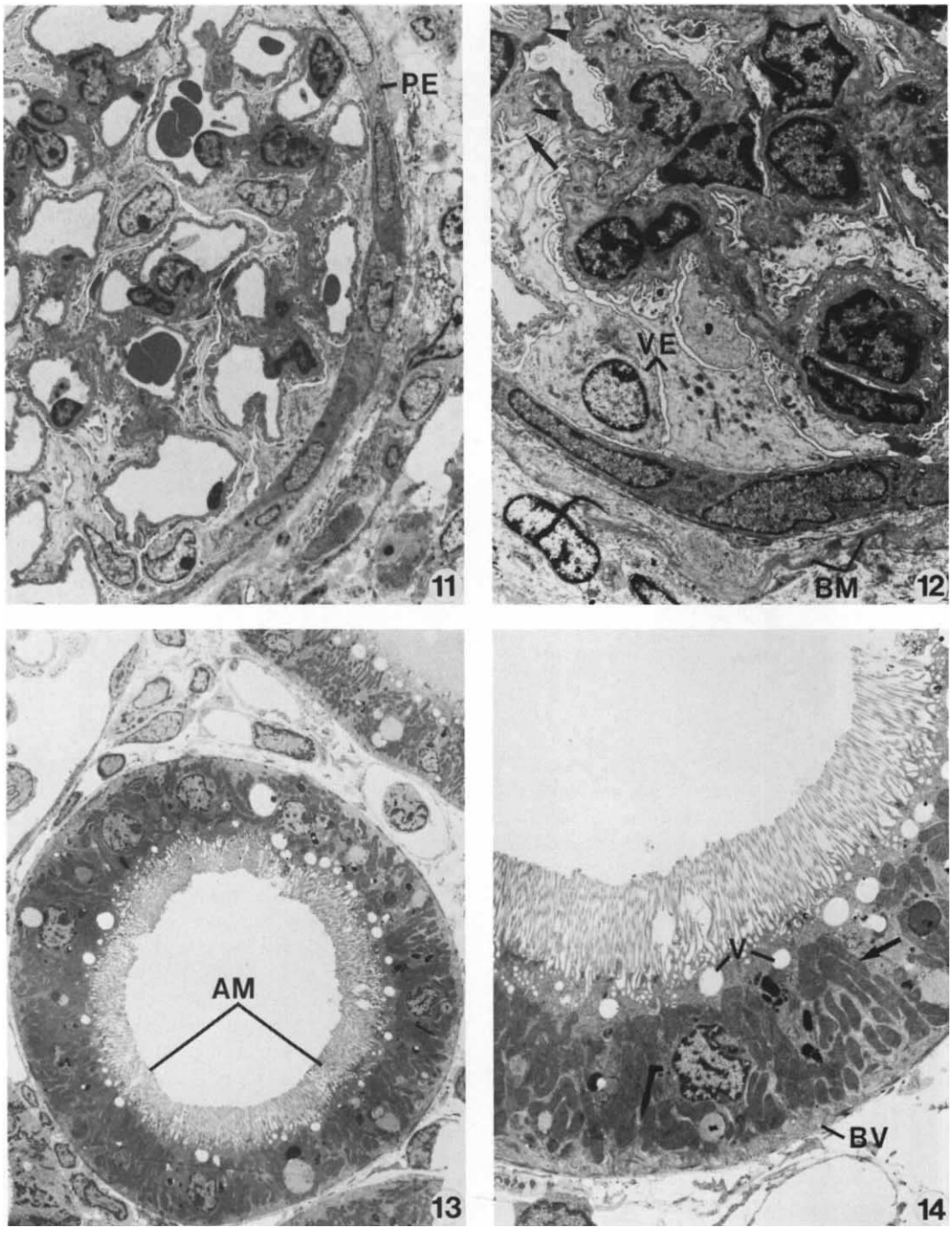
	Normal	Obstructed	Difference
One day of obstruction			
outer diameter μm	45.8 ± 0.4 (N = 4)	46.3 ± 0.5 (N = 4)	$P < 0.02$
lumen diameter μm	23.9 ± 0.6 (N = 4)	24.2 ± 0.6 (N = 4)	NS
cell height μm	11.0 ± 0.2 (N = 4)	11.1 ± 0.2 (N = 4)	NS
cell cross-sectional area μm^2	1200 ± 15 (N = 4)	1227 ± 21 (N = 4)	$P < 0.05$
One week of obstruction			
outer diameter μm	45.6 ± 0.4 (N = 5)	40.2 ± 1.9 (N = 5)	$P < 0.01$
lumen diameter μm	23.9 ± 0.8 (N = 5)	23.1 ± 1.6 (N = 5)	NS
cell height μm	10.9 ± 0.6 (N = 5)	8.6 ± 0.3 (N = 5)	$P < 0.01$
cell cross-sectional area μm^2	1185 ± 58 (N = 5)	852 ± 69 (N = 5)	$P < 0.01$
One month of obstruction			
outer diameter μm	46.5 ± 0.3 (N = 8)	31.3 ± 1.4 (N = 8)	$P < 0.001$
lumen diameter μm	22.6 ± 0.6 (N = 8)	20.8 ± 0.9 (N = 8)	$P < 0.01$
cell height μm	12.0 ± 0.4 (N = 8)	5.2 ± 0.6 (N = 8)	$P < 0.001$
cell cross-sectional area μm^2	1300 ± 38 (N = 8)	429 ± 54 (N = 8)	$P < 0.001$

