Glomerular Endothelial Cells in Uranyl Nitrate-induced Acute Renal Failure in Rats

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ABSTRACT In uranyl nitrate (UN)-induced acute renal failure (ARF) glomerular ultrafiltration coefficient (K_f) decreases because of unknown reasons. Since transport of water across the glomerular capillary wall occurs predominantly extracellularly through the endothelial fenestrae (EF), a reduction in the diameter and/or the density of EF can reduce the extracellular filtration area and the glomerular K_f. To examine this possibility, ARF was induced in rats by intravenous administration of UN in low (15 mg/kg) and high doses (25 mg/kg). Fenestral density ($\bar{x}\pm$SEM) per 5 cm^2 from the scanning electron micrographs (×30,000) was 107±10, 103±9, and 101±11 at 2, 7, and 17 h after the intravenous administration of bicarbonate saline to the control rats. In the low-dose UN group the EF density was 91±2, 52±8, and 45±11 at 2, 7, and 17 h after the injection, whereas for the high-dose group at corresponding time intervals the EF density was 95±3, 54±9, and 44±10. Fenestral diameters, in Angstrom units ($\bar{x}\pm$SEM), were 751±53, 765±43, and 764±37 at 2, 7, and 17 h after the injection of bicarbonate saline to control rats. At corresponding intervals after the administration of UN, the fenestral diameters were 501±61, 472±28, and 438±98 for the low-dose group and 525±43, 470±39, and 440±56 for the high-dose group. 2, 7, and 17 h after the injection of UN, fenestral area of the low-dose group decreased to 52.1, 30.1, and 24.6% of the controls, whereas in the high-dose group, the fenestral area declined to 54.3, 30.2, and 23.6% of the controls. Administration of UN (15 mg/kg) to sodium-loaded rats did not alter renal function or endothelial cell morphology. It is suggested that in UN-induced ARF the morphological alterations in endothelial cells reduce the K_f of glomerular capillaries by reducing the filtration area.

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INTRODUCTION

Reduction in ultrafiltration coefficient (K_f) of glomerular capillaries is one of the several abnormalities that has been identified in uranyl nitrate (UN)[1]-induced acute renal failure in rats (1–6). However, the reason for the decline in glomerular capillary K_f is not understood. Transport of solutes and water across the glomerular capillary wall occurs predominantly through the endothelial fenestrae (EF) (7, 8). Therefore, a reduction in the density and/or the size of the fenestrae could result in a decrease in the extracellular filtration area and the K_f of glomerular capillaries. This possibility was examined by a sequential evaluation of renal function and glomerular morphology in rats given UN. In an attempt to dissociate the functional from the morphological alterations, similar studies were performed in sodium-loaded and sodium-depleted rats after the administration of UN.

METHODS

This study was divided into two parts. In the first part the effects of UN on renal function and glomerular morphology were studied at intervals of 2, 7, and 17 h after the intravenous administration of UN in low dose (15 mg/kg) and in high dose (25 mg/kg). In the second part of the study, the effects of UN in sodium-loaded and sodium-depleted rats were studied at 17 h after the intravenous administration of UN (15 mg/kg). Female Sprague-Dawley rats weighing between 200 and 300 g were anesthetized with an intramuscular injection of ketamine HCl (10 mg/100g body wt). A group of 13 normal control rats were given 0.5 ml of NaCl-$NaHCO_3$ isotonic solution i.v. in an exposed femoral vein. From the controls, renal tissues were obtained from five rats after 2 h, from four rats after 7, and from four rats after 17 h of NaCl-$NaHCO_3$ injection. 16 rats were similarly given 15 mg/kg UN in 0.5 ml NaCl-$NaHCO_3$ isotonic solution. From this group, renal tissue was obtained from six rats after 2 h and from five rats each after 7 and 17 h after the injection of UN. 15 rats were given

[1] *Abbreviations used in this paper*: EF, endothelial fenestrae; FENa, fractional excretion of Na; GFR, glomerular filtration rate; UN, uranyl nitrate.

high-dose (25 mg/kg) UN and 2, 7, and 17 h later, the renal tissue was obtained from five rats at each period. In all these studies, 2 h before the collection of renal tissues, renal functions were measured.

