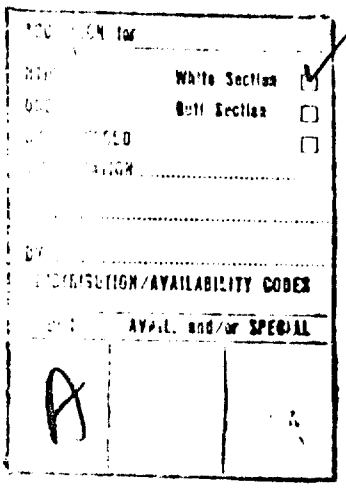

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EXPERIMENTAL SEPTIC SHOCK: MODELS AND MECHANISMS

L. B. Hinshaw, B. Benjamin, D. D. Holmes, B. Beller,

L. T. Archer, J. J. Coalson, and T. Whitsett

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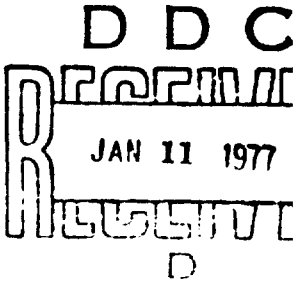

University of Oklahoma Health Sciences Center
Depts. of Physiology & Biophysics,
Pathology, and Medicine
Oklahoma City, Oklahoma

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ABSTRACT

The present study was designed to develop a nonhuman primate model more relevant to the clinical entity of septic shock. Experiments were conducted on young adult baboons, unrestrained, and maintained at a light plane of pentobarbital anesthesia. Responses of animals infused with E. coli endotoxin or live E. coli organisms were evaluated during a 24-hour period or until death. Results suggest significant differences between the two shock models: large dosages of endotoxin in contrast to those used in the canine species were required to elicit lethality characteristics. Hypoglycemia and hypoinsulinemia were regularly observed in live E. coli organism induced shock; however, hyperglycemia was a consistent hallmark in the endotoxin infused model. Renal fibrin thrombi were present only after E. coli administration while tubular necrosis was found following both organism and endotoxin infusions. Renal morphologic changes induced during shock were prevented by heparin administration. Liver dysfunction was indicated by elevations of blood levels of enzymes and morphologic alterations. Pulmonary function did not appear to be abnormally affected, although respiratory alkalosis and metabolic acidosis were regularly observed in both models. Significant differences in responses between the models should elicit caution in the application of findings in nonhuman primates to the human patient.

Considerable recent interest has been focused on the development of a research animal model more closely resembling the clinical entity of septic shock. Animals, including rats administered endotoxin (9,18), dogs given endotoxin (1,2,14) or live E. coli organisms (10,11,13), and nonhuman primates receiving endotoxin (4,5,15,21) or live E. coli (8,12,16), have recently been studied and exhibit a variety of hemodynamic, metabolic, hematologic and morphologic abnormalities. Special emphasis has centered around energy deficits in septic and endotoxin shock and has involved glucose and insulin interrelationships (1,3,6,8,10,12,14,15,19,22,23). Perfusion deficits (4,5,7,16,21) and coagulation abnormalities (16,17,21) have been reported to encompass in particular the renal, hepatic, and pulmonary systems with severe pathophysiological effects on the liver circulation and metabolism (7,9,11,17,18,20).

The primary objective of the present report was to assay the separate responses of a nonhuman primate to E. coli endotoxin and live E. coli organisms with particular emphasis on defining hemodynamic and metabolic pathophysiological changes which may aid in the understanding of the mechanisms of clinical septic shock.

METHODS

Experiments were carried out on sixteen young adult baboons (Papio anubus), weighing between 7.2 and 16.5 kg. Animals were prepared for experimentation as previously reported (12). The main aspects of the procedure were that unrestrained animals were maintained under the lightest possible level of sodium pentobarbital anesthesia; body temperature was controlled; animals were turned periodically from side to side and con-

tinuously observed up to 24 hours or death. Blood glucose, insulin, lactate, pH, pO_2, pCO_2, various enzymes, and mean arterial systemic pressures were monitored during the period of shock. Plasma glucose was determined with a Beckman glucose analyzer with an accuracy of ±3 mg%; plasma insulin was obtained by radioimmunoassay (Phadebas insulin test; Pharmacia, Uppsala, Sweden); lactate concentrations were achieved utilizing a modified procedure previously described (12); blood gases and pH were obtained from an Instrumentation Laboratories blood gas analyzer; while various other blood constituents including certain enzymes and metabolites were determined by chemical survey on a Technicon autoanalyzer (Technicon Instrument Corp., Terrytown, N.Y.).

Solutions of live E. coli organisms, Type B, were prepared for infusion by utilizing organisms stored in the lyophilized state. Cell suspensions in saline were adjusted to a predetermined density with a Coleman spectrophotometer. Viability counts of the inoculum were determined by appropriate dilutions and incubation. Table 1 lists the intravenously administered dosages of E. coli organisms and survival times in six baboons reported in the present study. Organism suspensions averaging 5 cc/kg volume and 4.3×10^{10} organisms/kg were infused during an average period of 90 minutes. Mean survival time was 11 hours. A separate group of seven baboons received intravenous infusions of E. coli endotoxin (Difco, Detroit, Michigan; B-8 strain). Table 1 shows the dosages and survival times of this group. Endotoxin was infused during an average time of 120 minutes at a mean volume of 9 cc/kg and an average concentration of 25 mg/kg. Four animals survived the 24-hour test period while three others died at an average time of 19 hours. It is of interest that the LD_{100} of this strain of endotoxin

in dogs is 2.5 mg/kg, while even a dose of 40 mg/kg in one baboon did not result in its death during a 24-hour period. A separate group of three animals served as controls, receiving infusions of saline in place of organisms or endotoxin.

Specimens of kidney and liver were fixed in 10% neutral buffered formalin, cut at 6 μ and stained with hematoxylin plus eosin (H&E) following standard procedures. In addition, sections of kidnev were stained with Mallory's phosphotungstic acid hematoxylin (PTAH) for demonstration of fibrin thrombi as derived in the AFIP Manual of Histologic and Special Staining Techniques (Armed Forces Institute of Pathology, 2nd Edition, 1949; The Blakison Division, McGraw-Hill Book Co., Inc.). Examination of tissue samples by light microscopy was conducted without prior knowledge of the experimental treatment of the tissue (blind procedure).

Statistics of a limited nature were carried out using a paired student t test, in which certain values of parameters in shocked animals were compared to the initial control, zero time quantities.

