contrast to the sarcomas produced after malignant transformation of hamster tissue *in vitro* by polyoma virus, the tumors were predominantly undifferentiated carcinomas with areas of adenocarcinoma, sarcoma and, in one animal, well-differentiated epidermoid carcinoma. SV40 was recovered from the infected cultures and from one of 2 tumors tested.

The authors are grateful to Mr. William J. Branigan, Miss Frances J. Paul and Miss Janeen Dougherty for technical assistance and to Mr. G. Gsell for photomicrographs.

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Received August 13, 1962. P.S.E.B.M., 1962, v111.

Endotoxin Shock in the Primate.* (27781)

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Endotoxin shock is important as an experimental model for septic shock. It is characterized in most species by hypotension(1) which is sufficient by itself to limit the chances for survival. Studies in the dog have shown this to result largely from hepatosplanchnic pooling with a consequent fall in venous return and cardiac output(2,3). But in monkeys, as well as in cats and rabbits, there is no evidence of such hepatosplanchnic pooling(4) so that hypotension in these species has not been entirely explained.

Since the effects of endotoxin in the monkey are more likely to resemble those in man, an explanation for the monkey's response is of particular interest. The present study concerns the effect of endotoxin and subsequent artificial alterations in venous return on cardiac output and total peripheral resistance in the monkey.

Methods. Eight rhesus monkeys (*Macaca mulatta*) weighing 3.4 to 5.7 kg were anesthetized with intravenous sodium pentobarbital, 30 mg/kg. Pressures were measured by Statham transducers and recorded by a direct writing oscillograph. Arterial pressure (BP) was taken from a femoral artery. Central venous pressure (CVP) was measured with a polyethylene catheter passed through the internal jugular vein to the superior vena cava. This catheter was also used for injection of indocyanine green to obtain dye dilution curves for calculation of cardiac output (CO). Dye was injected in 1-ml volumes, containing 1.25 mg of indicator, and the curves were recorded from blood aspirated through a 150 mm long, 0.86 mm I.D. polyethylene catheter inserted through the left common carotid artery to the aortic arch. Optical density changes of this blood were measured with a Colson densitometer(5) and recorded by the oscillograph. Dye dilution curves were replotted on semilogarithmic paper, and the cardiac output was calculated by the method of Hamilton *et al.*(6). Calibration of the densitometer system was done by drawing

* This work was supported by grants from the Chicago Heart Assn. and Am. Heart Assn.

through the densitometer a 5-ml control sample and three 5-ml samples of blood to which known amounts of dye had been added. These dilutions were made from a 20-ml blood sample obtained at the end of the experiment. Previous studies in the dog had shown that concentration deflection curves made from blood obtained before administration of endotoxin were essentially the same as those made from blood obtained preterminally. Loss of blood was kept to a minimum by calibrating with blood obtained at completion of the experiment, and by returning the blood for each dye dilution curve immediately after its inscription. Total peripheral resistance (TPR) was expressed as the ratio of mean arterial pressure in mm Hg to cardiac output in l/min/kg.

After a control period, lipopolysaccharide from *E. coli* (Difco) was given intra-arterially or intravenously. Pressures and CO were then followed until near death, or in 2 instances, for 2 and 6 hours. The effects of acute changes in venous return were studied by the withdrawal of arterial blood and by infusion of blood or 6% dextran. In 3 of the 8 experiments the thorax was opened with a sternum splitting incision and pressures were followed in the pulmonary artery and left atrium. The respirator used in these 3 experiments kept expiratory pressure at the atmospheric level.

Results. Lethality. In 2 unanesthetized monkeys, endotoxin caused emesis, diarrhea and prostration, but was not lethal at dose levels fatal to dogs (5-10 mg/kg). However, of the 8 anesthetized monkeys which underwent preparative surgery for pressure and CO determinations before being given endotoxin, only 1 had to be deliberately sacrificed. Average survival time was 167 minutes (range 111-370). A dose of 5 mg/kg of endotoxin was used except for 2 monkeys given 1 mg/kg and 10 mg/kg.