The urinary bladder was catheterized with a polyethylene tubing (PE 50) and the urine obtained was discarded. A 2-h timed urine collection was obtained and a 2-ml blood sample was drawn at the midpoint of urine collection. Urine volume, osmolality (by freezing point depression method [9]), sodium concentration (by flame photometry [10]), and creatinine concentrations (11) of serum and urine samples were measured. Fractional excretion of Na (FENa) was calculated. At the end of the experiment, left renal artery was catheterized. 30 ml of 0.9% NaCl was infused into the kidney, followed by 30 ml of 2.5% glutaraldehyde in 0.075 M sodium cacodylate HCl buffer at pH 7.4, using a steady pressure of 90 mmHg. Before a steady pressure could be achieved, the perfusion pressure fluctuated between 80 and 100 mmHg. After *in situ* fixation, portions of the cortex were cut into 1-ml cubes and further fixed in the original fixative for an additional 24 h. Renal tissues were assigned numbers and further preparation and reading of the sections were done without the knowledge of the group of rats to which the tissue sections belonged. The small blocks of tissue were routinely prepared for transmission electron microscopy and viewed on a Philips EM-200 electron microscope (Philips Electronic Instruments, Mahwah, N. J.). The larger pieces of tissue were washed in sodium cacodylate HCl buffer for 1.5 h, dehydrated in a series of graded alcohols to 100% ethanol, fractured in liquid nitrogen, transferred to a Samdri critical point dryer and dried with liquid CO_2. The tissue was attached to an aluminum stub and placed in a vacuum evaporator with a rotating stage for coating with gold palladium. Specimens were examined and photographed in a scanning electron microscope (Autoscan; ETEC Corp., Hayward, Calif.) operating at an accelerating voltage of 20 kV. To avoid selection bias, all the capillary loops of the first 10 glomeruli encountered were sequentially photographed from each specimen. The first 10 photographs from each specimen were used for quantitative studies. The photographs were taken at a minimal tilt (angle, <5°) so that the perspective error, that is, the difference in magnification between the foreground and background of the image when the specimen is tilted, would be negligible. Hilliard (12) has shown that at small tilt angles (<10°) and high magnifications the perspective error is small. To quantitate the perspective error, we photographed a calibration gold grid at a magnification of 30,000 and tilt angles of 1°, 5°, 10°, and 20°. The area of the same 20 grid spaces was measured from the photographs taken at different angles. Compared to the grid area at 0° tilt, the error was found to be 1.5% at 5°, 3.0% at 10°, and 4.5% at 20°. Thus a maximum error of 1.5% could have resulted from this mechanism.

We next considered the error that could have resulted from computing EF density per unit area from the plane photograph of the curved capillary wall where the real area of the curved wall would exceed the apparent area on the micrograph. The degree of curvature (θ) of the capillary segment was calculated from $\theta = S \times 360/2\pi r$, where S is the arc length and r is the radius. With 5 cm at 30,000 magnification as length and 8 μm as the average radius of capillary, an angle of 11.9° was obtained and the length of the curved segment (L) was calculated from $L = \pi r\theta/180$. The area on the plane micrograph differed from the calculated area of the capillary wall by less than 1%. To quantitate the density of endothelial fenestrae in the glomerular capillary loops, the number of fenestrae in the central 5-cm² area was counted from the 9 × 9 cm Polaroid scanning electron micrograph prints (Polaroid Corp., Cambridge, Mass.). All micrographs were photographed at a fixed magnification of ×30,000. Each capillary wall had to meet two criteria before it was photographed: (*a*) the tilt angle of the capillary had to be minimal (<5°), and (*b*) only the attenuated portion of the endothelial cell could be visible and not the cell body. To determine the diameter of the EF, the diameters of 25 fenestrae located in the center of the micrograph were measured from the first 10 scanning electron micrograph of each specimen, and the mean values for each rat and the groups were calculated and the significance of differences was assessed by Student's *t* test. The percentage of abnormal capillary loops in the glomeruli were obtained as a percentage of loops with morphologic abnormalities to the total number of loops. From the central 5-cm² area of the first 10 scanning electron micrographs from each specimen, the aggregate area of EF was measured by planimetry, the mean for each group was calculated (13), and the results were expressed as a percentage of the mean aggregate EF area found in the control rats.

