selves regardless of the final extent of tissue damage incurred or the physical impairment involved. For example, it has been reported (9) that 17-keto steroid excretion of rabbits given tuberculous meningitis rose slightly during the early stage of infection but remained at essentially normal levels at the height of the disease. If this is correct, then chronic illnesses such as emphysema, arthritis and possibly certain cancerous states might be unaccompanied by adrenocortical effects. On the other hand, some diseases of acute onset, such as certain infections (pneumonia, meningitis) or myocardial infarction may have concomitant adrenocortical activation and such activation could, indeed, contribute to their outcome. These possibilities are under examination.

1. Selye, H., Proc. Soc. Exp. Biol. and Med., 1959, v102, 403.
2. Guze, L. B., Goldner, B. H., Kalmanson, G. M., Yale J. Biol. Med., 1961, v33, 372.
3. Kalmanson, G. M., Hubert, E. G., Guze, L. B., Proc. Soc. Exp. Biol. and Med., 1963, v113, 918.
4. Breslau, A. M., Gonick, H. C., Sommers, S. C., Guze, L. B., Am. J. Pathol., 1964, v44, 679.
5. Gonick, H. C., Foos, R. Y., Rubini, M. E., Guze, L. B., J. Clin. Invest., 1963, v42, 937.
6. Guze, L. B., Kalmanson, G. M., Proc. Soc. Exp. Biol. and Med., 1961, v108, 496.
7. Geller, E., Yuwiler, A., Schapiro, S., Biochim. Biophys. Acta, 1964, v93, 311.
8. Duncan, D. B., Biometrics, 1957, v13, 164.
9. Buskina, V. A., Prob. Endocrin. Hormonal Therap., 1962, v4, 23.

Received February 8, 1966. P.S.E.B.M., 1966, v122.

Response of the Bear to Endotoxin.* (31164)

LURA A. SOLOMON, DALE A. REINS, DONALD D. HOLMES AND LERNER B. HINSHAW
Veterans Administration Hospital, University of Oklahoma Medical Center, and Civil Aeromedical Research Institute, Oklahoma City

This laboratory has been particularly interested in responses of different species of animals to endotoxin(1-5). Marked dissimilarities in vascular responses and tissue alteration have been observed between dogs, cats, rabbits, monkeys† and chickens(1-5). The response of the monkey to endotoxin is in marked contrast to that of the dog since hepatosplanchnic pooling in the monkey is not observed while shock in the dog is characterized by a sharp rise in portal pressure and extensive abdominal visceral pooling. Marked vascular changes were noted in the pulmonary bed of the monkey, cat, and rabbit(2). Gross differences found between animal species in response to endotoxin create difficulties in comparing data from a given species with the suspected responses in man(5). Information gained about responses in various species of animals to endotoxin would be of benefit in determining mechanisms operating in shock and in understanding the etiology of changes occurring in man. The present study was concerned with vascular and tissue responses of the bear to endotoxin.

Methods. Three adult American black bears (*Ursus americanus*) weighing between 96 and 173 kg fasted 24-48 hours were carefully restrained in a gorilla squeeze cage and administered sodium pentobarbital intraperitoneally followed by an intravenous injection. The total dose varied from 25-40 mg/kg body weight.

The animals were then placed in the supine position on a large operating table, and catheters were placed in the aorta (*via* the femoral artery), portal vein (*via* the splenic vein following a laparotomy) and right ventricle or pulmonary artery (*via* the jugular vein). Pressures at these 3 sites were continuously recorded by means of Statham pressure transducers on a Sanborn direct writing recorder. Heart rates were also monitored. An indwelling catheter was placed in the femoral vein for the injection of anesthetic, endotoxin and for procurement of blood samples required for pH and hematocrit determinations. *E. coli*

* Research supported by USPHS Grant HE-09381.
† Cercocebus torquatus atys; rhesus.

