Fall 8-1983

The role of adrenomedullary hormones in survival of the adrenalectomized mongolian gerbil, Meriones unguiculatus

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THE ROLE OF ADRENOMEDULLARY HORMONES IN SURVIVAL OF THE ADRENALECTOMIZED MONGOLIAN GERBIL, *MERIONES UNGUICULATUS*

A THESIS

SUBMITTED TO THE GRADUATE FACULTY

OF THE UNIVERSITY OF RICHMOND

IN CANDIDACY

FOR THE DEGREE OF

MASTER OF SCIENCE IN BIOLOGY

AUGUST, 1983

BY

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B.S., UNIVERSITY OF RICHMOND, 1983

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ABSTRACT

The effects of adrenalectomy and catecholamine replacement therapy on survival were studied in *Meriones unguiculatus*, the Mongolian gerbil. Adrenalectomized gerbils that received epinephrine lived significantly longer than the controls untreated adrenalectomized gerbils) and animals that received either norepinephrine or a combination of epinephrine and norepinephrine. Results also indicated that these epinephrine-treated animals lost more depot fat than either controls or other groups receiving treatment. In spite of the short survival benefit given by epinephrine, the mechanisms governing the critical adrenal dependency in this species remain unknown.

ACKNOWLEDGEMENTS

I would like to express my gratitude to each of my committee members for their assistance and guidance throughout this research. I would like to thank Janet Nolin for her interest in this research and the unique contribution her extensive knowledge of endocrinology provided. I am grateful to the guidance and motivation offered by Dr. William S. Woolcott. I also wish to thank Dr. Joseph C. Mitchell, Dr. Jacob Van Bowen, and Mr. H. Gilpin Brown for their direction in the statistical analyses of the data. I am grateful to Dr. David W. Towle for the use of his laboratory equipment and for his endless patience and counsel. Thanks are extended to Safia Baggia, Anne Bennett Jefferson, Andrew Horne, and Robert Daniels for their assistance during the surgical phase of the research.

My deepest gratitude and respect goes to my advisor, mentor, and friend, Dr. Francis B. Leftwich. His untiring enthusiasm and patience vastly contributed to this unique learning experience.

Finally, for his encouragement, faith, and loyal support, I express a very special gratitude to my husband, Ben.

INTRODUCTION

Meriones unguiculatus, the Mongolian gerbil, is a small desert rodent inhabitant of the semi-arid regions of Mongolia and northern China. It resembles the more commonly known *Mesocricetes auratus*, the golden hamster, and both belong to the mammalian family Cricetidae (Lawlor, 1979). Since its introduction to the United States in 1949, the Mongolian gerbil has become the subject of research in the areas of osmoregulation and adrenal dependence.

Although Hagood (1982) subjected gerbils to high sodium, low sodium, and sodium-free diets for 60 days, no evidence of physiological stress was found, based on urine and plasma levels of sodium, potassium, and chloride. The gerbil, however, has a low tolerance for adrenalectomy, surviving only four to five days (Cullen and Scarborough, 1970). Comparatively, non-desert mammals, e.g., the white rat, typically survive up to 17 days following adrenalectomy (Cowie, 1949).

The lower survival time in gerbils without adrenals prompted an investigation of their adrenal glands, revealing an adrenal-to-body-weight ratio of three to four times that of the white rat (Cullen, et al., 1971). Under conditions of high sodium

intake (6% NaCl drinking solution), an increase in mitotic figures was noted in the zona fasiculata of the adrenal gland, which suggested increased production of glucocorticoids (Freeman and Leftwich, 1981). This was accompanied by substantial fat and muscle depletion. Additionally, it was noted that replacement therapy with mineralocorticoids (aldosterone, deoxycorticosterone) following adrenalectomy failed to produce significant long-term survival in gerbils (Cullen and Scarborough, 1970), whereas non-desert mammals under similar conditions live an apparently normal lifetime (Pincus and Thimann, 1950). Research involving cortisol, a glucocorticoid shown to be highly effective in prolonging life in adrenalectomized white rats, was undertaken with adrenalectomized gerbils. This agent also failed to produce long-term survival in adrenalectomized gerbils (Cullen and Scarborough, 1970; Kozub and Leftwich, 1982; Baggia, 1983; Jefferson, 1983). The ineffectiveness of cortisol was unexpected, as it had been previously demonstrated that white rats placed under adrenal stress showed an increased secretion of glucocorticoids, followed by an increase in mobilized free fatty acids from depot fat and subsequent conversion of muscle proteins to blood glucose (Exton, et al., 1972).

