# Endotoxin Shock *

## A Manifestation of Intravascular Coagulation

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IN PREVIOUS experiments it was demonstrated that the intra-aortic injection of incompatible blood, amniotic fluid, or thrombin in the dog resulted in an immediate drop in the arterial blood pressure. This drop, was reversible, and the pressure usually returned to normal spontaneously in 15 to 45 minutes.[4, 8] It was also observed that under certain conditions a secondary fall in the blood pressure occurred a short time later with ultimate death of the animal.[4, 5] Autopsy regularly showed hemorrhagic gastro-intestinal lesions similar to those occurring subsequent to the administration of endotoxin. Because the clinical and pathological picture of endotoxin shock seemed identical to that produced by the injection of incompatible blood, amniotic fluid, and thrombin, and since the latter substances were shown to cause intravascular coagulation [4-6, 8] with resulting changes in the clotting mechanism,[7, 11] it seemed desirable to investigate endotoxin shock utilizing the same methods which had been used for the study of incompatible blood and thrombin shock.[4-8, 11]

### Methods

Fifty mongrel dogs of both sexes were anesthetized with sodium pentobarbital. Records of the arterial blood pressure were made on a Sanborn Recorder from a large size polyethylene catheter inserted into the right femoral artery. The vena caval presure was also measured in eight animals from a polyethylene tubing introduced through the femoral vein. A small-sized catheter inserted into the left femoral artery up to the level of the thoracic aorta was used to inject endotoxin and to withdraw blood samples. Each dog was given 4.0 mg. of *Escherichia coli* endotoxin per kilogram of body weight diluted to 60 ml. with saline. The injection was given over a five-minute period using a mechanical syringe in order to insure a constant, even injection. The endotoxin was prepared by the Department of Bacteriology at Walter Reed Army Institute of Research as follows:

*E. coli* was isolated from a dog later used in this study. Biochemical reactions of this organism were checked and only organisms from smooth colonies were used. A somatic antigenic analysis indicated that this organism was not a member of any of the known or suspected pathogenic groups, or of groups 01 through 025. Organisms

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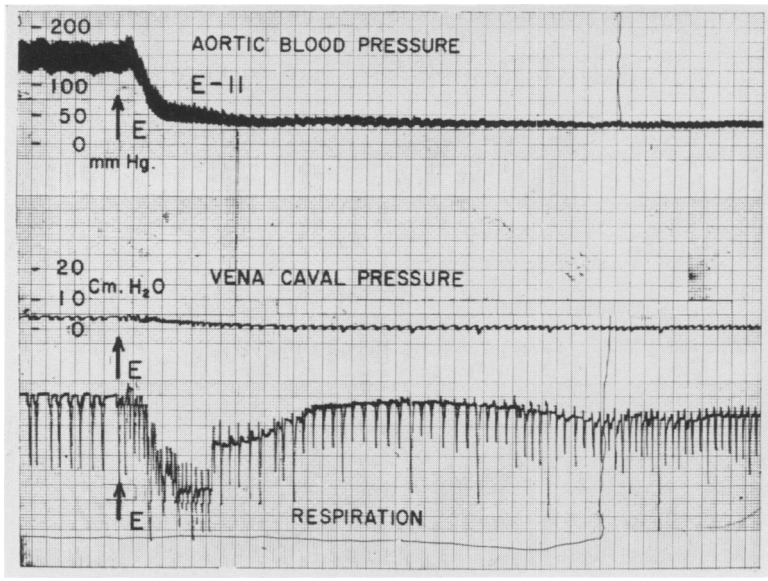


FIG. 1. Recording of Group A dog given endotoxin at point of large arrows. The upper record shows the typical brief rise and then dramatic fall of aortic blood pressure following endotoxin injection. Note that the pulse pressure before injection was about 50 mm. Hg and decreased after injection to 10–15 mm. Hg. The drop in both systolic pressure and pulse pressure persists for many minutes. The middle record shows the pressure in cm. of $H_2O$ of the vena caval blood. Before endotoxin it was about 4 cm. and it dropped to essentially zero after injection. The lower record shows respiration which was markedly affected by the injection.

were grown in Peptone Phosphate Broth (Difco–Detroit, Mich.), and the bacteria were harvested and processed as described by Noyes *et al.*[12] Sterilization of the endotoxin was effected by filtration through membrane filters prior to animal injections. The nitrogen content of the endotoxin was 1.1 per cent by weight as determined by Nesslerization after digestion with selenium-sulfuric acid. The $LD_{50}$ was 170 micrograms when injected intraperitoneally into 16- to 18-Gm. albino mice of the Bagg strain.

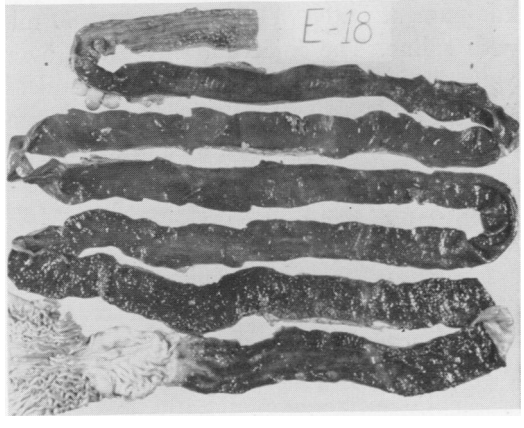


FIG. 2. Gastro-intestinal tract of dog dying three hours after injection of endotoxin. Note hemorrhagic necrosis of the mucosa, of the duodenum (below) jejunum, ileum and cecum (above).

