

Glomerular Dynamics and Morphologic Changes in the Generalized Shwartzman Reaction in Postpartum Rats

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ABSTRACT The roles of glomerular functional and morphologic changes were examined in the acute renal failure associated with generalized Shwartzman reaction in postpartum Munich Wistar rats. The susceptibility of postpartum rats to acute deterioration in renal function after a 2-h endotoxin infusion was found to be greater than in virgin litter mates: glomerular filtration rate fell by 93% in the former vs. 24% in the latter group ($P < 0.001$). In postpartum rats there were marked changes in platelet count and fibrinogen level ($P < 0.025$) compatible with consumption coagulopathy. Renal blood flow and glomerular filtration rate fell from 5.5 ± 0.9 and 0.74 ± 0.12 to 2.0 ± 0.7 and 0.12 ± 0.01 ml/min, respectively (both $P < 0.001$). Blood pressure did not change. Results of glomerular dynamics studies showed decreases in single nephron filtration rate from 28 ± 7 to 6 ± 4 nl/min and in glomerular plasma flow rate from 77 ± 26 to 23 ± 12 nl/min (both $P < 0.001$). Afferent net ultrafiltration pressure fell from 20 ± 3 to 5 ± 4 mm Hg due to a fall in glomerular capillary hydraulic pressure from 47 ± 1 to 29 ± 5 mm Hg ($P < 0.001$). There were four- and twofold increases in afferent and efferent arteriolar resistances, respectively. Less than 20% of glomeruli had evidence of fibrin deposition after 2 h of endotoxin infusion, a time when glomerular filtration rate was reduced by >90%. [1-Sar, 5-Ile, 8-Gly] angiotensin II infusion before endotoxin significantly protected glomerular filtration rate, 62 vs. 7% of control in rats with no preinfusion ($P < 0.01$) despite consumption coagulopathy and glomerular fibrin deposition similar to rats without pretreatment.

These data suggest that the early deterioration in renal function in the generalized Shwartzman reaction in the postpartum rat is due to major changes in glomerular dynamics induced by neurohumoral agents and that glomerular fibrin deposition plays a lesser pathogenetic role at this time in this disorder. The study does not address the pathogenesis of renal failure in pregnancy nor peripartum renal failure in another species.

INTRODUCTION

Postpartum acute renal failure, originally described by Robson et al. (1) and Wagoner et al. (2), is characterized by microangiopathic hemolytic anemia, consumption coagulopathy, and bilateral cortical necrosis. Microscopic studies have shown prominent deposition of fibrin and fibrinlike material in glomeruli and less frequently in afferent arterioles and the vasculature of other organs. Several investigators have pointed out the similarity between postpartum acute renal failure and the experimentally induced generalized Shwartzman reaction in rodents (3–6). The latter reaction is produced by two separate injections or a continuous infusion of endotoxin and is also characterized by microangiopathic hemolytic anemia, consumption coagulopathy, glomerular fibrin deposition, and bilateral cortical necrosis (7, 8). The observation that the pregnant animal is more sensitive to the development of the generalized Shwartzman reaction (5, 9–11) has been cited as support for a pathogenetic role of the Shwartzman reaction in postpartum acute renal failure. On the other hand, it has not been shown that animals in the postpartum period have increased sensitivity to develop the generalized Shwartzman reaction similar to that observed in the pregnant state. The absence of such a relationship would make an association between the generalized Shwartzman reaction and postpartum acute renal failure doubtful,

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since the latter has been reported to occur up to several weeks after delivery. In addition, while a great number of pathological studies have been carried out showing fibrin deposition in the kidneys after induction of the Shwartzman reaction, no studies have been performed that have examined the pathophysiologic processes that occur within the kidney, nor has there been an attempt to relate pathophysiologic changes to the observed histological alterations.

In the present study, three sets of experiments were performed to examine these questions. First, postpartum Munich Wistar rats were compared to virgin rats of the same strain in their renal response to endotoxin infusion. Second, serial measurements were made of whole kidney function and glomerular dynamics to determine the pathophysiologic factors responsible for the acute deterioration in renal function. Third, histologic studies were carried out at various times in the course of induction of the generalized Shwartzman reaction to investigate the relationship of changes in renal function to changes in renal histology.

The results showed that there was an increased sensitivity to the generalized Shwartzman reaction in postpartum rats. The major pathophysiological changes were decreases in glomerular plasma flow and glomerular capillary pressure. The early decline in glomerular filtration rate (GFR) was partially prevented by angiotensin II blockade. There was a poor chronologic correlation between the onset of renal dysfunction and detectable changes in renal morphology.

SNFF	Single nephron filtration fraction
SNGFR	Single nephron glomerular filtration rate (nl/min)
V	Tubular fluid flow rate

METHODS

Susceptibility of postpartum rats to the generalized Shwartzman reaction. Eight age- and weight-matched littermate virgin and 10-d postpartum Munich Wistar rats weighing 175–250 g were surgically prepared for clearance measurements after pentobarbital anesthesia as described (12). Inulin was infused through a left jugular vein catheter at a rate sufficient to give plasma concentrations of 50–100 mg/100 ml. A right femoral artery catheter was placed for the recording of blood pressure using a pressure transducer (model 267B, Hewlett-Packard Co., Palo Alto, Calif.) and recorded on a Hewlett-Packard recorder (model 7720B). A catheter was placed in the left ureter for measurement of urinary flow rate and urinary inulin concentration. After a 45-min equilibration period, a 100 μ l blood sample was obtained from the tail vein between two timed collections of 50 μ l of urine. *E. coli* 026B lipopolysaccharide endotoxin was then infused at 0.65 mg/h for 2 h into the right femoral vein. Repeat tail-vein blood and urine collections were then obtained. The total fluid volume received was 1.5 ml/h for both virgin and postpartum rats. Tail-vein blood (0.3 ml) was also taken for measurement of prothrombin time, fibrinogen level, and platelet count before and after endotoxin infusion.

A separate group of six virgin and six 10-d postpartum rats were infused with endotoxin for 2 h through a left femoral catheter while the animals were conscious in restraining cages. After infusion, the catheter was removed, the femoral vein ligated, and the rats returned to metabolic cages. 48 h after endotoxin infusion, all rats were killed and their kidneys removed for detection of cortical necrosis by light microscopy.