To dissociate the functional from the morphological alterations induced by UN in the second part similar studies were performed on sodium-loaded and sodium-depleted rats. 13 rats were housed in individual metabolic cages. Of these, six rats were given normal diets but their drinking water was replaced with 1% NaCl. Five rats were given low-sodium diets (ICN Nutritional Pharmaceuticals, Cleveland, Ohio) and distilled water to drink, whereas the two controls were given standard food and water. After 3 wk of acclimatization, 15 mg/kg UN in 0.5 ml bicarbonate saline was given intravenously to the experimental rats, whereas an equal volume of bicarbonate saline was given to controls. After the administration of UN, experiments as outlined earlier were performed with the addition that two indwelling catheters were placed, one in the jugular vein and another in a femoral artery. In the jugular vein, [^{14}C]inulin (30 μCi/ml) in 5% mannitol was infused at a rate of 0.9 ml/h·100 g rat body wt for 45 min to achieve equilibrium and then the infusion was continued

TABLE I

Renal Functional Parameters from the Control, the Low-Dose, and the High-Dose Groups at 2, 7, and 17 h after Injection

	Saline controls				15 mg/kg UN				25 mg/kg UN			
	n	Creatinine clearance	FENa	Urinary osmolality	*n*	Creatinine clearance	FENa	Urinary osmolality	*n*	Creatinine clearance	FENa	Urinary osmolality
		μl/min/100 g	*%*	*mosmol/kg*		*μl/min/100 g*	*%*	*mosmol/kg*		*μl/min/100 g*	*%*	*mosmol/kg*
2 h	5	830±52	0.68	1067±620	6	251±47*	8.2*	336±410*	5	163±73*	8.5*	425±439*
7 h	4	780±89	0.89	1286±722	5	193±76*	4.6*	464±301*	5	118±98*	3.8*	517±216*
17 h	4	742±124	0.75	1438±519	5	158±89*	7.3*	726±271	5	128±101*	6.1*	395±261*

All values are expressed as $\bar{x}\pm$SD. *n* refers to number of animals.

* Significant difference from control at $P < 0.05$.

TABLE II

EF Density/5 cm², EF Diameter in Å (×30,000), and the Percentage of Abnormal Capillaries in Normal Controls and the UN-injected Rats at 2, 7, and 17 h after Intravenous UN

	2 h			7 h			17 h		
		Density	Diameter		Density	Diameter		Density	Diameter
Controls	(n = 50)	107±10	751±53	(n = 40)	103±9	765±43	(n = 40)	101±11	764±37
15 mg/kg UN	(n = 60)	91±2*	501±61*	(n = 50)	52±8*	472±28*	(n = 50)	45±11*	438±98*
25 mg/kg UN	(n = 50)	95±3	525±43*	(n = 50)	54±9*	470±39*	(n = 50)	44±10*	440±56*
		Abnormal capillaries/total capillaries ×100							
15 mg/kg		36%			69%			80%	
25 mg/kg		47%			71%			93%	

The values are expressed as $\bar{x}$±SEM. n refers to the number of micrographs analyzed.
* Significant difference from controls at $P < 0.05$.

through the experiment. In the next 2 h, two 1-h samples of 1 ml blood each were drawn by continuous aspiration through the catheterized femoral artery and two 1-h urine collections were obtained. Radioactivity in the samples of serum and urine was counted and glomerular filtration rate (GFR) was calculated by the methods outlined in an earlier publication (14). Sodium concentration in the urine and serum samples was measured by the methods cited earlier and FENa was calculated. Morphological studies were performed as outlined earlier employing similar methods for the collection and analysis of data. Statistical methods of analysis on the functional and the morphological data included nonpaired t test (13), one-way analysis of variance, Newman-Keuls multiple comparison tests (15), and nonparametric analogue of the one-way analysis of variance with nonparametric comparison test (16).

