tween seminal plasma and spermatozoa could not be obtained with immunological technics. Evidence which would make it seem likely that the dominant antigenic material is derived from the fluid constituents of the semen rather than from the spermatozoa is presented. Human spermagglutinating sera do not give complement fixation tests with seminal plasma or spermatozoa, but they produce a zone of precipitation with seminal plasma as antigen in the agar diffusion test.

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Received June 6, 1956. P.S.E.B.M., 1956, v92.

Hemodynamic Effects of Vasopressor Agent (Metaraminol)* on Hypotension in Dogs Produced by Endotoxin. (22559)

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The mechanism of hypotension which occurs during the course of overwhelming infections has been studied intensively both in patients and experimentally in animals(1-5). The very striking hemodynamic changes which are sometimes observed in patients with bacteremia due to Gram-negative organisms have been attributed to the action of endotoxins which are liberated on dissolution of bacteria(6) and experimental shock may be readily produced by the administration of endotoxins derived from various Gram-negative bacteria. We had previously observed that intravenous injections of endotoxins, such as those obtained from *Escherichia coli* or *Brucella melitensis*, uniformly cause a prompt decline in arterial blood pressure in the anesthetized dog(7). This marked fall of blood pressure was shown to be the result of a corresponding fall in cardiac output without decrease in peripheral resistance. When total venous return was measured, the decreased cardiac output was found to be due to a marked deficiency in venous return(5,8). These changes were further correlated with a sharp increase in liver and intestinal weights (9). Our observations led to the tentative conclusion that the initial cardiovascular disturbances caused by various Gram-negative endotoxins in the dog are the end result of massive venous pooling in visceral organs(8).

The value of vasopressor agents in the treatment of shock has been controversial. Rashkind and co-workers(10) reported that norepinephrine normally increases venous return in the dog. Von Euler(11) expressed the opinion that norepinephrine has important vasoconstrictor effects on both arterial and venous vasculature thereby favoring effective circulation in patients with shock. Clinical experience with a related sympathomimetic amine, metaraminol (Aramine), has shown that this new vasopressor substance was effective in the management of shock associated with bacteremia(12). In an attempt to gain further insight into the influence of vasopressor agents on the course of shock, the effect of metaraminol on venous return in dogs was

* Metaraminol was supplied as Aramine by Medical Division, Sharp and Dohme, Division of Merck & Co., West Point, Pa.

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TABLE I. Volume of Blood Pooled after Injection of Endotoxin into Dogs.

	No. of dogs	Time after inj. of endotoxin (min.)	Vol pooled, ml/kg Mean	Range
Controls	6	5	40.6	22- 61
		10	58	28- 82
		30	79.6	43-114
Animals receiving metaraminol	5	5	24.8	16- 31
		10	23.4	20- 31
		30	19.4	11- 31

studied after the administration of endotoxin.

Materials and methods. Observations were made following the intravenous injection of *E. coli* endotoxin of the Boivin type or a suspension of the dried bacterial cells which had been grown on synthetic media. The method for preparing the endotoxin has been described elsewhere(13). The dried bacterial cells, suspended in an equal volume of saline, were prepared according to a method described by Braude *et al.*(14). Previous experiments in intact animals had demonstrated that a profound fall in blood pressure and marked elevation of portal vein pressure regularly followed the intravenous injection of 5 mg/kg of purified endotoxin or 0.3 ml of bacterial suspension(5). This was the dosage used in the present experiments. Direct measurements of the venous return were made by a method more fully described elsewhere(5,8). Briefly, blood was diverted from the superior and inferior vena cavae to a cylindrical reservoir and pumped at a constant rate from the reservoir to the right atrium. The azygos vein had been ligated so that all blood returned to the heart was passed through the reservoir. The volume in the reservoir was continuously recorded. Because the amount of blood pumped from the reservoir to the right atrium was kept constant, changes in the reservoir volume were the result of quantitative changes in venous return. The system was initially filled with blood from a donor animal and measured quantities of blood were added when pooling in the animal caused depletion of the reservoir.