RESULTS

The first set of figures illustrates changes in mean systemic arterial blood pressure, plasma glucose, and insulin concentrations in baboons receiving infusions of E. coli organisms, endotoxin, or saline (control group). Figure 1 shows the responses of three control animals to saline infusion. Mean pressures and insulin values are relatively constant compared to control, zero time quantities ($p>0.05$), while glucose concentrations are increased above control at 5-9, 11, and 14 hours following the onset of saline infusion ($p\leq0.05$). Figure 2 gives the changes in mean

systemic pressure, plasma glucose, and insulin in six baboons intravenously infused with E. coli organisms. Pressures are significantly reduced from control at each hour, from zero time values up to termination of experiments at 15 hours ($p \leq 0.05$). Glucose concentrations are decreased from 5 to 10 hours ($p \leq 0.05$), while mean insulin values are insignificantly altered from zero time quantities ($p > 0.05$), due to large variations of control values. Each individual baboon, however, demonstrated notable reductions in insulin concentrations at all times after infusion of E. coli in contrast to its own zero time control value (for doses of E. coli see Table 1). Figure 3 presents mean changes in systemic arterial pressure, plasma glucose, and insulin in seven baboons intravenously infused with E. coli endotoxin (see Table 1 for dosages). Mean systemic pressure is significantly reduced from control zero time values from 1 to 24 hours ($p \leq 0.05$). Glucose is elevated above control at 1, 2, 14, 15, and 18-20 hours post-injection ($p < 0.05$), while there are no significant differences in mean insulin concentrations.

Figure 4 arrays the changes in pH, pO_2, pCO_2, and HCO_3^- in the three types of studies with a total of 16 baboons. There are no significant differences in pH as compared to the control, zero time values in each of the groups, although individual baboons given E. coli organisms exhibit depressed pH in the terminal stages of shock (6-15 hours). Mean pCO_2 is decreased at 4 and 6 hours ($p \leq 0.05$) in E. coli infused animals, at 4 and 16 hours in the endotoxin treated group ($p \leq 0.05$), and is not changed in the control group. Mean pO_2 is not altered from control in any group ($p > 0.05$), while HCO_3^- is depressed at 4, 6, and 8 hours, and 4 and 16 hours in the E. coli organism and endotoxin groups, respectively.

Tables 2-4 represent findings pertaining to alterations in certain blood constituents including enzymes, lactate, and potassium. Table 2 shows

some of these responses of baboons to infused endotoxin or live organisms. Endotoxin-treated animals revealed significant increases in LDH (lactic dehydrogenase) and alkaline phosphatase ($p \leq 0.05$). Marked elevations in SGOT (serum glutamic oxalacetic transaminase) and F-LDH (% of total LDH) are observed in animals receiving both E. coli organisms and endotoxin ($p \leq 0.05$). Saline-infused animals demonstrate minimal alterations in SGOT, F-LDH, LDH, alkaline phosphatase, and potassium during a 24-hour observation period, indicating adequate stability of the control preparation. All individual animals receiving either endotoxin or organisms reveal elevated plasma K^+ concentrations as death approaches, but the increases in each group are not statistically significant.

Elevations in blood lactate are evident in all animals administered endotoxin or organisms, except in animal #3 administered live E. coli, in which lactate measurements were not made. Significant increases at 24 hours were observed in all surviving baboons administered endotoxin in contrast to the controls receiving saline alone in which only minimal changes were seen.

A variety of coagulation defects have been previously reported in septic shock patients (17) and nonhuman primates administered live E. coli (16) or endotoxin (21). Thrombi and necrosis of kidney and intestine have been commonly encountered lesions in human patients with septic shock (17), while microthrombi within glomeruli and necrosis of the proximal convoluted tubular epithelium of the kidney have been observed in nonhuman primates (21). It was thought to be of interest to determine whether or not renal lesions were present in endotoxin and live-organism shock models and if present to pretreat with heparin in subsequent studies. Figure 5a is a

section of a kidney from baboon #6, administered live E. coli organisms but without heparin, and dying in 11 hours. Fibrin thrombi are seen in the glomeruli. Figure 5b is a higher magnification of the same kidney section shown in the previous figure, revealing massive fibrin deposition. Figure 6 is a section of kidney from baboon #10, administered endotoxin without heparin pretreatment and dying in 23 hours. Cortical hemorrhage and necrosis is observed. Figure 7 presents a section through the renal cortex of baboon #5, administered live E. coli endotoxin and dying in 14 hours. Extensive tubular necrosis is demonstrated. Heparin was administered to a separate group of baboons prior to infusion of endotoxin, live organisms, or saline. Animals receiving such treatment are indicated in Table 1. Heparin dosages were 1 ml/kg body weight intravenously administered 15 minutes before shock, with 2 ml volumes given at the beginning of each hour (1000 units/ml). Although no differences in response of any measured parameter of the present study were observed, and no adverse gross tissue changes were seen as a result of the heparin treatment, renal lesions described above in Figures 5-7 were entirely absent. Heparin administration therefore prevented all signs of renal morphologic abnormality as determined with light microscopy. On the other hand, renal functional abnormalities were not modified with heparin administration. This is shown in Table 4, in which modest and progressive increases in BUN, endogenous creatinine and uric acid were not modified with heparin treatment in either endotoxin or live organism induced shock. Heparin treatment did not appear to improve the hemodynamic status or survival time and did not modify glucose, insulin, or enzyme changes in any animal receiving live organisms or endotoxin. For these reasons baboons, in each of the shock models, included both heparinized and non-heparinized animals. The results are consistent with

the probability that the adverse systemic hemodynamic status, including systemic hypotension and renal arteriolar vasoconstriction, were dominant features in depressing renal function. Hepatic morphologic changes were similar in both shock models and included tissue swelling, centrolobular focal necrosis, hydropic changes, and subcapsular hemorrhage.

DISCUSSION

Considerable concern has been expressed in recent years regarding the selection of an experimental animal model which effectively reveals a similar pathogenesis as seen in human septic shock (12). Questions have arisen about the selection of a proper animal species, the means of eliciting shock, the influence of anesthesia, and the duration of study in laboratory experiments designed to determine the mechanism of septic shock as applied to human patients. The purpose of this study was to select a species of animal, the baboon, already demonstrated to best show the pathophysiological alterations seen in man (8,12,15). The particular contribution of this report was to further evaluate the suitability of the animal as a shock model by extending the time of observation during shock, utilizing the lowest possible level of anesthesia in the unrestrained animal, and contrasting the hemodynamic, metabolic, and hematologic responses to separate infusions of E. coli endotoxin and live E. coli organisms, while administering the agents as infusions rather than in bolus form. It was hoped that data obtained from the study would aid in providing a clearer understanding of the underlying mechanisms operating in the human patient. Results emphasized the importance of monitoring parameters during many hours of observation, since an adequate picture of the pathogenesis of shock cannot be readily obtained during an acute period such as 6 to 8 hours of observation.