RESULTS

2 h after the UN administration, its effect on renal functions were evident from the changes in urinary os-

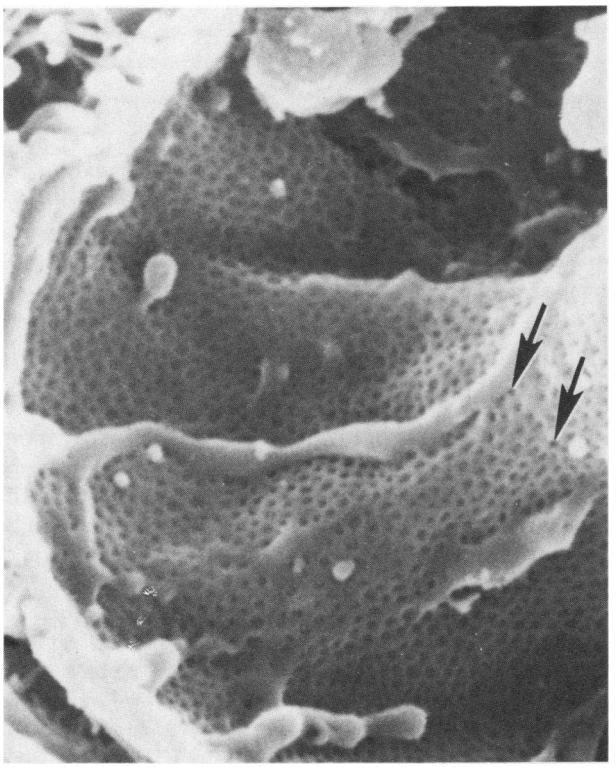

FIGURE 1 Scanning electron micrograph of a capillary loop from a control animal. The glomerular endothelium is characterized by numerous, regularly shaped fenestrae (arrows). An occasional cell process is seen. ×15,000.

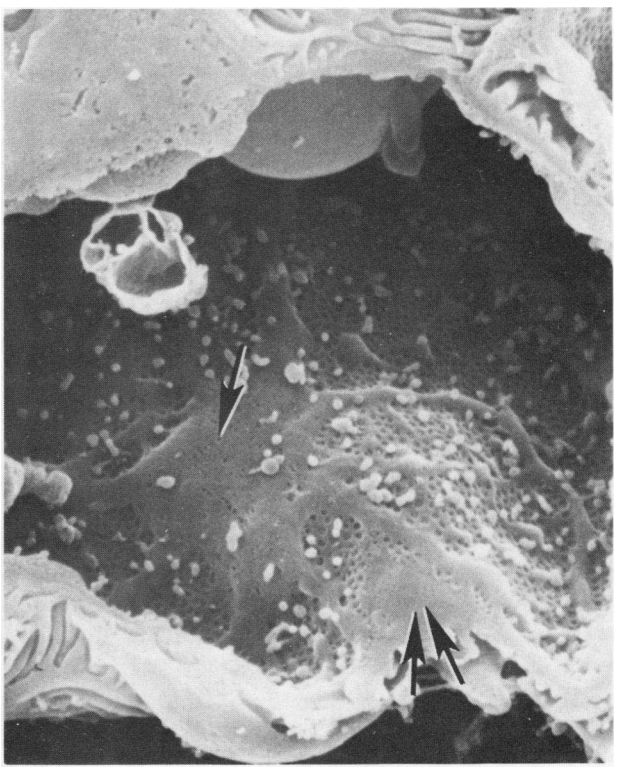

FIGURE 2 The glomerular endothelium 2 h after UN treatment at the low dose showed a reduction in the size (arrow) and density (double arrow) of fenestrae. ×14,500.

molality, creatinine clearance, and FENa. The fall in creatinine clearance and the increase in FENa show that the renal failure had begun at 2 h after the administration of UN (Table I). Renal function declined further at 7 and 17 h after the administration of UN (Table I).

From the scanning electron micrographs, the diameters of the capillaries cut horizontally were measured in each specimen to determine if in various groups the capillaries were variably dilated. The average capillary diameters from the rats of various groups were comparable. The data regarding EF density and diameter from control, low-dose and high-dose groups are presented in Table II. In controls, normally fenestrated endothelial cells were seen by scanning electron microscopy (Fig. 1). 2 h after injection of UN, a reduction in the size and density of EF and the appearance of microvilli on endothelial cell surface were the only morphologic abnormalities found (Fig. 2). At this time, the changes were localized to small areas of the luminal surface (Fig. 3). The percentage of abnormal to total capillary loops at different time intervals are shown in Table II. Epithelial cells were normal (Fig. 3). Although these changes were readily seen by scanning electron microscopy, by transmission electron microscopy the glomerular structure appeared normal.

