inhibition was found in each of the 2 trials at 10 mg and in the single trial at 20 mg. On the basis of these data, the antiandrogenic activity of tetra-n-butyllead is judged to be of the order of the reference standard progesterone.

Tetra-n-butyllead was studied for other possible hormonal activities with negative results. The compound, when administered by injection, was not estrogenic at doses up to 100 μg in the immature mouse using the uterus as the endpoint(5). At a total dose of 0.1 μg estrone elicits a highly significant uterine increase. Tetra-n-butyllead was also inactive as an antiestrogen at the 3 mg total dose level in the estrone stimulated immature mouse assay also employing the uterine endpoint(6).

Summary and conclusion. Tetra-n-butyllead exhibited antiandrogenic activity in the testosterone stimulated castrated mouse using the weight of the seminal vesicles as the endpoint. The compound is neither an estrogen nor an antiestrogen under the conditions of the experiments.

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Received May 6, 1964. P.S.E.B.M., 1964, v116.

Evaluation of Protection with Phenoxybenzamine Against Lethal Endotoxin Shock.* (29450)

F. D. MASUCCI AND L. B. HINSHAW
Environmental Physiology Branch, Civil Aeromedical Research Institute, Federal Aviation Agency, and Department of Physiology, University of Oklahoma Medical Center, Oklahoma City

The characteristic hypotension encountered in shock has been traditionally treated with vasopressors such as norepinephrine and metaraminol(1,2,3). Paradoxically, microscopic observations of blood vessels *in vivo* during shock have indicated excessive vasomotor activity with decided constriction of arteries and arterioles(4,5). These observations, together with other evidence of adrenergic involvement in shock(2,4,6), have led investigators to employ anti-adrenergic drugs to counteract shock irreversibility.

The most frequently employed anti-adrenergic agent has been phenoxybenzamine (Dibenzyline†). Most studies have reported lengthened survival time using phenoxybenzamine before induction of bacteremic shock (2,7,8), although pretreatment with 6 mg/kg phenoxybenzamine did not protect mice from lethal endotoxin shock(7). Phenoxybenzamine administered after induction of bacteremic shock has been demonstrated to be both beneficial(9,10) and detrimental(1,3). Phenoxybenzamine treatment has had such success in experimental animal shock therapy that it is presently being administered to patients (12,13). This situation emphasizes the need for a critical evaluation of the efficacy of phenoxybenzamine in shock therapy.

The present study was designed to evaluate the effect of pre- and post-treatment with phenoxybenzamine on survival of dogs given lethal injections of endotoxin.

Method. Adult mongrel dogs were maintained in air-conditioned kennels during these experiments. Dogs were divided into groups to test the survival value of pre- and post-treatment with phenoxybenzamine in bacteremic shock. Shock was induced in all groups by administration of 1 to 3 mg/kg *E. coli* endotoxin (Difco) dissolved in 10 cc saline. All injections were initiated through

* Research supported in part by U.S.P.H.S. grant.
† Appreciation is expressed to Smith, Kline and French for a generous supply of Dibenzyline.

the femoral veins and when a blood sample was drawn, pH was determined. The anesthetic, when used, was sodium pentobarbital (30 mg/kg) unless otherwise indicated. Dogs surviving over 7 days were considered permanent survivors. Experimental and control groups were organized as follows:

A. *Pretreatment studies.* Group 1 (10 dogs)—Control: Animals received no phenoxybenzamine before administration of 3 mg/kg endotoxin.

Group 2 (8 dogs) 24 hour pretreatment: Animals were pretreated with phenoxybenzamine (5 mg/kg body weight in 20 cc saline) 24 hours before administration of 3 mg/kg endotoxin.

Group 3-A (5 dogs)—1 hour pretreatment: Animals were pretreated with phenoxybenzamine (5 mg/kg body weight in 20 cc saline) and immediately infused with 30 cc/kg body weight Dextran (Cutter Laboratories) over a period of one hour. Endotoxin 3 mg/kg was then administered.

Group 3-B (5 dogs)—1 hour pretreatment: Animals were pretreated with phenoxybenzamine (5 mg/kg body weight in 20 cc saline) 1 hour before administration of 3 mg/kg endotoxin.

Group 3-C (8 dogs)—1 hour pretreatment: Animals were pretreated with phenoxybenzamine (5 mg/kg body weight in 100 cc saline) 1 hour before administration of 3 mg/kg endotoxin.