Adrenal dependency traditionally has been considered a function of the secretions of the adrenal cortex (glucocorticoids and mineralocorticoids), with the possible effects of the catecholamines epinephrine and norepinephrine (secretions of the adrenal medullae) largely ignored. As adrenal medullary hormones serve several functions, e.g., maintain basal blood pressure, provide the overall tone of the sympathetic nervous system, and interact with the glucocorticoids in carbohydrate metabolism, an investigation of the effects of epinephrine and norepinephrine on survival in the adrenalectomized Mongolian gerbil would possibly provide insight into the problem of adrenal dependency in gerbils.

MATERIALS AND METHODS

Thirty-five male *Meriones unguiculatus*, 13-18 weeks of age, were obtained from Tumblebrook Farms, West Brookfield, Mass. Gerbils were housed individually in standard 8"x8"x10" wire-mesh cages and given Purina laboratory chow (Ralston Purina Co., St. Louis, Mo.) and tap water *ad libitum*. Temperatures ranged from 21-24^{o}C throughout the experiment; photoperiods of 14-hour light/10-hour dark were maintained throughout the pre- and post-operative periods. All animals were acclimated to these conditions for five days after receipt from the supplier.

Gerbils were randomly divided into groups of seven. At the beginning of the experiment, all animals were bilaterally adrenalectomized in a one-stage operation. Treatment consisted of either epinephrine, norepinephrine, a combination of epinephrine and norepinephrine, or epinephrine and norepinephrine with alternate-day supplements of cortisol (Table 1). A sham group was not included in the present experiment, as sufficient data were generated in prior similar experiments (Cullen and Scarborough, 1970; Baggia, 1983; Jefferson, 1983).

On the day of surgery, sodium pentobarbital, 60 mg/kg, was injected intraperitoneally to induce

general anesthesia. A one-stage bilateral adrenalectomy, using a dorsal approach, was made for the excision of each adrenal. Following removal, the periadrenal area was examined for any remaining adrenal tissue. The incisions were closed with interrupted sutures of 3-0 silk. After completing the adrenalectomy, a small incision was made into the subcutaneous tissue of the dorsal neck permitting insertion of the osmotic minipump. This incision was closed in the manner described above.

The control group (untreated adrenalectomized gerbils) was divided into two sections to permit separate controls on each operative day. Animals that received epinephrine and norepinephrine, respectively, underwent surgery on the first day, as did four control animals. Gerbils that received the combination therapies underwent surgery on the fourth day, as did the remaining three control animals.

Epinephrine and norepinephrine were delivered by means of the Alzet^{TM} Osmotic Minipump, Model No. 2001 (Alza Corporation, Palo Alto, Ca.). This device permitted continuous infusion of the drug via implant into the dorsal subcutaneous tissue. Model No. 2001 is designed with a 200 µl reservoir volume and a nominal delivery rate of 1 µl/hr. Epinephrine and

norepinephrine were obtained as the bitartrate salt from Sigma Chemical Co., St. Louis, Mo. Both catecholamines were prepared in 0.9% NaCl and 0.1% ascorbic acid. This particular vehicle was selected to provide suitable stability for administration of these amines (Kleinjans, et al., 1981); however, a two day incubation (35°C water-bath, in an amber air-tight bottle) of the diluted catecholamines resulted in oxidation in each case. Catecholamines were re-prepared using a vehicle of 0.9% NaCl and 0.4% ascorbic acid (Kasamatsu, et al., 1979). As suggested by these authors, this increased content of ascorbic acid more effectively helped to suppress auto-oxidation of the epinephrine and norepinephrine.

Based on an average body weight of 60.0 g, epinephrine was prepared to yield a concentration of 0.25 µg/µl, while norepinephrine was similarly prepared to yield a concentration of 0.72 µg/µl. The infusion rate for epinephrine was 0.07 µg/kg/min, and norepinephrine was infused at 0.2 µg/kg/min. As previously mentioned, the nominal delivery rate of the osmotic minipump was 1 µl/hr. Dosages were selected in an attempt to approximate the normal resting rate of secretion by the mammalian adrenal medullae (Guyton, 1961). No specific dosages for gerbils or other desert mammals were available.

Control animals received the vehicle only, at the rate of 1 µl/hr. The group that received a combination of epinephrine, norepinephrine, and cortisol (Table 1) received only the epinephrine and norepinephrine via the osmotic minipump. The cortisol was administered subcutaneously, 1 mg every other day during the post-operative period, beginning on the operative day. Cullen and Scarborough (1970) found this dosage of cortisol to be the most effective in promoting survival in adrenalectomized gerbils. As the cortisol was prepared in propylene glycol, this vehicle was simultaneously administered subcutaneously to all other groups on corresponding days as a control.