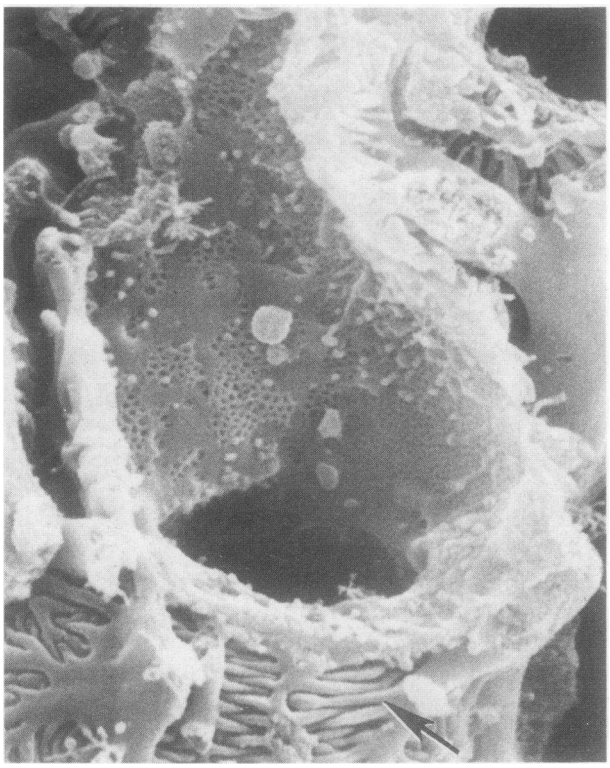

FIGURE 3 The endothelium showed the same changes after 2 h at high dose. The visceral epithelium showed no changes (arrow). ×14,000.

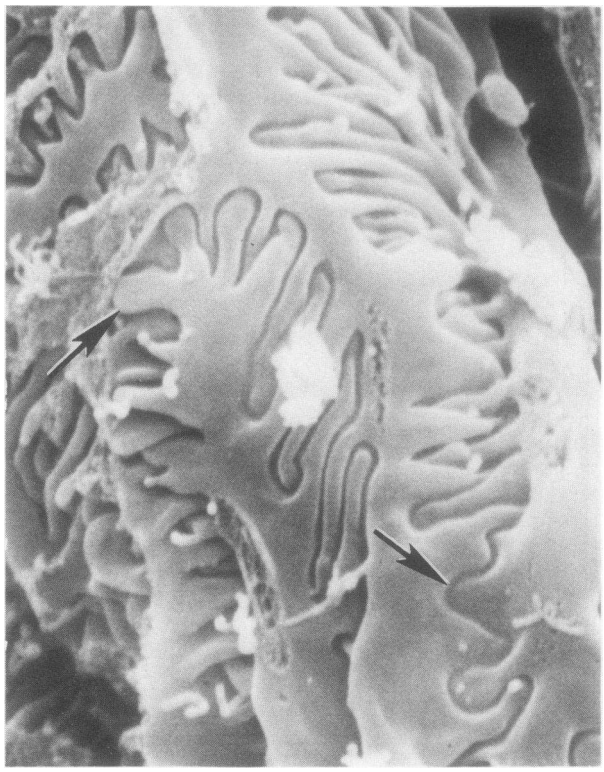

FIGURE 4 By 7 h, foot processes showed swelling (arrows) along focal areas of the capillary loops. ×16,000.

At 7 h after the administration of UN, swelling of epithelial cell foot processes was noted in a few areas (Fig. 4). Endothelial alterations had progressed and now involved larger areas (Fig. 5). The EF density and diameters at 7 h differed significantly when compared to the EF values obtained at 2 h ($P < 0.05$). The changes seen in high- and low-dose groups were similar (Table II). By 17 h, epithelial changes were more pronounced (Fig. 6) and the endothelial cells were altered in even larger areas (Fig. 7 and 8). However, the measured density and diameters of EF did not significantly differ from those obtained at 7 h. By transmission electron microscopy, although the epithelial cell alterations were readily seen, the alterations in the morphology of endothelial cells were equivocal. The aggregate EF area at 2, 7, and 17 h after the injection of UN, expressed as a percentage of the EF area of saline-injected controls, is shown in Table III. EF area declined progressively with time. However, in both low- and high-dose groups, the decrement in area was similar.