The dogs were divided into two groups: Group A (25 dogs) received endotoxin alone. Group B (25 dogs) received herapin in addition to endotoxin. The experiments were carried out on paired animal preparations, one dog receiving the endotoxin alone, the other receiving 12 mg. of 1 : 1,000 herapin per kg., intravenously, ten minutes before the administration of endotoxin. The toss of a coin immediately before the experiment decided which dog was to receive herapin. The last eight heparinized dogs were given a lower dosage of herapin consisting of 6.0 mg./kg. before endotoxin and 3.0 mg./kg. one hour after endotoxin. Blood samples were taken before injection of any material, and at 20 and 60 minutes after the administration of endotoxin. In Group B, an additional blood sample was taken ten minutes after the administration of herapin just preceding the endotoxin injection. The following determinations were done on the blood samples: 1) pH; 2) $pCO_2$; 3) fibrinogen; 4) platelet count; 5) prothrombin time; 6) thromboelastogram; 7) clotting time; 8) prothrombin time; 9) antithrom-

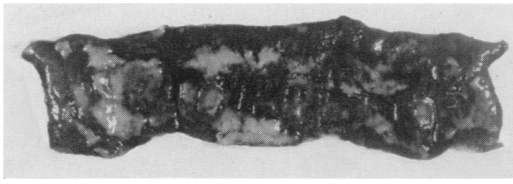

FIG. 3. Section of ileum of dog dying three hours after injection of endotoxin. Note white areas of dead superficial mucosa (pseudomembrane) which are peeling off leaving a raw hemorrhagic mucosa.

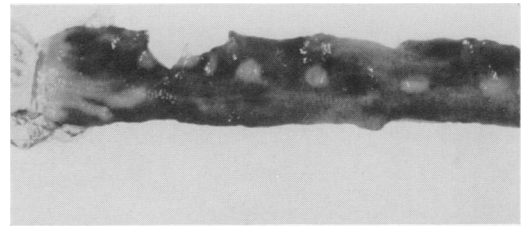

FIG. 4. Duodenum of dog dying three hours after injection of endotoxin. Note in addition to the hemorrhagic mucosa that there are four discrete ulcerations completely through the mucosa.

bin titration; 10) protamine titration; 11) thromboplastin generation; 12) labile factor; 13) lactic acid level; and 14) hematocrit. Most of these studies will be reported in another publication [3] and not be discussed in detail here. Autopsies and histologic studies were carried out on all cases of fatality.

## Results

**Group A (Endotoxin).** In these animals the aortic blood pressure, after an initial brief rise, always plummeted from a mean of about 150 mm. Hg to depths ranging from 25 to 60 mm. Hg 30 to 45 seconds after the intra-aortic injection of endotoxin. At the same time, the pulse pressure narrowed down from a control level of about 50 mm. Hg to ranges of 10–15 mm. The drop in the blood pressure lasted for several minutes and was then followed by a slow climb (Fig. 1). The narrowed pulse pressure likewise persisted for a similar interval and then began to slowly widen toward normal. Both pressures approached their control levels within 20 to 40 minutes in most animals. In a few animals recovery from the phase of hypotention was only slight. Concomitant with the precipitous fall of the arterial blood pressure, the inferior vena caval pressure dropped from preinjection levels of 4 to 5 cm. water to almost zero (Fig. 1). Respiration was also markedly affected, and frequently, there was an initial brief period of apnea. In four animals manual artificial respiration was applied for several minutes until spontaneous respiration was resumed. Hyperpnea ensued, persisting throughout the duration of the experiment (Fig. 16).

A secondary drop in the arterial pressure was observed to occur in most dogs starting about 40 to 50 minutes after the injection of the endotoxin. This was slow and gradual as compared to the dramatic earlier drop. Furthermore, it displayed no signs of reversibility and eventually culminated in the animals' demise. Many dogs remained deeply asleep and all 25 succumbed

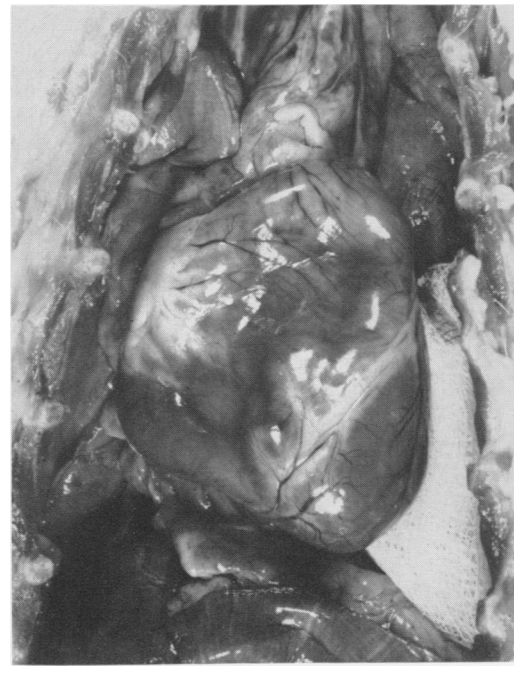

FIG. 5. Undisturbed heart of dog dying after injection of endotoxin. Note that the right heart (on the left) is completely collapsed and concave.

