A Micropuncture Study of the Early Phase of Acute Urate Nephropathy

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ABSTRACT The early pathophysiological changes in acute urate nephropathy were investigated in a rat model using micropuncture, clearance, and morphologic methods. Plasma urate was increased from 1.2±0.6 to 20.1±3.1 mg/100 ml ($P < 0.001$). Urinary urate rose from 24.3±5.1 to 142.2±21.0 mg/100 ml ($P < 0.001$). Renal plasma flow and glomerular filtration rate fell to 17 and 14% of control values, respectively, and urine flow rate decreased from 11.3±4.8 to 4.2±2.2 μl/min (all $P < 0.005$) Superficial nephron filtration rate fell less than that of the whole kidney (70 vs. 86%). Both proximal and distal tubular pressures were increased from 10.6 to 26.1 mm Hg and from 7.2 to 24.7 mm Hg, respectively ($P < 0.005$). Efferent arteriolar and peritubular capillary pressures were increased twofold. Vascular resistance beyond the peritubular capillaries increased from 4.8×10^9 to 21.6×10^9 dynes s/cm^5. Extensive deposits of uric acid and urate were found in the tubular system and vasa recti from the corticomedullary junction to the tip of the papilla.

It is concluded from these experiments that not only tubular obstruction in the collecting ducts, but also obstruction of the distal renal vasculature, are the primary early pathogenetic events in acute urate nephropathy.

INTRODUCTION

Acute urate nephropathy, the clinical designation for marked hyperuricemia and acute renal failure, is a well-known syndrome most frequently encountered in the course of hematologic malignancies (1–8). Evidence from in vitro biochemical experiments and in vivo morphologic studies (9–16) suggest that the renal shutdown is due to tubular obstruction from precipitation of excessive filtered and (or) secreted urate. However, some investigators have concluded that hyperuricemia per se may have acute nephrotoxic effects apart from the production of tubular uric acid deposits (15, 17). Still others have measured substantial decreases in the clearance of para-aminohippurate (PAH) [1] in patients with leukemia and hyperuricemia, suggesting that an alteration in renal hemodynamics may be of pathogenetic significance (18). Thus, it is possible that factors other than tubular obstruction with uric acid are important in the development of acute urate nephropathy.

Investigation of the pathogenesis of this disorder has been difficult. All commonly used experimental species produce an hepatic enzyme, uricase, which converts uric acid to allantoin (12). Thus, in most animal forms nucleic acid breakdown products are ultimately excreted as allantoin which is several times more soluble than uric acid, the end product of human nucleic acid metabolism. A second problem in designing a model of acute urate nephropathy is the relative insolubility of uric acid, which limits the systemic load of this substance that can be administered acutely without considerable volume expansion (17).

To circumvent these technical impediments to an investigation of the pathogenetic events in this disorder, we employed a model in which both micropuncture and clearance methods could be used to study animals in a control phase and shortly after producing hyperuricemia

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[1] *Abbreviations used in this paper:* GFR, glomerular filtration rate; PAH, para-aminohippurate; RBF, renal blood flow; SNGFR, single nephron glomerular filtration rate.

comparable to that occurring in man. This was accomplished by giving intraperitoneal and intravenous injections of oxonic acid, a uricase inhibitor, and a bolus injection of the highly soluble lithium salt of uric acid. The effects of lithium and oxonic acid on renal function were found to be negligible within the time period of the experiments.

The results indicate that the early pathophysiologic changes in acute urate nephropathy are due to an obstructive process from precipitated uric acid and urate, which involve not only the collecting ducts but also the distal renal vascular complex.