Experiments to determine whole kidney and glomerular dynamics in the generalized Shwartzman reaction. 14 littermate 10-d postpartum Munich Wistar rats weighing 200–265 g were prepared for clearance and micropuncture studies as described (13). Catheters were placed in the right jugular and right femoral vein and the right femoral artery as in the previous set of experiments. A catheter was placed in the left ureter and a small diameter flow probe (E.P. model 401D, lumen Diam 1.5 mm, Carolina Medical Electronics, Inc., King, N. C.) was placed about the left renal artery and connected to a square wave electromagnetic flow meter (model 501, Carolina Medical Electronics, Inc.) for measurement of renal blood flow. The method described by Arendshorst et al. (14) was used for calibration. After a 45-min period for stabilization of plasma inulin levels, base-line measurements of glomerular filtration rate and renal blood flow were made. 2-min collections of late proximal tubular fluid were made with 8 μ m o.d. oil-filled pipettes. Using a servo-null pressure monitoring device (Instruments for Physiology and Medicine, San Diego, Calif.), an electronic transducer (Statham Instruments, Inc., Oxnard, Calif. model P23Db), and a direct writing recorder (Hewlett-Packard model 7702B) hydraulic pressures were measured in glomerular capillaries, efferent star peritubular capillaries, and proximal tubules. At least three measurements were made in each animal. Two to five samples of efferent arteriolar blood were collected using 14 μ m o.d. oil-filled pipettes that had been coated with a 1:10 (vol) solution of Dow-Corning 1107 fluid (Dow-Corning Corp., Midland, Mich.) and trichloroethylene. Tail-vein blood samples (10 μ l) were taken at the beginning and end of the series of efferent arteriolar blood collections. The animals were then infused via the femoral

GLOSSARY

AII	Angiotensin II
AP	Arteriolar pressure
BP	Arterial blood pressure (mm Hg)
C _A	Afferent arteriolar protein concentration
C _E	Efferent arteriolar protein concentration
EABF	Efferent arteriolar blood flow
FF	Whole kidney filtration fraction
GBF	Glomerular blood flow
GFR	Whole kidney glomerular filtration rate (μ l/min)
GPF	Glomerular plasma flow (nl/min)
Hct _A	Arterial hematocrit (percent volume)
K _{UF}	Glomerular permeability coefficient (nl/s per mm Hg)
P _E	First-order efferent peritubular capillary hydraulic pressure (mm Hg)
P _{GC}	Glomerular capillary hydraulic pressure (mm Hg)
P _T	Proximal tubular hydraulic pressure (mm Hg)
P _{UF_A}	Afferent net ultrafiltration pressure (mm Hg)
P _{UF_E}	Efferent net ultrafiltration pressure (mm Hg)
Π _A	Afferent arteriolar oncotic pressure (mm Hg)
Π _B	Bowman's space oncotic pressure (mm Hg)
Π _E	Efferent arteriolar oncotic pressure (mm Hg)
R _A	Afferent arteriolar resistance (dynes·s/cm ⁵)
R _E	Efferent arteriolar resistance (dynes·s/cm ⁵)
R _{TA}	Total arteriolar resistance
RBF	Renal blood flow (ml/min)

vein with endotoxin for two h as in the preceding set of experiments and the measurements described above were repeated.

The same experimental procedures were carried out in a separate group of 12 animals that were infused with a pharmacologic agent with vasodilator properties before endotoxin to determine the effect of this maneuver on renal function, coagulation, and fibrin deposition. Six animals were infused with dibenzylamine, (2.5 mg/kg, Smith, Kline & French Laboratories, Philadelphia, Pa.) given as a bolus. The other group of six rats was given a continuous infusion of 2 μ g/min per kg of [1-Sar, 5-Ile, 8-Gly] angiotensin II (AII) (Bachem Inc., Torrance, Calif.) before and during endotoxin exposure. GFR and platelet count were measured before and after infusion of the vasodilator and 2 h after infusion of endotoxin.

Experiments to detect renal histologic changes. Five groups of 10-d postpartum litter-mate Munich Wistar rats were studied for light, immunofluorescent, and electron microscopically detectable renal morphologic abnormalities. Group I was composed of six animals that had undergone the above experimental protocol except that 0.9% saline was substituted for endotoxin. Group II consisted of six rats from the above experimental protocol that had been infused with endotoxin. Both Group I and II animals were killed at 2 h after beginning the respective infusions and their kidneys prepared for the microscopic studies described below. Group III was six rats treated identically to those in Group II except that endotoxin was given for 6 h before killing. Group IV and V were the six rats pretreated with dibenzylamine and six rats pretreated with [1-Sar, 5-Ile, 8-Gly]AII, respectively.

Analytic techniques and calculations. Plasma and urine inulin were measured with a Technicon Autoanalyzer (Technicon Instruments Corp., Tarrytown, N. Y.). Tubular fluid inulin was estimated by the micromethod of Vurek and Pegram (15) as modified for this laboratory (16). Platelet count, prothrombin time, and fibrinogen levels were determined by standard techniques adapted for microliter quantities of sample (17-19). Protein concentrations of efferent arteriolar and femoral artery plasma samples were determined in duplicate with an ultramicrocolorimeter using a microadaptation (20) of the method of Lowry et al. (21).

Single nephron glomerular filtration was calculated as

$$\text{SNGFR} = (\text{TF}/\text{P})_{\text{in}} \cdot V, \quad (1)$$

where $(\text{TF}/\text{P})_{\text{in}}$ and V refer to the tubular fluid to plasma inulin ratio and the tubular fluid flow rate, respectively.

Single nephron filtration fraction was determined by the equation

$$\text{SNFF} = 1 - (\text{C}_A/\text{C}_E), \quad (2)$$

where C_A and C_E denote afferent and efferent arteriolar protein concentrations, respectively.

$$\text{GPF} = \text{SNGFR}/\text{SNFF}, \quad (3)$$

where GPF refers to glomerular plasma flow.

Blood flow rate per single afferent arteriole or glomerulus was calculated as

$$\text{GBF} = \text{GPF}/(1 - \text{Hct}_A), \quad (4)$$

where Hct_A , the hematocrit of afferent arteriolar blood, was taken to be equal to the femoral arterial hematocrit.

Efferent arteriolar blood flow rate was determined as

$$\text{EABF} = \text{GBF} - \text{SNGFR}. \quad (5)$$

Resistance per single afferent arteriole was derived from the formula

$$R_A = [(\bar{A}P - \bar{P}_{GC})/\text{GBF}] \times (7.962 \times 10^{10}), \quad (6)$$

where the factor 7.962×10^{10} is used to give resistance in units of dynes \cdot s/cm⁵ when $\bar{A}P$ and \bar{P}_{GC} are expressed in millimeters of mercury and GBF in nanoliters per minute.

Resistance per single efferent arteriole was derived from the formula

$$R_E = [(\bar{P}_{GC} - \bar{P}_T)/\text{EABF}] \times (7.962 \times 10^{10}). \quad (7)$$

Total arteriolar resistance for a single pre- to postglomerular vascular unit was

$$R_{TA} = R_A + R_E. \quad (8)$$

An estimate of the net ultrafiltration pressure at the afferent end of the glomerular capillary (P_{UF_A}) was determined using the expression

$$P_{UF_A} = \bar{P}_{GC} - \bar{P}_T - \Pi_A. \quad (9)$$

An estimate of the net ultrafiltration pressure at the efferent end of the glomerular capillary (P_{UF_E}) was determined using the equation

$$P_{UF_E} = \bar{P}_{GC} - \bar{P}_T - \Pi_E. \quad (10)$$

Eqs. 9 and 10 assume that the colloid osmotic pressure of fluid in Bowman's space is negligible. This assumption has been validated by the finding in this strain of rats that the protein concentration of fluid in Bowman's space is <200 mg/100 ml; accordingly, Π_B is well below 1 mm Hg. Mean glomerular transcapillary hydraulic pressure difference was calculated as

$$\Delta P = \bar{P}_{GC} - \bar{P}_T. \quad (11)$$

The glomerular ultrafiltration coefficient (K_{UF}) was determined using the block iteration technique described by Blantz (22).