Dosages and lethality effects of E. coli endotoxin and live organisms. Infusions of live organisms at a mean dosage of 4×10^{10} organisms/kg resulted in all baboons dying within 15 hours. This observation compares favorably with previous findings in our laboratory in dogs administered live organisms at an average dosage of 1×10^{9} organisms/kg in which 17 of 29 animals were non-survivors (13), and with the results of Griffiths et al. in which seven of 20 dogs died within 12 hours following live E. coli administration at a dosage of 10^{9} organisms/kg (10). A discrepancy appears to exist, however, between the baboon and canine survival responses to endotoxin: the LD_{100} for E. coli endotoxin used in the present study is 2.5 mg/kg in dogs, whereas 16 to 20 times this dosage was required to kill two of three baboons within 24 hours. To explain this difference, it is possible that the reticuloendothelial system of the baboon may be more effective than that of the dog in removing endotoxin from the circulation.

Glucose-insulin relationships in endotoxin and live organism induced shock. The second aspect of interest was the difference in glucose and insulin values in animals receiving endotoxin versus live organisms. The effect of infused live organisms at an LD_{100} level was to elicit systemic arterial hypotension which was sustained at values between 40 and 60 mmHg. Mean plasma glucose increased for the first several hours, then progressively fell to hypoglycemic levels, approximating values of 50% or lower, while insulin concentrations declined markedly and remained low in all animals. Hypoglycemia and hypoinsulinemia were not merely terminal events in shock, but were observed during a large portion of the time the animal was in shock, including the terminal period. These findings are consistent with previous observations in baboons administered live organisms (8,12). Hypoglycemia has been reported in adult human subjects (1,19) and in the

human newborn (23) in septic shock. Hypoinsulinemia has been described in patients with low cardiac outputs in septic shock (6) and in clinical hypovolemic shock (3). There appears to be a close association between depressed plasma insulin levels and impending death in both experimental and clinical septic shock, while glucose levels may be variable. Early hyperglycemia followed by progressively developing hypoglycemia has been reported in baboons administered live E. coli (8,12) in the presence of sustained low plasma insulin concentrations. Live E. coli organism shock in dogs (10) has resulted in depressed glucose blood levels, and recent work in progress in this laboratory in unanesthetized dogs has demonstrated a profound degree of hypoglycemia.

In contrast, animals receiving infusions of endotoxin did not demonstrate hypoglycemia or hypoinsulinemia, and although mean systemic pressure fell significantly, it remained stabilized at a higher level, between 50 and 75 mmHg. Hyperglycemia of a short duration, as also seen in the live organism series, was a prominent finding in the endotoxin-treated group, and a delayed progressive increase in blood glucose concentration occurred from 6 to 24 hours. One animal receiving endotoxin (#9) demonstrated hypoglycemia and hypoinsulinemia during the terminal stage of shock. These findings suggest that hypoglycemia and hypoinsulinemia are hallmarks of endotoxin and live organism shock only when the state of shock is severe and when death is imminent. On the other hand, hyperglycemia concomitantly occurring with hypoinsulinemia, termed "pseudodiabetes", may suggest a deficiency in glucose transport into vital cells. Cowley and others evaluated significant biochemical parameters in 300 shock patients and found that blood glucose was highest in the patients eventually dying (7). Insulin values were not reported. Cavanagh and Rao administered

endotoxin to baboons at a dosage of 7 mg/kg and observed no changes in blood glucose for 2 hours after injection (4).

Blood gases, bicarbonate, lactate, and pH changes in endotoxin shock and live organism induced shock. pH remains relatively constant in animals in both forms of shock until terminal periods of shock are approached, at which time it falls by approximately 0.1 pH unit. This finding was reported by Horwitz and others (16) in baboons administered 10^{10} live E. coli organisms/kg in a shorter study of 4 hours' duration. Their data suggested that acidosis resulted from the effects of inadequate tissue perfusion. Both aortic pressure and cardiac output were notably depressed (16) as was also found by others (4) following endotoxin administration in baboons. The pH of the baboon is maintained within more nearly normal limits in shock (12) in contrast to the canine species (1,2,14).

pCO_2 was found to decline in most baboons in the present study, due to hyperventilation during the course of shock. There was no evidence of respiratory depression although data indicate the presence of metabolic acidosis. Lowered pCO_2 in baboons given live E. coli organisms was reported by Cryer's group (8). pO_2 remained relatively constant in baboons given endotoxin or live organisms in the present study, except in the terminal state of shock. Pulmonary complications seemed not to be a factor in contributing to the demise of the animals, although terminal CNS depression appeared to perform a late adverse role in gas transport. Horwitz et al. (16) reported no changes in pO_2 in baboons receiving 10^{10} organisms/kg during a 4-hour period, and values reported by Holper and others in similar studies on the baboon confirm the normality of pO_2 in experimental septic shock (15). Awake dogs administered live E. coli organisms at an LD_{60} dose demonstrate relatively constant pO_2 values,

while pCO_2 steadily falls in both surviving and non-surviving animals (13).

Bicarbonate concentrations were found to be depressed and lactate concentrations were seen to steadily rise, following both live organism and endotoxin induced shock in the baboons of the present study. Similar findings have been reported by others in baboons administered endotoxin (4) and E. coli organisms (12,16).