METHODS

Surgical preparation. Male Wistar rats (weight 280–310 g), maintained without food overnight but allowed free access to water, were anesthetized with pentobarbital (60 mg/kg i.p.). Supplemental doses of pentobarbital (5–10 mg/kg i.v.) were given as necessary during the studies. After anesthesia oxonic acid (250 mg/kg) was injected intraperitoneally. The animals were placed on a thermostatically controlled heated surgical table (37°C). Tracheostomy was performed and polyethylene catheters placed in the jugular vein and femoral artery. Isotonic Ringer's solution containing inulin, PAH, and oxonic acid was infused through the jugular vein catheter at 50 μl/kg per min. Oxonic acid content of the infusate was adjusted to deliver 2 mg/kg per min. The concentrations of inulin and PAH were sufficient to give plasma levels of 50–100 mg/100 ml and 2–4 mg/100 ml, respectively. The femoral artery catheter was attached to a pressure transducer (model 267B, Hewlett-Packard Co., Palo Alto, Calif.) and blood pressure was recorded on a Hewlett-Packard recorder (model 7702B). A polyethylene catheter with a hooked tip was positioned in the left renal vein via the right femoral vein for measurement of renal PAH extraction as previously described by this laboratory (19). The left kidney was then dissected free of surrounding connective tissue and placed in a Lucite cup (E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.) affixed to the surgical table. Agar at 37°C was layered about the free margins of the kidney and the surface was bathed with physiologic saline warmed to 37°C. A PE-50 catheter was inserted into the ureter for collection of urine samples. 1 h before the experiment, 1 ml of blood was removed from the femoral artery and replaced with an equal volume of isotonic Ringer's solution. Aliquots of this blood equal in volume to samples taken for inulin, PAH, and urate analysis were returned to the animal during the study to maintain stability of hematocrit.

Acute studies. After a 1-h period to allow equilibration of plasma inulin and PAH levels, samples of femoral artery (0.4 ml) and renal venous blood (0.1 ml) were obtained between two timed 50-μl collections of urine. Concentrations of inulin, PAH, and urate were determined on blood and urine samples. In addition, osmolality and pH were determined on urine samples. Timed collections of tubular fluid were made from four or five last proximal tubular loops with oil-filled micropipettes (8–10 μm OD) as previously described (20). Hydrostatic pressures were measured in proximal and distal tubules, efferent arterioles, and peritubular capillaries with a servo-null pressure measuring apparatus (Instrumentation for Physiology and Medicine, San Diego, Calif.). Initial identification of distal tubules was made from their characteristic small, thin appearance. After pressure measurements were obtained, identification was confirmed by the injection of FD and C green no. 3 (Keystone Ingham Corp., Cerritos, Calif.) into proximal loops of surrounding nephrons and then observing the delayed return of the colored material in the tubular loop studied. After these control determinations, lithium urate, prepared by dissolving uric acid in a warmed solution of saturated lithium carbonate and adjusted to pH of 7.4, was injected into the jugular catheter over 5 min. The total dose was 300 mg/kg delivered in a volume of 3 ml. Femoral artery blood (0.3 ml) and urine were obtained within 5 min of the injection to determine urate concentrations. After 1 h, repeat femoral artery and renal vein blood and ureteral urine collections for inulin and PAH concentration were obtained. Repeat tubular fluid collections were made from two to five new last proximal tubular sites. During collection, the intratubular pressure existing in that tubule was monitored with a pressure pipette just distal to the oil block. Fluid collection was controlled to maintain pressure constant. Hydrostatic pressures were remeasured in proximal and distal tubules, efferent arterioles, and peritubular capillaries. The kidneys were then removed, sectioned in a plane parallel to their long axis, and examined under a dissecting microscope for crystal deposition. One-half of each kidney was photographed to document gross pathology; the other half was subdivided for microscopic analysis. The latter studies consisted of light microscopy on hematoxylin-eosin-stained sections preserved in 90% alcohol and phase contrast and polarized light examination of frozen sections.

Fresh sections of liver, spleen, and skeletal muscle also were examined for the presence of crystal deposition to determine if the precipitation of urate was a nonspecific phenomenon unrelated to the biochemical environment of the kidney.

In a second group of rats an identical protocol was followed, except that a saturated solution of lithium carbonate in a dose of 133 mg/kg in 3 ml was substituted for lithium urate. The molar quantities of lithium and oxonic acid were the same as in the urate injection protocol. These studies were performed to assess the acute effects on renal function of lithium carbonate and oxonic acid per se, independent of that due to urate.

Balance studies. To determine the more prolonged effects of urate infusion on renal function, 10 rats were maintained in balance cages for 1 wk. Body weights, plasma urea nitrogen, and potassium were measured from 1 day before to 6 days after the intravenous infusion of lithium urate (300 mg/kg) and the intraperitoneal injection of oxonic acid (250 mg/kg). Body weight was maintained constant with intraperitoneal injection of 0.9% saline as necessary. Similar balance studies were carried out in animals given lithium carbonate (133 mg/kg i.v.) and oxonic acid (250 mg/kg i.p.). At the conclusion of the balance studies the animals were sacrificed and renal morphology evaluated with a dissecting microscope.