Weights were obtained on all animals on the day of surgery, and readings were continued daily throughout the experiment. Readings were taken at the onset of the light phase of the photoperiod each day. All weights recorded were corrected for the implanted filled-pump weight.

Repeated attempts were made to obtain systolic blood pressure readings using caudal sphygmography. A Programmed Electro-Sphygmomanometer, Model No. PE-300 (Narco Scientific, Houston, Tx.) adapted with a small-laboratory-animal occluding cuff, was used. This instrument is commonly used for measurement of indirect systolic and diastolic blood pressures in

small laboratory animals. However, this unit failed to give readings on the gerbils, possibly due to a stress-induced reduction of blood flow through the tail. Details of the procedure are contained in the Appendix.

Upon the death of each animal, a necropsy was performed. The peri-adrenal area was re-examined for the presence of any adrenal tissue left during surgery. One gerbil in the epinephrine/norepinephrine/cortisol group was found to have a small amount of adrenal tissue; a continued survival beyond the experimental post-operative period atypical of the other group members had suggested the presence of some adrenal tissue. It is well documented that a complete cortex can be regenerated from these few remaining cells (Turner and Bagnara, 1976). It was, therefore, necessary to delete this gerbil from the experiment. During necropsy, all osmotic minipumps were removed, and the contents of each was examined for discoloration which would indicate denaturation. No discoloration was observed.

In order to determine if the addition of the catecholamines would enhance the animals' ability to mobilize depot fat for energy, a study was made to examine the amount of depot fat at necropsy. All mesenteric fat visible below the diaphragm was

removed and immediately frozen to help prevent lipid degradation (Johnson, 1971). Total lipid content was determined by a separation procedure using chloroform and methanol (Johnson, 1971).

The experimental variables analyzed statistically included survival and percent-change in body weight. As several of the gerbils died following the third day, percent-changes in body weights were uniformly calculated for the third-day weight, as a percent of the initial weight. Terminal body weights were not used because of the daily weight loss in animals that survived beyond the third day. Differences in depot fat, as a percent of initial body weight, were noted but not statistically analyzed due to differences in survival. A one-way analysis of variance was performed to determine the presence of any significant differences between groups. If significant differences were present, a Duncan's Multiple Range test was performed at $p = 0.05$ to determine which groups differed significantly.

RESULTS

Of the animals receiving replacement therapy, only the epinephrine-treated group ($\bar{x}$ = 6.0 days) survived significantly longer than the control group (untreated adrenalectomized gerbils) ($\bar{x}$ = 4.6 days). Both the epinephrine-treated group and the animals that received norepinephrine ($\bar{x}$ = 5.6 days) survived significantly longer than either the epinephrine/norepinephrine-treated group ($\bar{x}$ = 3.6 days) or the combination group supplemented with cortisol ($\bar{x}$ = 4.0 days) (Fig. 1). No gerbils lived beyond six days.

All animals lost weight daily from the time of surgery until death. It should be noted that none of the animals were observed to eat or drink following the first post-operative day. All groups lost weight at approximately the same rate through the first post-operative day (Fig. 2). It is interesting to observe that both combination groups appeared to curb their rate of weight loss beginning on day 2. This contrasts with the almost continuous rate-of-weight-loss demonstrated by the controls and the groups receiving epinephrine and norepinephrine, respectively. The unsupplemented combination group, which had the shortest survival, also demonstrated the least percent change in body weight.

As measured by percent of initial weight lost (WL), gerbils receiving epinephrine ($\bar{x}$ = 14.4% WL) or norepinephrine ($\bar{x}$ = 15.2% WL) lost weight at about the same rate as the controls ($\bar{x}$ = 14.5% WL) throughout their respective survival times. Animals that received combination therapies lost weight at about the same rate, with the cortisol-supplemented group sustaining more weight loss ($\bar{x}$ = 10.5%) than the non-supplemented group ($\bar{x}$ = 7.7%). Based on third-day weights measured as percent of initial weight lost (Fig. 3), none of the gerbils receiving treatment had a significantly greater loss in weight than did the control animals ($\bar{x}$ = 10.5% WL).

All gerbils in each group lost depot fat (Table 2). Previous research on sham adrenalectomized gerbils has demonstrated that these animals retain their stores of depot fat compared to adrenalectomized gerbils maintained on either cortisol or aldosterone (Baggia, 1983). Although these data could not be statistically analyzed, it should be noted that the animals that received epinephrine and lived the longest lost comparatively more depot fat. While there was no significant difference in survival between gerbils that received epinephrine and those that received norepinephrine, it was noteworthy that the epinephrine-treated group lost approximately four times the amount of depot fat as gerbils that received norepinephrine. Furthermore, the mean initial body weights of these two groups differed by less than three grams.