Group 3-D (6 dogs)—1 hour pretreatment: Animals were pretreated with phenoxybenzamine (0.5 mg/kg body weight in 100 cc saline) 1 hour before administration of 3 mg/kg endotoxin.

Group 3-E (10 dogs)—1 hour pretreatment: Animals were first injected with 2 mg/kg body weight of morphine sulphate. One hour later they were pretreated with phenoxybenzamine (0.5 mg/kg body weight in 100 cc saline). After another hour 3 mg/kg endotoxin was injected.

B. *Post-treatment studies.* Group A (5 dogs)—Control: Dogs were anesthetized and injected with 1 mg/kg endotoxin. Blood samples were drawn at time of injection and 5 hours post-endotoxin.

Group A-1 (5 dogs): Dogs were anesthetized and injected with 1 mg/kg endotoxin. Eighty minutes later phenoxybenzamine (1 mg/kg in 50 cc saline) was infused for 20 minutes. Plasma (50 to 75 cc/kg), freshly obtained from a blood donor dog, was infused from 110 to 160 minutes after endotoxin. Blood samples were drawn pre-endotoxin and 5 hours post-endotoxin.

Group A-2 (11 dogs): Dogs were anesthetized and injected with 1 mg/kg endotoxin. Ninety minutes later phenoxybenzamine (0.5 to 1 mg/kg in 250 cc Dextran) was slowly infused for 90 minutes.

Group B (7 dogs)—Control: Dogs were treated as in Group A, except for the use of 3 mg/kg endotoxin which was administered 1.5 to 2 hours after anesthetization.

Group B-1 (9 dogs): Dogs were treated as in A-1 with 3 mg/kg dose of endotoxin.

Group B-2 (5 dogs): Dogs were anesthetized and injected with 3 mg/kg endotoxin. Twenty minutes later phenoxybenzamine (1 mg/kg in 50 cc saline) was infused for 40 minutes. Plasma (50 to 75 cc/kg), freshly obtained from a blood donor dog, was also administered 20 minutes after endotoxin and continuously infused for 4 hours. Central venous pressure was monitored with a cannula placed approximately at level of the right atrium.

Results. A. *Pretreatment studies.* Table I shows the results of pretreatment with phenoxybenzamine on survival of dogs given a lethal dose of endotoxin. There was no marked increase in number of survivors or mean survival time, although different dosages, times of administration, and dilutions of phenoxybenzamine were employed. After endotoxin injection the 10 dogs not pretreated with phenoxybenzamine had a 10% survival and a mean survival time of less than one day. Of the 6 groups pretreated with phenoxybenzamine, Group 3-C showed the greatest number of survivors.

B. *Post-treatment studies.* Table II shows results of post-treatment with phenoxybenzamine on survival of dogs administered either 1 or 3 mg/kg endotoxin. There was no marked difference in number of survivors or mean survival time between control and experimental groups. The number of survivors

TABLE I. Effect of Pre-treatment with Phenoxybenzamine on Survival of Dogs Receiving 3 mg/kg of *E. coli* Endotoxin.

	Group*	Survivors/Total treated	Survival (%)	Mean survival time (days)
1.	Control: no pretreatment	1/10	10	<1
2.	24 hr pretreatment: 5 mg/kg phenoxybenzamine in 20 cc saline	0/8	0	<1½
3-A.	1 hr pretreatment: 5 mg/kg phenoxybenzamine in 20 cc saline	0/5	0	<1½
3-B.	5 mg/kg phenoxybenzamine in 20 cc saline, 30 cc/kg Dextran infused for 1 hr	0/5	0	<1
3-C.	5 mg/kg phenoxybenzamine in 100 cc saline	2/8	25	<1½
3-D.	.5 mg/kg phenoxybenzamine in 100 cc saline	1/6	17	<1¼
3-E.	.5 mg/kg phenoxybenzamine in 100 cc saline after 1 hr treatment with 2 mg/kg morphine	2/10	20	<¾
4.	Total pretreated	5/42	12	<1¼

* Mean group weights, all exp, 14-17 kg.

in control groups was slightly greater than that in treated groups; duration of survival was slightly longer in treated groups as compared to control groups.

A comparison of the 5-hour post endotoxin pH changes was made between dogs which survived and dogs which died. There was a significantly greater decrease in pH in dogs which died. The mean pH decrease of those dying was 0.29; those that lived 0.05.