Analytical methods. Plasma and urine inulin and PAH were measured with a Technicon AutoAnalyzer (Technicon Instruments Corp., Tarrytown, N. Y.). Plasma potassium was determined by flame photometry (Instrumentation Laboratory, Inc., Lexington, Mass.). Urea nitrogen concentration was measured spectrophotometrically by the method described by Coulombe and Favreau (21). Urate content was tested by a colorimetric uricase method (American Monitor Corp., Indianapolis, Ind.) and urine osmolality determined with a model 3L osmometer (Advanced Instruments, Inc., Needham Heights, Mass.). A radiometer

Copenhagen pH meter 26 (The London Co., Cleveland, Ohio) was used to test urine pH. Tubular fluid inulin was estimated by the micromethod of Vurek and Pegram (22) as modified for this laboratory (23).

Because of an observed decrease in PAH extraction associated with urate deposition in the kidney, radiolabeled microspheres were used to confirm the accuracy of the clearance techniques to estimate renal plasma flow in three rats (24). A catheter was positioned in the left ventricle via the right carotid artery and constant withdrawal of femoral artery blood was performed with a Harvard pump (Harvard Apparatus Co., Inc., Millis, Mass.). In the control phase, ^{85}Sr-labeled microspheres (sp act 12.54 mCi/g) at a concentratoin of 0.97 mg/ml in 10% dextran were given as a bolus injection in the left ventricle (total dose 0.29 mg in 0.3 cm^3). Femoral artery blood was simultaneously withdrawn at a constant rate of 200 μl/min for 1 min. ^{141}Ce-labeled microspheres (sp act 12.92 mCi/g) were substituted for ^{85}Sr at the same concentration and total dose for estimation of renal blood flow during the experimental phase. At the conclusion of the experiment both kidneys were removed, decapsulated, and counted in a Bio-Gamma Counter (Beckman Instruments, Inc., Fullerton, Calif.) along with the femoral artery blood samples. Renal blood flow (RBF) was taken as the quotient of the total kidney counts per minute per femoral blood counts per minute × femoral artery blood withdrawal rate (expressed in microliters per minute). These results were compared with the PAH clearance and extraction determinations after the latter were factored for the hematocrit to give RBF. The mean RBFs by the clearance and microsphere techniques during control were 7,216±864 and 6,464±759 μl/min, respectively; during the experimental phase the values averaged 1,974±424 and 1,785±355 μl/min, respectively. While the results with these two methods varied significantly ($P < 0.05$) by an average 12%, the differences were consistent and the percentage decreases after urate injection were similar. Therefore, the clearance measurements were considered adequate to estimate the relative changes in RBF in these studies.

The paired *t* test was used to compare results between control and experimental phase of the studies and the unpaired *t* test was used to compare the data between the lithium carbonate- and lithium urate-treated animals. Data are expressed as means±1 SD.

RESULTS

Lithium carbonate control studies. The clearance and micropuncture date from rats given bolus injections of lithium carbonate revealed no significant effect of this agent on renal function. Arterial blood pressure, renal plasma flow, glomerular filtration rate (GFR), urine volume, urine osmolality, and arterial blood hematocrit were unchanged. Similarly, the single nephron glomerular filtration rate (SNGFR), promimal tubule absolute reabsorption, tubular, and peritubular vascular pressures remained constant. There was a significant, albeit slight, increase in urine pH from 5.6±0.4 to 6.6±0.5 ($P < 0.01$). Thus with the exception of urine pH, lithium carbonate had no apparent effect on any of the measured parameters of renal function at 1 h after injection.

Lithium urate studies. The control clearance and micropuncture measurements for rats given lithium urate (shown in Tables I and II) were similar to those for animals given lithium carbonate. After injection of the urate salt, plasma levels increased from 1.2±0.6 to 20.1±3.1 mg/100 ml ($P < 0.001$).[2] Urinary urate increased from 24.3±5.1 to 142.2±21.0 mg/100 ml ($P < 0.01$). Arterial blood pressure remained constant. At 1 h renal plasma flow and GFR had fallen to 17 and 14% of control values, respectively. The decrease in these two parameters was essentially parallel with no significant change in filtration fraction. Urine volume decreased from 11.3±4.8 to 4.2±2.2 μl/min ($P < 0.005$). Urine osmolality fell slightly ($P < 0.025$) and urine pH

[2] It was anticipated that a higher postinfusion value would be found, since the rats each received 90 mg of urate and had an average extracellular fluid volume estimated at 70 ml. It is possible that, in addition to precipitation within the kidney, residual uricase activity was present despite oxonic acid, or that the space of distribution of the injected urate approached that of total body water as has been suggested by studies in humans (10).

