TABLE II. Alazopeptin; Lederle Aa223.

No. of rats	Day of dose, i.p.	Mother's wt gain		Uteri total implants	Fetuses: Live	Fetuses: Stunted	Resorbed	Surviving placentas	Mothers with total resorbed litters	Litter wt	Fetus: Wt	Fetus: Length
14	7 & 8 .3 mg/kg	+8.3	a	126			129	85	14			
			b	9	0		9					
			c				100	67.5	100			
28	7 & 8 .5 mg/kg	+8.6	a	273	2	2	271	102	26			
			b	9.75			9.7			2.25	2.7	2.8
			c		.6	100*	99.4	37.4	93			
16	11 & 12 .5 mg/kg	+6.75	a	162			162	132	16			
			b	10.1	0		10.1	8.25				
			c				100	81.5	100			

a = Total b = Per mother c = % of total * % of live.

surviving fetuses of Group 2 were stunted and showed on clearing a retarded skeletal development, evidenced by absence of ossifying centers of supraoccipital and nasal bones, as well as metacarpal diaphysis 2, 3, 4 and 5.

Discussion. The present observation significantly demonstrates the sensitivity of the early embryo to A., a fact to be considered in chemotherapeutic efforts using this compound as antibiotic or antitumor agent in man. Furthermore, A. like O-Diazo-Acetyl-L-serine and 6-Diazo-5-oxo norleucine(2,3) permits the control of reproduction by either preventing proper implantation of the fertilized ova or destruction of the implanted embryos in the early phases of gestation without severely intoxicating the mothers.

Summary. Alazopeptin had the following toxicity in the adult Long-Evans rat: (1) Single LD_{50} of 150 mg/kg, the 5 LD_{50} of .3 mg/kg. (2) Alazopeptin destroyed *in utero* entire litters of Long-Evans rats (at time of implantation) when given i.p. on 7th and 8th day of gestation in doses of .3 mg/kg. (3) And in doses of .5 mg/kg i.p. (at mid term) when given on 11th and 12th day of gestation. (4) Placental remnants frequently survived the fetuses and were found at term. (5) The lethal dose of A. to the fetus of .5 mg/kg was approximately 1/30 of the LD_{50} for the mother animal.

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Received December 30, 1957. P.S.E.B.M., 1958, v97.

Cardiovascular Responses to Norepinephrine in Acute Adrenal Insufficiency.* (23912)

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Since Elliot's observations(1) on responses of adrenalectomized cats to various pressor agents, numerous investigators have concerned themselves with the problem of cardiovascular reactivity in adrenal insufficiency. A summary of the work on cardiovascular responses to sympathomimetic stimuli in adrenal insufficiency appears in the review by Ramey and Goldstein(2). An impairment in the vas-

* Aided in part by grant from Committee on Research of the Council on Pharmacy and Chemistry, Am. Medical Assn.

TABLE I. Increase of Force of Cardiac Contraction (g) following I.V. Norepinephrine (μg/kg).

Dose	Mean value ± S.D. Control	Adrenx	"p" value
.1	17 ± 15	12 ± 8	>.5
.5	49 ± 31	35 ± 18	>.3
1.0	68 ± 35	57 ± 24	>.4
2.0	75 ± 51	73 ± 28	>.9
3.0	79 ± 50	79 ± 26	>.9
4.0	79 ± 49	81 ± 24	>.9
5.0	80 ± 47	81 ± 24	>.9

cular responses to epinephrine and nor-epinephrine in adrenalectomized animals has been claimed by some investigators(3-5) but denied by others(6,7). Cardiac responses have not been thoroughly studied. The clinical observation of impaired pressor responses to nor-epinephrine in certain cases of traumatic or surgical shock with restoration of responses by adrenal steroid therapy has renewed interest in this problem(8).