DISCUSSION

While the extended survival time of adrenalectomized gerbils treated with epinephrine over that of the control group (untreated adrenalectomized gerbils) was statistically significant, the period was very brief. The cause of this extension may be due to this compound's actions on the cardiovascular system and its glycogenolytic and lipolytic effects. Unlike norepinephrine, epinephrine produces increased blood flow to the muscles and liver, where there is an accelerated rate of glycogenolysis. Epinephrine not only stimulates glycogen breakdown directly but also inhibits glycogen synthesis in the liver, thus directing all available glucose residues and precursors into the production of free blood glucose. This hyperglycemia is enhanced by an epinephrine-induced stimulation of a lipase in fat cells to break down triacylglycerols to yield free fatty acids which bind to serum albumin (Lehninger, 1975). The critical instability of the vascular system following bilateral adrenalectomy may be partially reduced by epinephrine's ability to increase cardiac output and, consequently, elevate systemic blood pressure (Remington, 1951).

The fact that epinephrine-treated animals survive longer than those receiving norepinephrine was expected. It is well documented that epinephrine has approximately ten times as great a metabolic effect in mammals as norepinephrine and has the ability to increase the metabolic rate to as much as 150 percent above normal (Guyton, 1961). Although both of these amines act to elevate blood pressure, norepinephrine achieves its pressor effects through its ability to greatly increase the total peripheral resistance, thereby elevating arterial pressure a corresponding amount (Guyton, 1961). In this sense, the vasoconstriction seen in muscle capillary beds, coupled with an inability to significantly affect both liver and muscle glycogenolysis, would limit the effectiveness of this amine in reducing an energy crisis of any kind. The lack of a significant difference in survival between the norepinephrine-treated animals and the control group might be expected; however, the absence of a significant difference between animals receiving norepinephrine and those given epinephrine was unexpected. The reasons for their comparable survival times are unknown.

Gerbils in all treatment groups demonstrated daily weight losses until death. Based on third-day weights,

however, as previously noted, no significant differences were found among the groups. Following adrenalectomy, weight losses for the first two to three days are likely due to desiccation, as has been reported for *Gerbillus gerbilus*, the jerboa, another desert rodent (Burns, 1956). This rapid weight loss during the first two days was observed in all postoperative animals. The treatment regimens used appeared to have no effect on this rapid initial decline in weight.

Gerbils that received the combination of epinephrine and norepinephrine lost less weight than any other group after the second day. The cortisol-supplemented group demonstrated more weight loss than the unsupplemented combination group after the second day; however, the rate of weight loss in both combination groups was considerably less than in the controls or the singly treated groups. The combination group supplemented with cortisol would be likely to exhibit more weight loss than the unsupplemented animals. The gluconeogenic activity of cortisol would result in a wasting of muscle tissue, while both epinephrine and cortisol would act to mobilize free fatty acids, producing a reduction in fat pad mass.

Both the epinephrine-treated animals and the group receiving norepinephrine followed a weight-loss pattern similar to the control animals, continuing with a sharp decline in weight after the second day. Because the majority of the epinephrine in the circulation is derived from that synthesized in the adrenal medulla (Wurtman and Axelrod, 1965), this similarity in daily weight loss is unclear. Moreover, in the absence of significant glycogenolytic activity, it is also unclear as to why the animals receiving norepinephrine also followed this pattern of daily weight loss.

The loss of depot fat seen in all groups tested is to be expected in the animal under stress. Although these data were not statistically analyzed, the gerbils that received epinephrine lost comparatively more depot fat, which may possibly correlate with their longer survival. As the easily mobilized supply of glycogen approaches exhaustion, an animal under stress must turn to other non-carbohydrate sources of energy. These energy sources are provided by the processes of gluconeogenesis, utilizing proteins from muscles, and lipolysis, using triglycerides from the fat depots, particularly in the abdominal and subcutaneous regions (Lehninger, 1975). Although survival times did not vary

significantly between the epinephrine-treated animals and the group given norepinephrine, the epinephrine-treated animals were able to more successfully mobilize depot fat. The stimulation of a lipase in fat cells to break down triacylglycerols to yield free fatty acids constitutes one of the major roles of epinephrine and would serve to explain the results demonstrated for the depot fat (Lehninger, 1975). It is interesting to note that all other treatment groups had more residual depot fat at necropsy than the control animals. A lessened survival would partially account for this additional depot fat. As the animal continues to live and demand energy, the supply of depot fat would diminish accordingly. However, the gerbils receiving norepinephrine lived longer than the controls, yet had approximately three times the depot fat at necropsy. As mentioned previously, both the epinephrine-treated animals and the norepinephrine group had similar survival times, yet the norepinephrine group retained approximately four times the depot fat of the gerbils receiving epinephrine. Apparently, the mechanism which functioned to promote survival in the gerbils receiving norepinephrine did not depend on an ability to mobilize depot fat.