TABLE I

Clearance Results for Rats Given Lithium Urate

Rat no.	BP		P_{urate}		RPF		GFR		V		U_{urate}		U_{osm}		U_{pH}		Hct	
	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp
	mm Hg		*mg/100 ml*				*μl/min*				*mg/100 ml*		*mosmol/liter*				%	
1	106	95	0.5	17.6	3,612	429	933	98	20.4	6.5	16.3	145.6	1,244	596	5.6	6.0	47	46
2	130	130	1.1	25.2	2,467	250	760	90	6.6	0.2	21.1	151.1	920	600	6.0	6.0	44	44
3	120	130	0.6	16.4	4,603	356	1,203	67	8.8	3.3	27.4	162.0	840	742	5.5	6.1	50	51
4	120	120	1.7	19.4	3,670	664	938	108	11.1	5.5	23.4	106.7	956	630	5.0	6.1	48	48
5	110	110	2.1	21.4	2,188	625	601	178	11.1	5.1	28.1	158.8	1,040	780	5.4	5.8	44	45
6	120	120	1.4	20.3	2,572	954	723	154	9.6	4.5	29.7	128.7	770	645	5.6	5.9	51	48
Mean	117	118	1.2	20.1	3,186	546	860	116	11.3	4.2	24.3	142.2	961	665	5.5	6.0	47	47
±1 SD	9	13	0.6	3.1	926	254	212	42	4.8	2.2	5.1	21.0	166	77	0.3	0.1	3	3
P value	NS		<0.001		<0.005		<0.001		<0.005		<0.001		<0.025		<0.05		NS	

Abbreviations: Cont, control period before urate infusion; Exp, experimental period 1 h after urate injection; BP, mean arterial blood pressure; P_{urate}, plasma urate concentration; RPF, renal plasma flow; V, urine flow rate; U_{urate}, urinary urate concentration; U_{osm}, urine osmolality; U_{pH}, urine pH; Hct, arterial blood hematocrit.

TABLE II

Micropuncture Measurements in Rats Given Lithium Urate

Rat no.	SNGFR		Jv		P_{PT}		P_{DT}		P_{EA}		P_C	
	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp
	nl/min						*mm Hg*					
1	35.0	3.6	17.9	1.8	6.5	28.4	6.0	24.4	11.3	24.0	8.0	19.3
	(5)	(3)	(5)	(3)	(6)	(5)	(3)	(5)	(4)	(4)	(4)	(4)
2	20.9	10.7	11.4	3.5	17.1	29.5	16.9	—	18.8	24.3	14.5	18.5
	(4)	(3)	(4)	(3)	(4)	(5)	(4)	—	(5)	(2)	(2)	(4)
3	49.3	14.3	25.0	10.1	8.1	29.4	6.7	26.0	15.0	26.3	10.4	18.8
	(4)	(3)	(4)	(3)	(4)	(5)	(3)	(3)	(3)	(3)	(8)	(6)
4	33.9	8.6	22.6	4.8	12.2	22.0	—	—	17.5	27.0	12.6	18.1
	(4)	(3)	(4)	(3)	(5)	(13)	—	—	(3)	(4)	(7)	(6)
5	21.6	10.5	11.0	5.7	10.1	17.6	9.5	17.0	15.5	30.3	9.9	16.2
	(4)	(2)	(4)	(2)	(4)	(8)	(1)	(1)	(4)	(3)	(5)	(3)
6	22.4	13.0	11.7	5.1	10.1	29.6	8.5	29.5	13.5	28.0	10.0	17.4
	(4)	(4)	(4)	(4)	(5)	(4)	(2)	(3)	(2)	(2)	(5)	(4)
Mean	29.7	10.1	15.6	5.1	10.6	26.1	7.2	24.7	14.2	26.4	10.9	18.1
±1 SD	11.5	3.7	6.6	2.8	3.7	5.1	1.2	5.3	2.6	2.3	2.3	1.0
P value	<0.005		<0.005		<0.005		<0.005		<0.001		<0.001	

Abbreviations: Cont, control period before urate infusion; Exp, experimental period 1 h after urate infusion; Jv, proximal tubule absolute reabsorption; P_{PT}, proximal tubule hydrostatic pressure; P_{DT}, distal tubule hydrostatic pressure; P_{EA}, efferent arteriole hydrostatic pressure; P_C, peritubular capillary hydrostatic pressure.
Numbers in parentheses represent the number of observations.

rose minimally from 5.5±0.3 to 6.0±0.1 ($P < 0.05$). Hematocrit was unchanged.

