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PROLONGED SHOCK IN THE BABOON SUBJECTED TO INFUSION OF 'E. COLI--ETC(U)
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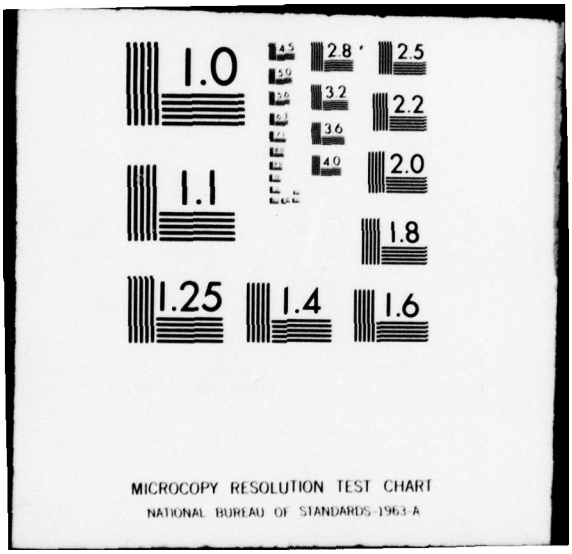
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(9) TECHNICAL REPORT, NO. 136

(6) PROLONGED SHOCK IN THE BABOON SUBJECTED TO INFUSION OF E. COLI ENDOTOXIN.

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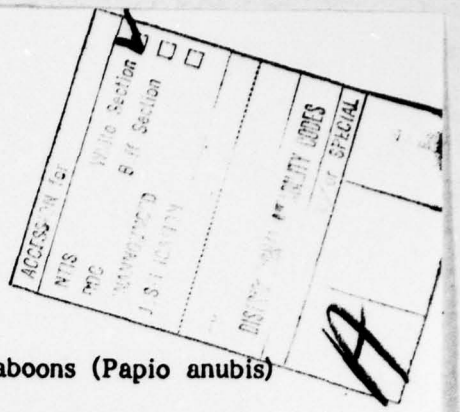
INTRODUCTION

Recent reports have indicated that severe hematologic abnormalities occur during septic shock. Thrombocytopenia, hypofibrinogenemia, and prolongation of the prothrombin and partial prothromboplastic times are associated with disseminated intravascular coagulation (1-8) in this form of shock. Pathologic findings in clinical studies have occasionally included the presence of fibrin thrombi in various organ systems (9-11). A report by Coalson and others utilizing live E. coli organisms in baboons elicited a lesion of diffuse fibrin thrombi in renal glomeruli (12). Hinshaw et al. reported the presence of renal fibrin thrombi in baboons subjected to E. coli shock (13). Hoffman and others described light and ultrastructural changes in livers of baboons following lead and endotoxin administration and noted fibrin deposition (14). Selmyer's group (15) reported the presence of fibrin thrombi in the renal glomeruli of baboons at 4 hours after endotoxin administration; however, no other studies have described this lesion in baboons administered endotoxin.

The purpose of the present study was to characterize the morphologic findings of the subhuman primate after endotoxin and to correlate these findings with physiologic and hematologic data during an observation period of twenty-four hours. Heparin was administered in some animals to determine whether the disseminated intravascular coagulopathy could be reversed and serve as an effective treatment modality.



MATERIALS AND METHODS

Experiments were performed on ten healthy adolescent baboons (Papio anubis) weighing 10.4—16.5 kg. Animals were fasted overnight, restrained gently by means of a squeeze cage device, administered sodium pentobarbital 20-25 mg/kg intravenously, and provided with an endotracheal tube. Femoral vessels were cannulated for measurement of pressures, administration of fluids and endotoxin, and for sampling of blood. Animals were unrestrained, positioned on a heating pad and observed constantly during a 24-hour period unless death intervened. Minimal amounts of additional anesthesia were administered when animals demonstrated visible movements of head and limbs. Ringer's lactate was infused at a rate of 80 cc/kg/24 hrs in order to satisfy minimum body fluid requirements. Arterial pressure and heart rate were registered on a Sanborn recorder. Oxygen and carbon dioxide partial pressures and pH were determined on an Instrumentation Laboratories blood gas analyzer. Arterial blood glucose concentrations were estimated with Dextrostix reagent strips and confirmed with a standard chemical procedure. A "Chem 18" survey (Technicon Instrument Corporation, Tarrytown, N.Y.) was utilized for albumin, plasma enzymes, creatinine, and blood urea nitrogen measurements. Insulin blood values were determined by radioimmunoassay and lactate concentrations were obtained with a procedure modified from an earlier report (16).