Values are means ± SD (number of tubules). Normal and obstructed nephrons were compared by paired t-tests.

interstitium surrounding the tubules included the presence of inflammatory cells and an increase in the number of interstitial cells.

Changes after one month of obstruction (Figs. 21–24) were dramatic. A further reduction in cell height occurred, and focal to complete loss of brush border was seen. Remaining brush border microvilli were greatly reduced in length. Cell nuclei were flattened. The cells possessed large autophagic lysosomes and other vacuoles containing debris. The number of mitochondria appeared to be reduced and they were often oriented parallel to the basement membrane. Basolateral interdigitations and basal microvilli were fewer. The outer circumference of tubule cross sections was irregular. The tubule basement membrane was thickened and layered. The interstitium was widened, and extensive interstitial fibrosis was present. The interstitium contained inflammatory cells (neutrophils, lymphocytes). Segments upstream to and downstream from a wax block both show atrophic changes at this time; however, these changes are less severe in the upstream segments.

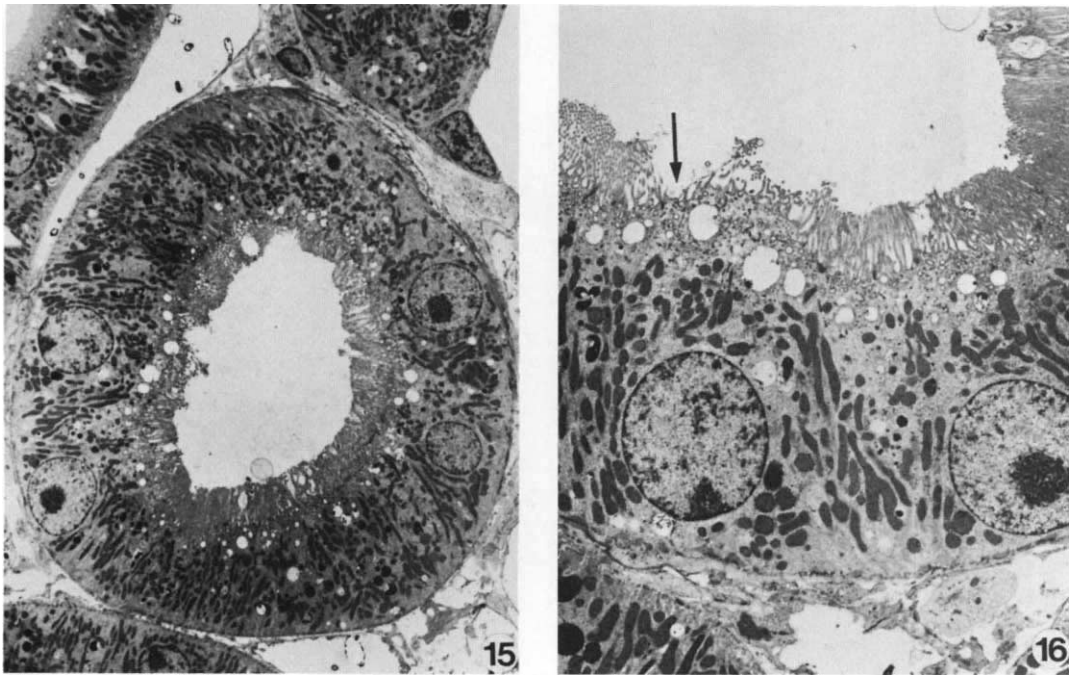
The dimensions of proximal tubules of normal and obstructed nephrons are summarized in Table 2. After one week of obstruction, outer diameter, cell height, and cell cross-sectional area were significantly decreased. Lumen diameter was not different from normal. The cell cross-sectional area in ob-