Discussion. Previous investigations have demonstrated increased survival time in endotoxin shock with phenoxybenzamine treatment(2,7,9,10). The present study utilized dosages and times of administration similar to other investigations(2,9,10), and also included dosages not previously reported. None of the regimens indicated any survival benefits comparable to previous studies and suggests that phenoxybenzamine does not promote increased survival in endotoxin shock.

The efficacy of the therapeutic use of vasopressor drugs in shock has been questioned by investigators who believe that elevation of blood pressure is of little benefit if it is accomplished by vasoconstriction(3,11). These investigators feel that additional vasoconstriction imposed by vasopressor amines

TABLE II. Effect of Post-treatment with Phenoxybenzamine on Survival of Dogs Given a Lethal Dose of *E. coli* Endotoxin.

	Group	Survivors/Total	Survival (%)	Mean survival time (days)
A.	Control: No phenoxybenzamine, with 1 mg/kg endotoxin	3/9	33	<½
A-1.	Post-treatment: Phenoxybenzamine (1 mg/kg in 50 cc saline) 80 min after 1 mg/kg endotoxin; plasma (50-75 cc/kg for 50 min) 110 min after endotoxin	1/5	20	<1¼
A-2.	Post-treatment: Phenoxybenzamine (1 mg/kg in 250 cc Dextran for 90 min) 90 min after 1 mg/kg endotoxin	2/11	18	<1
B.	Control: No phenoxybenzamine, with 3 mg/kg endotoxin	1/7	14	<¾
B-1.	Post-treatment: Phenoxybenzamine (1 mg/kg in 50 cc saline) 80 min after 3 mg/kg endotoxin; plasma (50-75 cc/kg for 50 min) 110 min after endotoxin	0/9	0	<1
B-2.	Post-treatment: Phenoxybenzamine (1 mg/kg in 50 cc saline) 20 min after 3 mg/kg endotoxin; plasma (50-75 cc/kg for 4 hr) 20 min after endotoxin	0/5	0	<1

may critically reduce blood flow to important vascular beds. The use of phenoxybenzamine in treatment of shock is based on the assumption that blockade of the vascular constrictor response to adrenergic agents released in shock may contribute to survival(7,9,11). If phenoxybenzamine prevents vasoconstriction imposed by humoral vasopressors and consequently increases blood flow in shock, the present study indicates that this increased flow to critical vascular beds does not promote survival.

Summary. The survival value of both pre- and post-treatment with phenoxybenzamine was evaluated in dogs given lethal injections of *E. coli* endotoxin. Pretreatment with either 1 or 5 mg/kg phenoxybenzamine did not promote survival after injections of endotoxin. Post-treatment with phenoxybenzamine and plasma was also of no therapeutic value in promoting survival after lethal injections of endotoxin.

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Received May 6, 1964. P.S.E.B.M., 1964, v116.

Enhanced Antibody Formation in Experimental Acute and Chronic Liver Injury Produced by Carbon Tetrachloride or Allyl Alcohol.* (29451)

FIORENZO PARONETTO AND HANS POPPER

Department of Pathology, Mount Sinai Hospital, New York City

In human hepatic diseases the stimulation of mesenchyma has been demonstrated by morphological techniques(1). This stimulation also involves immunologically competent cells which are included in the reticuloendothelial system(2,3). Although serum elevation of gamma globulin is common, its antibody nature is still in question. After immunization of patients with liver disease, some observers(4,5) have found increased antibody production, but others(6) do not confirm this finding. Histological techniques have demonstrated stimulation of the immunocytic or protein-forming part of the reticuloendothelial system in animals with acute liver injury caused by administration of CCl_4(7), or in those with chronic hepatic damage after ethionine feeding(8), or after exposure to CCl_4(9).

Therefore, a study was attempted of the immune response in mice with acute and chronic hepatic injury, using serological and immunocytochemical techniques correlated with pathological investigations.

Materials and methods. A total of 265 male Swiss-Webster mice, weighing an average of 30 g each, were divided into several groups (Tables I and II). CCl_4 was injected subcutaneously in the amount of 0.03 ml†,

* Supported by grants from Nat. Inst. of Arthritis and Metab. Disease, U.S.P.H.S., and by U.S. Army Medical Research and Development Command.

† Unless so stated, CCl_4 was not suspended in olive oil.