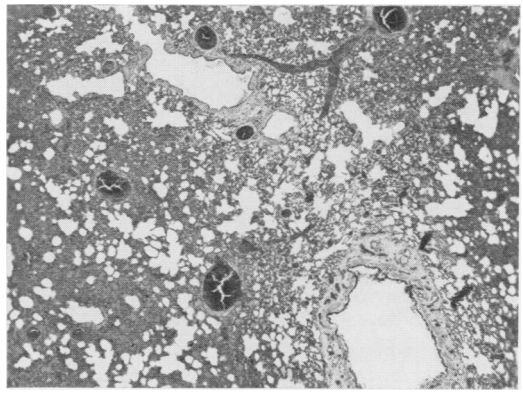

FIG. 6. Photomicrograph of lung of dog dying after injection of endotoxin. Note numerous thrombi in small pulmonary vessels and widespread hemorrhage and edema.

within two to 24 hours of the injection of endotoxin.

Autopsy consistently showed a marked hemorrhagic necrosis of the gastro-intestinal mucosa, usually most pronounced in the upper small bowel, but involving most or all of the alimentary tract (Fig. 2). Sloughing off of the superficial mucosal layers was frequently encountered in the terminal ileum leaving a hemorrhagic mucosa beneath (Fig. 3). In several animals numerous acute ulcerations were seen in various parts of the gastro-intestinal tract but mostly in the duodenal mucosa (Fig. 4). These appeared similar to the stress ulcers often seen in human autopsy material. There was moderate congestion of the liver, spleen and kidneys in all dogs, and in one animal hemorrhage in the pancreas was also noted. The lungs were heavy, moderately congested and contained numerous areas of hemorrhage: the right side of the heart was usually collapsed (Fig. 5), but otherwise normal. Histologic examinations disclosed numerous plugs consisting of fibrin and an amorphous collection of agglutinated red cells and platelets in the capillaries and small vessels of the lungs, liver gastro-intestinal mucosa, kidneys, pancreas and spleen (Fig. 6, 7). These were associated with focal necrosis in the liver (Fig. 8), infarction in the spleen (Fig. 9), and superficial necrosis, hemorrhage and ulceration in the gastro-intestinal mucosa (Fig. 10). Heart tissue appeared normal.

**Laboratory Data.** The blood coagulation mechanism was markedly altered. Blood clotted normally prior to the injection of endotoxin but frequently failed to clot for hours in the specimens taken 20 and 60 minutes after the injection (Fig. 11). Average silicone clotting time for pre-endotoxin blood was 10 minutes and 20 seconds. Average postinjection clotting time was several hours. There was a significant drop in the fibrinogen level (Fig. 12). This

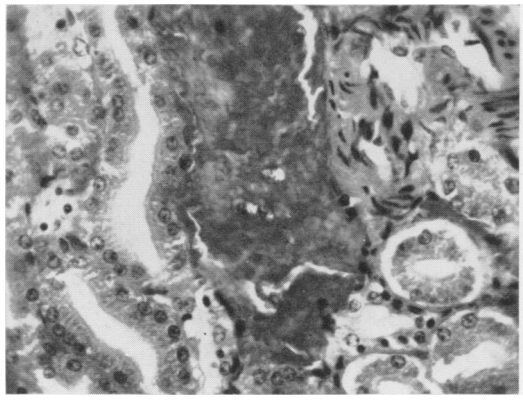

FIG. 7. High power photomicrograph of kidney of dog dying after injection of endotoxin. Note occlusion of small vessel by a plug or thrombus consisting of red cells agglutinated and firmly bound together.

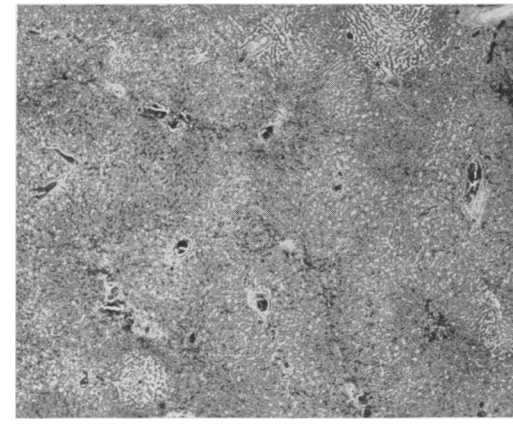

FIG. 8. Photomicrograph of liver of dog dying after injection of endotoxin. Note focal central necrosis around central veins occluded by thrombi.

finding did not account for the failure of the blood to clot in most cases. This abnormality was due apparently to endogenous heparin and low levels of other blood clotting elements. These were multiple and will be reported in detail elsewhere.[3] The decrease in levels of clotting elements is probably due to their being used up in a clotting episode.[3] In addition, there was activation of fibrinolysin in some cases (Fig. 13). There was a marked increase in lactic acid level of the blood after endotoxin and a swift production of a metabolic acidosis.[2]