Enzymatic, electrolyte, and metabolic concentrations indicative of organ dysfunction following infusions of endotoxin or live organisms. The presence of sustained systemic hypotension and metabolic acidosis with indications of accelerated anaerobic metabolism (2,11) as common factors in both baboon shock models of the present study suggest that liver and renal functions are depressed. This possibility is supported by elevations in SGOT and F-LDH seen in both shock models of the present study. Individual animals receiving either endotoxin or organisms revealed elevated plasma potassium concentrations as death approached. Modest increases in BUN, endogenous creatinine, and uric acid were observed in both endotoxin and live organism treated animals. Hepatic dysfunction and morphological pathology have been extensively documented in patients in shock. McGovern has studied tissues from patients dying in septic shock and has reported lesions in lungs, liver, intestine, heart, kidneys, adrenals, pancreas, and skin (17). Cowely et al., in a review of 300 patients including all major classifications of shock, have reported that the liver shows the most consistent and noteworthy pathologic changes (7). Their findings included dilatation and congestion of sinusoids and hepatic veins and necrosis of hepatic cells in both central and midzonal regions. Schumer and others have reported that E. coli endotoxin inhibits respiration

in human and rat liver mitochondria (20), while Mela et al. have found evidence for the elicitation of defective oxidative metabolism of rat liver mitochondria in E. coli endotoxin shock (18). This type of liver functional damage is further supported by findings from Filkins' group that hepatic gluconeogenesis is depressed in the rat subjected to endotoxin shock (9), and by others who have reported defects in the formation of glucose in dogs administered live E. coli organisms (10) and deranged liver metabolism causing deaths in dogs with E. coli bacteremia (11,13). Data from the present baboon series is consistent with a variety of reports indicating a significant degree of liver dysfunction in both endotoxin and live organism challenged animals. The failure of baboons to maintain a normal glucose concentration in live E. coli shock could be explained on the basis of a failure of hepatic gluconeogenesis. Hypoinsulinemia uniformly observed in baboons in live organism induced shock (8,12) could be explained on the basis of excessive sympathoadrenal stimulation with subsequent suppression of pancreatic insulin release and deficient blood perfusion of the pancreas resulting in its defective function.

There is considerable evidence for renal dysfunction in septic shock, and the present study documented fibrin thrombi deposition in glomeruli following live E. coli infusion and cortical hemorrhage and tubular necrosis in baboons administered endotoxin or live organisms. This pathology was entirely eliminated by pretreatment and repeated administration of heparin throughout the course of shock. Indicators of steadily developing renal dysfunction, however, were not influenced by heparin treatment: BUN, creatinine, and uric acid concentrations rose equally in heparinized and non-heparinized shocked baboons, and urine flow was uniformly absent in both groups. This latter observation suggests that renal dysfunction may

be a function of poor perfusion resulting from systemic hypotension, renal arteriolar vasoconstriction, and depressed blood flow. Cavanagh and Rao studied baboons subjected to endotoxin shock and described a precipitous decrease in renal artery flow within 3 minutes after endotoxin administration, which occurred without corresponding changes in aortic pressure and cardiac output (4). They concluded that the baboon kidney was a primary target organ in endotoxin shock and that the oliguria they observed was not simply due to a reduction in aortic pressure but probably resulted from a specific effect of endotoxin on the renal vasculature. Cavanagh and others (5) in a similar study in baboons recorded a fall in renal blood flow, a profound drop in platelet count and a marked increase in plasma norepinephrine levels within 3 minutes following intravenous injection of endotoxin. Plasma clotting time was shortened and stimulation of the fibrinolytic system occurred, suggesting that intravascular coagulation may perform a role in the pathophysiology of endotoxin shock in the baboon. Selmyer and his group administered E. coli endotoxin to baboons and recorded a sustained period of marked systemic hypotension. After 4 hours of shock, they observed microthrombi within glomeruli, necrosis of the proximal tubular epithelium and concluded that renal ischemia was secondary to decreased perfusion pressure (21).

Implications of these findings for application to human septic shock. The primary aspects of this investigation that bear directly on the suitability of the baboon as a shock model relevant to the clinical entity are as follows: (a) the control, non-shocked baboon, lightly anesthetized, unrestrained, and continuously monitored during a 24-hour period, is a very stable experimental preparation, showing minimal changes in hemodynamics,

metabolism, blood chemistry, organ function, and morphology; (b) differences were observed between endotoxin and live organism induced shock, but the significances of these are not clear. The live E. coli treated baboon appears to bear a closer similarity to the clinical entity of septic shock, particularly because of the persistent development of hypoinsulinemia, hypoglycemia, and renal lesions, including fibrin thrombi. The endotoxin treated model, on the other hand, exhibits many pathophysiological features common with the live organism treated animal, although doses of endotoxin required to elicit irreversible shock and death are inordinantly high.

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TABLE 1. Dosages of Endotoxin and Live E. coli Organisms and Survival Times in Baboons

Baboon No.	Dose of E. coli organisms per kg	Time of Survival (Hrs)
1*	9.7×10^{10}	15
2*	8.9×10^{10}	8
3	1.6×10^{10}	6
4	1.6×10^{10}	12
5	1.6×10^{10}	14
6	2.5×10^{10}	11
Baboon No.	**Dose of Endotoxin, mg/kg**	**Time of Survival (Hrs)**
7*	8	24
8*	12	24
9*	40	17
10	12	23
11	12	24
12	40	24
13	50	16
Baboon No.	**Saline Control, ml/kg**	**Time of Survival (Hrs)**
14	2	24
15*	8.2	24
16	5.9	24

* With heparin

TABLE 2. Responses of the Baboon to Infused Endotoxin or Live E. coli Organisms[a]

Parameter	Time During Shock (Hours)											
	Control		4		8		11-14		15-16		22-24	
SGOT (mU/ml)												
Saline Control	32(3)	3[b]	34(5)	3					65(19)	3	80(30)	3
E. coli	99(36)	6	142(45)	6	*282(47)	4	*501(131)	4				
Endotoxin	37(2)	7	* 79(9)	7					*712(240)	7	567(305)	5
F-LDH (% of total)												
Saline Control	163(31)	3	186(37)	3					207(26)	3	235(36)	3
E. coli	324(76)	6	*413(98)	6	*596(88)	4	1294(292)	3				
Endotoxin	218(23)	7	317(39)	7					*1483(371)	7	1216(515)	5
LDH (mU/ml)												
Saline Control	228(37)	3	275(55)	3					299(20)	3	342(44)	3
E. coli	621(227)	6	731(243)	6	975(146)	4	1705(343)	4				
Endotoxin	305(33)	7	519(86)	7					*2550(595)	7	1629(519)	5
Alkaline Phosphatase (mU/ml)												
Saline Control	458(249)	3	472(244)	3					*489(248)	3	453(193)	3
E. coli	707(176)	5	804(163)	5	981(127)	3	644(212)	3				
Endotoxin	312(116)	7	*558(113)	7					*527(107)	7	473(70)	5
K^+ (mEq/L)												
Saline Control	3.7(.4)	3	3.3(.6)	3					3.4(.5)	3	3.3(.2)	3
E. coli	3.7(.1)	5	*2.9(.3)	5	4.8(.7)	3	7.0(1.5)	3				
Endotoxin	3.4(.1)	7	3.2(.2)	7					4.4(.6)	7	4.2(.5)	5