Figs. 11 and 12. *Transmission electron micrographs of portions of a renal corpuscle from a nephron that had been blocked for one month.* All cell types appear altered. The visceral epithelium (VE) shows focal regions of podocyte fusion (arrow). The glomerular basement membrane (arrowheads) is folded and thickened; its thickness varies along a capillary loop. Some glomerular endothelial cells have lost their fenestrae. The parietal epithelium (PE) and the basement membrane of Bowman's capsule (BM) are thickened. The surrounding interstitium contains numerous inflammatory cells. Fig. 11: ×1,800, Fig. 12: ×4,000

Figs. 13 and 14. *Low and high power transmission electron micrographs of a proximal tubule S1 segment from a normal nephron.* The cells show characteristic ultrastructural features of this nephron segment: tall cells, long and densely packed apical microvilli (AM); apical vacuoles (V); numerous, elongated mitochondria (arrow); extensive basolateral interdigitations; and numerous basal microvilli (BV). Fig. 13: ×1,800, Fig. 14: ×4,000

structed nephrons averaged 72% of normal at this time. Marked decreases in tubule dimensions were seen after one month of obstruction. Cell cross-sectional area in obstructed nephrons was 33% of normal. In eight normal and eight one-month obstructed proximal tubules, we found an average of 4.8 ± 0.5 and 5.2 ± 0.4 nuclei per tubule cross section, respectively.



Figs. 15 and 16. *Low and high power transmission electron micrographs of an S1 segment from a nephron blocked for one day.* No obvious alteration in tubule cell ultrastructure was noted, except for a focal loss of apical microvilli. This loss of microvilli is clearly seen in Fig. 16 (arrow) which is a higher magnification of the same tubule as in Fig. 15. Fig. 15: ×1,800, Fig. 16: ×4,000