In the second part of the study, sodium-loaded and sodium-depleted rats were given UN (15 mg/kg). Blood urea nitrogen, inulin clearance and FENa of normal controls and UN-injected sodium-loaded and sodium-depleted rats are shown in Table IV. In sodium-loaded rats, administration of UN did not significantly reduce GFR (Table IV). In these rats the endothelial

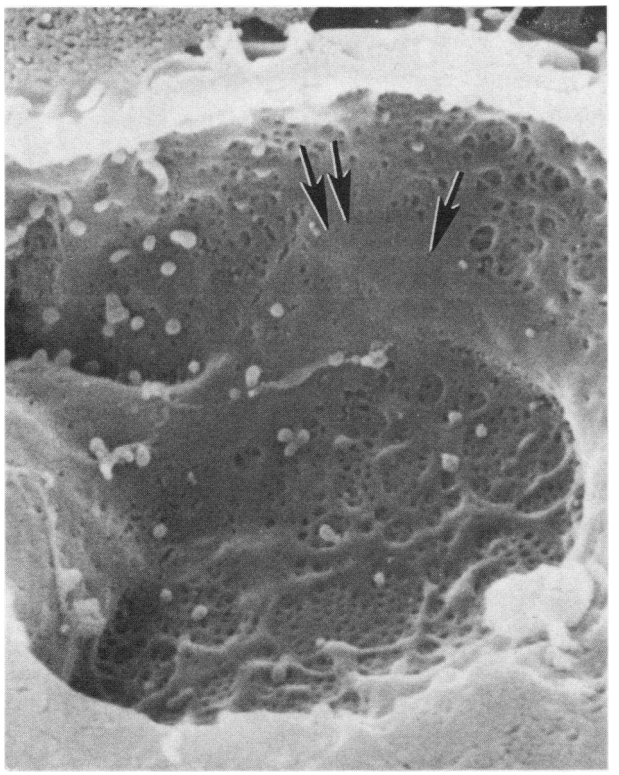

FIGURE 5 The glomerular endothelium showed changes by 7 h at the low dose of UN. Larger areas showed a reduction in the diameter (arrow) and density (double arrow) of fenestrae. ×15,000.

cell morphology was also normal. However, epithelial cells showed loss of the interdigitating cytoplasmic processes in some areas. The rats that were sodium-depleted developed marked reduction in GFR (Table IV). Sodium-depleted rats in contrast to the sodium-loaded rats, showed marked reduction in the EF density and diameter. Quantitative analysis of the EF changes in these rats is presented in Table IV. The results show that the sodium-expanded rats had no important reduction in EF density and diameter as compared to the controls. A severe reduction in EF area was found to have occurred in the sodium-depleted rats whereas no significant reduction had occurred in the EF area in sodium-expanded rats (Table IV).

DISCUSSION

Solutes move across the glomerular capillary walls through an extracellular pathway that sequentially consists of EF, glomerular basement membrane, the pores of slit diaphragms, and the filtration slits (7). A major portion of the water transported across the glomerular capillaries appears to follow the same pathway (8). A diminution in the size and the density of EF is anticipated to reduce the extracellular area for glomerular filtration and thereby reduce the capillary K_f, because K_f is a product of the hydraulic conductivity of the capillary wall and the filtration area. 2 h after the administration of UN, we found a reduction in EF diameter and density, whereas the glomerular K_f has been previously shown to decline in a similar model of acute renal failure at a corresponding interval (3). The temporal relationship between the structural and functional alteration suggests a cause and effect relationship. The correlation between the progressive reduction in EF area and GFR at 7 and 17 h after the administration of UN further supports this suggestion.

In glomerular capillaries, the total area of epithelial slit pores has been considered to be the major determinant of water permeability (8). In some models of acute renal failure epithelial alterations have been found and it has been suggested that these alterations may be responsible for the decline in glomerular K_f (4, 5). However, several observations are against this possibility. In our studies, glomerular epithelial cells were morphologically normal 2 h after the administration of UN, a time at which glomerular K_f has been found to be reduced (3). Similarly, in gentamicin-induced acute renal failure, despite normal epithelial cells, the glomerular K_f is reduced (17). In addition, we found similar, though less severe, alterations in the epithelial cells without an important reduction in the