Eight of the ten baboons received intravenous infusions of E. coli endotoxin (Difco, Detroit, Mich.; B-8 strain) during an average time of 120 minutes and a mean concentration of 25 mg/kg. The variation in dose reflects the finding that it took 16 to 20 times the LD100 dose used for dogs to kill the baboon in 24 hours. This dose variation could not be correlated with the degree of morphologic response. In four of the eight animals, heparin, 1000 units/kg body weight, was administered intravenously, 15 minutes before the onset of endotoxin infusion, with 2000 units administered at the beginning of

each subsequent hour. Table 1 lists the endotoxin dosages and baboon survival times. Control baboons received anesthesia and saline and one received heparin. Statistical analysis was performed using the Student's "t" test.

Blood samples for fibrinogen levels, total hemolytic complement, platelet counts, white blood cell counts, and red blood cell counts were taken at zero time and at specified intervals until death or sacrifice. Plasma fibrinogen levels were assayed using a modified Ratnoff-Menzie method (17). Sera total hemolytic complement levels were assayed using a modified Kabat-Mayer method (18). White blood cell and red blood cell counts were determined by Coulter counter. Platelet counts were performed by phase microscopy.

Four experimental animals and two controls survived 24 hours and were then sacrificed with pentobarbital sodium. The other animals died at 3, 6, 17, and 23 hours, and were autopsied immediately (Table 1). Tissue samples of lung, left ventricle, kidney and liver were placed in appropriate fixatives. Bouin's fixative was utilized for the light microscopic studies. Specimens were embedded in Paraplast and stained by hematoxylin and eosin and phosphotungstic acid hematoxylin (PTAH). Tissues for ultrastructural studies were placed in Zetterqvist's fixative, dehydrated in ascending grades of ethanol, and embedded in Epon 812 and Araldite. Thin sections were stained with lead citrate and uranyl acetate, and examined with an RCA-EMU-3G or Hitachi HS-9 electron microscope.

RESULTS

Physiological and Biochemical Data

Physiologic and biochemical results have been previously reported (13). In summary, the mean systemic arterial pressure in both the endotoxin and endotoxin-heparin treated groups progressively decreased from control values to 24 hours. There were no significant differences in pH in either group as compared to zero time values. Mean

HCO_3^- levels were decreased at 4 and 16 hours in both groups ($p \leq 0.05$). Mean pO_2 levels were not altered from zero time values in either series. Mean pCO_2 values were depressed at 4 and 16 hours in the endotoxin-heparin treated group and at 16 hours in the endotoxin-alone treated group ($p \leq 0.05$). Control animals showed relatively constant pH, pO_2, pCO_2 and HCO_3^- values. Endotoxin-treated group blood lactate levels were significantly increased at 16 hours and at 24 hours in both experimental groups ($p \leq 0.05$). Glucose levels were elevated above control at 15 hours post-injection in the endotoxin-alone treated group ($p \leq 0.05$). There were no significant differences in mean insulin concentrations in the experimental groups. The two control animals receiving saline infusions showed relatively constant glucose and insulin values.

SGOT, LDH, FLDH, alkaline phosphatase, BUN, creatinine, and uric acid parameters are represented in Table II. Control values remained relatively constant during the entire study. SGOT levels were significantly elevated at 4 hours in the endotoxin-treated group ($p \leq 0.05$). Mean LDH, FLDH, and alakine phosphatase were increased in both experimental groups at the 16-24 hour intervals. BUN levels in both experimental groups gradually increased and that of the endotoxin-treated group was significantly increased ($p \leq 0.05$) at 16 hours. Creatinine and uric acid levels were increased significantly at 4 hours in the endotoxin-treated group ($p \leq 0.05$).

Hematologic Data

Platelet counts, fibrinogen and complement levels, and white blood cell counts are summarized in Figures 1-4 and expressed as a percentage of the baseline value. Platelet counts decreased steadily throughout the 24-hour period in both experimental groups (Figure 1). One of the control animals showed thrombocytopenia throughout the period of observation. Fibrinogen levels initially decreased in both experimental groups, but the values in the endotoxin-heparin treated group increased starting at 60-120 minutes and showed a 100% increase above the normal control level by 24 hours. The fibrinogen

values in the endotoxin-alone treated group were decreased until 18-240 minutes at which time they increased toward the level of the endotoxin-heparin group (Figure 2). Fibrinogen concentrations in the two control animals showed minimal changes. Complement levels decreased progressively throughout the 24-hour period in both experimental groups (Figure 3). One of the control animals revealed a low initial complement level which progressively decreased, whereas the other control showed relatively constant levels during the study. White blood cell counts initially increased in the endotoxin-heparin group, decreased around 60-120 minutes, and again increased at about 180-320 minutes. The endotoxin-treated group showed a marked decrease at 15 minutes with gradual subsequent increases, but at 20-24 hours WBC's were again decreased (Figure 4). The WBC's of the two control animals showed minor alterations throughout the study.