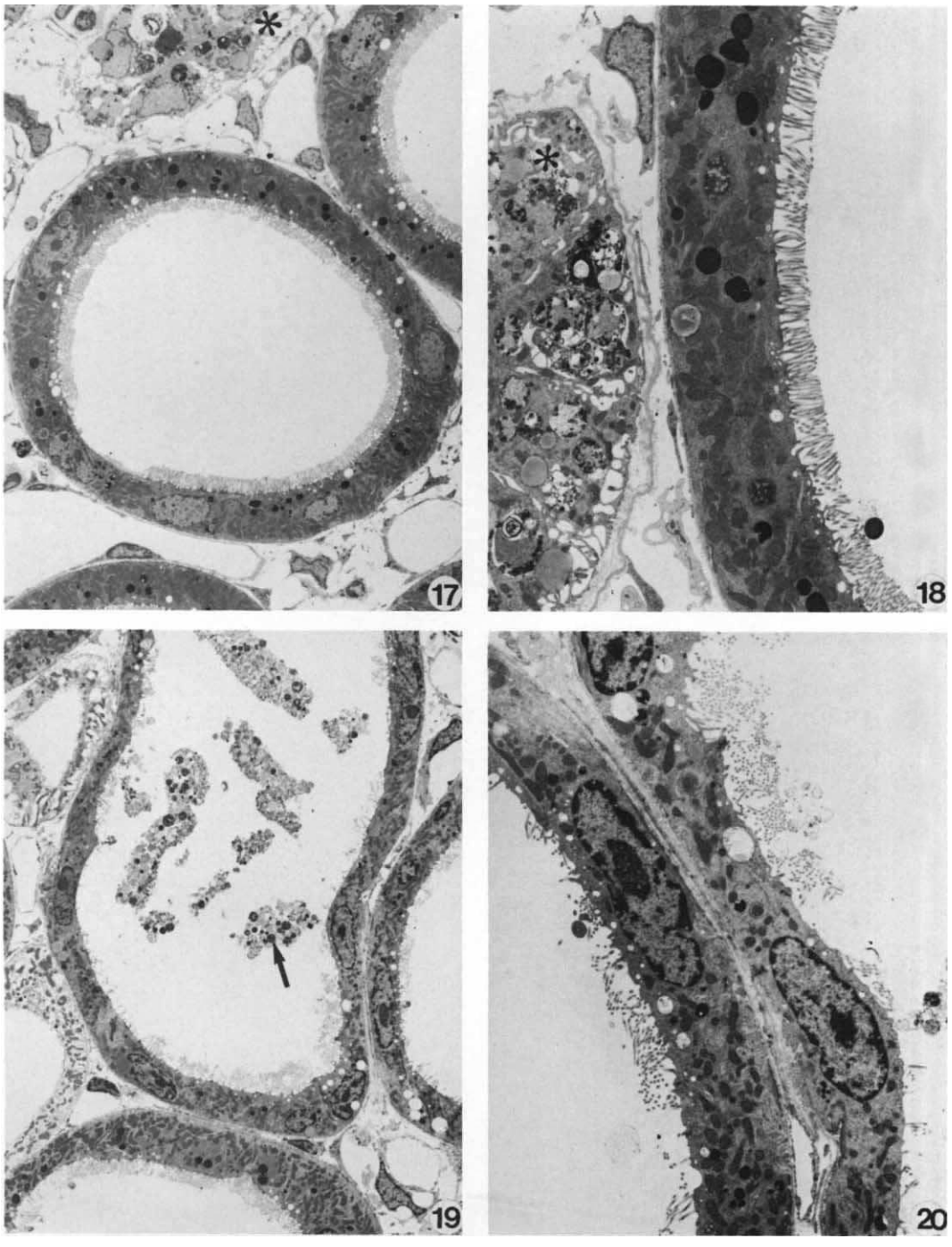
These nuclear counts are not significantly different ($P > 0.05$), and suggest that there was no loss of tubule cells. Assuming that tubule length did not change with obstruction and that there was no loss of tubule cells in cross section, our results suggest that the volume of individual tubule cells of obstructed nephrons was reduced to one-third of normal after one month of obstruction.

Discussion

The nephron changes observed after obstruction of single nephrons are remarkably similar to those seen after obstruction of the urinary tract [3, 12–18]. In both cases, nephron atrophy occurs and glomerular changes develop more slowly than tubular changes. The major changes observed in the glomerulus after one month of obstruction are a marked reduction in overall size, reduction in capillary number and size, fusion of podocyte foot processes, thickening of the basement membrane of Bowman's capsule, and periglomerular fibrosis. The proximal tubular changes common to both prolonged single nephron and urinary tract obstruction include a reduction in cell height, loss of apical microvilli, decreased complexity of basolateral membranes, and a reduced number of mitochondria. The tubular basement membrane is thickened, and cortical interstitial spaces are widened. Urinary tract obstruction is more complicated than is single nephron obstruction, because hydronephrosis produces distortion of the renal parenchyma [3]. The fact that obstruction of the whole kidney and obstruction of a single nephron have similar effects on ultrastructure suggests that the response of the whole kidney is largely determined by the response of its individual nephron units. With single nephron obstruction, the morphological changes were confined to the blocked nephron, and we never saw ultrastructural evidence that adjacent nephrons were affected.

Nephron obstruction may contribute to some of the changes in tubular and glomerular morphology observed in acute renal failure. In ischemia-induced acute renal failure, for example, tubule lumens become plugged by cell debris [1, 2, 19]. The kidneys, however, often recover from an acute ischemic insult within a week or so, and during this time, the morphological changes produced by obstruction alone appear to be relatively modest. If tubules are irreversibly blocked, however, then obstruction may contribute to nephron atrophy.

