Role of the Intestine in Endotoxin Shock.* (27151)

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Previous reports have dealt with the role of the intestine in irreversible endotoxin shock(1,2). Hemorrhagic necrosis of the bowel has been described and attributed to ischemia resulting from vasoconstriction and oligemia(3). Hemolysis, hemoconcentration and acidosis observed in this form of shock have also been accounted for by the action of endotoxin on the gut(4). Intestinal hypothermia, enterectomy and evisceration have been proposed as measures effective in reversing the course of shock(1,5,6). However, in contrast to previous observations(1,3,4), the present report suggests a beneficial role of the gastrointestinal tract in endotoxin shock.

Materials and methods. Adult mongrel dogs, anesthetized with 30 mg/kg sodium pentobarbital were used in all experiments. Femoral artery pressure was monitored with a Statham strain gauge and registered on a Sanborn recorder. Hematocrit, blood pH and plasma hemoglobin were determined periodically throughout the experiments. Following control readings dogs were given an intravenous dose of 2.0 mg/kg *E. coli* endotoxin (Difco). Animals in which identical experimental procedures were carried out, received no endotoxin and were sacrificed at approximately 8 hours after commencement of surgery, due to the non-sterile character of the experiments. At time of sacrifice mean systemic arterial blood pressures had not changed appreciably from control values in all these animals.

Fifty-six dogs were divided into 4 major groups each comprised of sham-treated and endotoxin-treated animals. *Group I.* Intact controls: Dogs given either a lethal dose of endotoxin or observed untreated. *Group II.* Enterectomy: The intestine was removed from the second portion of the duodenum to the distal rectum(1). One hour after this procedure was completed animals were injected with endotoxin or followed as sham experiments. *Group III.* Eviscerated, hepatic artery intact: The stomach, proximal duodenum, pancreas and spleen were removed as well as the intestine(7) but the arterial blood supply to the liver was carefully preserved. At one hour post surgery endotoxin was administered to all but the sham-treated animals. *Group IV.* Totally eviscerated: Procedures identical to those described in Group III were used with the exception that the hepatic artery was ligated.

Results. The effect of tissue removal on survival time in dogs given endotoxin is shown in Fig. 1. A statistically significant stepwise decrease in survival time is noted as an increased amount of tissue is surgically removed. Ranges in survival times were: intact dogs, 1-48 hr; enterectomized, 2.6-14 hr; eviscerated with hepatic artery intact, 1.3-8.3 hr; totally eviscerated, 1-3.2 hr. Sham-treated animals from all groups had no appreciable change in blood pressure 7 hours after the beginning of a one-hour control period, and were sacrificed at this time.

Table I is a summary of the overall results in 56 dogs. Mean values for changes in hematocrit, plasma hemoglobin and arterial blood pH are indicated. In intact dogs given endotoxin an increase in hematocrit, moderate hemolysis and a slight degree of acidosis are observed. Sham-treated dogs showed a minimum of hemoconcentration and hemolysis. Enterectomized dogs given endotoxin show approximately the same degree of hemoconcentration and hemolysis as intact animals, but a slightly greater degree of acidosis. Sham-treated animals of this group exhibited very small changes in these parameters. The largest degree of hemolysis and acidosis is seen in the eviscerated dog with the hepatic artery intact, although the rise in hematocrit is negligible. No significant change in plasma hemoglobin or blood pH was noted in the

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TABLE I. Effect of *E. coli* Endotoxin on the Intact Dog and on the Dog with Increasing Amounts of Visceral Tissue Removed.

	Intact dog		Enterectomy		Evisceration (hepatic artery intact)		Total evisceration	
	Exp.	Sham	Exp.	Sham	Exp.	Sham	Exp.	Sham
No. of animals	12	4	6	6	9	5	8	6
Mean change in hematocrit (units)	+8	0	+8	+3	+3	+3	+3	+9
Mean change in plasma hemoglobin (mg/100 cc) plasma	+22	+6	+36	+1	+75	-5	+24	+40
Mean change in blood pH	-.08	+.03	-.15	-.03	-.31	+.05	-.28	-.17

sham-treated animals of this group. Totally eviscerated dogs administered endotoxin showed minimal hemoconcentration but a significant degree of hemolysis and acidosis. Sham-treated animals of this last group exhibited similar changes, but in contrast to their experimental counterparts had no appreciable change in arterial blood pressure.