For light microscopy a 3-mm coronal section through the papilla was fixed in 10% formalin buffered at pH 7.0 with 0.1 mM sodium phosphate and embedded in paraffin. 4- μ m sections were stained with hematoxylin and eosin.

1-mm cubes of cortex were taken from each pole and midsection and fixed in 4% glutaraldehyde buffered with 0.1 mM sodium phosphate for electron microscopy. After postfixing in 2% osmium tetroxide, the tissue was dehydrated with alcohol and embedded in Epon 812 (Fisher Scientific Co., Pittsburgh, Pa.) and sectioned with a Sorvall MT-2 ultramicrotome (Dupont Instruments, Sorvall Biomedical Div., Newtown, Conn.). Tissue sections were transferred to uncoated copper grids and stained with uranyl acetate and lead citrate. For each kidney the initial three glomeruli identified from each pole and midportion were examined ($n =$ nine per kidney). Viewing and photomicrography were done with the Phillips 300 electron microscope (Phillips Electronic Instruments, Inc., Mahwah, N. J.).

For immunofluorescence studies, tissue was also taken from each pole and midsection of the kidney and frozen in Tissue-Tek frozen section embedding compound. 4- μ m sections were cut with the Minot rotary microtome in an International cryostat (International Equipment Co., Needham Heights, Mass.). Sections were incubated at 37°C for 2 h to promote adherence to glass slides and stored at -10°C. Before staining the tissue was fixed in acetone. Sections were incubated with fluorescein-conjugated antisera to rat immunoglobulin (Ig)G, complement (C)3, and fibrinogen (Meloy Laboratories, Inc., Springfield, Va.). The first three glomeruli identified from the midportion and both poles ($n =$ nine per kidney) were examined and photographed using a Leitz epi-

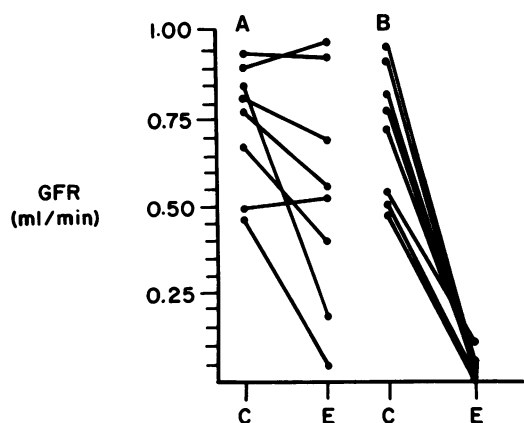


FIGURE 1 GFR in response to 2 h of endotoxin infusion in litter-mate virgin and postpartum rats. C refers to control period, E to experimental phase after endotoxin infusion. There was a small but significant decline in mean GFR in the virgin rats (A) while there was a uniform and significantly greater fall in mean GFR by 90% in postpartum rats (B).

illumination fluorescence microscope (E. Leitz, Rockleigh, N. J.). The percentage of glomeruli showing positive immunofluorescence was calculated and the intensity of immunofluorescent staining was scaled from 0 to 4+ without prior knowledge of the animal source.

Data are expressed as means \pm 1 SD. Comparisons of results between experimental periods and between groups were made with the paired and unpaired Student's *t* tests, respectively.

RESULTS

Susceptibility of postpartum rats to the generalized Shwartzman reaction. Fig. 1 shows the results of the first set of experiments in which the renal response to a 2 h infusion of endotoxin was compared between virgin and 10-d postpartum animals. The mean pre-infusion values of GFR were not significantly different between the two groups of rats (0.746 ± 0.184 vs. 0.713 ± 0.184 ml/min). After endotoxin infusion GFR

fell slightly to 0.596 ± 0.282 ml/min in the virgin rats ($P < 0.05$). In the postpartum rats GFR fell to a mean value of 0.035 ± 0.042 ml/min ($P < 0.001$). There was a significant difference in the GFR response between the two groups ($P < 0.001$). Severe bilateral cortical necrosis was found in all kidneys of postpartum rats that were killed 48 h after endotoxin infusion but not in virgin animals. These data demonstrated an enhanced susceptibility to the generalized Shwartzman reaction in postpartum rats.

Table I shows the results of coagulation studies carried out before and after endotoxin infusion in this same group of postpartum and virgin rats. In the postpartum animals hematocrits fell slightly but significantly from 47 ± 5 to $42 \pm 6\%$ ($P < 0.05$). Both the platelet count and fibrinogen concentration declined to approximately one-third of their respective control values ($P < 0.025$). Prothrombin time was increased from 19 ± 2 to 23 ± 3 s ($P < 0.025$). There were slight declines in platelet count and fibrinogen concentration in virgin rats. There were no changes in hematocrit or prothrombin time. Platelet and fibrinogen changes were significantly greater in postpartum than in virgin rats (both $P < 0.01$).

Whole kidney and glomerular dynamics. Changes in whole kidney dynamics for the group of 14 rats that underwent this portion of the study are shown in Table II. There was no significant fall in systemic blood pressure. On the other hand, renal blood flow,¹ GFR and FF declined significantly (both $P < 0.001$). The urine flow rate fell from 6 ± 3 to 1 ± 1 μ l/min ($P < 0.001$).

Measurement of single nephron glomerular dynamics are shown in Tables III and IV. GPF rate declined from 77.2 ± 25.8 to 22.5 ± 11.6 nl/min. Nephron filtra-

¹ RBF results using the electromagnetic flow probe technique were compared with those obtained with the microsphere method. No significant differences were found between the control or postendotoxin results.