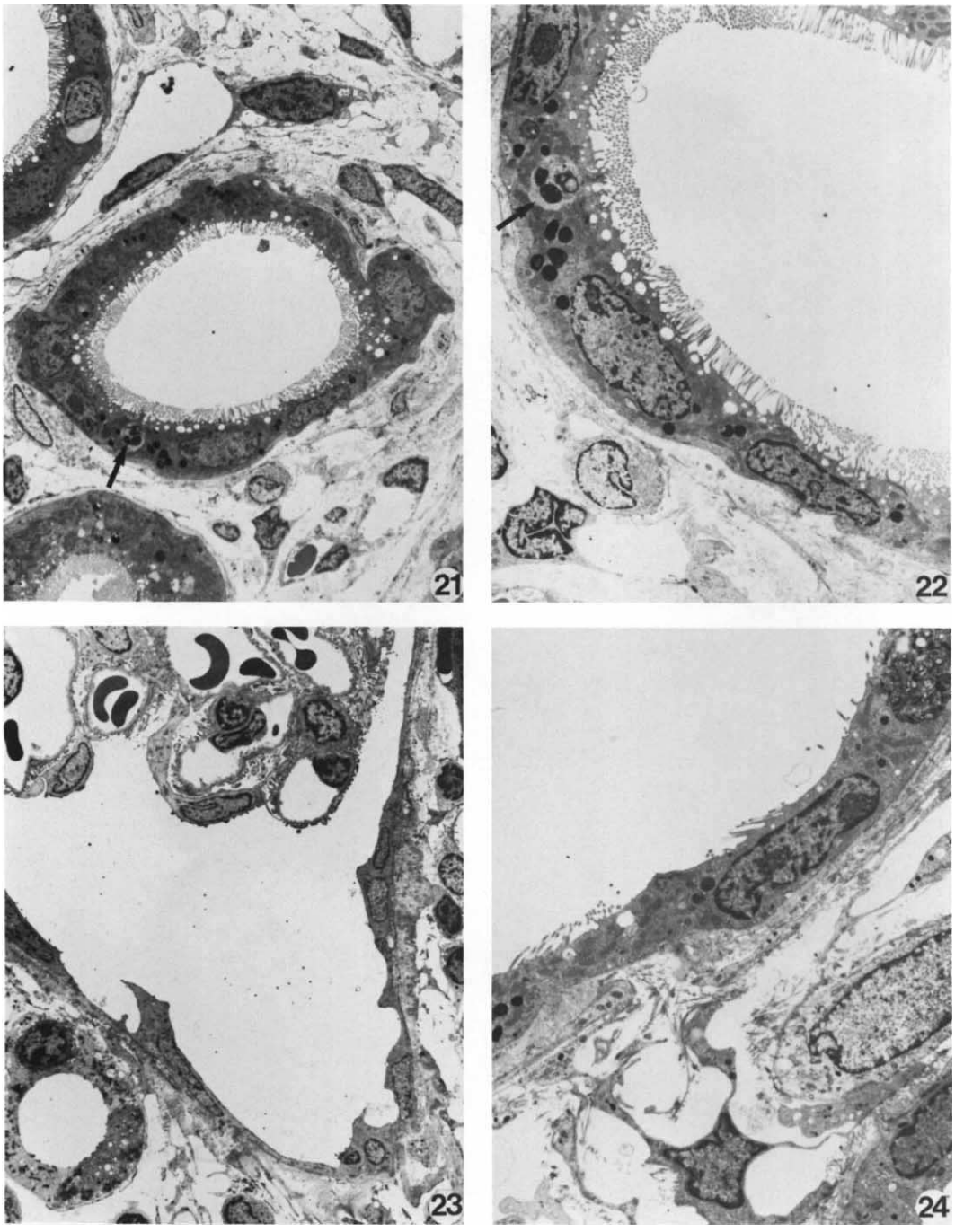
Tubule obstruction has also been postulated to play a role in cystic disease of the kidney [4]. Micropolyps have been noted at the outflow end of renal cysts in animal models and in human autosomal dominant polycystic kidney disease [4, 5, 20–22]. These micropolyps are thought to cause *partial* obstruction of tubular fluid flow. The obstruction has been postulated to lead to an increased resistance to outflow, increased intraluminal pressure, and ballooning of nephrons to form cysts [4]. In the present study, we produce *complete* nephron obstruction. Different results might be produced by partial versus complete single nephron obstruction. Chronic complete ureteral obstruction produces greater decrements in glomerular filtration rate than does partial ureteral obstruction [23]. We have previously demonstrated [24] that chronic, complete single nephron obstruction results in a decrease in single nephron glomerular filtration rate. This fall in glomerular filtration may explain why we did not see an expansion of the tubule lumen upstream to a complete block (Table 2). The effects of partial obstruction on single nephron structure and function and the role of partial obstruction in cyst development need further study.



