A Further Note on the Mechanism of Action of Endotoxin.* (31782)

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Death from endotoxin is the result of injury to vascular muscle, which leads to a progressive decline in venous return, and consequently to a fall in cardiac output that is incompatible with survival(1). In a previous communication evidence was given that the injury to vascular muscle by endotoxin is inflicted indirectly, *i.e.*, by virture of its neurotoxic action, and not because of any direct action upon this muscle(2). The experimental data in support of this view are: (a) the severity and lethality of peripheral vascular collapse produced by 2000 gamma of an endotoxin given intravenously is equalled by that following 100 gamma injected subdurally(3), and by that following one or two gamma of endotoxin placed in direct contact with the coeliac ganglion(4,5); (b) in an animal dead from endotoxic shock the tissues of a denervated area including vascular muscle are free of the injuries that are present in a corresponding area that is not denervated. Thus, prophylactic denervation of the splanchnic viscera by coeliac blockade prevents hemorrhagic necrosis of the intestinal mucosa except *in the distal half of the colon*(6).

Coeliac blockade also prevents death from a lethal dose of endotoxin. This is because the elimination of vasoconstriction in this area not only preserves the integrity of the liver and spleen, but allows better access for the clearance and detoxification of circulating endotoxin by the RE system in these tissues.

The foregoing evidence for the neurotoxic hypothesis notwithstanding, one can expect considerable hesitation in accepting it because of other potentially lethal effects on the vascular system that might be the result of direct action of the endotoxin (*e.g.*, myocardial necrosis, degeneration of intima, capillary rupture, changes in platelets, leukocytes, titer of circulating plasminogen and fibrinogen) and that might also be prevented by preserving liver function. We, therefore, thought it worthwhile to explore this possibility by using the heart-lung preparation in the dog, which is an appropriate experimental model because it is a denervated preparation in which endotoxin can be brought to act as directly as possible on the cardiovascular apparatus(7). Accordingly, 4 experiments were performed on 4 heart-lung preparations in dogs (weight range from 12 to 16.5 kg). Anesthesia was induced with an intraperitoneal injection of sodium pentobarbital (35 mg/kg). After isolation of the heart and lungs, the lungs were ventilated with a mixture of 95% oxygen and 5% carbon dioxide at a rate of 20 per minute with a tidal volume of 250 to 300 ml.

The arterial resistance was set to give a mean arterial pressure of 100 mm of mercury. Left atrial pressure was measured directly with a water manometer from a cannula inserted in the atrial appendage; right atrial pressure was recorded *via* a cannula at entrance of the inferior vena cava. Pulmonary arterial pressure was measured *via* a cannula in the main pulmonary artery leading to a strain gage transducer and Grass amplifier.

The cardiac output was measured with a Shipley-Wilson recording rotameter and was initially set at a level of 600 to 700 ml/minute. The heart rate was determined from electrocardiographic tracings. The total blood volume of the system averaged 1,020 ml. Blood temperature ranged from 37.9 to 38.4°C in all experiments, with a range no greater than $\pm$ 0.1°C in any one temperature.

After baseline hemodynamic data were obtained bacterial endotoxin (*Salmonella enteriditis* MLD 1 mg/kg, b.w.) was injected into the tubing leading into the right atrium. The doses used in these 4 experiments were 6, 10, 25, and 30 mg, respectively, *i.e.*, the equivalent of one or more lethal doses in each instance.

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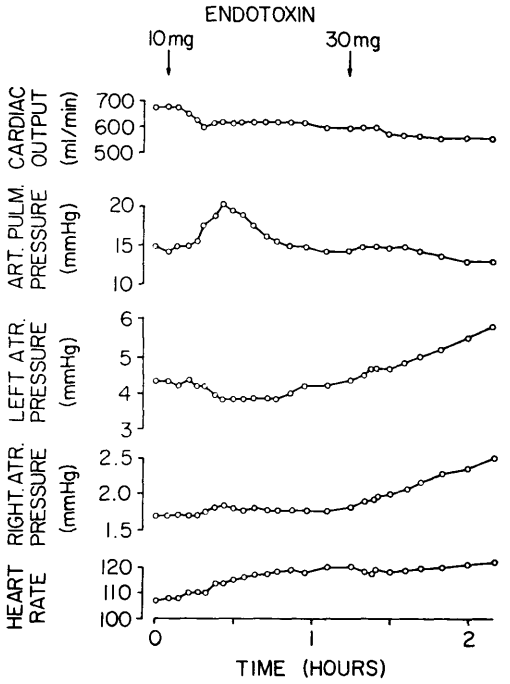

FIG. 1. Hemodynamic data on a heart-lung-preparation treated with intravenous endotoxin.

In the experiments with doses of 6 mg and 30 mg of endotoxin respectively, there were no changes in any of the hemodynamic parameters during a 2 hour period following the injection. In the experiment with 10 mg of endotoxin there was a slow rise in the mean pulmonary arterial pressure from 15 mmHg to a maximum of 21 mmHg over a period of 20 minutes, followed by a return to the pre-injection value after 30 minutes (Fig. 1). This was accompanied by a slight fall in systemic output and in left atrial pressure. An additional 30 mg of endotoxin injected some 60 minutes after the first dose did not produce any noteworthy effect. In the fourth experiment, in which 25 mg of endotoxin was injected, there was also a rise in mean pulmonary artery pressure from 12 mmHg to a maximum of 18 mmHg after 20 minutes, with a return to control values in 30 minutes. A fall in systemic output from 625 to 600 ml/minute without change in atrial pressures occurred. In none of the experiments was there a significant change in heart rate or rhythm.

Comment. If the endotoxin exerted a negative inotropic action, one would have expected myocardial depression. This did not occur, and there was no evidence of loss of vascular tone. The absence of any change whatever in 2 experiments, and of minimal transient effects in the other two experiments, confirms observations showing that bacterial endotoxins do not produce significant damage by direct action upon the heart or blood vessels.

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