11. Box, H. K., *Oxygen Insufflation in Periodontal Diseases.* Charles Thomas, Springfield, Ill., 1955.

12. Brill, N., Krasse, B., *Acta Odont. Scand.*, 1958, v16, 223.

13. Nilsson, I. M., Sjoerdsma, A., Waldenström, J., *Lancet*, 1960, 1322.

14. Nilsson, I. M., Skanse, B., Gydell, K., *Acta Med. Scand.*, 1957, v159, 463.

15. Sjoerdsma, A., Nilsson, I. M., PROC. SOC. EXP. BIOL. AND MED., 1960, v103, 533.

16. Fosdick, L. S., Piez, K. A., *J. Dent. Res.*, 1953, v32, 87.

17. Krasse, B., Brill, N., *Odont. Revy*, 1960, v11, 152.

18. Schultz-Haudt, S. D., *Observations on the Acid Mucopolysaccharides of Human Gingiva.* Thesis. Oslo Univ. Press, Oslo, 1957.

19. Meyer, K., Hoffman, P., Linker, A., in *Connective Tissue, Thrombosis and Atherosclerosis.* Ed. by Irvine, H., N. Y. and London, 1958.

20. Brill, N., Björn, H., *Acta Odont. Scand.*, 1959, v17, 11.

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Supplementary Role of Hydralazine in Reversal of Endotoxin Shock with Metaraminol and Hydrocortisone. (26309)

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Endotoxin shock in the dog can be reversed with a combination of a pressor agent and hydrocortisone, but there still remains the problem of decreased renal function due to reduced renal blood flow(1,2). Because hydralazine has been shown to increase renal blood flow(3-6), the following experiments were designed to measure the additive effect of this agent with metaraminol and hydrocortisone in reversal of canine endotoxin shock.

Methods. Four groups of adult male mongrel dogs, anesthetized with Na Pentobarbital (30 mg/kg), were injected intravenously with a standardized lethal dose of *Escherichia coli* endotoxin, as previously described(1). Measurements of blood pressure and urine output were made continuously for 9 hours, along with hourly determinations of hematocrit and arterial blood pH. Hydralazine,* metaraminol,† and hydrocortisone‡ were administered alone or in combination at that time after endotoxin administration when the animal was manifesting shock with a blood pressure of less than 70 mm Hg systolic, and anuria or oliguria of less than 4 ml/hr.

Group 1 consisted of 12 control dogs given 0.55 mg/kg of endotoxin intravenously. Group 2 involved 6 dogs given the same dose of endotoxin but treated with varying doses of hydralazine according to the output of urine measured at 30 minute intervals. Group 3 included 10 dogs given the lethal dose of endotoxin and then treated with metaraminol and hydrocortisone. Groups of control animals were not treated with either metaraminol or hydrocortisone alone, since previous studies had shown that neither agent reversed endotoxin shock(1). The fourth group of 10 dogs injected with the lethal dose of endotoxin were given hydralazine, and a combination of hydrocortisone and metaraminol in amounts identical to Group 3. That is, one hundred mg of hydrocortisone was infused intravenously, followed by a 1% solution of metaraminol in amounts that maintained systolic blood pressure between 90 and 100 mm of Hg. Hydralazine was administered at varying periods of time after injection of endotoxin.

To clarify the time-dose relationship of hydralazine in the fourth group of animals, it is necessary to review briefly the hemodynamic effects of endotoxin in the dog. Immediately following injection of endotoxin a

* Supplied as hydralazine HCl by Research Dept., Ciba Pharmaceutical Products, Inc., Summit, N. J.

† Supplied as Aramine Bitartrate 10% by Research Division, Merck, Sharp and Dohme, Philadelphia, Pa.

‡ Supplied as Solu-Cortef by Upjohn Co., Kalamazoo, Mich.

precipitous drop in systolic blood pressure occurs, due in large part to the hepatosplanchnic pooling of blood(7). Either of 2 characteristic hemodynamic patterns follow this initial hypotensive period, and each were observed in the present study. The first type of response is recovery of the blood pressure to pre-endotoxin levels, and is associated with oliguria or anuria. When this pattern was present, hydralazine was injected in order to correct the flow of urine, before hydrocortisone and metaraminol were administered for sustaining the blood pressure. The second pattern of response differs from the first in that the initial hypotension is prolonged, and in such instances hydrocortisone and metaraminol were administered first in order to support the blood pressure, followed by administration of hydralazine.

Results. None of 12 control dogs given endotoxin survived beyond 24 hrs. The mean hourly measurements are incorporated in Fig. 1. The fulminating course of these animals was marked by hypotension, severe oliguria, hemoconcentration, acidosis, and output of an acid urine.

Although none of the 6 animals in Group 2 treated with hydralazine survived, 2 findings were in contrast to those in the control group. The characteristic acidosis did not appear, and output of urine was consistently greater, although the hypotension persisted. Data on this group are presented in Table I, showing blood pressure and output of urine in relation to administered dose of hydralazine.