Figs. 17–20. *Transmission electron micrographs (low and high power) of proximal tubule S1 segments from two different nephrons that had been blocked for one week.* The degree of cell damage was variable from one nephron to another (compare Figs. 17 and 18 to Figs. 19 and 20). The nephron depicted in Figs. 19 and 20 shows a more severe loss of apical and basal microvilli; also cell debris (arrow) is present in the tubule lumen. In Figs. 17 and 18, the proximal tubule segment downstream from the block (asterisk) is visible, and it shows extensive cell damage. Fig. 17: ×1,800, Fig. 18: ×4,500, Fig. 19: ×1,800, Fig. 20: ×4,500

The morphological changes produced in tubule segments upstream and downstream to a short wax block were remarkably different after one day of obstruction. Signs of severe injury were seen in downstream segments [8], whereas upstream changes were minimal. The fact that such different effects were seen upstream and downstream to a block strongly suggests that the results obtained are not simply due to a toxic effect of the wax, but are rather related to interruption of tubule fluid flow. We previously suggested that abrupt cessation of fluid flow in some way was responsible for the severe downstream changes [8]. Continued filtration and reabsorption upstream to a block may help to preserve nephron structural integrity.

The pathogenetic mechanisms which lead to nephron atrophy



Figs. 21–24. *Transmission electron micrographs (low and high power) of proximal tubule S1 segments from two different nephrons that had been blocked for one month.* The degree of change was highly variable from one nephron to another, and even along the same tubule. An inflammatory cell is seen within the tubule wall (arrow). Figs. 23 and 24 show a severely altered proximal tubule at the urinary pole of a renal corpuscle. Fig. 21: ×1,800, Fig. 22: ×4,000, Fig. 23: ×1,800, Fig. 24: ×5,000

following tubule obstruction are not known with certainty, but three interrelated factors may play a contributory role: 1) changes in blood flow, 2) disuse atrophy, and 3) inflammatory responses.

Chronic obstruction of the lumen of single nephrons results in a fall in glomerular blood flow. After one day glomerular blood flow is 2/3 of normal, and after one week of obstruction, it is 1/3 of normal [25, 26]. Glomerular blood flow after one month of single nephron obstruction has not been measured. In the dog, chronic obstruction of one ureter produces similar changes in whole kidney blood flow [27]. After one day of ureteral obstruction, renal blood flow is 2/3 of normal, after 6 days, 1/3 of normal, and after one month, 1/6 of normal. By analogy, we presume that glomerular blood flow in single blocked nephrons

is very low after one month of obstruction. The shriveled appearance of the glomerulus at this time is consistent with this idea. The cause of the fall in blood flow with single nephron obstruction is not completely known; we have presented evidence that an increase in locally produced angiotensin II may play a role [25, 26]. The S1 segment of superficial nephrons is perfused mainly by the efferent arteriole of its own glomerulus [28], so it is likely that peritubular capillary blood flow is reduced with prolonged tubule obstruction. A reduction in blood flow might contribute to the morphological changes. We rarely saw cell necrosis, however, a common finding with ischemic injury [1, 2]. Furthermore, the work demands on the tubule are reduced as filtration rate falls. Therefore, the oxygen supply to a blocked nephron might be adequate for its needs. A reduction in blood flow is probably not the sole cause of nephron atrophy.