[a]Mean (±SE)

[b]Number of animals

*Significantly different from control, zero time value ($p \leq 0.05$)

TABLE 3. Effects of Infused E. coli Organisms and Endotoxin on Blood Lactate Concentrations in Baboons

Baboon No.	Time During Shock (Hours)													
	Control	6	7	8	11	12	13	14	15	16	17	22	23	24
E. coli														
1	5.9						86.0		(Died)					
2	9.4		125.7	(Died)										
3	9.2	(Died)												
4	22.2			35.6		(Died)								
5	6.7			36.6				65.0	(Died)					
6	14.7			55.6	(Died)									
Endotoxin														
7	8.2									26.5				21.9
8	4.9									57.6				76.6
9	8.2									53.9	(Died)			
10	7.3									42.5		115.3	(Died)	
11	10.0									37.2				45.9
12	23.4									46.6				47.5
13	--								57.1	(Died)				
Saline Control														
14														
15	4.1									2.3				11.4
16	6.2									7.8				7.5

TABLE 4. Effects of Heparin Administration on Responses of Baboons to Infused Endotoxin or Live E. coli Organisms[a]

	Time During Shock (Hours)											
	Control		4		8		11-14		15-16		22-24	
E. coli												
No Heparin												
BUN	15.0(2.3)	3[b]	19.3(5.2)	3	23 (4)	2	30 (6)	5				
Creatinine	1.0(.1)	4	1.5(.1)	4	2.7(.2)	3	4.1(.2)	3				
Uric Acid	.5(.1)	4	.7(.1)	4	1.2(.2)	3	3.3(.9)	2				
With Heparin												
BUN	14 (2)	2	19 (5)	2	36	1	32	1	35	1		
Creatinine	1.0(.2)	2	1.6(.6)	2	2.9	1	3.2	1	3.9	1		
Uric Acid	.6(.2)	2	.5(.3)	2	.8	1	.8	1	3.2	1		
Endotoxin												
No Heparin												
BUN	14 (1.4)	4	18.5(1.0)	4					36.5(4.7)	4	43.3(5.0)	3
Creatinine	1.1(.1)	4	1.8(.1)	4					3.4(.9)	4	3.5(1.3)	3
Uric Acid	.2(.1)	4	.7(.1)	4					.7(.1)	4	1.2(.5)	3
With Heparin												
BUN	12.3(1.3)	3	15.7(2.9)	3					29.7(5.2)	3	46 (22)	2
Creatinine	.9(.1)	3	1.1(.1)	3					1.5(.2)	3	1.8(.7)	2
Uric Acid	.2(.1)	3	.4(.2)	3					.4(.2)	3	.2(.1)	2

[a]Mean (±SE)

[b]Number of animals

Legends for Figures

Figure 1. Mean values ±SE, of mean systemic arterial blood pressure (MSAP; mmHg), plasma glucose (mg%), and insulin (μU/ml plasma), in three control baboons administered saline in place of endotoxin or live E. coli organisms.

Figure 2. Changes in mean systemic pressure, plasma glucose and insulin in six baboons intravenously infused with live E. coli organisms (For doses of E. coli, see Table 1).

Figure 3. Changes in mean systemic pressure, plasma glucose and insulin in seven baboons intravenously infused with E. coli endotoxin (see Table 1 for doses).

Figure 4. Changes in pH, pCO_2, pO_2 and HCO_3^- are presented in the three types of studies with a total of 16 baboons.

Figure 5a. Section of kidney from baboon #6, administered live E. coli organisms, dying in 11 hours. Animal was not administered heparin.

Figure 5b. This is a section of the same kidney shown in Figure 5a, showing an enlarged glomerulus with increased magnification.

Figure 6. Section of kidney from baboon #10, administered endotoxin, dying in 23 hours. Animal was not administered heparin.

Figure 7. Section through renal tubules of baboon #5, administered live E. coli endotoxin, dying in 14 hours. Animal was not administered heparin.