Six of the 10 animals in Group 3 treated with the combination of hydrocortisone and metaraminol survived. On the other hand, 8 of 10 animals in Group 4 survived when given hydralazine in addition to hydrocortisone and metaraminol. Measurements in this group of animals are shown in Table II. Eight of the 10 animals were given hydralazine before hydrocortisone and metaraminol, that is, there was a tendency for the blood pressure to approach normal after the initial decline but oliguria was severe. Two deaths occurred in this group. Two animals received hydralazine after steroid-pressor

TABLE I. Systolic Blood Pressure and Urine Output in 6 Dogs Given a Lethal Dose of *E. coli* Endotoxin and Treated with Hydralazine. Determinations recorded for control period of 1 hr and then hourly post-endotoxin.

Time of observation	Dog No. and wt (kg) 1 12.4			2 11.6			3 10.4			4 8.7			5 13.7			6 13.2			Mean values		
	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.
Control	170	6.4		200	9.1		205	10.5		185	10.3		160	16.4		115	.6		172	8.9	0
15 min. post-endo.	55			65			50			60			70			45					0
1 hr *idem*	140	12.5		180	7.9		65	5.6		150	3.0	.9	70	.0	3.0	50	.1		109	4.9	2.0
2 " "	130	3.3	.6	80	.2	3.0	50	.0	3.0	125	7.2	6.0	70	2.0		45	.0	1.4	83	2.1	2.8
3 " "	80	.2	1.8	120	1.0	3.0	60	.0	3.0	130	14.7		75	.5	2.4	65	.0	2.8	88	2.7	2.4
4 " "	82	.1	2.0	150	.0	4.3	75	.0		135	16.5		130	8.2		115	.0	3.0	114	4.1	1.8
5 " "	95	.2	1.2	160	.0		65	.0	3.0	145	13.8		125	.6		143	10.0		122	4.1	2.1
7 " "	65	.4	4.2	125	.2	1.3	55	.0		135	12.0		115	.0		155	13.2		108	4.2	2.7
9 " "	90	.0		95	.0		85	.2	2.2	110	7.6		160	.0		150	11.7		117	2.0	2.2
Total hydralazine (mg)			9.8			11.6			11.2			6.9			5.4			7.2			8.7
Survival post-endotoxin		18.0 hr			18.0 hr			18.5 hr			23 hr			24 hr			18.5 hr				

BP = Systolic blood pressure; UO = Urinary output in ml; Hyd. = Hydralazine in mg.

therapy, and both survived. Mean average hourly determinations of this group receiving all 3 agents are compared (Fig. 1) with the untreated control animals, those receiving only hydralazine, and those animals receiving only hydrocortisone and metaraminol. The most significant feature in the hydralazine-hydrocortisone-metaraminol treated animals was the marked volume of urine recorded in comparison to the other groups.

TABLE II. Systolic Blood Pressure and Urine Output in 10 Dogs Given a Lethal Dose of *E. coli* Endotoxin and Treated with Metaraminol, Hydrocortisone, and Hydralazine. Determinations recorded for a control period of 1 hr and hourly after endotoxin.

Time of observation	Dog No. and wt (kg)																					
	1*			2			3*			4*			5*									
	11.0			9.0			10.0			11.3			11.3									
	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.							
Control	210	8.6		202	11.1		164	10.8		125	9.4		170	9.8								
15 min. post-endo.	55			70			40			35			65									
1 hr *idem*	95	2.2	.9	155	8.3	.6	95	19.4	.9	65	.0		55	15.9	.9							
2 " "	95	10.8		85	14.6		110	20.8	.9	85	1.2	.4	115	2.3								
3 " "	110	.8		100	8.5		135	32.4		130	10.0		105	.5								
4 " "	125	9.5		145	22.1		145	36.0		165	16.6		125	.2	.4							
5 " "	150	11.6		140	49.0		140	51.8		165	19.2		135	.0	1.2							
7 " "	125	13.7		130	19.9		120	66.2		125	20.4		140	13.8	1.6							
9 " "	130	10.1		140	40.2		120	38.5		125	22.6		135	8.4								
Total hydralazine (mg)			.9			.6			1.8			.4			4.5							
Survival post-endotoxin	Permanent			Permanent			Permanent			Permanent			Permanent									