As evidenced, both epinephrine and cortisol provide the animal under stress with mechanisms for obtaining energy. By attempting to simulate the resting secretion rate of catecholamines by the adrenal medullae, following Guyton (1961), and by further incorporating the adrenal cortical hormone cortisol, as used by Cullen and Scarborough (1970), it was the proposal of the present research that some measure of significant survival would be demonstrated in the gerbils receiving the epinephrine/norepinephrine combination, supplemented with cortisol. On the contrary, this group had significantly less survival than the animals given epinephrine, which appeared to be the most capable of coping following adrenalectomy. Additionally, it was thought that the presence of cortisol would be advantageous, as many effects of catecholamines are dependent on adrenocortical secretions (Hingerty and Boyle, 1972). It must be remembered, however, that no dosage levels for either catecholamine secretion or adrenal cortical secretion have been established for the Mongolian gerbil. Possibly, with different dosages, long-term survival could be achieved in the gerbil. For that matter, the rate of secretion of adrenal hormones in the laboratory-housed gerbil might be entirely different than that

of the gerbil found in the wild. Considering that the normal habitat of the gerbil contrasts sharply with the typical laboratory environment, it is not unlikely that the laboratory-housed gerbil has undergone a compensatory increase in adrenal mass to cope with his foreign environment.

Additionally, a determination of the major cortical and medullary secretions in the gerbil should be investigated. Evidence suggests that perhaps cortisol is only one of the major glucocorticoids synthesized by the gerbil. Oliver and Peron (1964) found that the gerbil produces equal quantities of cortisol and 19-hydroxy-11-deoxycortisol. More recently, a 19-norhydroxylase was isolated in the mitochondria of the gerbil adrenal (McCarthy and Dickinson, 1980). Although epinephrine and norepinephrine are considered the major secretions of the adrenal medulla, it is now known that many more compounds, including enkephalins, are found there (Livett, et al., 1981). Several of these more newly discovered compounds may have far more profound effects than the well-known secretions, which are more widely investigated. Based on the results of the present research and those of similar studies, it is likely that the key to the gerbil's critical

adrenal dependence will unfold only through extensive investigation of both traditional and newly discovered replacement compounds.

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Table 1. Post-operative replacement therapy used in adrenalectomized *Meriones unguiculatus* according to group*.

GROUPS				
ADX - No Replacement (Control)**	Epinephrine	Norepinephrine	Epinephrine/ Norepinephrine	Epinephrine/ Norepinephrine/ Cortisol

*For all groups, N = 7 except the Epinephrine/Norepinephrine/Cortisol group, where N = 6.

**Divided into two sections to permit separate controls on both operative days.

Table 2. Effect of catecholamine replacement therapy on depot fat in adrenalectomized *Meriones unguiculatus*.

Treatment Group*	Mean Survival (Days)	Mean Initial Body Wt. (g)	Mean Terminal Body Wt. (g)	Mean Depot Fat (g)	Depot Fat/ Initial Body Wt.
Control	4.6	53.3	47.5	0.11	0.0022
Epinephrine	6.0	55.2	47.2	0.09	0.0016
Norepinephrine	5.6	58.0	50.5	0.39	0.0066
Epinephrine/ Norepinephrine	3.6	55.4	51.2	0.47	0.0084
Epinephrine/ Norepinephrine/ Cortisol	4.0	58.7	51.3	0.19	0.0030

Figure 1. The effects of catecholamines on survival in adrenalectomized *Meriones unguiculatus* ± Standard Deviation. For the epinephrine group, all animals lived six days (N = 7). For the Epinephrine/Norepinephrine/ Cortisol group, N = 6. Means underscored by the same line do not differ significantly at p = 0.05.

$\bar{x}$ = mean survival (days)

Legend - Treatment Groups

A = Control (no treatment)