**Group B (Heparin Plus Endotoxin).** In this group of 25 dogs, 12 survived and 13 died within 24 hours. Of the eight dogs given the reduced and divided heparin dosage six (75 per cent) survived. The initial blood pressure responses were variable. In one animal there was no significant drop (Fig. 14). In four the drop in the mean pressure was slight 10 to 30 mm. Hg (Fig. 15). In the remaining animals a marked fall occurred. This was similar to, but not as marked as, that observed in Group A dogs. The recovery started sooner and proceeded faster than in Group A (Fig. 16). The diastolic pressure returned to 75 per cent of the control levels in an average time of 4.9 minutes in these animals, as compared to a mean of 29.1 minutes in Group A dogs. Statistical analysis of these readings shows a "t" value of 3.25,

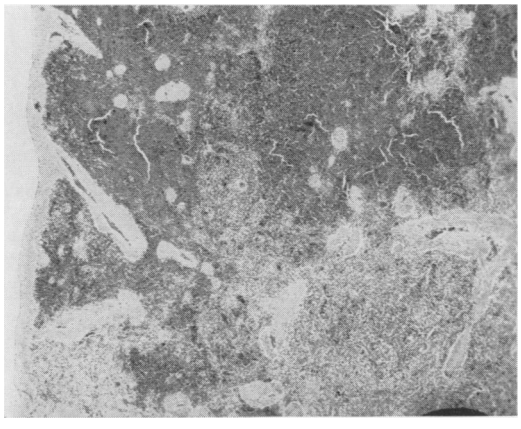

FIG. 9. Photomicrograph of spleen of dog dying after injection of endotoxin showing edge of infarct.

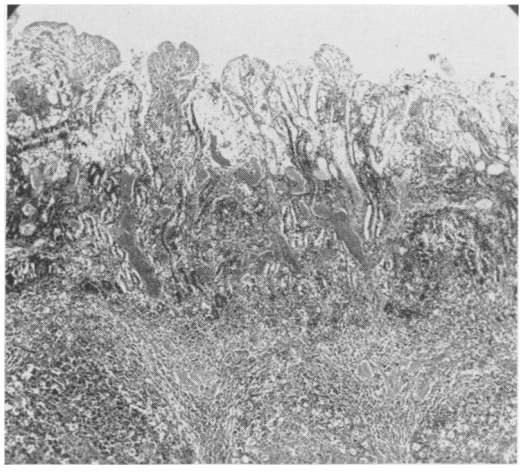

FIG. 10. Photomicrograph of intestine of dog dying after intra-aortic injection of endotoxin. Note necrosis of superficial mucosa, and numerous thrombi in the lower mucosa.

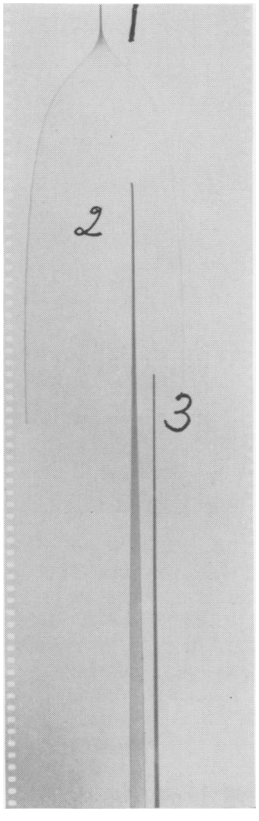


FIG. 11. Thromboelastogram of blood of dog taken (1) before injection of endotoxin, (2) 20 min. after endotoxin and (3) 60 min. after endotoxin. Note the normal configuration of the record in the first specimen with normal clotting time. Both the 2nd and 3rd specimens never clotted, as shown by the long narrow records.

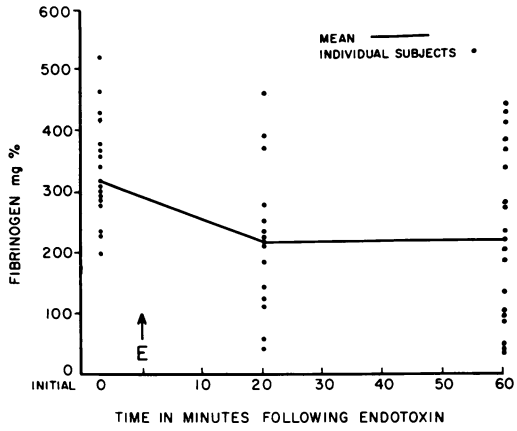


FIG. 12. Fibrinogen levels of Group A dogs given *E. coli* endotoxin at point of arrow marked "E." The individual determinations are recorded as dots and the average drawn in a heavy line. Note an average drop of 100 mg.% after endotoxin injection. Also note the many recorded readings below 100 mg.% after endotoxin.

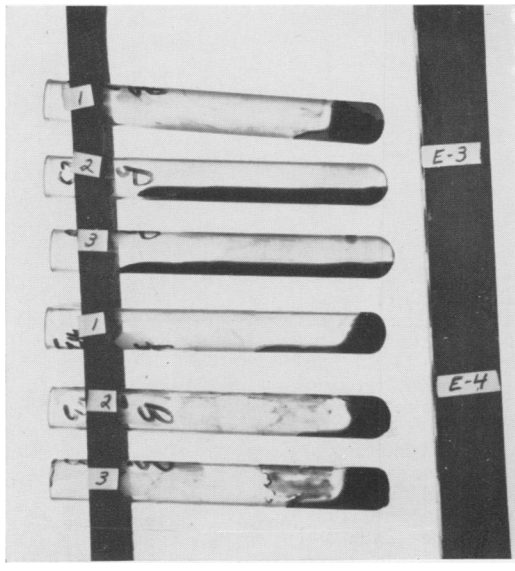


FIG. 13. Blood of two dogs (E-3 and E-4) given endotoxin. The upper three tubes are from one dog, Tube 1 being taken before endotoxin injection, Tube 2 20 minutes following injection and Tube 3, 60 minutes following injection. All tubes were allowed to clot although Tubes 2 and 3 took some time. After incubation at 37°C. for 24 hours, the tubes were turned on their sides. Note that contents of Tubes 2 and 3 are liquid, denoting lysis of the clot. Similar tubes for dog E-4, below, failed to demonstrate fibrinolysin.