The mean SNGFR after urate was 30% of control (Table II). Absolute reabsorption of proximal tubular fluid fell in proportion to SNGFR. The mean tubular fluid to plasma inulin ratio during control and after urate injection was 2.12±0.54 and 2.03±0.62, respectively. These values represented fractional reabsorptions of 53 and 51% which were not significantly different. Proximal tubular pressure rose from 10.6±3.7 to 26.1± 5.1 mm Hg ($P < 0.005$). There was a similar increase in distal tubular pressure from 7.2 ± 1.2 to 24.7±5.3 mm Hg ($P < 0.005$) indicating that the level of obstruction was beyond the accessible distal tubule. Efferent arteriolar and peritubular capillary pressures also were significantly elevated, both reaching nearly twice control levels.

Balance studies. The results of plasma urea nitrogen, potassium, and urate determination for rats observed for 6 days after injection of either lithium carbonate or lithium urate are shown in Fig. 1. None of these measurements changes with the former infusate. After infusion of the latter, plasma urate was 15.5±2.4 mg/100 ml at 2 h and fell to levels similar to the lithium carbonate-treated group by the 3rd day. Plasma urea nitrogen rose to a peak level of 84±28 mg/100 ml on the 2nd day and plasma potassium reached 11.1±2.0 meq/liter on the 3rd day in urate-treated rats. Two of

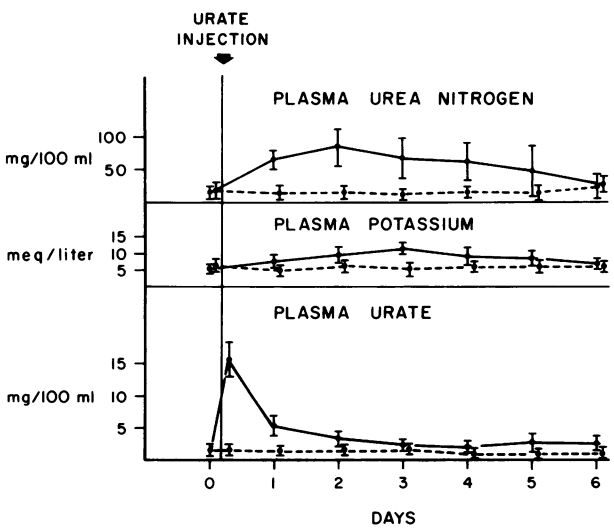

FIGURE 1 Plasma urea nitrogen, potassium, and urate concentrations before and for 6 days after injection of lithium monourate and oxonic acid (solid line). For comparison, the same data is shown for animals receiving injections of lithium carbonate and oxonic acid (interrupted line). Data is expressed as the mean±1 SD for 10 rats in each group.