Disuse atrophy [29] may be another explanation for the involution of the glomerular and tubule unit. As blood flow and filtration rate fall, the reabsorptive work done by the tubule also decreases. The changes in tubule morphology (a decrease in apical and basolateral membrane surface area and a reduction in size and number of mitochondria) are consistent with a decrease in tubule transport activity. The tubule may need the constant stimulation of reabsorptive work to maintain its normal structure. The mechanisms involved in this postulated relation between cell activity and cell structure are not known.

A third explanation for the changes observed relates to a possible inflammatory response. As early as one day after obstruction, we noticed occasional inflammatory cells (neutrophils, lymphocytes) in the glomerulus and near the blocked tubule. These cells were associated only with blocked nephrons. It is unlikely that their presence was related simply to the presence of a foreign substance in the tubule lumen, since they were found far from the wax blocks. It is important to note that we used sterile techniques, and never saw evidence of bacterial infection. The stimulus causing accumulation of inflammatory cells is not known; possibly it is related to alterations in the metabolic state of the epithelial and endothelial cells as a result of the fall in glomerular blood flow. The presence of inflammatory cells in the kidney after urinary tract obstruction is characteristic of this disorder [3, 12, 13, 30]. These cells are known to release proteases and other enzymes and to produce oxygen-derived free radicals [31]; these and other chemical agents may damage the nephron. Stimulated inflammatory cells produce increased amounts of arachidonic acid metabolites, which can affect blood flow [30]. Activated lymphocytes stimulate fibroblasts to proliferate and may lead to increased interstitial collagen and mucopolysaccharides [32]. This will result in increased diffusion distances between tubule cells and capillaries, impaired nourishment of the tubule cells, and tubule atrophy [16, 17]. Inflammatory responses may contribute importantly to the nephron atrophy that occurs with prolonged tubule obstruction.

In conclusion, chronic obstruction of single tubules leads to tubular and glomerular atrophy. Factors which contribute to this atrophy may be a reduction in blood flow, disuse, and inflammation. Further studies are needed to define the contributions of these various factors to the morphological changes produced by tubule obstruction. Prolonged tubule obstruction may be an important cause of nephron atrophy in renal disease.

Acknowledgments

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References

1. Oliver J, MacDowell M, Tracy A: The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and the ischemuric episode. *J Clin Invest* 30:1307–1440, 1951
2. Kreisberg JI, Venkatachalam MA: Morphologic factors in acute renal failure, Chapter 2, in *Acute renal failure* (2nd ed), edited by Brenner BM, Lazarus JM, New York, Churchill Livingstone, 1988, p. 45
3. Strong KC: Plastic studies in abnormal renal architecture. V. The parenchymal alterations in experimental hydronephrosis. *Arch Pathol* 29:77–119, 1940
4. Gardner KD Jr: Pathogenesis of human cystic renal disease. *Ann Rev Med* 39:185–191, 1988
5. Bernstein J, Evan AP, Gardner, KD Jr: Epithelial hyperplasia in human polycystic kidney diseases: Its role in pathogenesis and risk of neoplasia. *Am J Pathol* 129:92–101, 1987
6. Oliver J: *Architecture of the kidney in chronic Bright's disease.* New York, Hoeber, 1939
7. Vaamonde CA, Pardo V: Multiple myeloma and amyloidosis, Chapter 80, in *Diseases of the kidney* (4th ed), edited by Schrier RW, Gottschalk CW, Boston, Little, Brown and Company, 1988, vol. 3, p. 2439
8. Evan AP, Tanner GA: Proximal tubule morphology after single nephron obstruction in the rat kidney. *Kidney Int* 30:818–827, 1986
9. Gutsche H-U, Müller-Suur R, Hegel U, Hierholzer K, Lüderitz S: A new method for intratubular blockade in micropuncture experiments. *Pflügers Arch* 354:197–202, 1975
10. Tanner GA, Evan AP: Effects of proximal tubule obstruction on glomerular and tubular morphology. *Xth Int Congr Nephrol Abstracts,* London, UK, 1987, p. 489
11. Maunsbach AB: Observations on the segmentation of the proximal tubule in the rat kidney. Comparison of results from phase contrast, fluorescence and electron microscopy. *J Ultrastruct Res* 16:239–258, 1966
12. Nagle RB, Bulger RE, Cutler RE, Jervis HR, Benditt EP: Unilateral obstructive nephropathy in the rabbit. I. Early morphologic, physiologic, and histochemical changes. *Lab Invest* 28: 456–467, 1973
13. Nagle RB, Johnson ME, Jervis HR: Proliferation of renal interstitial cells following injury induced by ureteral obstruction. *Lab Invest* 35:18–22, 1976
14. Nagle RB, Bulger RE: Unilateral obstructive nephropathy in the rabbit. II. Late morphologic changes. *Lab Invest* 38:270–278, 1978
15. Møller JC, Skriver E, Olsen S, Maunsbach AB: Ultrastructural analysis of human proximal tubules and cortical interstitium in chronic renal disease (Hydronephrosis). *Virchow Arch A* 402: 209–237, 1984
16. Møller JC, Skriver E: Quantitative ultrastructure of human proximal tubules and cortical interstitium in chronic renal disease (hydronephrosis). *Virchow Arch A* 406:389–406, 1985
17. Møller JC, Jørgensen TM, Mortensen J: Proximal tubular atrophy: Qualitative and quantitative structural changes in chronic obstructive nephropathy in the pig. *Cell Tiss Res* 244:479–491, 1986
18. Ninomiya H, Nakamura T: Renal vascular changes in hydronephrosis in rats: scanning electron microscopy of resin casts of glomerular capillaries. *Exp Anim* 37:153–158, 1988
19. Tanner GA, Sophasan S: Kidney pressures after temporary renal artery occlusion in the rat. *Am J Physiol* 230:1173–1181, 1976
20. Gardner KD, Jr, Evan AP: Renal cystic disease induced by diphenylthiazole. *Kidney Int* 24:43–52, 1983