significant at the 1.0 per cent level. The systolic and pulse pressure readings of both groups were also subjected to statistical analysis and the differences were found to be significant at the 1 per cent level. Mean readings in both groups are charted in Figures 17 and 18. Additional significance is provided by the fact that all the mean pressure readings of the heparinized dogs in the post endotoxin period were significantly higher than any of those in the non-heparinized group. The secondary fall starting after 40 or 50 minutes, which was prominent in Group A, was only slight in Group B (Fig. 17, 18) and intimated that these dogs had a better chance of survival. The respiratory disturbances (apnea followed by hyperpnea) were not nearly so prominent as in Group A (Fig. 16).

Autopsy findings were generally different from those of Group A. The lesions in the gastro-intestinal mucosa were usually extremely mild (Fig. 19) in comparison to those in Group A (Fig. 2). Petechial hemorrhages were encountered in the heart and other organs in 10 animals. This may have been related to possible overdosage of heparin. In the lungs, only a few very small petechiae were seen as opposed to the large areas of discoloration and hemorrhage in Group A. Microscopic sections showed none of the obstructing intravascular thrombi noted in the previous group of animals (Fig. 20), and there was no hemorrhagic necrosis evident in the liver.

Blood coagulation studies were rendered impossible since heparin was used. However, determination of fibrinogen showed that, while heparin itself caused a moderate drop in fibrinogen, there was no further drop in this element after the injection of endotoxin (Fig. 21). The fibrinogen drop associated with the administration of heparin is probably related to the precipitation of this protein by heparin as described by Godal.[1] Despite the fall caused by heparin in this group of animals, there was not post-endotoxin fibrinogen readings of less than

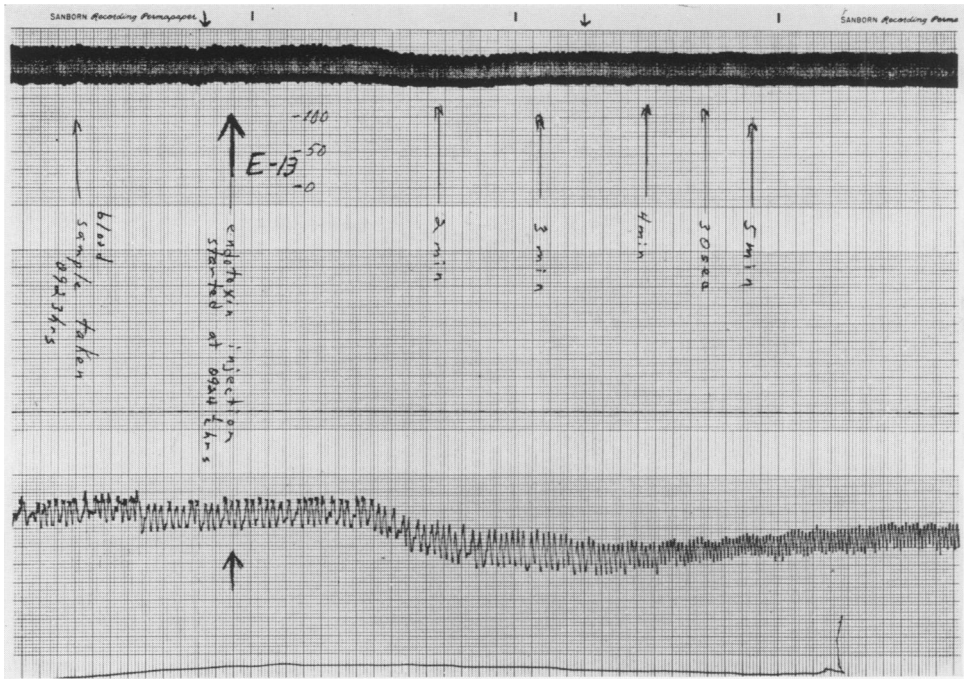


FIG. 14. Record of dog given endotoxin at arrow after previous intravenous injection of 12 mg./kg. of heparin. Note the very slight effect on blood pressure above and respiration below. This is only an occasional finding.