B = Epinephrine

C = Norepinephrine

D = Epinephrine/Norepinephrine

E = Epinephrine/Norepinephrine/Cortisol

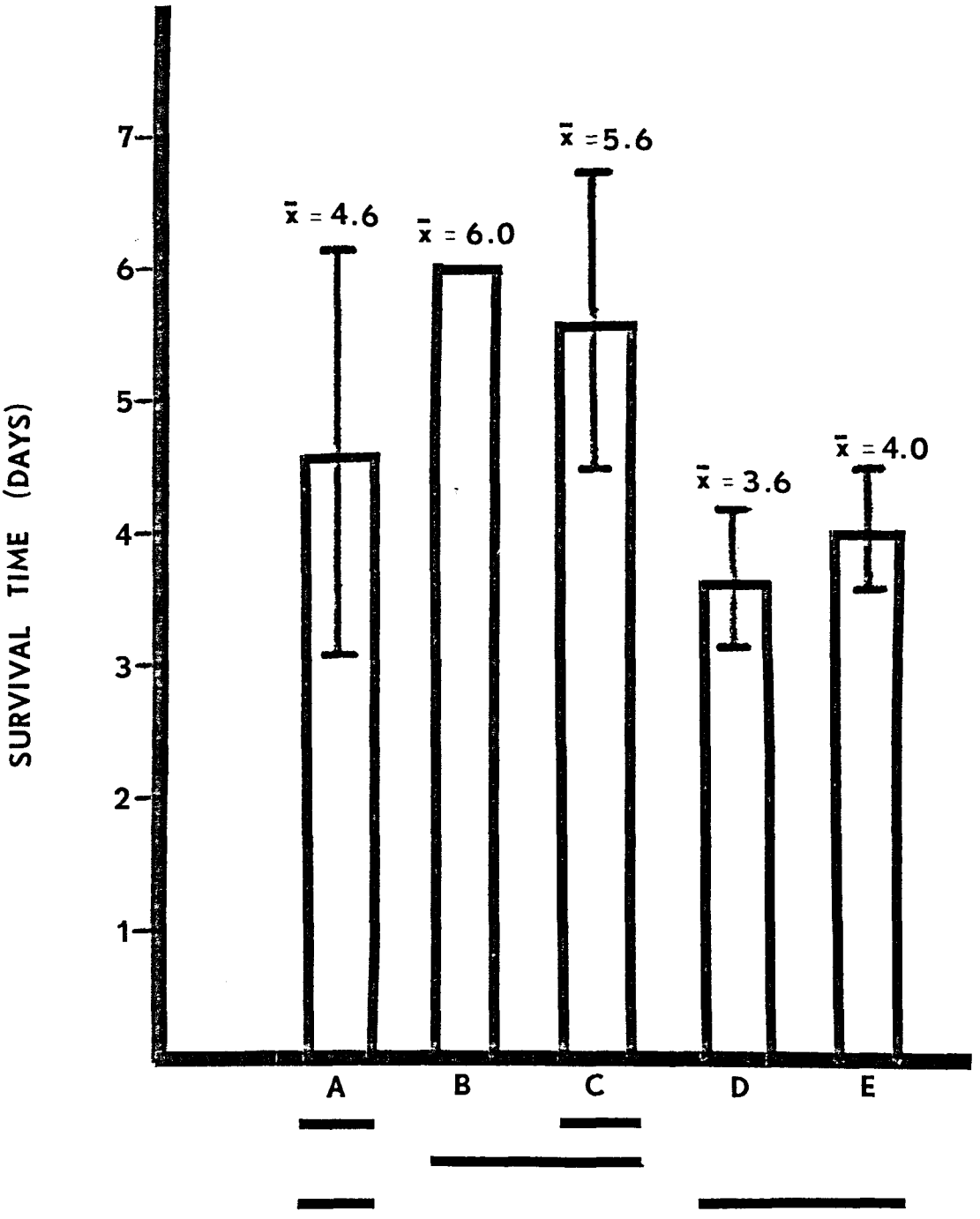

SURVIVAL TIME (DAYS)
7
6
5
4
3
2
1
x̄ = 4.6
x̄ = 6.0
x̄ = 5.6
x̄ = 3.6
x̄ = 4.0
A
B
C
D
E

Fig. 2. The effect of catecholamines on daily weight changes in adrenalectomized *Meriones unguiculatus*, calculated as a percent of initial body weight.