Morphologic Data

Controls: Both control animals demonstrated occasional foci of congestive atelectasis in the lung, and ultrastructurally, no sequestration of poly-platelet aggregates was present. The liver of one control animal showed the presence of a few fibrin strands within the sinusoids. Hepatocytes from both controls showed a few fat droplets, well-preserved mitochondria, and some glycogen stores. Light and electron microscopic findings of heart and kidney were within normal limits.

Experimentals

Lungs: Specimens from the four endotoxin-treated animals showed only a few sites of focal atelectasis and/or edema. Only a few polymorphonuclear leukocytes (polys) were present within the capillary bed. The small venules of the lung were ectatic and occasionally contained polymorphonuclear leukocytes. A single fibrin thrombus was found in one of the pulmonary arterioles in one of the animals. Ultrastructurally, the lungs of these four animals were similar and showed a few polys within the alveolar capillary beds. Occasionally, free specific granules were seen floating in the plasma

within the capillary lumina, but the characteristic platelet-poly aggregates seen in acute shock lung studies were not present. The underlying endothelium exhibited focal sites of edema; no actual disruption or endothelial loss was present. No fibrin was found in the lung capillaries by electron microscopy. In the four baboons which received endotoxin plus heparin, the consistent light microscopic finding was focal atelectasis. One animal showed focal hemorrhage and another animal showed a single fibrin thrombus in one of the pulmonary muscular arteries. Ultrastructurally, a few polys, occasional free specific granules and a few platelets were seen.

Heart: The endotoxin-alone treated group showed minimal pathologic myocardial changes at the light microscopic level. In two of the animals, the intramyocardial vessels were ectatic, but no white cells or platelets were present within the lumina. Ultrastructurally, the findings varied from essentially normal architecture to sites in which intramyocardial fiber edema, increased contraction bands, focal mitochondrial edema, and lipid droplets were seen (Figure 5). The capillaries did not contain any aggregates of platelets or polys, but showed occasional underlying endothelial edema. In the endotoxin-heparin group, three of the hearts evaluated by light microscopy were within normal limits. One of the hearts showed some venous dilatation. Ultrastructural lesions in three of the four hearts included increased contraction bands, focal mitochondrial edema, and mild intrafiber edema. One of the hearts showed essentially normal ultrastructural architecture.

Liver: Light microscopic specimens obtained from the livers of the endotoxin-treated group showed retention of intact lobular architecture. In three of the animals, individual hepatocytes showed mild to moderate vacuolization whereas the remaining liver showed fatty change. In two of the animals, there were marked numbers of polymorphonuclear leukocytes within dilated sinusoids. In the other two animals, the sinusoids were ectatic and contained polymorphonuclear leukocytes, and fibrin thrombi were

suspected on hematoxylin and eosin preparations. The PTAH stain showed definitive fibrin thrombi in one of these animals, whereas, it was inconclusive in the second. Ultrastructural findings in all four of these animals revealed that the hepatic sinusoids contained aggregates of fibrin, cellular debris, polys, and platelets (Figure 6). The surrounding Kupffer cells were vacuolated and frequently showed cellular membrane disruption. The sinusoidal endothelium was severely edematous and focally lost. The hepatocytes revealed varying degrees of cell injury. Most contained lipid droplets and vacuoles. The vacuoles frequently contained fragmented membrane material and plasma-like products. Glycogen depletion was noted throughout the hepatocytes. Many of the mitochondria were markedly edematous, and some showed outer mitochondrial membrane rupture. Bile canaliculi and the spaces of Disse showed no significant alterations. Hepatic changes in endotoxin-heparin treated baboons included marked sinusoidal dilatation with poly sequestration. Fibrin thrombi were not seen on any of the light microscopic preparations. The hepatocytes in all four of these animals showed marked vacuolization and increased lipid droplets. Ultrastructural findings in the specimens obtained from the endotoxin-heparin treated baboons revealed no evidence of fibrin thrombi in the sinusoids. Multiple polys, free cytoplasmic granules, and cellular debris were seen in the sinusoids with surrounding Kupffer cell edema and/or fragmentation; endothelial edema and focal disruption were also present (Figure 7). Some hepatocytes contained mitochondria with normal configurations, while in other hepatocytes, mitochondria were severely edematous. Many hepatocytes contained vacuoles and a few lipid droplets. Glycogen depletion was noted throughout all of the hepatocytes.