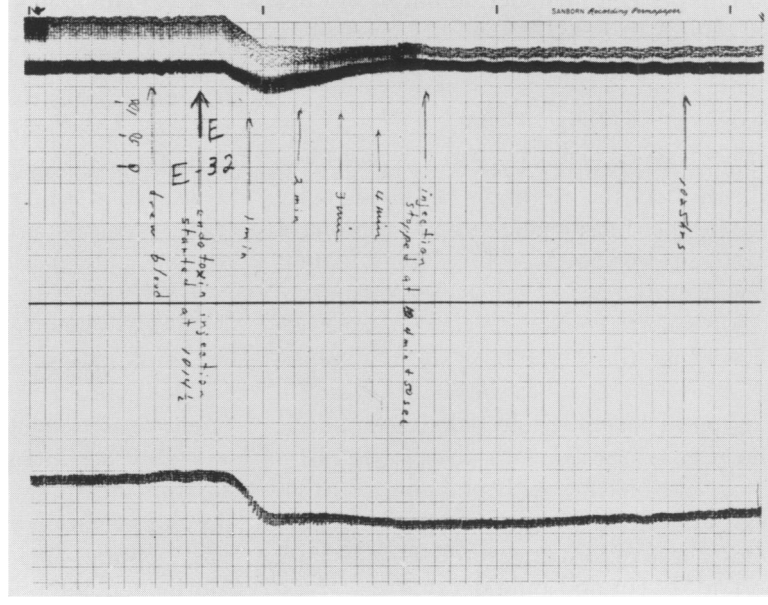


FIG. 15. Record of dog given endotoxin injection after previous heparinization. Note the slight transient fall in blood pressure above and mild effect on respiration below. This is only an occasional finding.

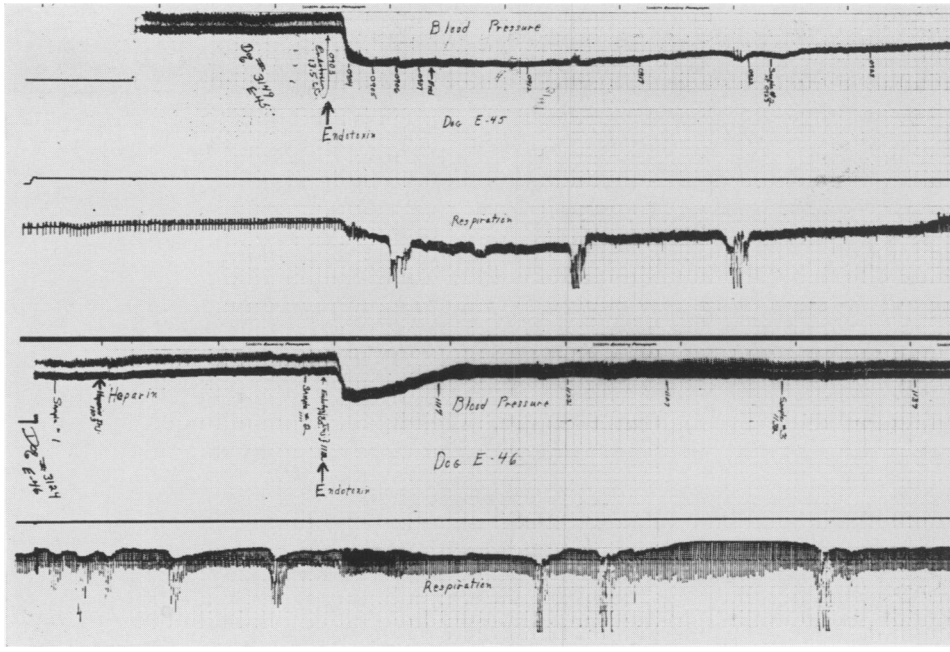


FIG. 16. Record on typical paired dogs, E-45 and E-46, below. Dog E-45 received no heparin. Dog E-46 received heparin at arrow at the left of 3rd channel. Both dogs received endotoxin at arrow marked "E." Note that the non-heparinized dog's pressure dropped precipitously and remained low during the entire record. The pulse pressure also remained low during the entire record. Note that the heparinized dog's pressure (3rd channel) while it dropped markedly after the endotoxin injection, recovered quickly and demonstrated essentially normal diastolic and pulse pressures within a few minutes. Statistical analysis of these differences show significance to the less than one per cent value. Note also that the respiration was markedly affected in the non-heparinized dog (2nd channel) with a severe hyperpnoea starting soon after the endotoxin injection. This occurred to a much less extent in the heparinized animal (4th channel).

100 mg. per cent, whereas about ⅓ of dogs in Group A dropped below that level (Fig. 12, 21).

## Discussion

The data provided by these experiments indicate that the respnose of the mongrel dog to the intra-aortic administration of endotoxin, appeared to be similar to that elicited by the use of other clotting agents. In a previous communication,[4] it was reported that the immediate drop in blood pressure incident to the intra-aortic administration of incompatible blood or amniotic fluid was associated with an episode of intravascular clotting with plugging of capillaries and small vessels in the lungs and liver. There was a measured rise in both the portal vein and pulmonary artery pressures.[4] This phenomenon was attributed to the obstruction of the flow of blood in the liver and lungs by the formed thrombi. Pulmonary obstruction decreases venous return to the left heart. The acute portal obstruction and generalized peripheral vasoconstriction cause a decrease in the inferior vena caval pressure, as was noted in the present experiments. This decreases the venous return to the right heart. The decreased venous return to both the left and right heart contributes to a diminished cardiac output. The circulatory embarrassment caused by these thrombi could conceivably be intensified by associated vasospasm; the spasm being possibly mediated by the liberation of smooth muscle stimulating peptides incident to the hydrolysis of fibrinogen into fibrin under the influence