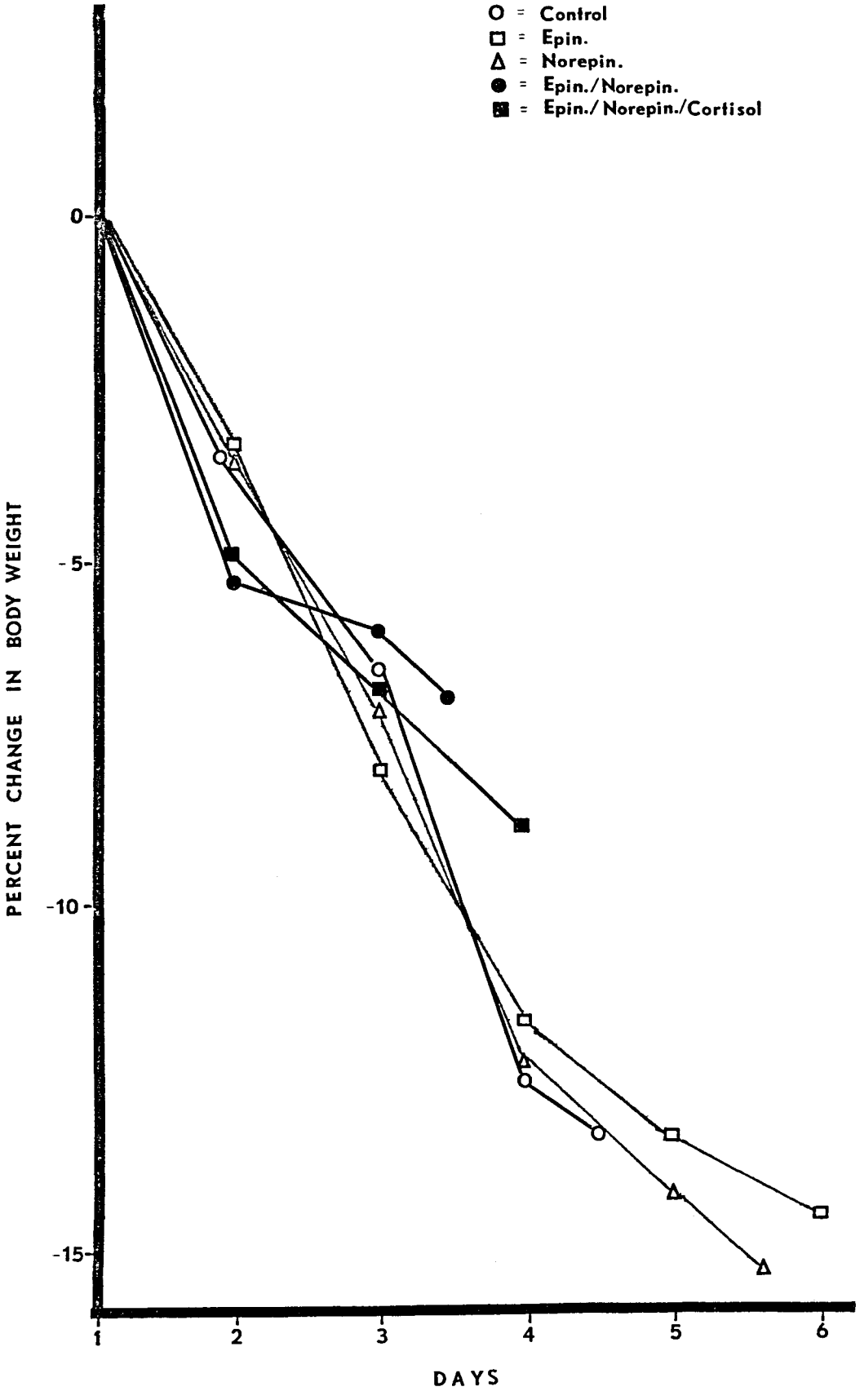

O = Control
□ = Epin.
△ = Norepin.
● = Epin./Norepin.
■ = Epin./Norepin./Cortisol
0
-5
-10
-15
PERCENT CHANGE IN BODY WEIGHT
1
2
3
4
5
6
DAYS

Figure 3. The effects of catecholamines on weight loss in adrenalectomized *Meriones unguiculatus* based on the third-day weight as a percent of initial body weight ± Standard Deviation (N = 7) - For the Epinephrine/Norepinephrine/Cortisol group, N = 6