Kidneys: In the four endotoxin-treated animals, there was no evidence of glomerular fibrin thrombi deposition. In three of the four animals, a proximal convoluted tubular lesion consisting of tubular dilatation, increased epithelial eosinophilia, presence of cytoplasmic hyaline droplets, and proteinaceous material in the lumina was present

(Figure 8). The remaining kidney specimen showed severe proximal tubular necrosis accompanied by focal hemorrhage and edema within the surrounding interstitium. This animal did not show any evidence of fibrin thrombi. In the four baboons which received endotoxin-heparin, light microscopic examination of the renal specimens revealed no glomerular fibrin deposition. In only one of the four specimens was there significant tubular dilatation. Otherwise, the findings were increased eosinophilia of the proximal convoluted tubular cells and increased protein within the proximal convoluted tubular lumina. No fibrin thrombi were seen in the large renal vessels. Ultrastructural findings in both the endotoxin-alone and the endotoxin-heparin treated groups revealed no fibrin thrombi within the glomeruli. Glomerular changes included occasional sites of edema in the epithelial podocytes and endothelium. Occasional glomeruli would show red blood cell congestion within the capillary loops. The proximal convoluted tubular epithelium in all the animals showed increased numbers of vacuoles and lysosomes. Cytoplasmic and microvillous edema with focal sites of microvillous loss were present. Proteinaceous and membranous debris were present in the tubular lumina.

DISCUSSION

The present study indicates that endotoxin, either with or without heparin, does not elicit renal glomerular fibrin thrombi at the time intervals studied. Selmyer et al. (15), however, found renal fibrin thrombi in the baboon at 4 hours after injection of endotoxin, 21mg/kg. In our endotoxin-treated group, both uric acid and creatinine values were significantly different from baseline values at 4 hours suggesting an underlying renal lesion. One of our animals died at 3 hours and no renal thrombi were present. However, this animal had been treated with heparin. The other survival times ranged from 17 to 24 hours. The clot-lysis time in baboons is reported to be 24-30 hours (19). Perhaps fibrin thrombi were present during the earlier hours in our study, but fibrinolysis occurred later and they dissolved. Bellar and Graeff (20) studied the deposition of glomerular fibrin in

the rabbit after infusion with endotoxin (0.66 mg/100 ml of E. coli endotoxin at a rate of 30-50 mg/kg/hr over a 14-hour period), and animals sacrificed after 5 hours had no fibrin in the kidneys, whereas animals which died or were sacrificed between 8 and 14 hours showed deposition of glomerular fibrin thrombi. Interestingly, they noted that animals infused for a period of 14 hours and then sacrificed at 34 or 48 hours showed no glomerular fibrin deposition, but some animals demonstrated renal cortical necrosis. They suggested that the rabbit, even with its poor fibrinolytic system, could lyse fibrin in the kidney after the infusion had ended. Although none of the kidneys in this study showed granular thrombi, cortical tubular epithelial damage was present, a finding also reported by Selmyer et al. (15).

The striking finding in this study was the alterations in the liver. Both experimental groups demonstrated severe hepatocyte injury. Fat droplets, edematous mitochondria, glycogen loss, dilated endoplasmic reticulum, and increased cytoplasmic vacuoles were present and are similar to the findings described in other endotoxin liver studies (21-24), and in toxic chemical (25,26) and anoxic liver studies (27,28). Hepatic fibrin thrombi were seen consistently in the endotoxin-treated group, whereas no hepatic fibrin thrombi were seen in animals treated with endotoxin-heparin.

Boler and Bibighaus (21), White et al. (24), and McKay et al. (29) reported that fibrin was seen in the hepatic sinusoids of dog and rat livers. Levy et al. (22) described fibrin in the vacuoles of mouse hepatic cells, although none was described within the sinusoids. No fibrin was described in the livers of the endotoxin-treated dogs in the study by Rangel et al. (23). There does not appear to be an experimental study in the subhuman primate in which the effect of heparin on the deposition of hepatic thrombi following endotoxin infusion has been studied. The results from this 24-hour endotoxin baboon model indicate that if heparin is administered before endotoxin injection, and if maintenance doses of heparin are utilized, hepatic fibrin thrombi are not present in comparison to baboons not treated with heparin in which hepatic fibrin thrombi are seen.