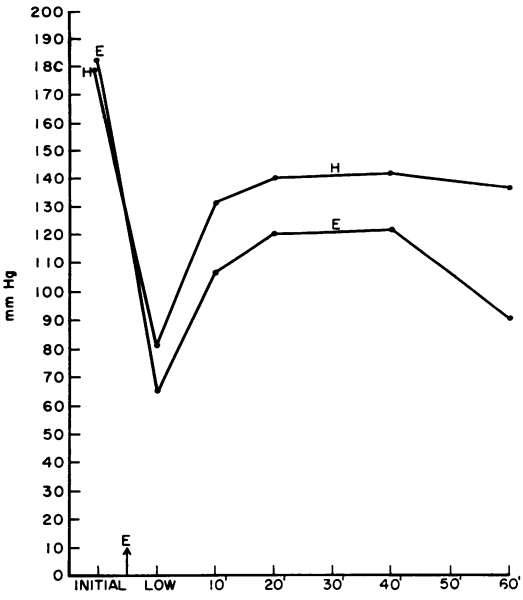


FIG. 17. Average systolic blood pressure of preheparinized dogs (H) and non-heparinized dogs (E) injected with endotoxin at arrow E. Note that the average initial fall was less in the heparinized dogs and recovery more rapid. Also note that there was a tendency for the pressure to show a secondary fall in the nonheparinized dogs whereas this was only slight in the heparinized dogs.

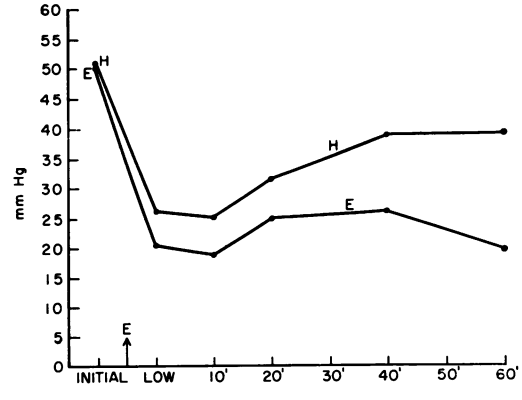


FIG. 18. Average pulse pressure of pre-heparinized dogs (H) compared with non-heparinized dogs (E) injected with endotoxin at arrow "E." Note that the heparinized dogs did not fall as low as the non-heparinized dogs and recovered more rapidly. Also note that there was a marked tendency for the pulse pressure to show a secondary fall in the non-heparinized dogs whereas this did not occur in the heparinized dogs.

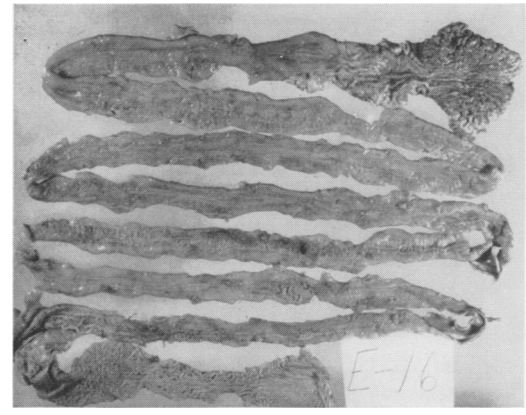

FIG. 19. Gastro-intestinal tract of pre-heparinized dogs dying after injection of endotoxin. Note relatively normal gastrointestinal mucosa as compared with non-heparinized dogs Figure 2.

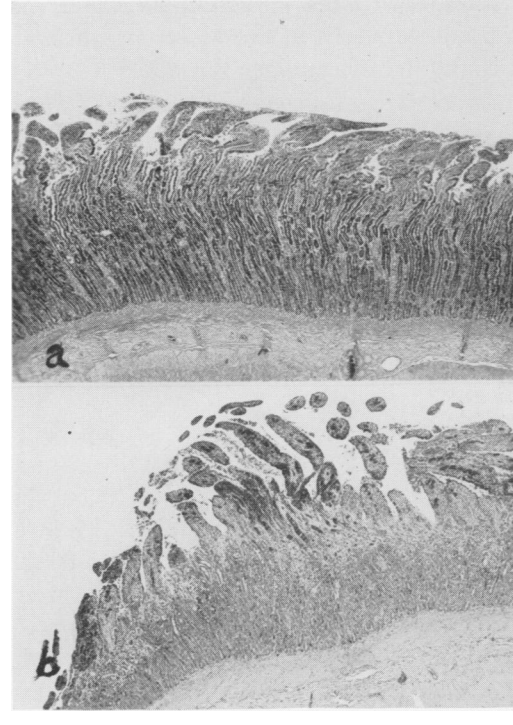


FIG. 20a. Gastric mucosa of pre-heparinized dog dying after injection of endotoxin. Contrast the lack of thrombi and hemorrhage with the dark areas in the lower picture. b. Gastric mucosa of non-heparinized dog showing areas of thrombi and hemorrhage in the villi.