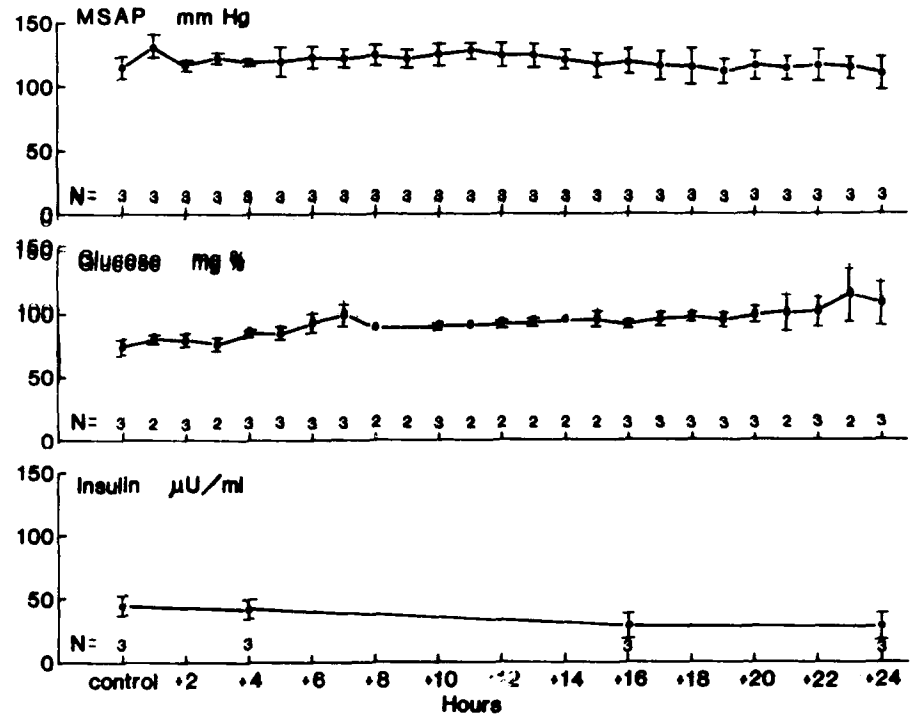

FIGURE 1

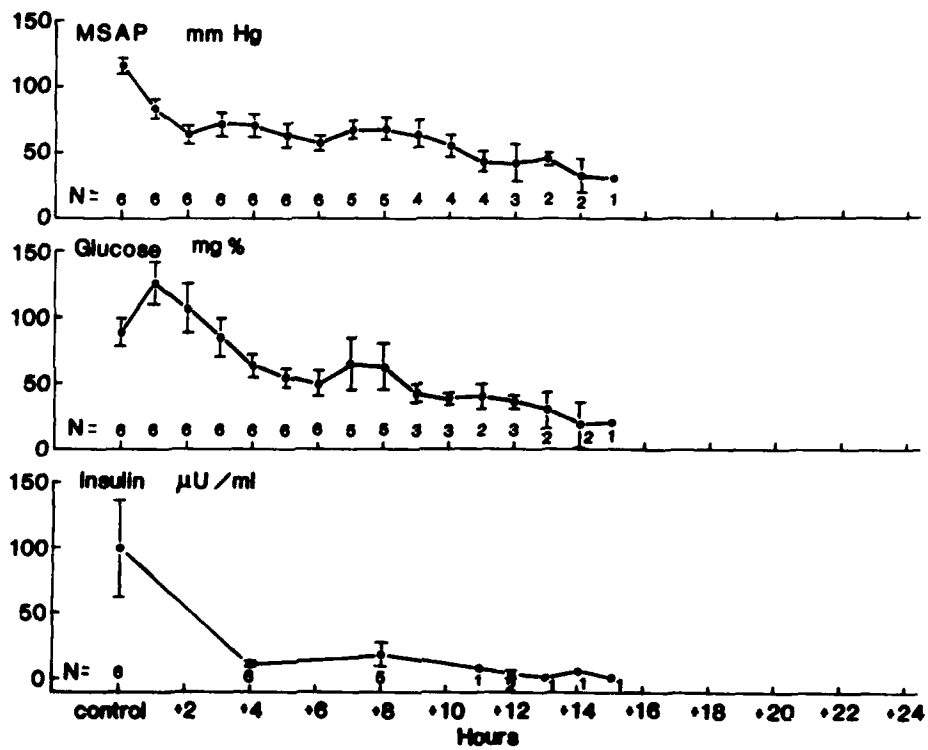

FIGURE 2

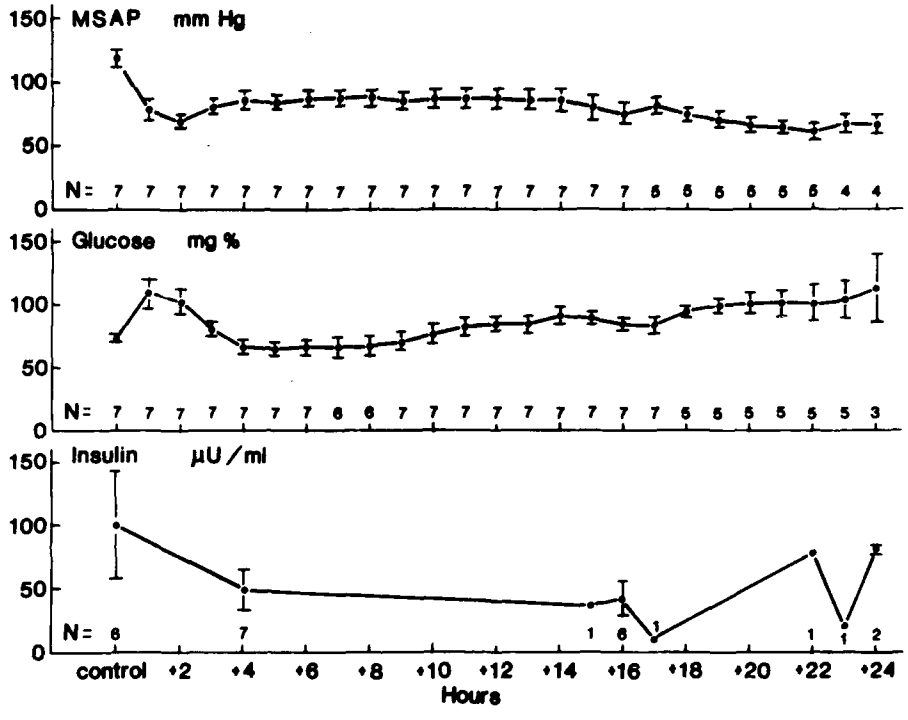
MSAP mm Hg
150
100
50
0
N= 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 5 5 5 5 5 5 4 4
Glucose mg %
150
100
50
0
N= 7 7 7 7 7 7 7 6 6 7 7 7 7 7 7 7 7 5 5 5 5 5 5 3
Insulin µU/ml
150
100
50
0
N= 6 7 1 6 1 1 1 2
control +2 +4 +6 +8 +10 +12 +14 +16 +18 +20 +22 +24
Hours