Although heparin prevented the appearance of microthrombi in the liver, the survivability of the heparin-treated group was not increased. Hepatocyte damage in the two groups was comparable, indicated by both morphologic and serum enzyme parameters. The precise mechanism by which endotoxin effects its damage in liver cells remains unclear.

Several authors have noted the ability of heparin to induce leukocytosis (30, 31). This heparin effect may explain the 15-minute interval elevation of WBC's in the endotoxin-heparin treated group as compared to the endotoxin-alone treated group which shows the more classical leukopenia following endotoxin infusion. Recently, several reports have indicated that the presence of leukocytes is required for triggering endotoxin-induced generalized intravascular coagulation (32-36). This finding supports earlier reports (37, 38) which indicated the importance of leukocytes in mediating intravascular coagulation. Leukocytes have also been shown to possess antiheparin activity (39). Lipinski et al. (34) have suggested that fibrin monomer formation is prevented by heparin, thus preventing the interaction of circulating fibrin monomers with granulocytes which would result in fibrin formation.

Decreased fibrinogen levels have been noted within the first 8 hours in live-organism septic baboon models (40-42) and in one endotoxin baboon study (43). The fibrinogen levels of both experimental groups in this study decreased at 15 minutes. However, in the endotoxin-heparin group fibrinogen levels rose again after 15 minutes and were 100% above normal by 20-24 hours. The fibrinogen levels of the endotoxin-treated group continued to decline through 4 hours but then increased again. Several investigators have reported that endotoxin injection causes an increase in plasma fibrinogen levels (44-48).

The thrombocytopenia noted in this study has been seen in other baboon septic models including both live-organism and endotoxin-induced shock (40,41,43). Fearon et al. (49) have reported that there is activation of C3 and the terminal complement

sequence of C5-C9 occurring primarily by the properdin pathway in patients with gram-negative septicemia who develop shock. Kane et al. (50) have reported that the thrombocytopenia in shock is complement-related. In this study both experimental groups revealed decreased total hemolytic complement levels in association with the progressive thrombocytopenia. Other significant morphologic findings in this chronic endotoxin-septic model in the baboon were the lack of a significant cardiac lesion and acute pulmonary lesion described in the past by multiple investigators (51-53). The sequestration of platelets and polys within the alveolar capillary bed was not a striking lesion in the 17-24 hour lung specimens. No significant degree of pulmonary edema was present in these animals at the light microscopic level, and only focal edema of the endothelium was seen at the electron microscopic level.

The findings in this 24-hour endotoxin shock model would indicate that if heparin is administered before endotoxin injection, and if maintenance doses of heparin are utilized, fibrin thrombi will not be present in the livers of baboons in comparison to those not treated with heparin in which hepatic fibrin thrombi are seen. It is not known if hepatic thrombi ever occurred in the endotoxin-heparin group which subsequently underwent fibrinolysis, or if heparin actually prevented their formation. The underlying hepatocyte damage in the two groups was not significantly different at the ultrastructural level. Although the use of heparin in this study did prevent the appearance of microthrombi in the liver, it did not increase overall survivability in the heparin-treated group when compared to the non-heparin treated group. Our study would add some indirect evidence to the work of the many investigators who have suggested that an intact reticuloendothelial system is of importance in overall survivability in shock.

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Table 1

Dosages of *E. coli* Endotoxin and Survival Times in Baboons

Endotoxin without heparin treated group

Baboon Number	Dose of Endotoxin, mg/kg	Time of Survival (hrs)
659	12	23
660	12	24
662	40	24
663	50	16

Endotoxin with heparin treated group

Baboon Number	Dose of Endotoxin, mg/kg	Time of Survival (hrs)
652	8	24
654	5.5	3
656	12	24
661	40	17

Saline Controls

Baboon Number	Saline Control, ml/kg	Time of Survival (hrs)
658*	8.2	24
664	5.9	24

*with heparin

Table II

Liver and Renal Responses in Baboon Endotoxin Shock (mean S.E.)