Adult mongrel dogs were used and all experiments were done under pentobarbital anesthesia in a dosage of 30 mg/kg. Arterial pressures were measured in the femoral artery. Pressures were recorded by means of Statham strain gauge manometers and a Sanborn polyviso recorder. Endotoxin was injected into the venous tubing leading to the right atrium. Purified *E. coli* endotoxin was used in 2 control and 3 treated dogs. The suspension of bacterial cells was employed for the remaining experiments. In this and earlier studies, the hemodynamic response to either preparation was found to be approximately the same.

Atropine sulfate in a dosage of approximately 0.5 mg/kg was given immediately after injection of endotoxin to 3 of 5 experimental animals. This agent alone had previously been shown to have no significant effect on venous return but it prevented arrhythmias of vagal origin produced by metaraminol which had invalidated several earlier experiments. Metaraminol in a dosage of 0.025 mg/kg was injected into the venous tubing after the sharp decline in venous return had clearly established itself. The initial dose was injected at approximately 3½ minutes (2-6 minutes) and supplementary doses were injected directly into the reservoir at 1½ to 8 minute intervals thereafter.

Results. The volume of blood pooled in the body of 6 control and 5 metaraminol-treated dogs is indicated in Table I. Results of these measurements are also illustrated in Fig. 1, where the heavy lines indicate the mean values and the shaded areas the spread of individual cases. It will be noted that following the injection of endotoxin, there was a rapid early loss of blood and a continued more gradual loss in the control series. The same pattern occurred initially in the test group. However, metaraminol promptly prevented further pooling and its effect is already apparent at 5 minutes. In the following 25 minutes small supplementary doses of metaraminol were added and the venous return was slightly increased indicating that some reversal of storage was occurring. The loss of blood due to pooling should be corrected for slight bleeding from the operative sites, but this correction would not minimize the differences shown.

Discussion. The initial circulatory dis-

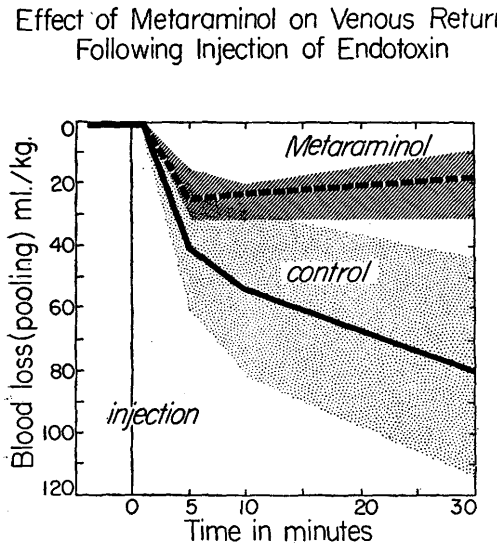

FIG. 1. Effect of metaraminol on venous return following inj. of endotoxin. Endotoxin was inj. at time zero. Metaraminol was inj. shortly thereafter when the sharp decline in venous return had begun.

turbance produced by endotoxin has been traced to the pooling of large quantities of blood in specific venous channels, particularly in the liver and intestine. The precise mechanism and location of this effect of endotoxin have not been investigated fully. It would appear that metaraminol has a selective effect on the venous vasculature which prevents and/or reverses pooling of blood in these vessels. Vasopressor agents may have a specific dilating action on hepatic veins and thereby counteract massive pooling in the splanchnic bed brought about by their constriction(15). The use of vasopressor agents in the treatment of various forms of shock has been criticized on the grounds that these substances increase vasoconstriction to an undesirable degree and potentiate shock by further stagnation of blood(16). To the contrary, this study in dogs has shown that a pressor drug augments rather than decreases venous return under the circumstances studied.

Conclusions and summary. The early shock produced in the dog by the injection of Gram-negative endotoxin is the result of venous pooling and greatly diminished venous return. Intravenous administration of metaraminol (Aramine) prevented further pooling. Venous return was effectively increased and the mechanism through which the shock was initiated was therefore counteracted.

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Received June 7, 1956. P.S.E.B.M., 1956, v92.