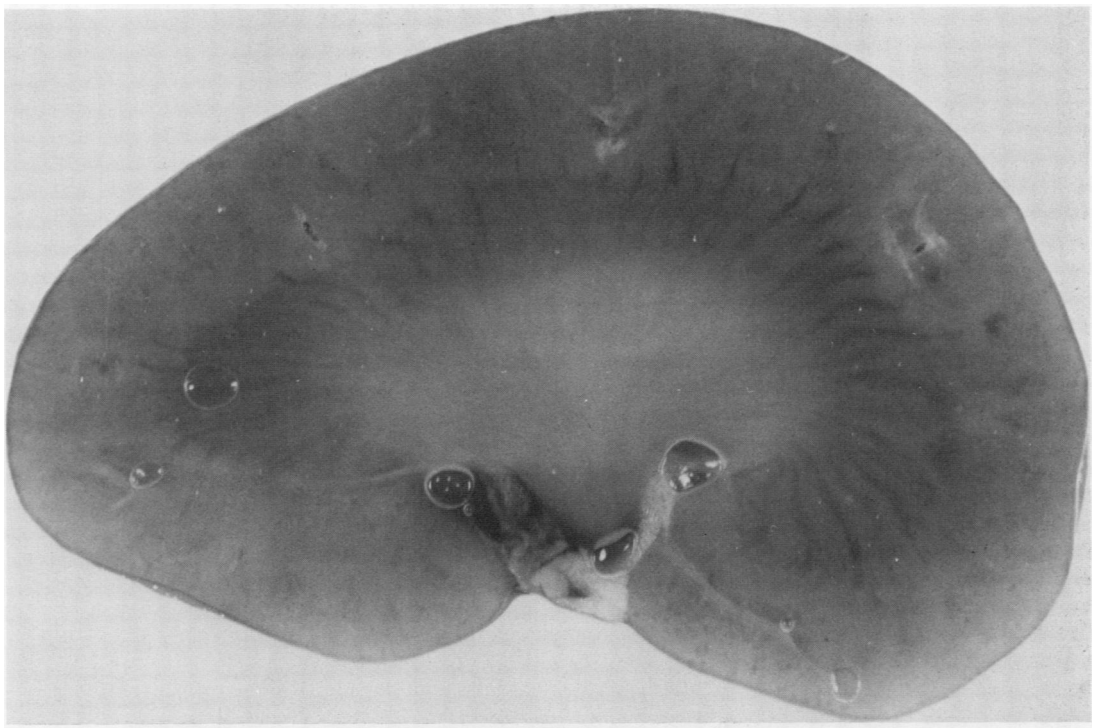

FIGURE 2 Gross appearance of the cut surface of the kidney of a rat given lithium carbonate. Both cortex and medulla are normal without evidence of crystal deposition. (× 10).

FIGURE 3 Gross appearance of the cut surface of the kidney of a rat given lithium monourate. There are scattered deposits in the cortex which become progressively more dense toward the papilla. (× 10).