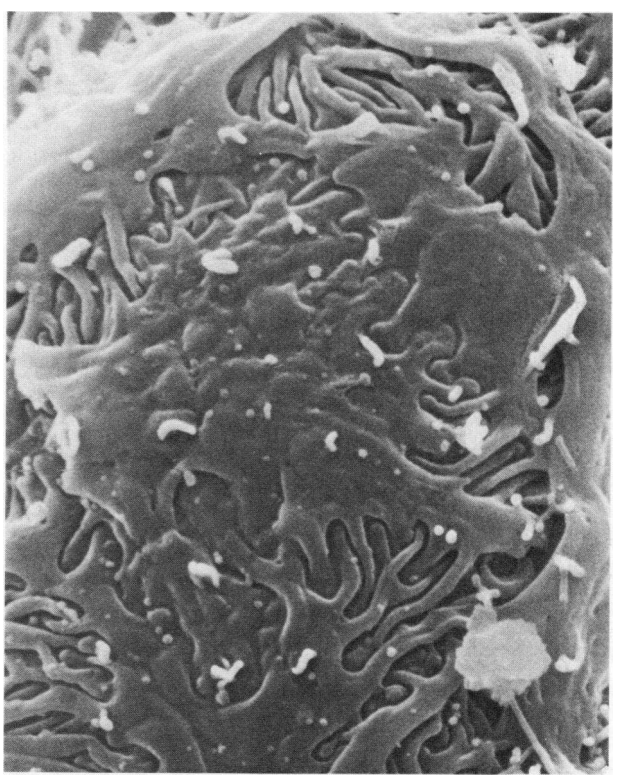

FIGURE 6 By 17 h extensive podocyte swelling was noted. More areas of swelling were seen at 17 h as compared to 7 h. ×14,000.

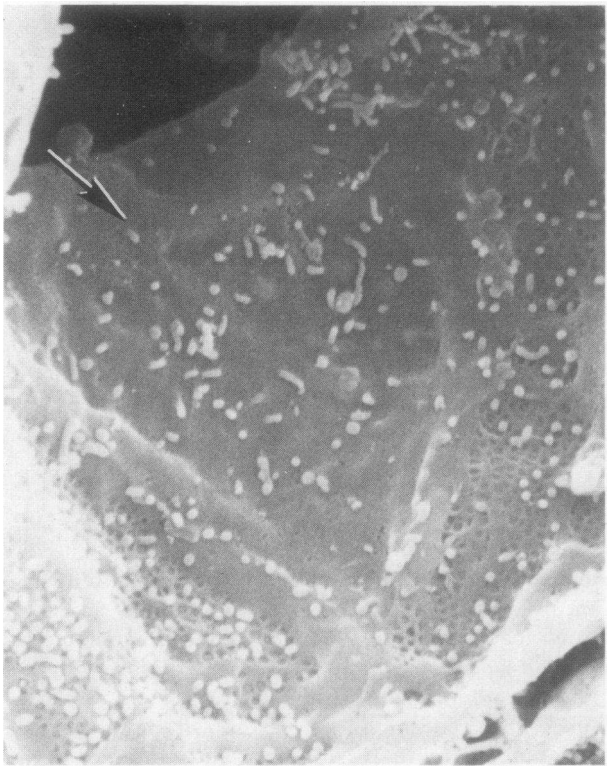

FIGURE 7 At 17 h in the low-dose group the fenestral diameter had not decreased further, however, larger areas appeared to become involved. Note area (arrow) with no fenestrae. ×16,000.