Methods. Seven graded doses of norepinephrine were given to each of 5 adrenalectomized and 8 control dogs. The doses ranged from 0.1-5.0 μg/kg i.v. The responses measured were the increases in pulmonary and systemic arterial blood pressures and in force of cardiac contraction. The experimental animals were adrenalectomized *via* the lumbar approach one side at a time. The operations were 5-8 days apart. Measurements were made on these dogs 2 days after the second operation, at which time the animals were less active, anorexic, weak, and less responsive to external stimuli. They had been given some salt in their drinking water after the second stage adrenalectomy but no hormone replacement. Half of the control group were sham adrenalectomized 2 days before making the measurements. They were active, strong, had good appetites, and generally appeared completely normal. Their responses were identical to the other half of the control group which were unoperated and so the two groups have been considered together as the controls. All measurements were made during light pentobarbital anesthesia with the chest open and with respirations maintained by a Starling type pump. Pulmonary and systemic arterial pressures were measured by P-23D Statham pressure transducers connected, *via* short polyethylene cannulae, to a branch of the left pulmonary artery and a femoral artery, respectively. The force of left ventricular contraction was measured by means of an arch strain gauge sutured to the ventricle according to the method of Boniface, Brodie and Walton (9). All recordings were made with a multichannel oscillographic recorder† after suitable amplification. The pressure transducers and arch strain gauge were calibrated for each experiment; their responses were also checked and found to be linear.

Results. The initial systemic arterial pressures were significantly lower ("p" value of <0.01) in the adrenalectomized group of animals (71/35 mm Hg) compared to the control group (121/77 mm Hg). The initial pulmonary arterial pressures were also lower in the adrenalectomized group (9/<1 mm Hg) compared to the control group (15/5 mm Hg); the difference was of borderline significance, however ("p" value between 0.05 and 0.1).

There were no significant differences between the two groups in either their cardiac (Table I) or pressor (Tables II and III) responses to the graded doses of norepinephrine. The *responses* are recorded as the *increases* above the initial values.

TABLE II. Increase of Femoral Arterial Pressure (mm Hg) following I.V. Norepinephrine (μg/kg).

Dose	Mean value ± S.D. Control	Adrenx	"p" value Systolic	Diastolic
.1	26/20 ± 9/8	18/14 ± 4/5	>.1	>.2
.5	53/39 ± 17/15	46/38 ± 21/18	>.5	>.9
1.0	73/42 ± 18/19	72/57 ± 28/24	>.9	>.2
2.0	110/61 ± 32/17	99/69 ± 32/28	>.5	>.4
3.0	108/72 ± 39/23	105/80 ± 21/16	>.8	>.4
4.0	135/78 ± 41/19	124/80 ± 19/15	>.5	>.8
5.0	142/82 ± 41/20	139/86 ± 22/21	>.9	>.7

† Electronics for Medicine, White Plains, N. Y.

TABLE III. Increase of Pulmonary Arterial Pressure (mm Hg) following I.V. Norepinephrine (μg/kg).

Dose	Mean values Control	Adrenx
.1	1.5/ .5	2/ .4
.5	4.5/1.0	5/2.0
1.0	8 /1.0	10/3.0
2.0	14 /1.0	15/4.0
3.0	17.5/1.0	20/6.0
4.0	18 /1.0	21/5.0
5.0	18 /1.5	22/3.5

In addition, preliminary experiments were done in which dose-response curves were obtained in control and in adrenalectomized dogs before and 2 hours after infusion of hydrocortisone (5-10 mg/kg i.v.) Hydrocortisone did not modify the dose-response curve in either group of animals within this time interval. In 2 of the adrenalectomized animals, autopsies were done and the heart carefully examined both grossly and microscopically. There was no evidence of any coronary artery or myocardial abnormality such as that reported by Hall and Cleghorn(13).

Discussion. The failure to demonstrate impaired pressor responses to nor-epinephrine in the adrenalectomized dogs is in contrast to the findings of Ramey, Goldstein and Levine (10). These investigators found impaired pressor responses to nor-epinephrine (0.25-1.0 μg/kg i.v.) in adrenalectomized dogs maintained 5 to 10 days post operatively on desoxycorticosterone acetate; they found in addition that adrenal cortex extract restored the responses to nor-epinephrine. Impaired pressor responses to epinephrine in adrenalectomized animals was reported by Remington *et al.*(6) and by Cleghorn *et al.*(11). On the other hand, Salmoiraghi and McCubbin(12) found no impairment in the pressor responses to either nor-epinephrine or epinephrine in untreated adrenalectomized dogs, 1-4 days post-operatively. Brown and Remington(7) recently found no impairment in hind limb vascular responses to epinephrine or nor-epinephrine in adrenalectomized dogs as indicated by flow/pressure ratios in the femoral arterial bed. In spite of this, they did observe diminished systemic arterial pressor responses in the adrenalectomized dogs compared to controls bled to approximately the same initial blood pressure levels. These investigators postulated that the diminished pressor responses were the result of impaired cardiac responses. The results of our study fail to show any impairment in left ventricular contractile force responses to nor-epinephrine in adrenalectomized dogs.