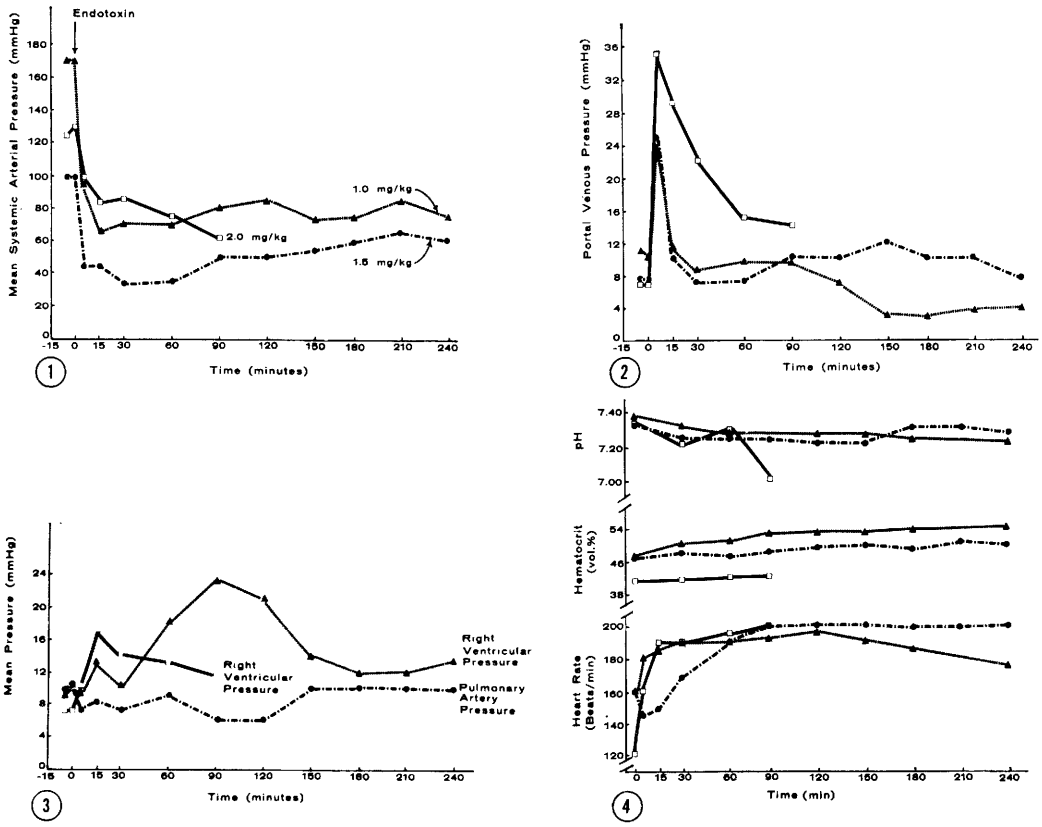

FIG. 1. Changes in mean systemic arterial pressures in bears following endotoxin.

FIG. 2. Alterations in portal venous pressures in bears given endotoxin. Endotoxin administered at zero time.

FIG. 3. Changes in pulmonary artery or right ventricular pressures in bears administered endotoxin. Endotoxin administered at zero time.

FIG. 4. Alterations in pH, hematocrits and heart rates in bears given endotoxin. Endotoxin administered at zero time.

endotoxin (Difco, Detroit, Mich.) was injected in doses varying between 1 to 2 mg/kg body weight. Animals were observed a minimum of 4 hours following endotoxin, unless death intervened, and were sacrified at the end of the 4-hour period. A post mortem examination was carried out at the time of death and tissue samples were prepared for histological evaluation.

Results. Fig. 1 presents changes in mean systemic arterial blood pressure following injection of endotoxin. Records from each of the 3 bears are shown separately. It is noted that by 5 minutes blood pressure had fallen significantly. In 2 bears pressures remained low (35-70 mm Hg) for 60 minutes, then gradually climbed, never reaching the control level. One bear died at 90 minutes post endotoxin, presumably from the effects of endotoxin. The latter bear had received the largest dose of endotoxin (2 mg/kg).

Fig. 2 depicts findings in portal venous pressure after endotoxin. Control values varied from 7 to 11 mm Hg. Pressures rose sharply in all bears with peak values at 5 minutes ranging between 23 and 35 mm Hg. Following the 5-minute peak pressures, portal venous pressures fell abruptly to approximately control levels by 30 minutes in 2 animals. The third animal, dying at 90 minutes, exhibited the greatest rise in portal venous pressure and failed to recover to the control level.