Blood pressure. Control BP's ranged from 73 to 123 (average 88) mm Hg, and differed by −11% (range −2 to −25%) from readings 30 minutes previously. After endotoxin the course of the BP was variable, but in all except an experiment where a first dose of only 1 mg/kg was given, the BP had fallen below control levels at 10 minutes (Fig. 1). The average level at this time was 58% of control, and the absolute BP varied from 24 to 85 mm Hg. In general, the pressure continued downwards, though in 4 instances there was a brief period of partial recovery after the early dip.

Cardiac output. The average control CO was 156 ml/min/kg (range 69-290). This differed by −5.8% (range −11 to +4%) from determinations made 6 to 37 minutes (average 20) previously. The CO (Fig. 2) did not fall as rapidly nor as far as did the arterial pressure. In all but 2 experiments the CO had fallen below control levels at 10 minutes (average 74, range 30-109 as percent of control). Variation in the subsequent downward trend is exaggerated in some curves by the effects of temporarily produced changes in blood volume (vid. Inf.).

Total peripheral resistance. Since BP fell more than CO, there was a distinct reduction in TPR after endotoxin (Fig. 3). Indeed, in 2 instances, the CO first rose slightly or stayed the same though the BP was falling. From 20 to 100 minutes after endotoxin, the TPR remained below control levels in every experiment. At 60 minutes it was 62% (range 44-87) of the control value. The TPR rose beyond control levels in 4 of the 7 experiments followed after 100 minutes.

Central venous pressure. The CVP (Fig. 4) rose slightly during the first 5 minutes after endotoxin in the closed chest experiments, probably as the result of changes in intrathoracic pressure related to the hyperpnea and bronchospasm produced by endotoxin. It did not rise in the open chest preparations. It subsequently fell slightly or remained at control levels except for an agonal rise in 2 instances.

Other parameters. Left atrial pressure remained below control levels for most of the period after endotoxin in 3 of 3 experiments. Pulmonary artery pressure rose during the first 10 minutes in 2 of the 3.

There were no consistent changes in heart rate. The mean circulation time and central blood volume were calculated by the method of Hamilton(7) for the 5 closed chest experiments. No striking trends were apparent. The central blood volume, however, had fallen

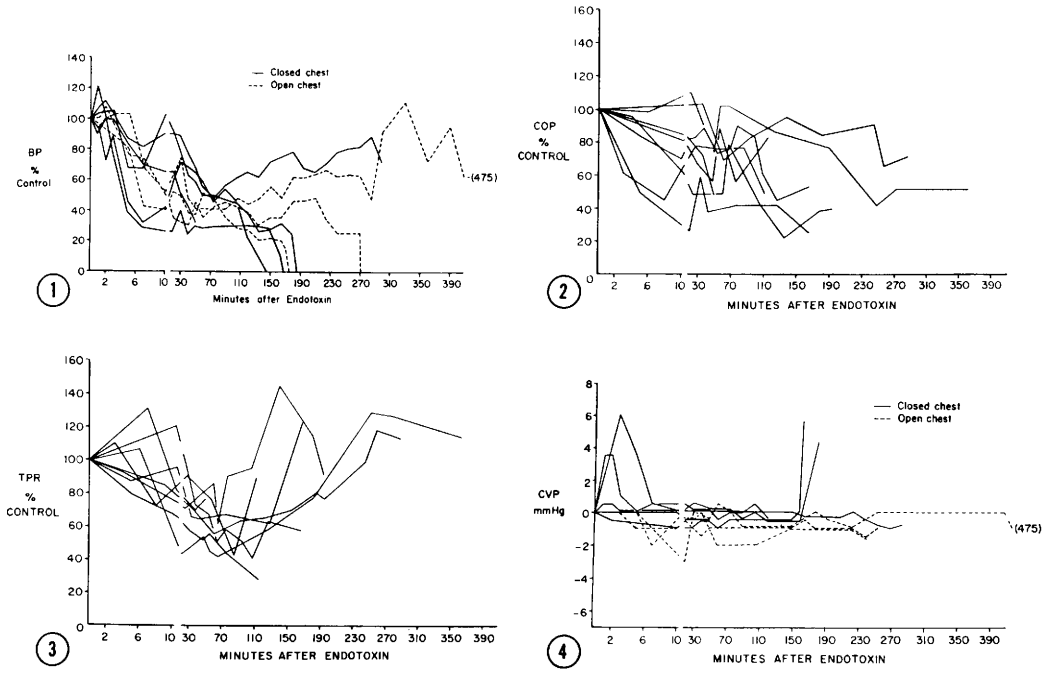

FIG. 1. Effect of endotoxin on mean arterial pressure expressed as % of control level. Note use of different time scale after 10 min.