Time of observation	Dog No. and wt (kg)															Mean values (dogs 1-10)		
	6*			7*			8*			9*			10*					
	12.0			9.6			10.0			10.0			15.0					
	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.	BP	UO	Hyd.
Control	200	8.2		225	11.6		180	10.2		142	10.5		145	10.6		176	10.1	0
15 min. post-endo.	45			60			50			50			45			52		0
1 hr *idem*	135	2.0	.9	140	12.8	.6	90	1.9	.9	75	4.1	.9	185	14.1	1.2	109	8.1	.78
2 " "	80	1.2	1.0	135	15.8		95	.1	.6	93	.3	1.8	160	26.2		105	9.3	.47
3 " "	105	2.3	.9	130	14.0		108	9.5	.9	115	.7		162	27.3		120	10.6	.18
4 " "	165	1.7		135	18.0		125	4.0	.5	135	7.8		145	19.4		141	13.5	.09
5 " "	185	21.9		155	10.4		145	11.3		130	12.0		140	15.0		148	19.0	.12
7 " "	180	40.0		150	12.5		165	9.8		125	13.0		135	13.0		137	21.0	.16
9 " "	150	40.3		160	9.3		165	10.1		130	18.6		140	12.8		139	23.0	0
Total hydralazine (mg)			2.8			.6			2.9			2.7			1.2			
Survival post-endotoxin	Permanent			Permanent			18 hr			16 hr			Permanent					

* Received hydralazine first. BP = Systolic blood pressure; UO = Urinary output in ml; Hyd. = Hydralazine in mg.

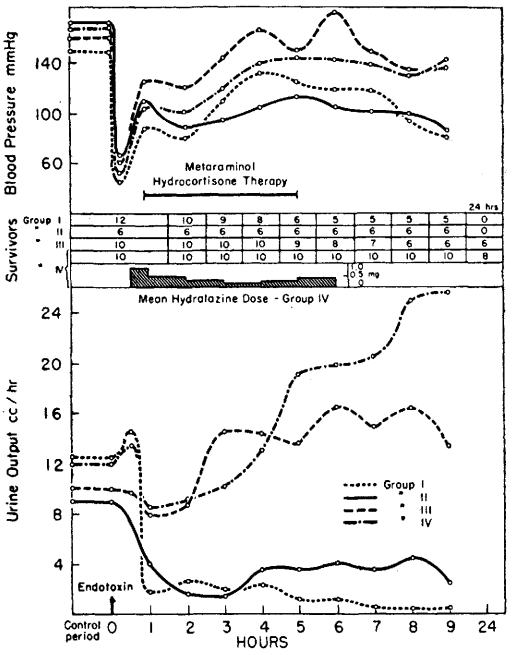

FIG. 1. Time-dose relationship of 4 groups of dogs given a lethal dose of endotoxin. Group 1 = untreated controls; group 2 = treated with hydralazine alone; group 3 = treated with hydrocortisone and metaraminol; group 4 = treated with hydrocortisone, metaraminol and hydralazine. Curves illustrate avg hourly blood pressure and output of urine. Animals surviving 24 hr after endotoxin are indicated for each group.

Discussion. In studies on the pathogenesis of canine endotoxin shock attempts have been made to reverse the peripheral vascular collapse with various agents. After onset of hypotension, and oliguria or anuria, the most consistently successful results obtained in this laboratory have followed administration of a combination of hydrocortisone and metaraminol. The present study has demonstrated that hydralazine will increase urine flow in dogs having severe hypotension. This is in contrast to the untreated control series of animals that had a higher blood pressure but a consistently lower output of urine. When the systemic pressure was supported with a pressor drug and steroid, hydralazine had a favorable effect on output of urine, even though the blood pressure was lower than in the pressor-steroid treated group. These results are of interest since hydralazine is usually employed as an anti-hypertensive drug.

Summary. Canine endotoxin shock is characterized in part by hypotension, oliguria, hemoconcentration and acidosis. The "shock" can be reversed in some animals with a combination of a pressor drug and hydrocortisone. The addition of hydralazine to this combination greatly augments the flow of urine, and possibly contributes to the survival of animals.

1. Spink, W. W., Vick, J., *Circulat. Res.,* 1961, v4, 184.

2. Hinshaw, L. B., Bradley, G. M., Carlson, C. H., *Am. J. Physiol.,* 1959, v196, 1127.

3. Reubi, F., *Helvet. Med. Acta,* 1949, v16, 297.

4. Freis, E. D., Rose, J. C., Higgins, T. F., Finnerty, F. A., Jr., Kelly, R. T., Portenope, E. A., *Circulation,* 1953, v8, 199.

5. Grob, D., McKusick, V. A., *Johns Hopkins Hosp. Bull.,* 1955, v96, 164.

6. Judson, W. E., Hollander, W., Wilkins, R., *Circulation,* 1956, v13, 664.

7. Weil, M. H., MacLean, L. D., Visscher, M. B., Spink, W. W., *J. Clin. Invest.,* 1956, v35, 1191.

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Presence of Two Glutamic-Oxalacetic Transaminases in Serum of Dogs Following Acute Injury of the Liver.* (26310)

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We have reported recently that human and animal tissues such as heart and liver contain 2 glutamic-oxalacetic transaminases

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