Attempts were made in each bear to obtain pulmonary artery pressure, but this was accomplished in only one animal. Fig. 3 illus-

trates changes in pulmonary artery or right ventricular pressures following endotoxin. Sharp rises in right ventricular pressure were observed in 2 bears, while pulmonary artery pressure fell in the third animal. Right ventricular pressure remained above control in the bear which died at 90 minutes.

Alterations in pH, hematocrit, and heart rate following endotoxin are shown in Fig. 4. A gradual drop in pH is seen in 2 animals while an abrupt fall is noted at 90 minutes in the bear which died at that time. Gradual and rather small increases in hematocrit were observed in 2 bears, the animal dying early showing no significant change in hematocrit. By 60 minutes all animals showed marked tachycardia which was sustained during the course of the experiments. There was no evidence of bradycardia in 2 bears while one animal experienced an early drop in heart rate.

Gross post mortem and histological examinations were carried out on each of the 3 bears. Pathological changes attributable to endotoxin were generally mild and primarily vascular in nature. The heart consistently showed subendocardial and myocardial hemorrhages. The liver exhibited central vein and sinusoid engorgement and scattered hemorrhages. There were also indications of early degenerative changes around many central veins in the liver. The gall bladder did not show any significant degree of edema; however, portal lymph nodes revealed slight edema. Moderate congestion was observed in the spleen and kidney. Hyperemia and occasional hemorrhages were seen in the adrenals, primarily in the outer cortex. Stomachs were normal. However, in the small intestines the mucosa showed mild hyperemia and a few scattered areas of necrosis. The submucosa also revealed slight hyperemia. Changes were more prominent in the duodenum than in the lower portions of the intestines. No changes of significance were seen in the lungs.

Discussion. Our results appear to place the bear in a position between the dog and the monkey with regard to tissue alterations due to endotoxin(2,7). The bear responds similarly to the dog with respect to portal hypertension and liver pooling(6,8) in contrast to the monkey which fails to show liver congestion(2,3). Changes in hematocrit were less than the dog and more than the monkey, thus placing the bear between these species (3,5,6,9). Heart rate changes differed from the dog in that early bradycardia was observed in only one bear in contrast to prominent bradycardia in the dog(9). Heart rate changes in the bear resembled those in the cat(2). The pH changes were similar to those seen in other species(3,7,9), acidosis being a consistent finding. Early increases were found in mean right ventricular pressure although the diastolic pressure remained fairly constant during the post-endotoxin period.

Findings from this study exemplify the complexity of species reactions to endotoxin and offer some support for the theory that common mechanisms operate in all species (10).

Summary. Anesthetized bears were administered intravenous injections of *E. coli* endotoxin. Systemic hypotension, portal hypertension, tachycardia and acidosis were regularly observed. Hepatic lesions similar to the dog were noted. These results, relatively unique to the bear, resembled selected findings previously reported from this laboratory in dogs, cats and monkeys. The observations stress the complexity of species reactions to endotoxin and suggest the operation of common mechanisms in the various species.

1. Hinshaw, L. B., Gilbert, R. P., Kuida, H., Visscher, M. B., Am. J. Physiol., 1958, v198, 631.

2. Kuida, H., Gilbert, R. P., Hinshaw, L. B., Brunson, J. G., Visscher, M. B., ibid., 1961, v201, v144.

3. Hinshaw, L. B., Jordan, M. M., Vick, J. A., J. Clin. Invest., 1961, v40, 1631.

4. Jordan, M. M., Hinshaw, L. B., Proc. Soc. Exp. Biol. and Med., 1964, v115, 455.

5. Hinshaw, L. B., Brake, C. M., J. Okla. State Med. Assn., 1964, v57, 421.

6. Jordan, M. M., Holmes, D. D., Hinshaw, L. B., J. Trauma, 1965, v5, 726.

7. Gilbert, R. P., Physiol. Rev., 1960, v40, 245.

8. Weil, M. H., MacLean, L. D., Visscher, M. B., Sping, W. W., J. Clin. Invest., 1956, v35, 1191.

9. Hinshaw, L. B., Brake, C. M., Emerson, T. E., Jr., Jordan, M. M., Masucci, F. D., Am. J. Physiol., 1964, v207, 925.

10. Visscher, M. B., Physiol. Phys., 1965, v3, 1.

Received February 9, 1966. P.S.E.B.M., 1966, v122.