Discussion. When *E. coli* endotoxin is administered to the intact dog a precipitous fall in blood pressure occurs(8) which is obliterated by removal of all or some of the visceral tissue. The eviscerated animal does not, however, appear to greatly differ from the intact dog as concerns hematocrit, blood pH and plasma hemoglobin changes. Furthermore,

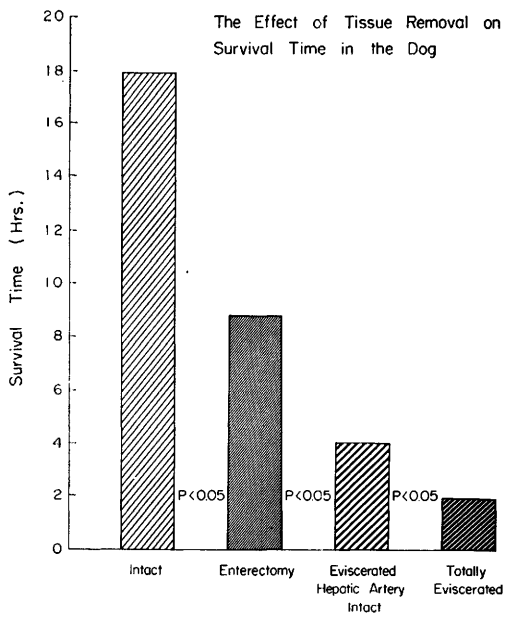

FIG. 1. Effect of visceral tissue removal on survival time in the dog administered endotoxin.

survival time is shortened and shock is potentiated by progressive excision of an increasing amount of visceral tissue. This observation is in opposition to the view that the bowel is of prime importance in development of irreversible endotoxin shock in the dog(1). If the latter view were true, one would expect that removal of the "shock" organ would not only result in a prolongation of life, but might actually prevent death due to endotoxin. Our results, however, indicate that the intestine provides a defense against the detrimental effects of endotoxin.

A possible explanation for the marked difference of our results with those of others is the fact that previous workers employed surgical procedures causing "profuse bleeding into the peritoneal cavity"(1) which necessitated fluid replacement with whole blood or dextran. This procedure has been found to increase survival time, thereby invalidating their results. In contrast, only a maximum of 25 cc of blood was recovered from the peritoneal cavity of any dog used in our experiments.

Data obtained in the monkey(9,10) support the view that the intestine is not the crucial organ responsible for development of irreversible shock, but that this phase of shock is due in large part to release of histamine. The detrimental effect of sympathomimetic agents released during endotoxin-induced hypotension has also been pointed out (1,2,11,12).

The absence of pathological changes of significant magnitude in the gut of the cat, rabbit and primate(9,10) is evidence that the intestine of the dog is unique in its response

to endotoxin. Findings of the present study support the view that the intestine of the dog does not play a major role in promoting development of the irreversible phase of endotoxin shock.

Summary. Previous reports have suggested that the gastrointestinal tract plays a major role in development of irreversible endotoxin shock in the dog. However, results presented here do not support this view but show a statistically significant stepwise decrease in survival time as an increasing amount of visceral tissue is removed from the dog. These data indicate that the gut of the dog is not the "shock organ" but rather serves a protective role in endotoxin shock. A possible mechanism for development of the irreversible phase of endotoxin shock in the cat, rabbit, dog and monkey is suggested.

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Tremorine Tremor in Chronic Spinal Rats. (27152)

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Everett and his co-workers, who discovered the characteristic properties of Tremorine (1,4-dipyrrolidino-2-butyne), reported that 5 to 20 mg/kg by any route of administration produced a marked, sustained tremor in all animals tested(1,2,3). The tremor was seen particularly in the head and limbs. They initially noted that acute spinal rats exhibited Tremorine tremors above the level of section, but none caudal to it. Nash and Emerson later reported that Tremorine (35 mg/kg, i.v.) given to 2-week chronic spinal cats would induce tremor and spasticity at all levels above and below the section(4). Kaelber and Hamel recently reported their inability to reproduce this "spinal" tremor in 2-week chronic spinal cats given Tremorine, 35 mg/kg, i.v.(5). They suggested that the phenomenon reported by Nash and Emerson may really have been the twitching of clonus associated with various mass reflexes commonly seen in chronic spinal animals.

The use of Tremorine as a tool for production of "spinal" tremor led us to plan a detailed study of the phenomenon, using more than 75 chronic spinal rats maintained up to one month post-operatively.

Methods. All operations were performed aseptically under ether anesthesia upon female Wistar albino rats weighing 200 g. Spinal cordectomy was accomplished by laminectomy and removal of a 2-3 mm segment of cord between the sixth and ninth thoracic vertebrae. Subsequent dorsal root sections in chronic spinal rats were performed either unilaterally or bilaterally by laminectomy and division of the dorsal root fibers central to the spinal ganglia of the fifth, sixth and

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