TABLE I
Coagulation Parameters in Virgin and Postpartum Rats

	Control	2 h after endotoxin	P value
Postpartum rats (8)			
Hct, %	47 \pm 5	42 \pm 6	<0.05
Platelet count, per mm^3	848,000 \pm 125,720	238,800 \pm 228,830	<0.025
Fibrinogen, mg/dl	80 \pm 30	33 \pm 30	<0.025
Prothrombin time, s	19 \pm 2	23 \pm 3	<0.025
Virgin rats (8)			
Hct, %	48 \pm 4	46 \pm 5	NS
Platelet count, per mm^3	814,550 \pm 141,200	706,850 \pm 187,340	<0.05
Fibrinogen, mg/dl	83 \pm 20	64 \pm 24	<0.05
Prothrombin time, s	20 \pm 2	21 \pm 2	NS

TABLE II
Whole Kidney Data before and after Endotoxin Infusion

Rat no.	Before endotoxin					After endotoxin				
	BP	RBF	GFR	FF	Hct	BP	RBF	GFR	FF	Hct
1	100	4.4	534	0.26	52±0 (2)	100	2.7	210±128 (2)	0.16	50±0 (2)
2	120	6.9	980±21 (2)	0.28	50±0 (2)	105	1.0	100	0.19	48±1 (2)
3	125	6.2	698±27 (2)	0.23	51±0 (2)	125	2.0	195	0.20	50±0 (2)
4	140	7.1	790±23 (2)	0.22	50±0 (2)	135	1.5	155	0.21	50±0 (2)
5	100	4.2	690±19 (2)	0.28	41±0 (2)	100	1.1	150±71 (2)	0.22	39±1 (2)
6	135	5.0	668±5 (2)	0.26	48±0 (2)	135	1.5	60	0.07	43±0 (2)
7	125	5.7	763±28 (2)	0.27	47±0 (2)	105	2.0	100	0.09	42±0 (2)
8	105	5.0	680	0.25	45±1 (2)	110	2.5	170	0.12	43±0 (2)
9	125	6.3	972±5 (2)	0.31	50±0 (2)	130	4.1	240±50 (2)	0.12	49±0 (2)
10	110	5.4	674±11 (2)	0.26	50±0 (2)	125	3.0	250±80 (2)	0.15	44±0 (2)
11	120	5.4	780±37 (2)	0.28	48±0 (2)	120	2.0	100	0.09	47±1 (2)
12	100	5.0	735±15 (2)	0.28	50±0 (2)	100	2.2	150	0.14	50±0 (2)
13	125	5.7	810±24 (2)	0.26	46±1 (2)	120	2.0	220±14 (2)	0.20	44±0 (2)
14	100	4.5	625±15 (2)	0.28	50±0 (2)	100	1.0	60	0.12	49±1 (2)
Mean±SD	116±14	5.5±0.9	743±121	0.27±0.02	48±2.9	115±14	2.0±0.9	155±65	0.15±05	46±4
						<i>P</i> < NS	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001

Data are expressed as mean±SD.

Numbers in parentheses are determinations in each animal.

tion rate fell from 28.0 ± 7.0 to 6.3 ± 3.7 nl/min. P_{GC} fell from 47.3 ± 1.0 to 29.0 ± 5.1 mm Hg. P_T initially had been 10.5 ± 0.6 mm Hg and averaged 7.0 ± 1.5 mm Hg following endotoxin. Efferent arteriolar pressures fell from 15.0 ± 0.6 to 8.0 ± 2.0 mm Hg. All of the changes in the above parameters were significant at $P < 0.001$. The Π_A did not change before and after endotoxin, but there was a decline in the Π_E ($P < 0.001$). The calculated afferent effective filtration pressure averaged 20.0 ± 3.0 before and 5.2 ± 4.3 mm Hg after endotoxin infusion ($P < 0.001$). The mean effective filtra-

tion pressure in control was 2.0 ± 1.7 mm Hg. A positive P_{UFE} was calculated for 11 of the 14 individual determinations. In the experimental phase P_{UFE} was -4.8 ± 4.4 mm Hg with 13 of the 14 individual values negative. Since a negative value for P_{UFE} is not physiologic, these values were assumed to be zero in determining a mean value for $\Delta\Pi$ and K_{UF} . Since filtration disequilibrium was found in the vast majority of postpartum rats under control conditions the calculated values of K_{UF} were unique values in all but three rats. After endotoxin, filtration equilibrium was clearly

TABLE III
Glomerular Dynamics before Endotoxin Infusion

Rat no.	SNGFR	GPF	SNFF	Π_A	Π_E	Π_B	P_{GC}	P_T	P_E	P_{UF_E}	R_A	R_E	K_{UF}
1	16.9±6.6 (5)	51.3	0.33	19.8	37.0	—	48±0 (3)	11.0±0 (5)	16.0±1 (4)	0	3.9	2.8	0.0493
2	43.0±12.1 (4)	142.8	0.30	19.3	33.6	—	47±1 (3)	10.3±0.5 (4)	15.0±0 (3)	3.2	2.0	1.1	0.0762
3	25.6±3.7 (5)	72.5	0.35	17.0	34.9	—	48±4 (2)	10.4±0.5 (5)	14.0±0 (2)	2.7	4.1	2.2	0.0416
4	37.9±5.7 (5)	112.4	0.34	19.8	37.7	—	49±3 (2)	11.5±1.2 (7)	16.0±0.9 (3)	-0.2	3.2	1.4	0.1065
5	24.5±3.6 (5)	57.7	0.42	12.3	31.7	—	46±0 (2)	10.7±1.2 (5)	15.5±0.7 (4)	3.7	4.4	3.3	0.0332
6	19.7±7.3 (3)	50.2	0.39	16.1	34.3	—	48±2 (3)	9.4±0.8 (5)	15.3±0.4 (2)	4.3	7.2	3.4	0.0249
7	34.1±5.9 (5)	91.3	0.37	16.5	33.6	—	46±1 (2)	10.0±0.4 (4)	16.0±0 (3)	2.4	3.7	1.7	0.0569
8	19.3±1.3 (5)	52.3	0.37	17.0	34.3	—	48±0 (2)	10.5±0.6 (6)	15.5±0 (2)	3.2	4.8	3.4	0.0287
9	31.1±8.0 (3)	77.4	0.40	16.5	36.3	—	46±1 (2)	10.1±0.2 (5)	15.8±0.4 (2)	-0.4	4.1	1.9	0.0729
10	26.6±4.0 (5)	72.3	0.37	17.9	36.3	—	47±1 (3)	10.5±0 (4)	15.0±0 (3)	0.2	3.5	2.2	0.0597
11	32.3±5.2 (5)	89.4	0.36	17.0	33.6	0	48	11.0±0 (6)	16.0±0.9 (4)	3.4	3.3	1.8	0.0485
12	25.5±3.0 (5)	70.0	0.36	17.4	34.9	0	47±0 (2)	11.0±0.5 (4)	15.0±0 (3)	1.1	3.0	2.2	0.0538
13	30.2±6.4 (5)	79.3	0.38	16.5	34.3	0	48	10.0±0.6 (5)	16.0±0.9 (3)	3.7	4.2	2.2	0.0415
14	22.3±4.0 (5)	61.9	0.36	17.9	35.6	0	46±0 (2)	10.0±0 (5)	15.0±0.3 (3)	0.4	3.5	2.4	0.0517
Mean±SD	28.0±7.0	77.2±25.8	0.36±0.03	17.2±1.9	34.8±1.6	0±0	47.3±1.0	10.5±0.6	15.0±0.6	2.0±1.7	4.1±1.3	2.4±0.8	0.0532±0.0214

Data are expressed as means or means±SD.
Numbers in parentheses are determinations in each animal.

present and all but one of the K_{UF} values represent minimum estimated. The mean values of K_{UF} for both groups were not numerically different. SNFF was $0.36±0.03$ before and $0.27±0.04$ ($P < 0.001$) after endotoxin. As GPF, SNGFR rate, and P_{GC} declined R_A increased from a control value of $4.1±1.3$ to $23.9±19.3 \times 10^{10}$ dynes·s/cm⁵. R_E increased from a control value of $2.4±0.8$ to $6.0±3.2 \times 10^{10}$ dynes·s/cm⁵.