We are unable to explain the inconsistencies referred to above. However, the following points can be made toward this end: 1) No 2 of the above experiments were carried out under the same experimental conditions. The duration, and undoubtedly the degree, of adrenal insufficiency varied widely. In some experiments animals were maintained on desoxycorticosterone and/or adrenal cortex extract; in other experiments the animals were untreated. Our own experimental conditions resemble most closely those attained by Salmoiraghi and McCubbin both as to duration (2 days *vs.* 1 and 4 days) of adrenal insufficiency and as to post-operative management (*ad lib.* diet; no replacement therapy); our results also coincide most closely with their results with regard to pressor responses. 2) The selected test dosages of epinephrine and nor-epinephrine vary widely; this point deserves special emphasis since Remington *et al.* (6) found reduced pressor responses to small, but not to large, doses of epinephrine. Few investigators attempted to obtain adequate dose-response curves. 3) In no study has there been adequate simultaneous evaluation of both cardiac and vascular responses.

With respect to the interpretation of our own results the following limitations deserve mention: 1) The pressor responses were measured as the increases in blood pressure above initial blood pressure levels. As pointed out under results, initial blood pressure in adrenalectomized animals was significantly lower than in the controls. The possible influence of variable initial pressure levels on the pressor responses is unknown; successful attempts to control this by making the control animals hypotensive would appear to depend on the way in which hypotension is produced, *i.e.*, it should be produced in a manner which is hemodynamically similar to the mechanism underlying the hypotension in adrenal insuf-

ficiency. 2) Cardiac contractile responses were also measured as increases in the force of left ventricular contraction above the initial level. Technical difficulties with the method precluded accurate comparison of initial contractile force, under conditions of identical fiber length and tension, between the control and experimental groups. 3) All measurements were made during anesthesia, with chest open, and during artificial respiration.

With the above limitations in mind, we conclude the following: 1) the adrenalectomized animals were in mild symptomatic adrenal insufficiency as indicated by general appearance and behavior, hypotension, and decreased tolerance to pentobarbital (the dose required for anesthesia being approximately one-half that required by controls). 2) Systemic and pulmonary hypotension is an early feature of experimental adrenal insufficiency. 3) There is no significant demonstrable impairment in pressor or cardiac contractile responses to norepinephrine in dogs with early (2 days) adrenal insufficiency which are not on replacement therapy. 4) The unimpaired cardiac contractile responses plus unimpaired pressor responses suggest, but do not prove, that the vascular responses to nor-epinephrine are also unimpaired. 5) The results afford no explanation for the hypotension present in adrenal insufficiency. Anatomical lesions in the heart do not necessarily accompany the hypotension.

Summary. Cardiovascular responses to norepinephrine have been studied in adrenalectomized and control dogs. The initial mean systolic and diastolic blood pressures of the adrenalectomized group in both femoral and pulmonary arteries were lower than those of the control group. There was no significant difference between the 2 groups in ability to respond to intravenously injected norepinephrine by an increase in force of cardiac contraction or by an increase in systemic or pulmonary blood pressure. Myocardial or coronary artery lesions did not occur in the 2 adrenalectomized animals examined.

The authors wish to acknowledge the helpful technical assistance of many members of the technical staff of the Departments of Physiology and Pharmacology.

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Received January 20, 1958. P.S.E.B.M., 1958, v97.

Retrograde and Forward Perfusion of Isolated Canine Lung Lobes.* (23913)

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The influence of mechanical factors on pulmonary vascular resistance has become established during recent years. Since the pulmonary vascular bed is an easily distensible system, it is not surprising that changes in transmural pressure exert a major influence on resistance to blood flow through this system. Because earlier studies have been made only on forward perfusion of intact or isolated lungs(1-5) it seemed of interest to investi-

* This work was supported in part by Research Grant H-1784 from the N.H.I., U.S.P.H.S. and Minnesota Heart Assn.