FIG. 2. CO changes after endotoxin expressed as % of control level. Note different time scale after 10 min. Some acute CO increases followed infusion of dextran, 5 ml/kg.

FIG. 3. TPR changes after endotoxin expressed as % of control level. Note different time scale after 10 min.

FIG. 4. CVP changes after endotoxin. Note different time scale after 10 min. The terminal acute rises in 2 experiments were associated with apnea.

below control levels by the latter part of each experiment.

Altering venous return. Cardiac output fell or rose markedly in response to decreasing or increasing the blood volume. The BP was less affected than the CO. The distinct (though brief) CO rise following infusion (Table I) indicated that the heart was quite capable of responding to an increase in venous return. The withdrawal of 5 ml/kg of blood was followed by an output fall of 36, 28 and 42% in 3 separate experiments.

Discussion. It has been shown that the reaction to endotoxin is different in various species(4). This is also true of prolonged hemorrhagic hypotension which, for example, does not cause the monkey to develop the hemorrhagic gut lesions found in the dog(8). Endotoxin effects in the monkey conform more to what is known of the human responses than to those seen in the dog. As in man, the early BP fall is relatively slow and less pronounced. There was a distinct decrease in TPR, quite the reverse of what would ordinarily be expected to occur with a decrease in flow(9). In man, the TPR is reduced in the mild pyrogen reaction, and it is frequently, though not always, below normal in patients with bacteremic shock(10,11). In dogs, on the other hand, the CO falls precipitously *pari passu* with the BP(3), although there is evidence that the TPR falls in the latter stages(12).

Endotoxin effects hypotension in the monkey through a fall in both TPR and CO. The fall in cardiac output is probably due to a diminished venous return: 1) This has been shown to occur in the dog and cat(1,3,4,12). 2) The CO increase after dextran infusion points to diminished venous return and not to myocardial failure as the factor responsible for the decreased CO. 3) The CVP did not rise and, if anything, tended to fall.

It seems unlikely that a fall in venous return would be due to blood volume depletion,

TABLE I. Effects of Infusion of 6% Dextran, 5 ml/kg.

Exp. No.	Control BP	BP change, %	CO change, %	TPR change, %	CVP change, mm Hg
1	50	+28	+121	-40	+ .5
4	37	+11	+ 15	- 4	+1.0
5	29	+14	+ 36	-16	+ .5
6	40	+28	+ 66	-28	+ .5
7*	25	+64	+ 57	+ 5	+1.0
Avg	36	+29	+ 59	-17	+ .7

* Blood given instead of dextran.

since the output started to fall at once in 6 of 8 experiments and since diminished blood volume has not been found to be an important factor in the early stages of the endotoxin response of other species(1). In contrast to the hemoconcentration seen in dogs, Hinshaw *et al.*(13) found that endotoxin causes the hematocrit to fall in monkeys. Patients with shock due to infection have been shown to have a normal blood volume(14). Any fall in venous return must, therefore, be due to a redistribution or trapping of blood. The site and mechanism of this are not known. It does not occur in the hepatosplanchnic area (4).

The decrease in TPR is presumably mediated through vasoactive agents released by endotoxin or through a change in vasomotor activity. Histamine could be one such agent, since it is a known vasodilator, its plasma level rises after endotoxin in monkeys and dogs, and it is capable of trapping blood by producing arteriolar dilatation and venous constriction(15).

Summary. Cardiac output, arterial pressure, central venous pressure and total peripheral resistance were measured in 8 rhesus monkeys before and after intravenous injection of gram negative bacterial endotoxin. Arterial pressure fell more than cardiac output, so there was a decrease in total peripheral resistance. Thus, the fall in pressure was due to a reduction of both cardiac output and total peripheral resistance. Since increasing the venous return by infusion caused the cardiac output to rise, and since the central venous pressure remained the same or fell after endotoxin, the decrease in cardiac output is presumed to result from a decreased venous return.

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Received August 13, 1962. P.S.E.B.M., 1962, v111.