Effects of dibenzylamine and [1-Sar, 5-Ile, 8-Gly]AII. Hematocrits, platelet counts, and GFR were the same before and after vasodilator infusion in either the dibenzylamine or [1-Sar, 5-Ile, 8-Gly]AII treated groups. Following dibenzylamine the mean arterial blood pressure (BP) fell significantly from $118±10$ to $98±6$ mm Hg ($P < 0.01$). This value was also significantly less than the mean value of $119±10$ mm Hg for the rats receiving no pretreatment shown in Fig. 1 ($P < 0.01$). The mean BP of $124±13$ mm Hg in the [1-Sar, 5-Ile, 8-Gly]AII-treated rats was not different

from the control measurements or from animals that received no pretreatment. The GFR following pretreatment and following endotoxin are shown in Fig. 2 and compared to those receiving no pretreatment. The GFR of $811±291$ and $688±108$ for the dibenzylamine and [1-Sar, 5-Ile, 8-Gly]AII-treated groups, respectively, were not different from the group that had no pretreatment. After endotoxin infusion there were significant falls in the GFR of the dibenzylamine-treated animals to $274±191$ ($P < 0.005$), and in the [1-Sar, 5-Ile, 8-Gly]AII-treated rats to $430±209$ ($P < 0.005$). The percentage fall in the dibenzylamine-treated group was similar to that in the animals that received no pretreatment (Fig. 2). However, the percentage fall in GFR was significantly less in the [1-Sar, 5-Ile, 8-Gly]AII-treated animals compared to the dibenzylamine treated rats ($P < 0.025$) and those receiving no pretreatment ($P < 0.001$). Before endotoxin platelet counts were $717,500±126,524$ and $760,000±212,132$ mm³ respec-

TABLE IV
Glomerular Dynamics after Endotoxin Infusion

Rat no.	SNGFR	GPF	SNFF	Π_A	Π_E	Π_B	Γ_{GC}	P_T	P_E	P_{URF}	R_A	R_E	K_{UR}
1	9.4±2.1 (2)	32.8	0.29	18.8	31.7	—	30	8.2±2.1 (6)	10.0±0 (2)	-9.8	8.5	2.8	0.2245
2	4.0±0.5 (4)	16.0	0.25	17.9	27.5	—	30±0 (2)	8.0±2.2 (7)	11.5±0.7 (2)	-5.5	19.4	5.5	0.0634
3	7.0±1.0 (5)	24.2	0.29	16.5	29.2	—	28	4.3±0.6 (5)	6.0±0 (3)	-5.5	16.0	4.2	0.0681
4	7.0±1.4 (4)	28.4	0.25	19.3	29.8	—	35±0 (2)	8.0±0.4 (5)	9.0±0.5 (4)	-2.8	14.0	4.2	0.0549
5	12.3±5.2 (5)	35.7	0.34	13.1	24.0	—	25±3 (2)	8.0±0.6 (7)	6.2±0.3 (3)	-7.0	10.2	3.3	0.1898
6	2.0±2.0 (2)	8.0	0.25	14.8	22.4	—	20±0 (2)	4.0±0.7 (6)	6.0±1 (4)	-6.4	65.2	9.7	0.1147
7	2.0±1.4 (2)	6.0	0.33	16.1	28.2	—	20±4 (3)	5.8±0.8 (4)	6.5±0.7 (2)	-14.7	64.3	13.0	-0.1193
8	7.0±2.5 (5)	28.0	0.24	16.1	24.5	—	35	7.0±0 (3)	10.0±0 (2)	3.5	12.2	4.7	0.0156
9	13.1±2 (4)	45.6	0.29	16.5	27.4	—	35±0 (2)	8.0±0 (4)	11.0±0 (3)	-0.4	8.4	2.5	0.0672
10	7.0±2.0 (3)	21.8	0.32	17.4	31.0	—	28±0 (2)	4.8±0.5 (4)	6.5±2 (2)	-7.8	19.6	5.3	0.0740
11	2.0±0 (2)	10.0	0.20	16.0	23.0	0	25±0 (2)	6.0±0.4 (6)	7.0±0.2 (3)	-4.0	40.1	8.5	0.0557
12	6.1±3.0 (4)	25.1	0.24	17.0	25.6	0	30±1 (3)	8.0±0.5 (6)	10.0±0.2 (5)	-3.6	11.1	3.6	0.0761
13	7.2±4.0 (4)	23.5	0.31	16.5	28.6	0	35±0 (2)	8.0±0.3 (5)	9.0±0.5 (5)	-1.6	16.1	6.0	0.0369
14	2.0±0.7 (2)	9.7	0.21	17.4	24.5	0	30±0 (3)	7.0±0.6 (7)	8.0±0.5 (5)	-1.5	29.3	10.3	0.0223
Mean±SD	6.3±3.7	22.5±11.6	0.27±0.04	16.7±1.6	27.0±3.0	0±0	29±5	7.0±1.5	8.0±2.0	-4.8±4.4	23.9±19.3	6.0±3.2	0.0674±0.0798
	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS

Data are expressed as mean or mean±SD.
Numbers in parentheses are determinations in each animal.

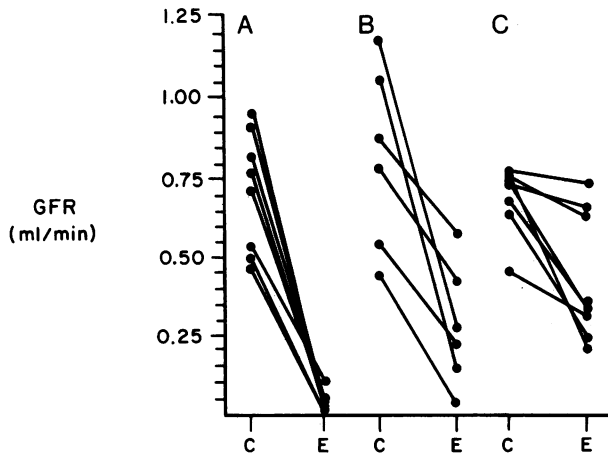


FIGURE 2 GFR in response to 2 h of endotoxin infusion in postpartum rats. Group A received no pretreatment before endotoxin infusion whereas Group B was pretreated with dibenzylidine and Group C was pretreated with [1-Sar, 5-Ile, 8-Gly]AII. The percentage fall in GFR was significantly less in the group receiving AII blockade compared with either the group receiving no pretreatment or that receiving dibenzylidine.

tively, after dibenzylidine and [1-Sar, 5-Ile, 8-Gly]AII. After endotoxin these same values were $250,000 \pm 43,778$ and $182,500 \pm 152,027$ mm³. Both falls in platelet counts were significant ($P < 0.025$) and similar to that in the rats with no pretreatment.