Parameter	Group	(N)	Baseline Value	Time (in hours) 3-4	15-18	20-24
SGOT	without heparin	4	36.5 ± 1.5	80.5 ± 4.7*	1024.2 ± 348.5	806.7 ± 486.3
	with heparin	4	36.7 ± 4.2	77.7 ± 21.8	295.0 ± 95.8	207.5 ± 89.5
	control	2	32.0 ± 3.0	34.0 ± 5.0	65.0 ± 19.0	80.0 ± 30.0
LDH	without heparin	4	298.5 ± 37.0	431.7 ± 41.7	2895.7 ± 914.9	1989.7 ± 781.0
	with heparin	4	314.3 ± 70.6	634.3 ± 190.8	2090.0 ± 786.2	1089.0 ± 616.0
	control	2	228.0 ± 37.0	275.0 ± 55.0	299.0 ± 20.0	342.0 ± 44.0
FLDH	without heparin	4	210.2 ± 21.8	288.0 ± 30.1	1772.5 ± 587.8	1583.0 ± 827.4
	with heparin	4	228.0 ± 51.4	354.7 ± 85.9	1097.7 ± 374.6	665.5 ± 309.5
	control	2	163.0 ± 31.0	186.0 ± 37.0	207.0 ± 26.0	235.0 ± 36.0
ALK. PHOS.	without heparin	4	457.0 ± 175.6	640.5 ± 178.4	671.3 ± 132.9	549.3 ± 31.6
	with heparin	4	336.0 ± 218.3	620.8 ± 192.9	335.0 ± 110.3	357.5 ± 152.5
	control	2	216.5 ± 108.5	236.0 ± 105.0	250.0 ± 119.0	275.5 ± 129.5
BUN	without heparin	4	14.0 ± 1.4	18.5 ± 1.0	36.5 ± 4.7*	43.3 ± 5.0
	with heparin	4	12.3 ± 1.3	15.7 ± 2.9	29.7 ± 5.2	46.0 ± 22.0
	control	2	9.5 ± 1.5	8.0 ± 2.0	9.0 ± 3.0	12.5 ± 7.5
CREATI-NINE	without heparin	4	1.1 ± 0.1	1.8 ± 0.1*	3.4 ± 0.9	3.5 ± 1.3
	with heparin	4	0.9 ± 0.1	1.1 ± 0.1	1.5 ± 0.2	1.8 ± 0.7
	control	2	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	1.1 ± 0.2
URIC ACID	without heparin	4	0.2 ± 0.1	0.7 ± 0.1*	0.7 ± 0.1	1.2 ± 0.5
	with heparin	4	0.2 ± 0.1	0.4 ± 0.2	0.4 ± 0.2	0.2 ± 0.1
	control	2	0.6 ± 0.3	0.4 ± 0.0	0.4 ± 0.1	0.4 ± 0.1

* significantly different from control baseline values ($p \pm 0.05$)

FIGURE LEGENDS

Figure 1. Changes in platelets following E. coli endotoxin infusion in baboons expressed as a percentage of baseline value (four animals with endotoxin alone and four animals with endotoxin-heparin).

Figure 2. Fibrinogen responses of the baboon following E. coli endotoxin infusion expressed as a percentage of baseline value (four endotoxin treated animals and four endotoxin-heparin treated animals).

Figure 3. Changes in total hemolytic complement following infusion of E. coli endotoxin in baboons expressed as a percentage of baseline value (four endotoxin treated animals and four endotoxin-heparin treated animals).

Figure 4. White blood count responses following infusion of E. coli endotoxin in baboons expressed as a percentage of baseline value (four endotoxin treated animals and four endotoxin-heparin treated animals).

Figure 5. Endotoxin-treated heart specimen. The mitochondria show focal edema (arrows). Multiple lipid droplets (L) are present and increased contraction bands are seen. Uranyl acetate and lead citrate; X 5700.

Figure 6. Endotoxin-treated liver specimen. In the cytoplasm of the hepatocyte there are a few lipid droplets (L), increased small vacuoles, and slightly edematous mitochondria. The nucleus is normal (N). Within the sinusoids, dark aggregates of fibrin (F) are seen intermixed with cellular debris. The arrows indicate sites of disruption of the sinusoidal endothelium. Uranyl acetate and lead citrate; X 5100.

Figure 7. Endotoxin-heparin treated liver specimen. The hepatocyte nucleus (N) is surrounded by cytoplasm which shows mild vacuolization, a few lipid droplets (L), and loss of glycogen stores. The sinusoids contain a degenerate polymorphonuclear leukocyte (P), free floating granules, and cellular debris (arrows). No fibrin thrombi are present. Uranyl acetate and lead citrate; X 7300.

Figure 8. Endotoxin-treated kidney specimen. The glomerulus is normal. The surrounding proximal convoluted tubules show severe cytoplasmic vacuolization. Proteinaceous and membranous debris are seen within the lumina. Hematoxylin and eosin; X 675.