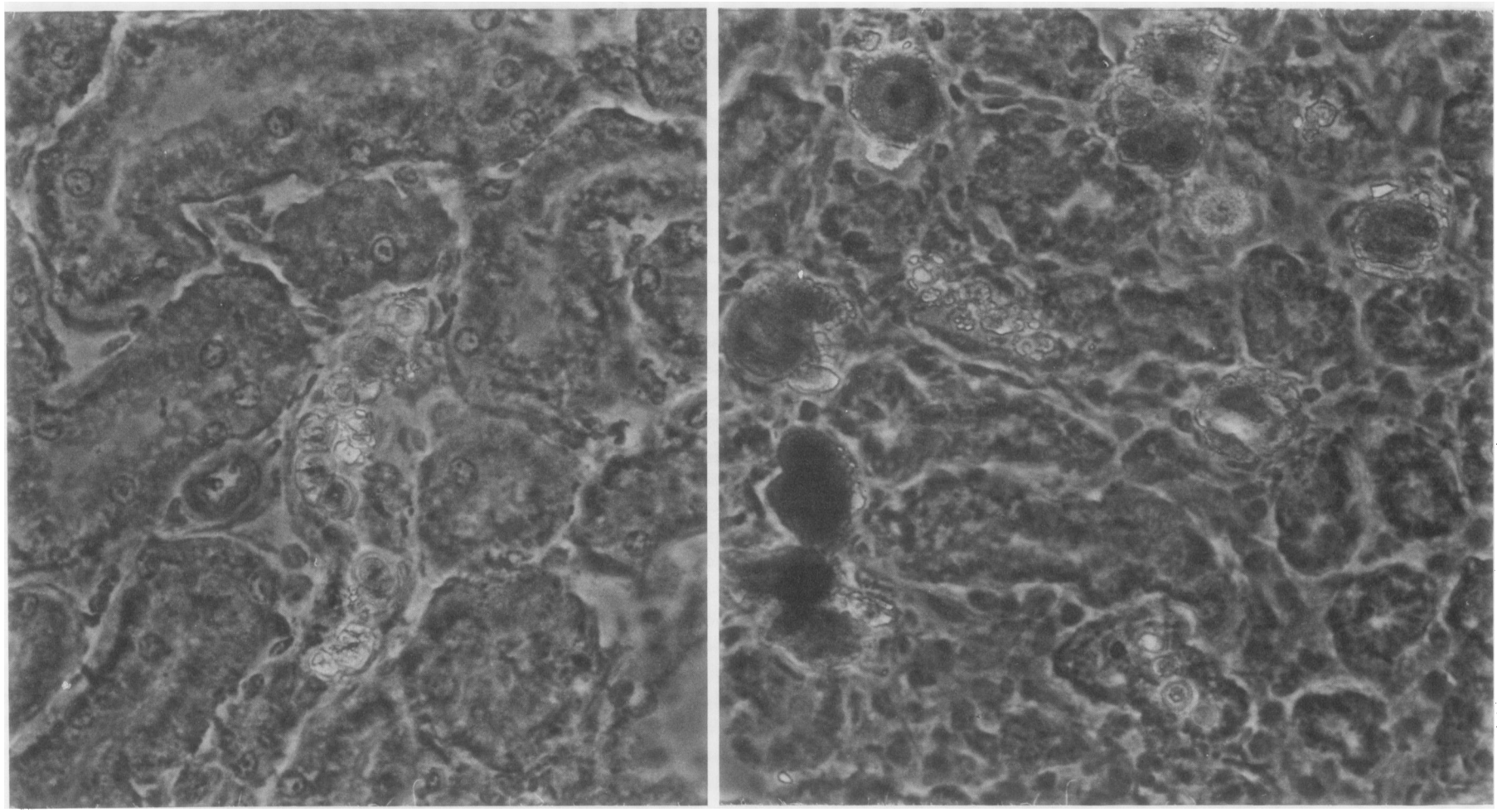

FIGURE 4 Phase contrast microscopic appearance of the region of the cortico-medullary junction of a rat given lithium monourate. The peritubular capillary in the section to the left is filled with deposited material. The section to the right shows the same amorphous crystalline material within both the microvasculature and tubules. (× 500).

the animals died on the 3rd day. In the remaining rats both plasma urea and potassium had returned to levels comparable to those in the control group by the 6th day.

Morphologic studies. Both the external and sectioned gross appearance of the kidneys of the lithium carbonate-treated rats were normal (Fig. 2). In the urate group, the kidneys were swollen with a slight external pallor. Occasional deposits of crystalline material were observed within the superficial tubules which appeared distended but otherwise intact. The cut sections revealed a strikingly uniform yellow-white deposition from the cortico-medullary junction to the tip of the papilla as shown in Fig. 3. By contrast the cortex had minimal crystal deposition. Examination of sections of the cortico-medullary junction, medulla, and papilla with phase-contrast microscopy demonstrated the presence of amorphous crystalline material not only packed in tubular structures but in adjacent blood vessels as well (Fig. 4). Deposits within the tubular structures were assumed to be uric acid rather than urate, because of the high solubility of the lithium salt and the strongly pH dependent solubility of uric acid (9, 10). Vascular deposits were considered to be sodium and (or) lithium[3] urate since their solubility is effected minimally by pH (25, 26). Precipitation resulted from concentrations exceeding their solubility in the ionic strength of the intravascular environment (14, 25). The control experiments with lithium carbonate and oxonic acid infusion excluded the possibility that the deposits were either of these substances or an insoluble carbonate salt. There was less evidence of material within tubules in the microscopic sections than there was on examination of the fresh specimens under the dissecting microscope. This difference has been noted by others (14) and probably represents loss of crystal material in fixing and processing the tissue. No interstitial crystals were seen and except for dilatation and the presence of deposits there were no morphologic abnormalities of tubules or vessels as judged by light microscopic examination of cortical and medullary sections stained with hematoxylin and eosin. The glomeruli did not appear abnormal. No crystals were observed in fresh sections of liver, spleen, or skeletal muscle.

The appearance of the kidneys 6 days after urate injection was similar to that observed in the acute studies. However, unilateral or bilateral hydronephrosis was an added finding in the two animals who died. Uric acid casts filled the upper portion of the ureters in both of these rats.

[3] Lithium urate solubility in vitro decreases by only 20% when pH is decreased from 9 to 5. Unpublished data.

DISCUSSION

Despite the restrictions of species difference that must be accepted in designing a rat experiment to simulate a human pathologic process, it seems that the model used in this study had a number of features that make it an acceptable reproduction of acute urate nephropathy. The plasma urate levels achieved were in the range reported in leukemia and lymphoma patients receiving chemotherapy who developed acute renal failure (6–8, 27).[4] The urinary urate concentrations also were similar to those found in the human disease (18). Urine flow rate fell to one-third of control acutely. The balance studies indicated that the rats had a moderate azotemia that remitted over the course of 6 days. Gross and microscopic examination of the kidneys revealed uric acid and urate deposition. Thus, both "clinical" and pathological changes in our model resembled closely those peculiar to the syndrome of acute urate nephropathy seen in man.

It was anticipated that the use of a lithium salt of uric acid as the agent infused might produce untoward alterations in renal function that would interfere with evaluation of the effects of urate. Several studies have documented impairment of kidney water metabolism by lithium salts (28–31). However, neither urine volume nor osmolality was significantly changed in the control animals given lithium carbonate. Moreover, no other measured parameters of kidney function were altered except for a slight alkalinization of the urine. This latter finding could have been a result of the alkaline nature of the lithium carbonate or a direct effect of lithium since the latter has been reported to cause renal tubular acidosis (32). In any case, no effects of lithium were observed which would have confused interpretation of the results of urate infusion.