21. EVAN AP, GARDNER KD JR: Nephron obstruction in nordihydroguaiaretic acid-induced renal cystic disease. *Kidney Int* 15:7–19, 1979
22. EVAN AP, GARDNER KD JR, BERNSTEIN J: Polypoid and papillary epithelial hyperplasia: A potential cause of ductal obstruction in adult polycystic disease. *Kidney Int* 16:743–750, 1979
23. WILSON DR: Pathophysiology of obstructive nephropathy. *Kidney Int* 18:281–292, 1980
24. TANNER GA: Nephron obstruction and tubuloglomerular feedback. *Kidney Int* 22, Suppl 12:S213–S218, 1982
25. TANNER GA, KNOPP LC: Glomerular blood flow after single nephron obstruction in the rat kidney. *Am J Physiol* 250:F77–F85, 1986
26. CARMINES PK, TANNER GA: Angiotensin in the hemodynamic response to chronic nephron obstruction. *Am J Physiol* 245:F75–F82, 1983
27. VAUGHAN ED JR, SORENSEN EJ, GILLENWATER JY: The renal hemodynamic response to chronic unilateral complete ureteral occlusion. *Invest Urol* 8:78–90, 1970
28. FAARUP P, RYØ G, SAELEN H: Selective capillary vascularization of the nephron in the rat kidney. *Acta Pathol Microbiol Scand* 80A:139–141, 1972
29. HINMAN F: Renal counterbalance. An experimental and clinical study with reference to the significance of disuse atrophy. *Trans Am Assoc Genito-Urinary Surgeons* 15:241–385, 1922
30. JONAS PE, DESCHRYVER K, OKEGAWA T, LEAHY K, NEEDLEMAN P: Presence of inflammatory cells associated with exaggerated arachidonic acid metabolism in renal injury. *Adv Prostaglandin Thromboxane Leukotriene Res* 12:65–73, 1983
31. WEISS SJ: Oxygen, ischemia and inflammation. *Acta Physiol Scand* Suppl 548:9–37, 1986
32. NEILSON EG, JIMENEZ SA, PHILLIPS SM: Cell-mediated immunity in interstitial nephritis. III. T lymphocyte-mediated fibroblast proliferation and collagen synthesis: An immune mechanism for renal fibrogenesis. *J Immunol* 125:1708–1714, 1980