FIGURE 3

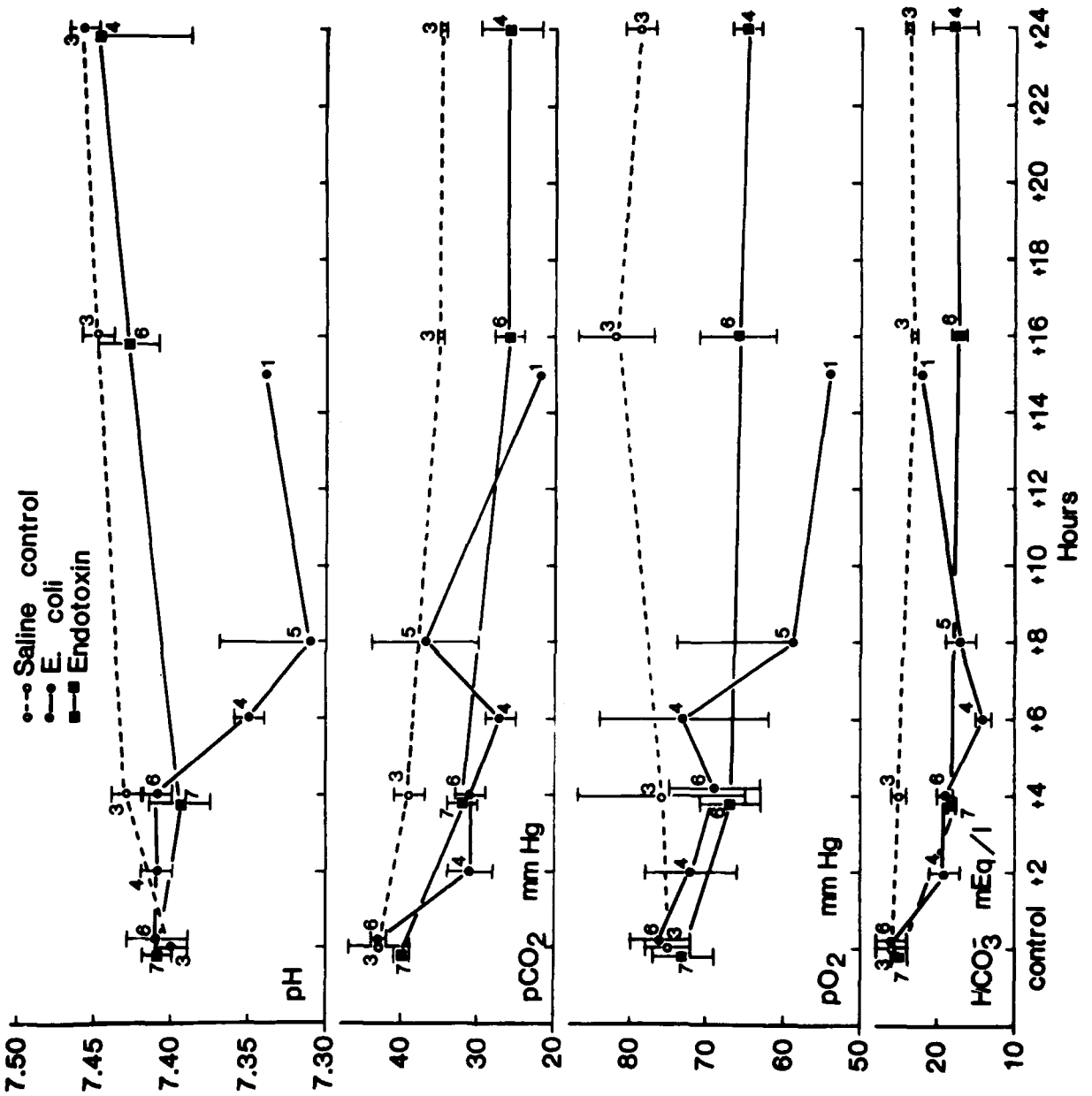
Saline control
E. coli
Endotoxin
pH
7.50
7.45
7.40
7.35
7.30
pCO2 mm Hg
40
30
20
pO2 mm Hg
80
70
60
50
HCO3- mEq/l
20
10
control
2
4
6
8
10
12
14
16
18
20
22
24
Hours