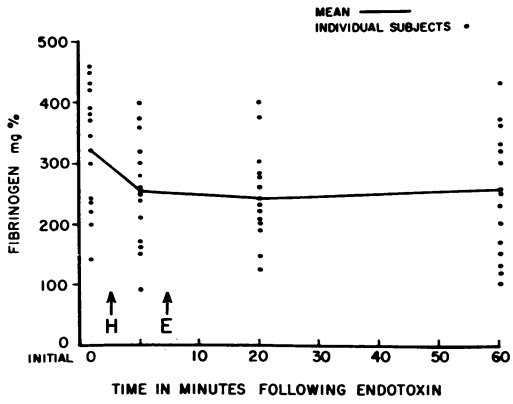


FIG. 21. Average fibrinogen levels in Group B dogs heparinized at arrow "H" and injected with endotoxin at arrow "E." Note drop in fibrinogen after heparin but lack of change in fibrinogen after endotoxin. Note lack of readings below 100 in this record as compared with the numerous low readings after endotoxin alone in Figure 12.

of the enzyme thrombin.[9] Recovery from this primary fall in blood pressure may be associated with the activation of fibrinolysin and antithrombin in the blood stream and washing out of capillary thrombi.[8]

As to the secondary and terminal fall in blood pressure, additional mechanisms resulting from the initiating factor of intravascular thrombosis are brought into play. The deleterious effect of the thrombi on the involved tissue is evidently determined in these animals not only by the extent and the duration of the thrombotic phase and associated vascular spasm but also by the capability of the tissue to withstand the greatly compromised oxygen supply. The gastro-intestinal mucosa, kidney, liver, and pancreas are relatively sensitive to anoxia and seem particularly susceptible to injury from an episode of intravascular clotting. Furthermore, the circulating blood after endotoxin injection is poorly oxygenated [8] and has a high lactic acid content,[2] which in itself may add insult to injury. The integrity of the gastro-intestinal mucosa appears to be a crucial factor in the survival of the dog for the first 24 hours. The severe damage sustained by this tissue was apparently responsible for the early demise of the animals that died. The superficial layers of the mucosa necrose and slough off leaving a raw surface which rapidly ooses blood and serum. This loss of blood and body fluids ultimately causes a fall in the blood pressure, which is usually terminal. In addition, the factors described in the initial fall in blood pressure may be still operating in part causing a decreased cardiac output. This secondary blood pressure fall appeared late in the experiment after the animal had already partially or completely recovered its control pressures. In some animals the two phases overlapped and the demise was therefore earlier. These changes were similar to those previously reported using injection of incompatible blood [5] or thrombin.[8] Lillehei [10] attributed these mucosal changes entirely to vasospasm. While there undoubtedly is a significant degree of spasm involved, it is believed this spasm is probably not the predominant underlying factor and could conceivably be secondary to the thrombosis as explained by Laki.[9] He isolated two peptides which were split off from the fibrinogen molecule by the enzyme thrombin. These peptides he found to stimulate smooth muscle.

The data strongly suggest that the use of heparin can greatly ameliorate the initial phase of immediate hypotension and enhance the recovery of the blood pressures (Fig. 17, 18). It is further demonstrated that this anticoagulant drug can avert the occurrence of the secondary and often terminal phase of hypotension, especially when the appropriate amount of heparin is used. This is evident by the over-all improved survival rate in the Group B dogs and particularly outstanding in the last eight animals of this group in which the proper dose of heparin was approached. The protective effect of heparin, as evaluated in these experiments, appears to be closely related to this drug's predominant known action, i.e. anticoagulation. This mode of action is strongly suggested by the fact that no intravascular thrombi were seen

in the heparinized dogs in contrast to the numerous thrombotic plugs noted in the vasculature of the non-heparinized dogs. These findings would further lend support to the contention that the pathologic physiology underlying endotoxin shock is predominantly initiated by intravascular thrombosis and its sequelae.

## Summary and Conclusion

Intra-aortic injection of *E. coli* endotoxin produces intravascular coagulation as evidenced by,

1. Decrease (due to using up) of blood clotting factors including, fibrinogen and other clotting elements.
2. Finding of thrombi in tissue sections.
3. Finding of focal necrosis and infarcts.
4. Prevention of these findings by preheparinization.

There is evidence that the immediate (reversible) fall in blood pressure after endotoxin injection is caused by a decreased cardiac output secondary to

1. Decreased venous return to the left heart because of acute cor pulmonale due to blockage of pulmonary capillaries by thrombi and associatated vasospasm.

2. There is decreased venous return to the right heart due to damming of blood in the portal system by thrombi in the liver, and associated vascular spasm contributing to a low inferior vena cava pressure, which is also partially due to increased peripheral resistance. This immediate blood pressure drop can be prevented in part by heparin. Recovery from it may be associated with appearance of fibrinolysin in the blood and lysis and washing out of the clots and plugs in the capillaries and small vessels.

There is evidence that the secondary (irreversible) fall in blood pressure and death is assisted by loss of blood and serum into the bowel lumen, caused by necrosis and sloughing of the superficial gastro-intestinal mucosa. This may be caused by ischemia and anoxia secondary to plugging of mucosal capillaries by clots and plugs. Factors described in the primary blood pressure fall may still be in partial operation. These probably include dominantly the decreased venous return to the right heart as evidenced by the finding of a collapsed right ventricle at autopsy. These changes may be largely prevented by preheparinization, but once they occur are irreversible due to mucosal tissue death. Acute ulcers frequently seen in the present experiments are apparently due to local infarction of mucosa and may be analagous to similar lesions frequently seen in human autopsy cases.

Focal necrosis of the pancreas, liver and other organs while prominent in the dog is not as prominent as the gastro-intestinal lesions. In humans this may be reversed. This may account for the dogs demise within 12–24 hours in irreversible shock whereas humans frequently die more slowly with focal necrosis of the liver and kidney.

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