Renal histologic changes. In the virgin rats killed 48 h after endotoxin, two showed areas of cortical necrosis in both kidneys. All postpartum animals had patchy to diffuse bilateral cortical necrosis. No significant architectural changes were noted by light microscopy in control rats (group I) or those that had been infused with endotoxin for 2 h and then immediately killed (group II). The group III rats that had been infused with endotoxin for 6 h and killed had evidence of fibrinlike material in the glomeruli but no evidence of necrotic changes within glomeruli or tubules. Electron microscopy of 54 glomeruli demonstrated scattered deposition of fibrin partially occluding some capillary loops in <50% of the glomeruli in group II. In group III fibrin was present more uniformly with nearly complete to complete occlusion of all glomerular capillary loops ($n = 54$). Representative electron micrographs for groups II and III are shown in Fig. 3. The results with immunofluorescence studies are shown in Table V and Fig. 4. There was a trace amount of fibrin in occasional glomeruli in control rats. Very focal and segmental evidence of fibrin, C3 and IgG was present in the kidneys of group II rats. In >80% of glomeruli there was no immunofluorescence. In addition, there was no immunofluorescent staining of arterioles or peritubular capillaries. By contrast the kidneys of group III rats had diffuse positive immunofluorescence within the capillary loops of nearly all glomeruli. Fibrinogen, C3, and

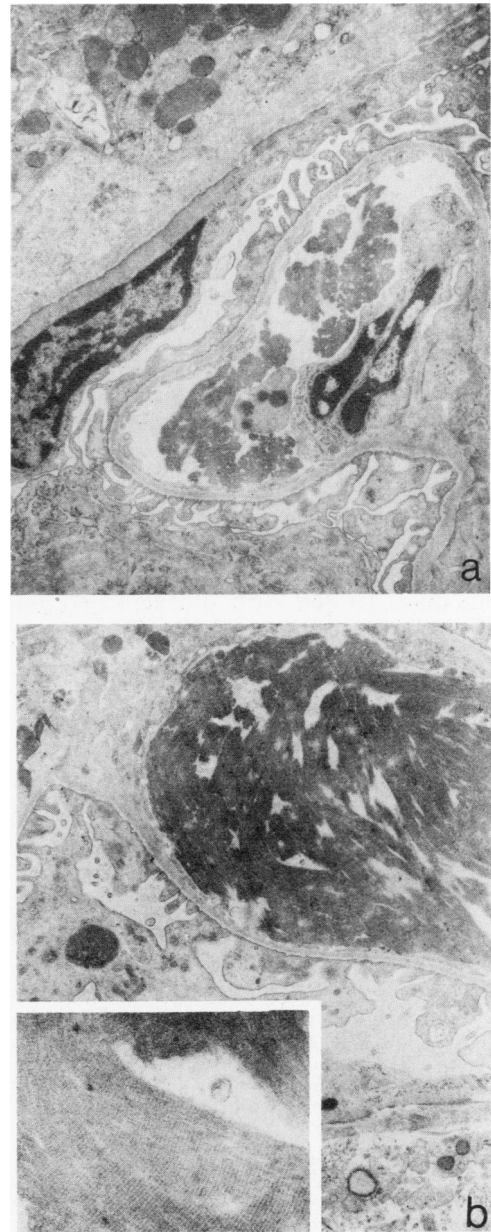


FIGURE 3 Electron micrographs of glomeruli in (a) a rat infused for 2 h with endotoxin, and (b) for 6 h with endotoxin. Fibrinlike material is partially occluding the capillary loop in the 2-h infused rat. In the 6-h infused animal the capillary loop is densely packed with the same electron dense material. The insert in the lower left hand corner is a magnified section ($\times 6$) of the deposited material in (b) showing the typical periodicity of fibrin ($\times 23,500$).

IgG all showed similar intensity. There was no immunofluorescent staining in arterioles or peritubular capillaries. In the rats that were preinfused with dibenzylidine and [1-Sar, 5-Ile, 8-Gly]AII positive immunofluorescent staining of 26 and 22% of glomeruli, respectively, with antifibrinogen antibody. This was a uniform finding in all sections observed. The density

TABLE V
Immunofluorescence Microscopy Results

Group	No. of rats	Percentage of glomeruli with fibrin deposition	Intensity of immunofluorescence
I Control (54)	6	3±3	trace
II 2 h endotoxin (54)	6	18±8	1+ to 2+
III 6 h endotoxin (54)	6	94±10	3+ to 4+
IV 2 h endotoxin-dibenzylidine (54)	6	26±12	1+ to 3+
V 2 h endotoxin-[1-Sar, 5-Ile, 8-Gly]AII (54)	6	22±9	1+ to 3+

Numbers in parentheses are the number of glomeruli examined in each group.

of immunofluorescence was intermediate between that of the group II and group III rats. There was no discernible difference between the staining patterns of those treated with dibenzylidine (group IV) or with [1-Sar, 5-Ile, 8-Gly]AII (group V). A typical glomerulus from a rat pretreated with [1-Sar, 5-Ile, 8-Gly]AII is shown in Fig. 5.

DISCUSSION

The generalized Shwartzman reaction is a pseudo-allergic phenomenon in which a preparatory and a challenge injection of endotoxin given at 24-h intervals will elicit a syndrome of consumption coagulopathy and varying degrees of organ failure involving the kidney, heart, lungs, brain, and liver (5, 9). Initial experiments (9) were carried out in rabbits in which sequential injections were used to elicit the pathologic process. Subsequently, the same generalized reaction has been demonstrated in other species by giving continuous infusion of endotoxin (5). When induced in pregnancy only a single injection of endotoxin in rabbits or a limited infusion of endotoxin in rats is necessary to cause the total spectrum of the generalized Shwartzman reaction.

The present study demonstrated an enhanced sensitivity to the renal dysfunction of the generalized Shwartzman reaction in Munich Wistar rats that were 10 d postpartum. After 2 h of endotoxin infusion GFR had fallen in all postpartum rats by 90%. This decline in function was significantly greater than the average 24% decline observed in matched control virgin animals. The marked change in renal function in the postpartum rats was accompanied by a slight decline in Hct_A and evidence for a consumption coagulopathy. In addition, the dose of endotoxin used caused bilateral renal cortical necrosis in animals that were sacrificed 48 h after infusion. The increased sensitivity to the generalized Shwartzman reaction in postpartum rats was similar to that reported for pregnant rats (5). While the relative hypercoagulation state of pregnancy

has been thought to predispose these animals to the generalized Shwartzman reaction (23), these or other predisposing factors have not been evaluated critically in the postpartum period. Nevertheless, an enhanced susceptibility of 10-d postpartum animals to the renal failure of the generalized Shwartzman reaction was apparent from this study.