FIGURE 4

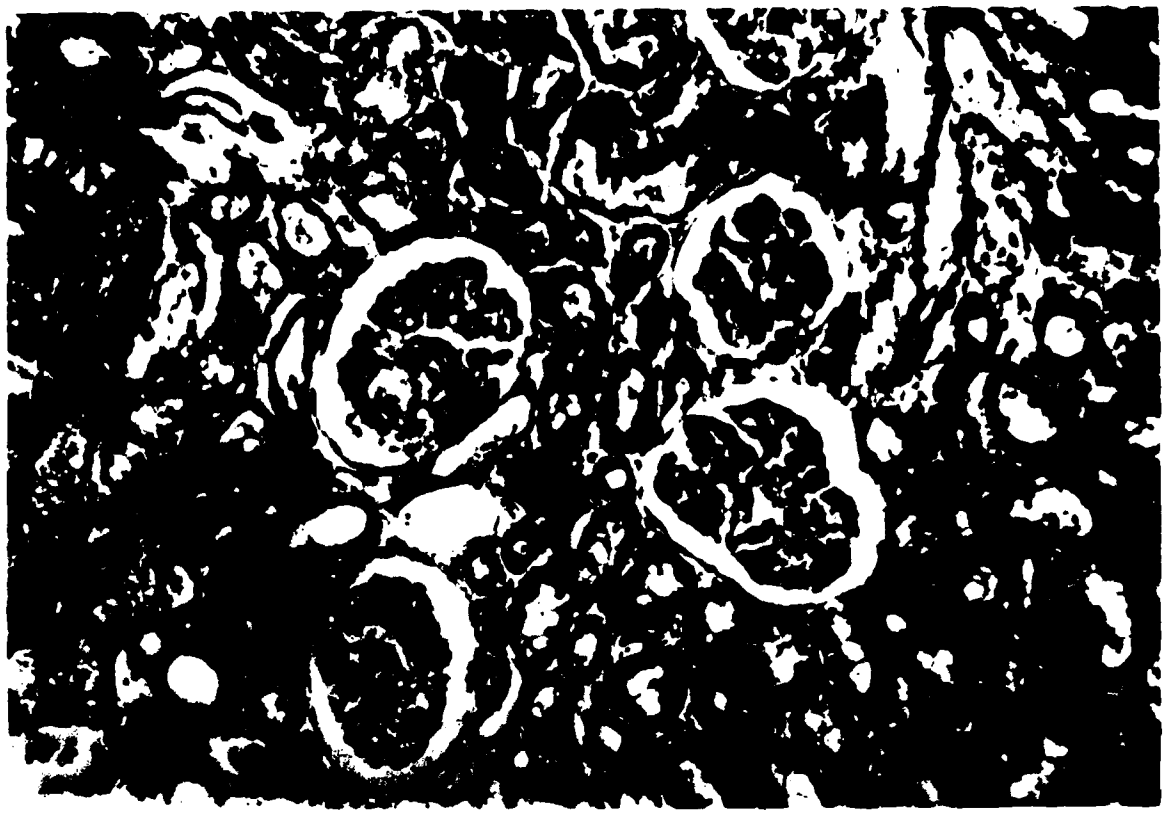

FIGURE 5A

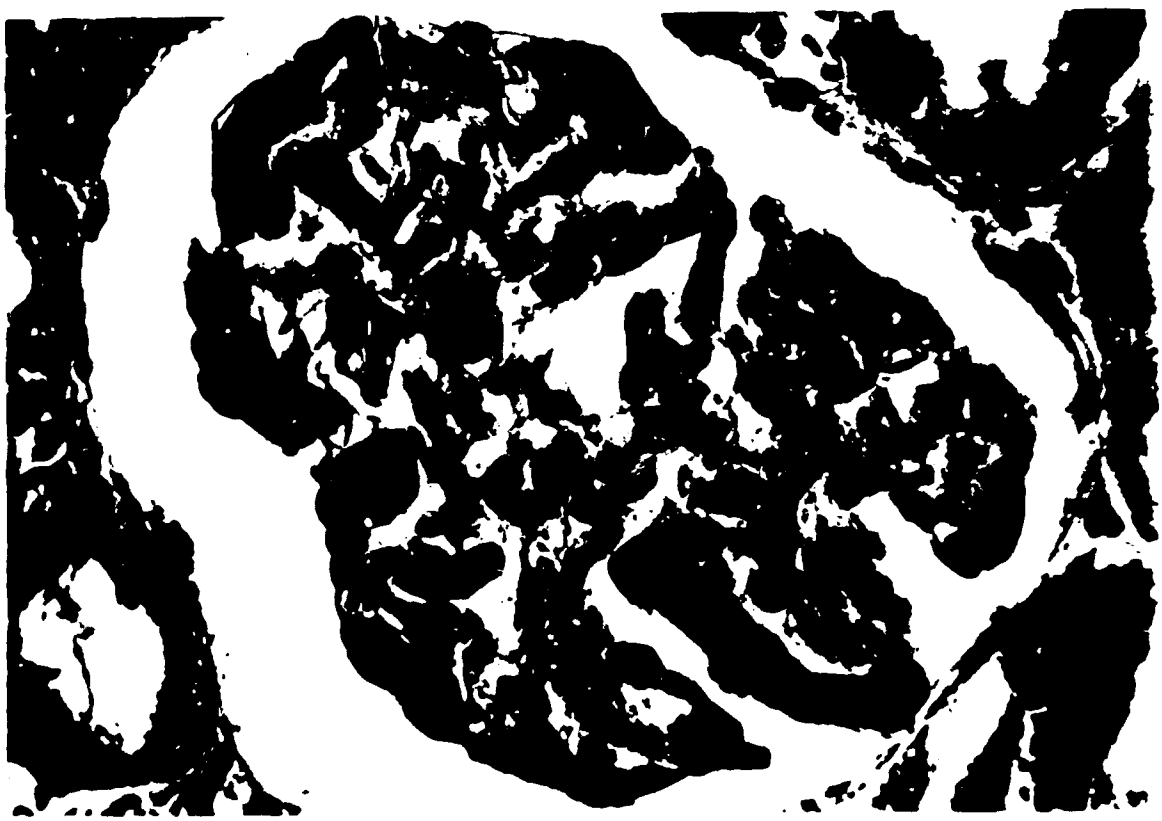

FIGURE 5B

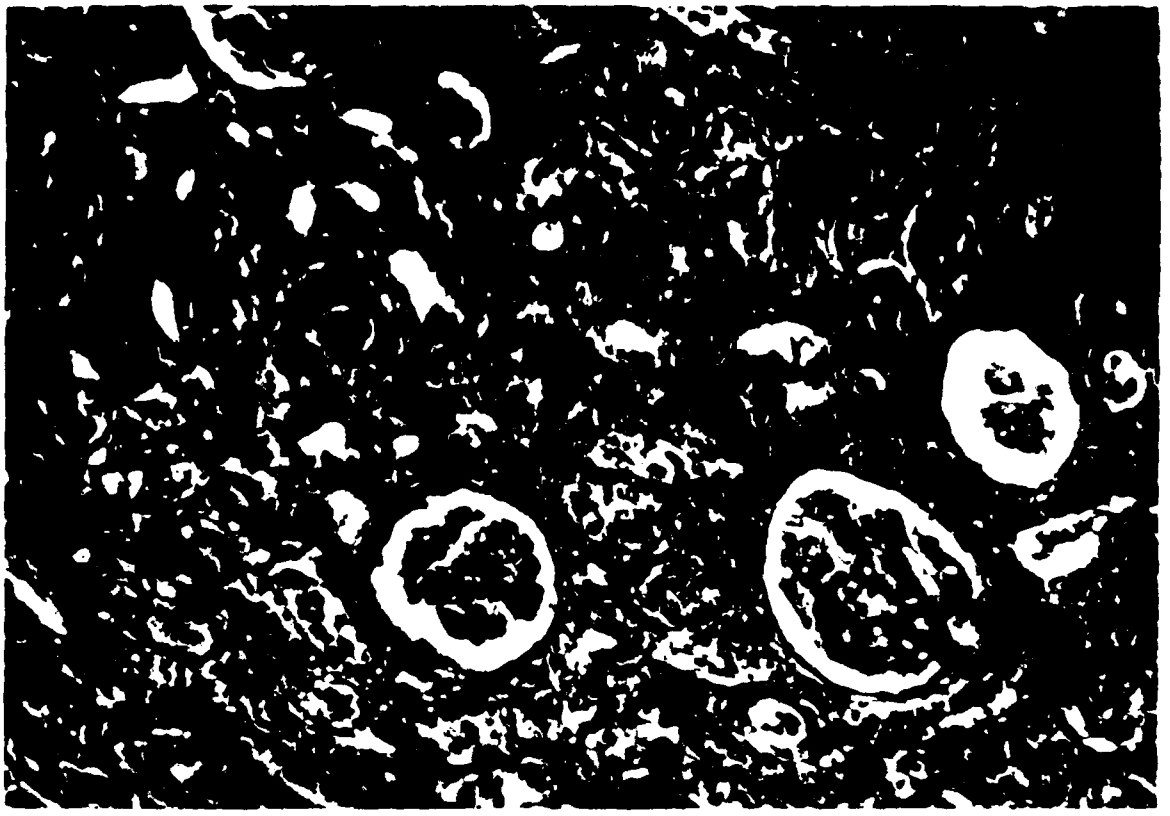

FIGURE 6

FIGURE 7

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13. ABSTRACT

The present study was designed to develop a nonhuman primate model more relevant to the clinical entity of septic shock. Experiments were conducted on young adult baboons, unrestrained, and maintained at a light plane of pentobarbital anesthesia. Responses of animals infused with E. coli endotoxin or live E. coli organisms were evaluated during a 24-hour period or until death. Results suggest significant differences between the two shock models: large dosages of endotoxin in contrast to those used in the canine species were required to elicit lethality characteristics. Hypoglycemia and hypoinsulinemia were regularly observed in live E. coli organism induced shock; however, hyperglycemia was a consistent hallmark in the endotoxin infused model. Renal fibrin thrombi were present only after E. coli administration while tubular necrosis was found following both organism and endotoxin infusions. Renal morphologic changes induced during shock were prevented by heparin administration. Liver dysfunction was indicated by elevations of blood levels of enzymes and morphologic alterations. Pulmonary function did not appear to be abnormally affected, although respiratory alkalosis and metabolic acidosis were regularly observed in both models. Significant differences in responses between the models should elicit caution in the application of findings in nonhuman primates to the human patient.

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