None of the means differed significantly at p = 0.05

$\bar{x}$ = mean percent weight loss

Legend - Treatment Groups

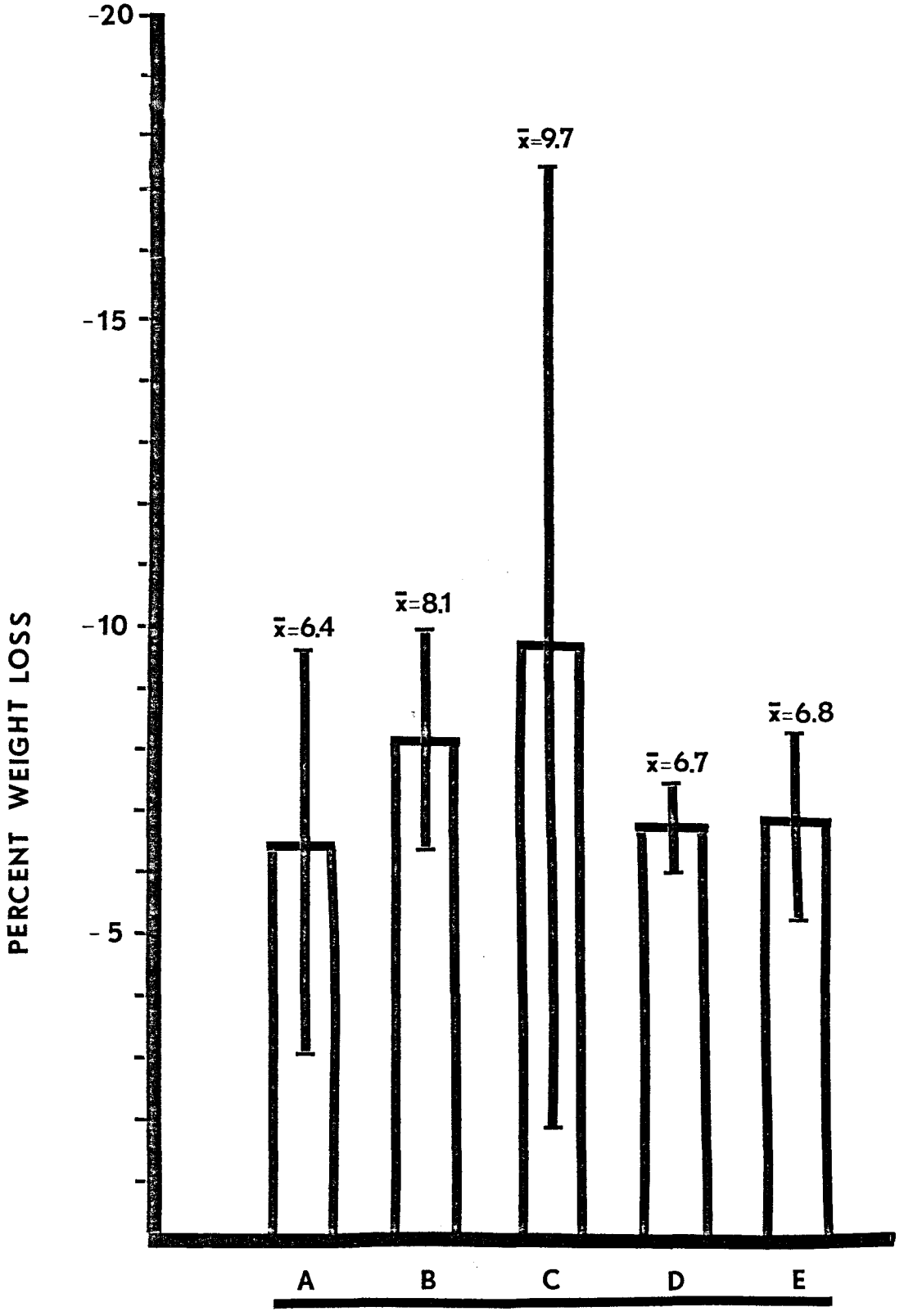
A = Control (no treatment)

B = Epinephrine

C = Norepinephrine

D = Epinephrine/Norepinephrine

E = Epinephrine/Norepinephrine/Cortisol



APPENDIX

Caudal Sphygmography

A Programmed Electro-Sphygmomanometer, Model No. PE-300 (Narco Scientific, Houston, Tx.), adapted with a small-laboratory-animal occluding cuff, was used to attempt systolic blood pressure readings on the gerbils. As this unit is commonly used for obtaining indirect systolic and diastolic blood pressures in small laboratory animals, it was hoped that this unit could be adapted to the gerbil as well. A plexiglass immobilizer was used to warm the animals for 10-15 min prior to obtaining readings (Diz, et al., 1981). When this measure alone proved to be ineffective, several modifications in the technique were employed. The animals' tails were shaved to permit better contact with the electrode. To enhance blood flow through the tail, additional warming with incandescent lights was provided. Finally, an additional amplifier was attached to the unit to help boost the signal. All of these measures proved ineffective. Because this unit could not be adapted to the gerbil, this experimental parameter was abandoned.

VITA

Carol Birkhead Ussery was born April 6, 1949 in Richmond, Va. Secondary education was completed in 1967 at Hermitage High School in Richmond. She attended Chowan College for one year, majoring in business education. From 1968 to 1970, she was employed by A. H. Robins Co., and from 1970 to 1972, by the Department of Laboratory Animal Medicine, Indiana University. She received her nursing education from Richmond Memorial Hospital and was licensed as a registered nurse in 1975. Following graduation, she worked as an emergency room nurse, a private scrub nurse, and an allergy nurse. She then resumed full-time undergraduate education at Westhampton College, receiving her B.S. degree in biology in 1981. She received the degree of Master of Science in biology from the University of Richmond in 1983. Throughout graduate school, she was employed part-time as a staff R.N. in the obstetrics and gynecology units of Henrico Doctors Hospital, Richmond. In August 1983, she will enter the School of Medicine at the Medical College of Virginia.