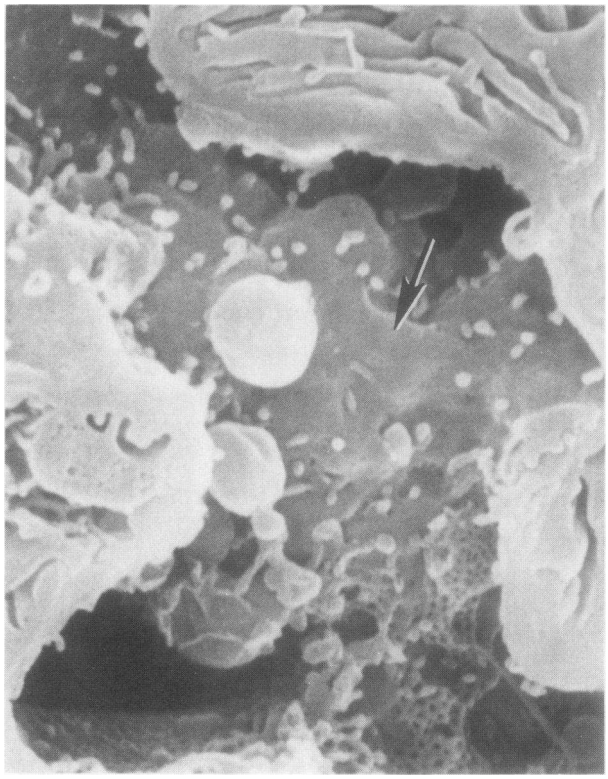

FIGURE 8 An extensive loss of fenestrae (arrow) was seen by 17 h at the high dose. ×15,500.

GFR by the administration of UN to sodium-loaded rats and in sodium-loaded dogs given mercuric chloride similar findings have been noted (6). These observations cast doubt whether the epithelial alterations, per se, are sufficient to decrease the glomerular filtration. We found changes in both the endothelial and the epithelial cells at 7 and 17 h after the administration of UN and the possibility remains that when such alterations occur together in both cells, a greater reduction in filtration area results.

Reduction in glomerular K_f can also occur from other mechanisms (18). It has been suggested that the contraction of glomerular mesangium can shorten and narrow the capillaries resulting in reduced surface area (19). In addition, glomerular K_f has also been suggested to decline because of a reduction in the hydraulic conductivity of the capillary wall when calcium, angiotensin II, vasopressin, cyclic AMP, and certain vasodilator drugs are infused in the renal artery (20–23). However, the possibility of reduced filtration area by the mechanism described here has not been fully excluded in these situations. A quantitative relationship between the filtration area and the rate of filtration has been derived from a model of glomerular ultrafiltration (24). It has been suggested that ~50% reduction in filtration area is needed to reduce the filtration rate (24). 2 h after the administration of UN, the EF area had declined to only 52%, whereas 7 and 17 h later, the EF area had declined to 30%, which could have been an important factor in reducing the GFR.

We administered UN to sodium-loaded rats in an attempt to dissociate the glomerular morphological from the functional alterations. In sodium-loaded rats, if the endothelial alterations had occurred without a reduction in GFR it would have been against the possibility that these alterations were a factor in reducing the GFR. Our inability to dissociate the two phenomena does not prove but is consistent with a cause and effect relationship. It is tempting to speculate regarding the reason for the failure of sodium-loaded rats to develop the functional or the morphological alterations. In sodium-

TABLE III

EF Area of UN-injected Rats Expressed as a Percentage of the EF Area of Saline-injected Controls at 2, 7, and 17 h after Injection

UN	2 h	7 h	17 h
15 mg/kg	52.1	30.1	24.6
25 mg/kg	54.3	30.2	23.6

TABLE IV

Renal Functional and Morphologic Parameters Obtained from Normal Controls given Bicarbonate Saline and from Sodium-depleted and Sodium-loaded Rats Given 15 mg/kg UN

	Control rats on regular diet (n = 2)	Low Na Diet and water drinking rats (n = 5)	Regular diet and saline drinking rats (n = 6)
BUN, *mg%*	18±3	35±7*	22±4
Inulin clearance, *μl/min/100 g body wt.*	793±104	92±41*	632±134
FENa, %	0.5±0.3	7.5±2.8*	8.9±4.3*
EF, *density/5 cm²*	105±10	43±15*	109±11
EF diameter, Å	763±31	473±59*	752±75
% EF area	100%	27.4%*	92%

All values are expressed as $\bar{x}$±SEM. Number of observations for BUN, inulin clearance, and FENa were twice the number of animals (n).

* Significant difference between the controls and the sodium-depleted and sodium-loaded rats.

loaded rats, a lower concentration of UN may have prevented the cellular injury. Alternatively, a reduction in the intrarenal generation of angiotensin by sodium-loading could have been responsible for the protection. The reverse of either of these two possibilities could account for the more severe alterations in sodium-depleted rats.

We propose that the endothelial cells play a role in the modulation of the glomerular capillary filtration area and that the structural alterations in endothelial cells are a factor in reducing the GFR in UN-induced acute renal failure.

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