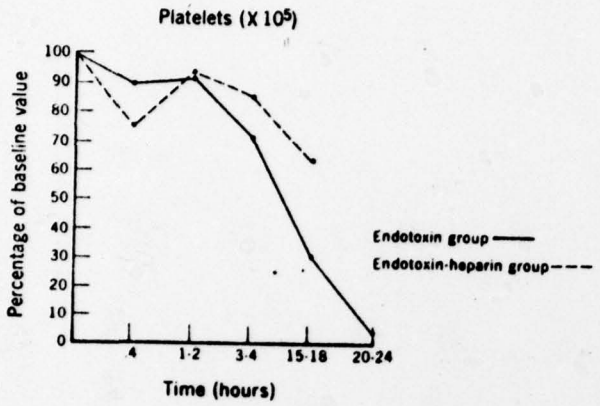

FIG. 1

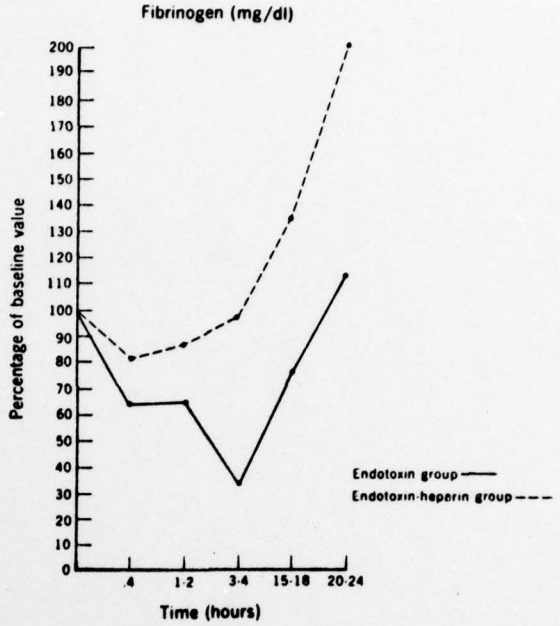

FIG. 2

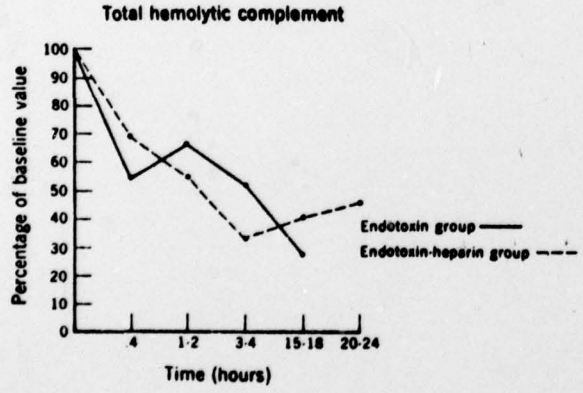

FIG. 3

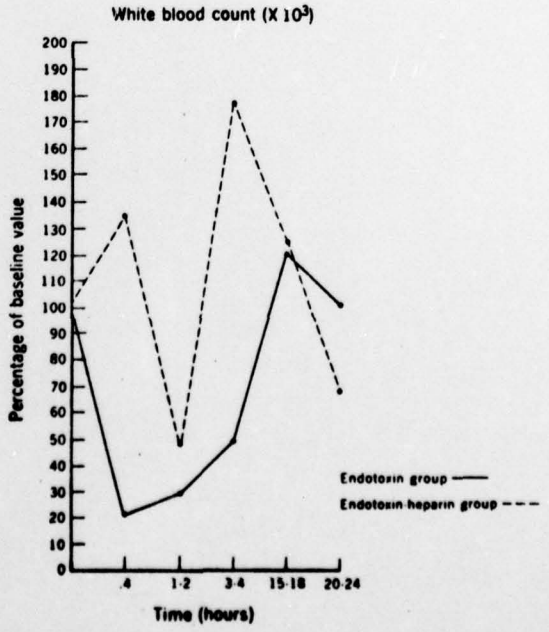

FIG. 4

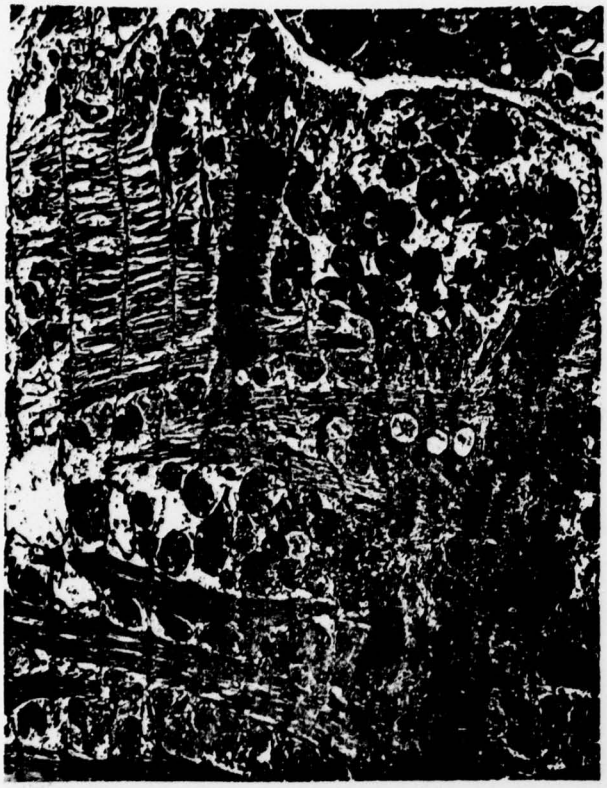

FIG. 5

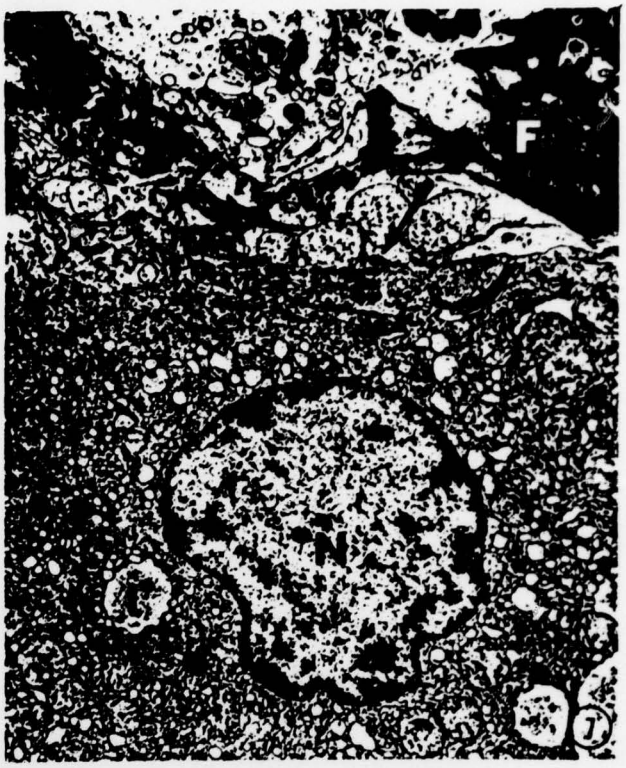

FIG. 6

FIG. 7

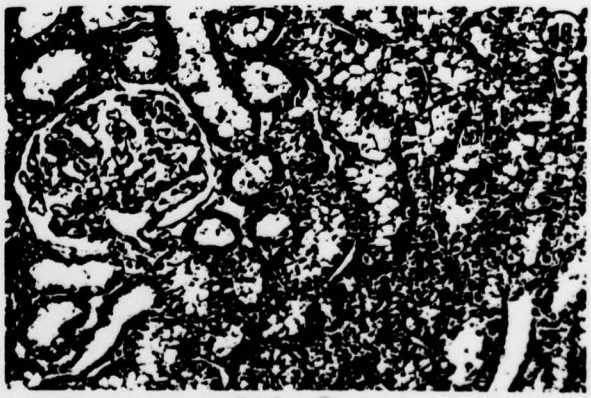

FIG. 8

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shock	serum enzymes
heparin treatment	subhuman primate
fibrin thrombi	baboon

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This study was designed to examine the response of the baboon during a 24-hour period following E. coli endotoxin infusion. Experiments were conducted on young adult baboons, unrestrained and maintained at a light plane of anesthesia induced with pentobarbital sodium. Light and electron microscopic studies on lung, heart, liver, and kidney were conducted; hematologic changes and physiologic responses were measured. The efficacy of heparin to prevent the coagulopathy and increase survivability was assayed. Hepatic sinusoidal

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fibrin thrombi with underlying hepatocyte cellular damage was seen in the endotoxin-treated group. In contrast, the experimental group receiving heparin showed no sinusoidal fibrin thrombi but demonstrated hepatocellular damage. Liver dysfunction was indicated by elevation of blood levels of enzymes. Glomerular fibrin thrombi were not present. Although heparin prevented the formation of hepatic thrombi in endotoxin-treated baboons, it did not increase survival. Platelet and complement levels decreased in both experimental groups, while wide variations in WBC and fibrinogen levels were observed. Polymorphonuclear leukocyte-platelet aggregations previously reported in the pulmonary vasculature during acute shock were not observed in the present study, and their absence may have been related to the longer time of survival.

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