Our finding of parallel increases in proximal and distal tubular hydrostatic pressures established the functional site of obstruction in this disorder at the collecting duct level. Previous morphologic study results have been conflicting in that both the ascending limbs of the loops of Henle and the collecting ducts have been reported as the primary sites of obstruction (11, 15, 17). Microscopically, it was difficult for us to distinguish collecting ducts and ascending limbs when a tubular structure contained uric acid deposits; however, there was no indication that physiological obstruction occurred before the distal tubule in any of the experiments. Similar pressure increases were found by Spencer et al. (33) in a more chronic hyperuricemic model. The fact that the collecting duct was the primary site of obstruc-

[4] The values in this study were two to three times those reported in other animal models in which uric and oxonic acid were added to the diet or given intraperitoneally (14, 16, 28).

tion in this model supports the recent observation that this tubular segment has the least compliance and is the major resistance site within the nephron (34).

In the present studies superficial nephron GFR was better preserved than that of the whole kidney. The former fell only to 30% of control while the latter decreased to 14% of its initial level. Such results suggested that there was a greater depression of deep nephron function. The disproportionate changes in superficial and deep nephron filtration rates correlate very well with the pathologic findings of dense deposits of uric acid in the medulla and papilla with relatively little deposition seen in the outer cortical zones.

The marked increases in efferent arteriolar and peritubular capillary pressures provided an explanation for the large decline in renal plasma flow that occurred in the presence of an unchanged renal perfusion pressure. The elevated peritubular vascular pressures indicated that a major fraction of the increased renovascular resistance was in the distal circulatory bed between the peritubular capillaries and the renal vein. Applying the formula given by Blantz et al. (35) and deriving the single nephron RBF from the whole kidney filtration fraction and SNGFR, the calculated resistance for this segment of the renal vasculature increased from a control value of 4.8×10^9 to 21.6×10^9 dynes s/cm^5. Some component of the increase in distal renovascular resistance may have been due to the urate deposits found in the vasa recti. However, since only a relatively small fraction of RBF courses through these vessels, a more likely explanation would be that the increase in distal vascular resistance was secondary to increases in tubular and interstitial pressure with compression of the vessels. Such an explanation would be in agreement with the finding of similar increases in efferent arteriolar and peritubular capillary pressures by Blantz et al. in a model of mechanical ureteral obstruction (35). Regardless of the relative importances of intrinsic and extrinsic mechanisms of blood vessel obstruction, a fall in RBF as a consequence of increased distal renal vascular resistance appeared to be an important factor in the pathogenesis of acute urate nephropathy. It is interesting to note that similar decreases in RBF were found by Rieselbach et al. (18) in a study of this syndrome in leukemia and lymphoma patients.

Although microscopic changes have been seen at 24 h in epithelial cells of rat tubules containing uric acid (15), nephrotoxicity did not appear to play an important role in the earliest phase of renal failure in our model. The change in proximal tubular reabsorption closely paralleled the decrease in SNGFR. This degree of glomerulotubular balance was qualitatively similar to that observed with mechanical occlusion of the ureter (36). Thus, the alteration in proximal tubular reabsorption could be accounted for largely by the factors operative in tubular obstruction without the need to invoke a nephrotoxic explanation. In addition no light microscopic abnormalities of tubular cell morphology were seen within the first 2 h after urate injection, a time at which renal function was severely impaired. Nephrotoxicity, however, may contribute to the later phases of acute urate nephropathy when pathologic changes in tubular cells and the interstitium are a prominent finding (13–15).

In summary, the findings of this study indicated that obstruction was the major pathogenetic event in the earliest stage of acute urate nephropathy. Functionally the site of tubular obstruction was at the collecting duct level. Both physiologic and morphologic studies suggested more extensive pathologic involvement of deeper nephrons. Uric acid and urate deposits occurred in tubular structures and vasa recti from the corticomedullary junction to the papilla. Vascular as well as tubular obstruction was a prominent early pathogenetic factor. The fractional fall in RBF was similar to that of GFR and in large part was the result of a major increase in vascular resistance beyond the efferent arterioles and peritubular capillaries. Both extrinsic compression and intrinsic urate occlusion appeared to be responsible for the change in renovascular resistance.

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