The mechanism whereby endotoxin infusion causes renal failure has not been examined functionally at the individual nephron level. A commonly held explanation has centered around the histologic changes in glomeruli where fibrin deposition has been a consistent finding (4-6, 24). It is thought that the obstruction of glomerular capillaries by fibrin deposits causes a primary cessation of glomerular filtration. The fibrin deposition process is a consequence of an endotoxin-induced consumption coagulopathy. To investigate the importance of these pathologic observations in the pathogenesis of the disease, the current study, while assessing whole kidney parameters, was focused primarily on the measurable physiologic alterations of glomerular dynamics. After 2 h of endotoxin infusion systemic blood pressure remained constant but there was a marked decline in renal blood flow. There was a similar marked fall in inulin clearance and urine flow rate. The residual fractional renal function as estimated from the inulin clearances for the whole kidney and superficial nephrons were 0.22 and 0.26, respectively. The similarity of these values indicated that changes measured from the superficial nephrons closely reflected those of the whole kidney.

There was a discrepancy between whole kidney and superficial nephron filtration fractions that was similar in control experiments and after endotoxin infusion. The mean control values for the whole kidney and superficial nephrons were 0.26 and 0.36, respectively; after endotoxin the FF was 0.15 and that for the single nephron 0.29. The finding of a difference in superficial and FF under hydropenic conditions is unlike the results obtained by Blantz (25) in a study of uranyl nitrate-induced acute renal failure in Munich Wistar

rats. In that study inulin extraction was used to estimate RBF. In the present study an electromagnetic flow probe was used and the results were confirmed by microsphere methods. The flow probe was repeatedly calibrated and there was no reason to suspect that the flow meter reading was inaccurate. Thus, it is likely

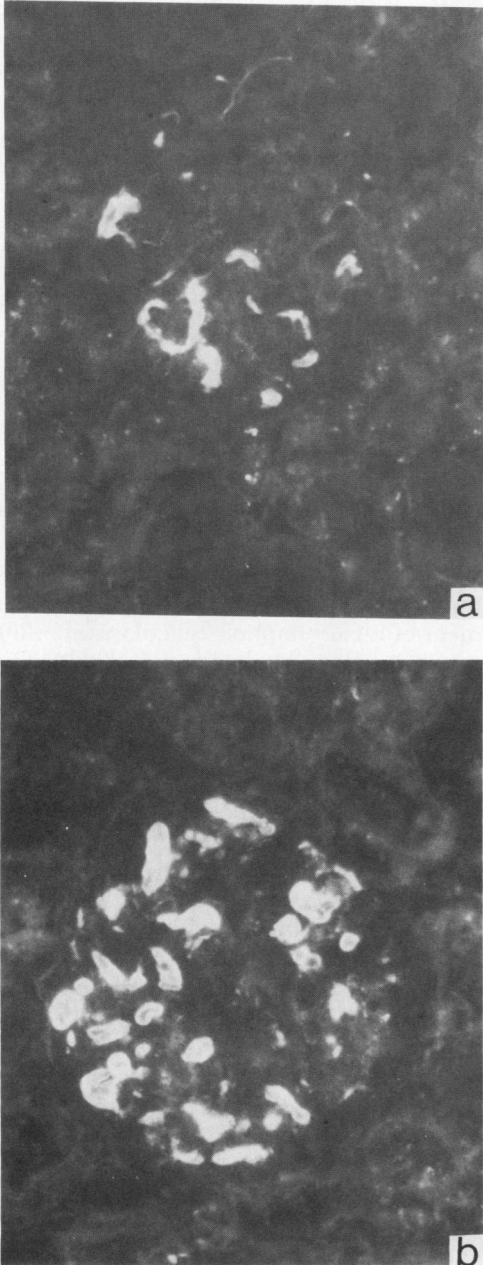


FIGURE 4 Immunofluorescence (anti-fibrinogen) of glomeruli in (a) a rat infused for 2 h with endotoxin, and (b) a rat infused for 6 h with endotoxin. Focal, scattered immunofluorescence is seen in the glomerulus of the former animal while dense immunofluorescence involving nearly all capillary loops is observed in the latter ($\times 300$).

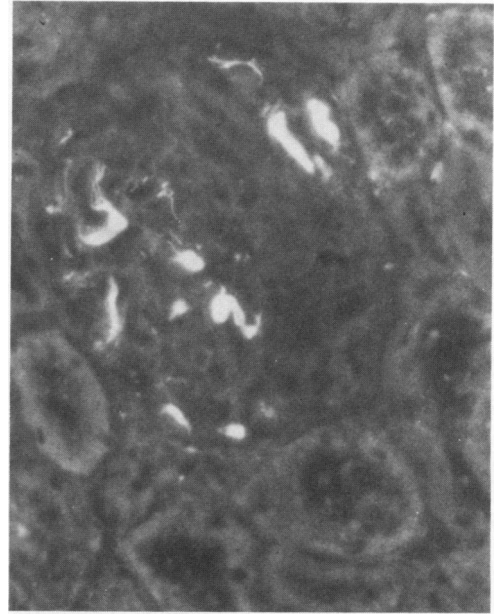


FIGURE 5 Immunofluorescent staining for fibrinogen in rats that received AII blockade before 2 h of endotoxin infusion. There is minimal scattered immunofluorescent positivity seen in the glomerulus; it is similar to that observed in animals that had received no pretreatment before endotoxin infusion ($\times 400$).

that in the group of rats studied there was a lower FF in deeper nephrons than in their superficial counterpart.

This relationship between superficial nephron and FF was also present after endotoxin infusion. It is possible that these filtration fraction values reflect the pregnant or postpartum state of the rats. Measurement of glomerular filtration forces revealed a decrease in glomerular plasma flow to one third of its control value after endotoxin. The P_{GC} fell from a mean value of 47 to 29 mm Hg. Under control conditions eight rats were at filtration equilibrium and six were not. Filtration disequilibrium in Munich Wistar rats under hydropenic conditions has been reported previously by Blantz and associates (26) and by Arendshorst and Gottschalk (27) although the majority of studies have found filtration equilibrium. Since the rats in the present study represented a mixture of animals meeting the conditions of both filtration equilibrium and disequilibrium, it was not possible to calculate a unique value of K_{UF} for the whole group. A unique value for the postpartum control rats that had a mean positive P_{UFE} was 0.0532 nl/s per mm Hg. After endotoxin where conditions of filtration equilibrium obtained (see below), a minimum value of K_{UF} was 0.0674 nl/s per mm Hg. These values were not significantly different and similar to those reported by others in Munich Wistar rats (28, 29).

The finding of a minimal to modest negative P_{UF_E} in 13 of the 14 rats after endotoxin, although consistent, can have no meaning in a transport system with physiologic driving forces that typify the glomerulus. The negative P_{UF_E} must represent a spurious result of either the ΔP or $\Delta \Pi$ at the efferent end of the glomerular capillary network. The albumin to globulin ratio was similar to that measured in plasma before endotoxin. It is possible that the surface glomeruli had disproportionately greater injury from endotoxin resulting in lower P_{GC} estimates. Higher values of Π_E may have reflected the greater probability of collecting blood from efferent arterioles originating from deeper nephrons. In any case, since a negative value of P_{UF_E} cannot exist physiologically, K_{UF} was calculated from a curve in which Π_E was equal to ΔP (filtration equilibrium) and, therefore, considered to be a minimal estimate of the ultrafiltration coefficient.

While tubular fluid back leak was not examined directly in this study, the marked decrement in the driving forces for ultrafiltration were considered adequate to explain the fall in inulin clearance that was measured (30). Moreover, there was no change in the rate of superficial nephron to FF after endotoxin. Both R_A and R_E were increased after endotoxin infusion explaining the decline in the GPF rate. However, because the increase in R_A was proportionately greater than R_E , the P_{GC} declined as well as the GPF. The changes in R_A and R_E could be explained by neurohormonal factors operating to change vessel diameter at these resistance sites. On the other hand, such resistance changes would also be measured if there were extensive fibrin deposition occurring from the afferent end to the efferent end of the same glomerular capillary network. In this situation intraluminal deposits of fibrin or fibrinlike material would act functionally much as neurohormonal factors in that they could actually alter afferent and efferent arteriolar effective vessel diameter by intraluminal channel narrowing. Thus, from functional measurements of glomerular dynamics one could not determine specifically whether the changes in R_A and R_E were the result of pathologic obstruction of capillary lumens or because of alterations in afferent and efferent arteriolar tone.

Although none of the previous experimental studies had examined kidneys with immunofluorescence and electron microscopy as early as 2 h after endotoxin infusion, it was anticipated that significant deposition of fibrin might be found 2 h after endotoxin infusion to account for the alterations in glomerular dynamics that were measured. Although fibrin deposition was detectable when residual renal function was negligible, the quantity of fibrin deposited was relatively small. Less than one fifth of glomeruli that were seen in immunofluorescent microscopy sections contained fi-

brin and the vast majority had no detectable staining for fibrin, C3, or IgG. To determine that the immunofluorescent technique itself was adequate to detect fibrin deposition, other animals were infused for 6 h with endotoxin before immunofluorescent studies were carried out. In those kidneys nearly all glomeruli had intense immunofluorescent labeling which involved all capillary loops within the glomeruli. Inasmuch as there was minimal evidence of fibrin deposition and there were no architectural abnormalities by light or electron microscopy after 2 h of endotoxin, there was a strong possibility that in the early phase of the acute renal dysfunction of the generalized Shwartzman reaction that factors other than, or in addition to, fibrin deposition within glomerular capillary lumens were responsible for the abrupt changes in R_A and R_E and the consequent decline in glomerular filtration. Despite the findings of Good and Thomas (31) that renal cortical necrosis could be prevented by pretreatment with heparin as determined by microscopic studies carried out 48 h after endotoxin injections in rabbits, there is other evidence that neurohormonal factors are involved in the renal changes of the generalized Shwartzman reaction. Müller-Berghaus and McKay (32) and Fine and associates (33) found that alpha-adrenergic blocking agents modified the magnitude of the fibrin deposition within the kidney after endotoxin infusion despite the development of a consumption coagulopathy. Similarly, Palmerio et al. (34) and Bolton and Atuk (35) prevented renal cortical necrosis in the denervated kidney with unilateral sympathectomy. Although none of these studies examined renal function, they did demonstrate a diminished fibrin deposition. Whereas these studies suggested that catecholamines caused renal vascular changes that predisposed to fibrin deposition, they did not examine renal function per se to detect an early functional alteration in renal hemodynamics that could have been induced by endotoxin but was not related to intravascular coagulation. In the present study both dibenzylamine, an alpha-adrenergic blocking agent, and [1-Sar, 5-Ile, 8-Gly]AII antagonist, were infused before endotoxin to assess the role of functional vasoconstrictive changes early in the course of endotoxin-induced acute renal failure. No protective effect of dibenzylamine on GFR could be found; however, mean blood pressure at the time of endotoxin infusion was significantly lower in this group of animals and, therefore, the protection of alpha adrenergic blockade was not completely excluded. With AII blockade there was significant protection of GFR with a mean value 62% of control compared with 7% in rats with no pretreatment. While 38% of glomerular function may have been lost because of fibrin deposition, the major fraction of renal function was retained with infusion of a

physiologic agent that apparently did not interfere with consumption coagulopathy or glomerular fibrin deposition. Immunofluorescent staining for fibrin was at least as intense and diffuse in glomeruli and platelet count declines were similar in [1-Sar, 5-Ile, 8-Gly]AII-preinfused rats when compared with those with no preinfusion. These data indicate that angiotensin blockade significantly preserves renal function after endotoxin infusion despite systemic evidence of a consumption coagulopathy and intrarenal deposition of fibrin.

It is known that endotoxin induces activation of prekallikrein, the complement system and catecholamine release by the kidney (36-39); however, it is not known at the present time the mechanism whereby endotoxin might stimulate the renin-angiotensin system. It is possible that renin activation is due to prostaglandin stimulation from kinins; however, there is no direct evidence to support such a process. Angiotensin blockade may reduce the effect of the renin-angiotensin, since the latter has been shown to be stimulated by ischemia (40). However, the protective effect of angiotensin blockade would not explain the initiation of ischemia following endotoxin. It is also possible that vasoconstrictive peptides such as serotonin are released in the process of platelet lysis that occurs in consumption coagulopathy (41). In this situation coagulopathy itself could initiate vasoconstriction before actual anatomic plugging of vessels. The present study suggests that, through an angiotensin-mediated mechanism, endotoxin causes changes in R_A and R_E which result in early deterioration in renal function in the generalized Shwartzman reaction. We suggest that these changes are independent of significant morphologic fibrin deposition, which appears to be a chronologically later phenomenon.

In summary, it has been found that the postpartum rat, like the pregnant rat, has a peculiar predisposition to developing the acute renal deterioration of the generalized Shwartzman reaction. In the early phase of rapid deterioration of renal function the mechanism seems to be a primary profound decrease in nephron filtration rate, which is due to decreases in glomerular plasma flow as well as glomerular capillary pressure. These changes in parameters of nephron filtration are the result of an increase in R_A and a lesser increase in R_E . Major alterations in renal function and glomerular dynamics occurred at a time when there was minimal evidence of fibrin deposition within the kidneys of these animals; glomerular filtration could be preserved with AII blockade. These findings suggest that the earliest functional changes in the acute renal failure of the generalized Shwartzman reaction in 10-d postpartum rats may be initiated by mechanisms that precede actual fibrin occlusion of

vessels and mediated by neurohormonal substances that result from endotoxin or consumption coagulopathy.

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